



**SOCIETÀ MEDICA
DI SANTA MARIA NUOVA**

IX EDIZIONE

**Giornate Mediche di
Santa Maria Nuova 2017**

L'Ospedale dei Fiorentini



**LA DIMISSIONE
OSPEDALIERA "RITARDATA":
Complicanze intraospedaliere
e criticità gestionali**

5-6 Ottobre 2017

**L'OTTIMIZZAZIONE GESTIONALE E TERAPEUTICA COME
STRUMENTO DELLA PREVENZIONE DELLE COMPLICANZE
E COME ACCELERATORE DEL PERCORSO DI DIMISSIONE**

***La corretta gestione
della terapia
antiaggregante e
anticoagulante
nel perioperatorio***



**Federica Marini
UO Anestesia e Rianimazione
Ospedale Santa Maria Nuova
Azienda Toscana Centro**

Peri-operative period

Perioperative period refers to the three phases of surgery:

Preoperative
Intraoperative
Postoperative

**Perioperative
period
± 30 days**

The goal of **Perioperative Care** is to provide better conditions for patients before operation, during operation and after operation.



2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

The Task Force for the management of atrial fibrillation of the European Society of Cardiology (ESC)

Developed with the special contribution of the European Heart Rhythm Association (EHRA) of the ESC



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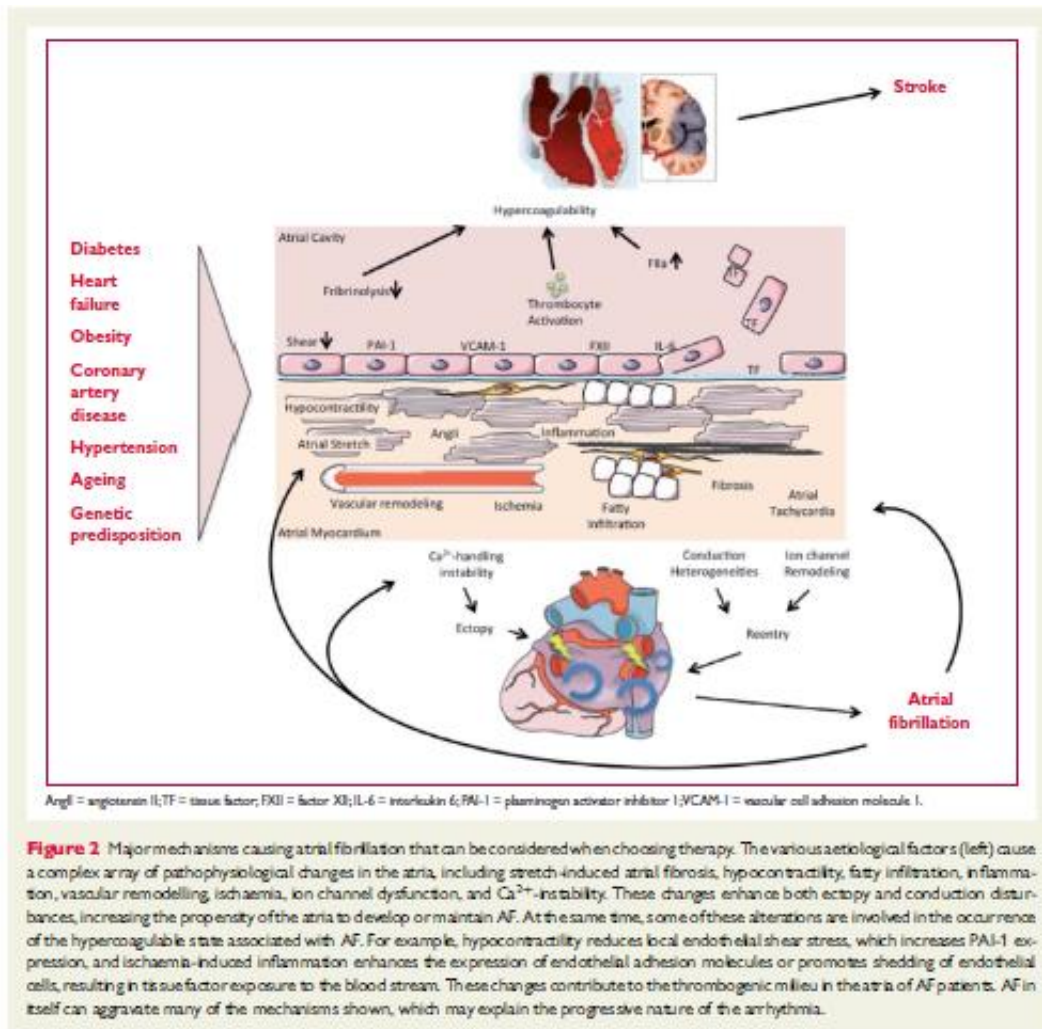
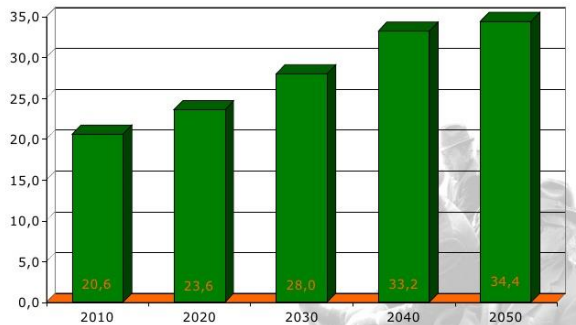


Figure 2 Major mechanisms causing atrial fibrillation that can be considered when choosing therapy. The various aetiological factors (left) cause a complex array of pathophysiological changes in the atria, including stretch-induced atrial fibrosis, hypocontractility, fatty infiltration, inflammation, vascular remodelling, ischaemia, ion channel dysfunction, and Ca²⁺-instability. These changes enhance both ectopy and conduction disturbances, increasing the propensity of the atria to develop or maintain AF. At the same time, some of these alterations are involved in the occurrence of the hypercoagulable state associated with AF. For example, hypocontractility reduces local endothelial shear stress, which increases PAI-1 expression, and ischaemia-induced inflammation enhances the expression of endothelial adhesion molecules or promotes shedding of endothelial cells, resulting in tissue factor exposure to the blood stream. These changes contribute to the thrombotic milieu in the atria of AF patients. AF in itself can aggravate many of the mechanisms shown, which may explain the progressive nature of the arrhythmia.

Le proiezioni demografiche

Proiezioni sull'incidenza percentuale della popolazione con oltre 65 anni 2010-2050 (ipotesi centrale)



Fonte: Istat, GeoDemo: Demografia in cifre, [http://demo.istat.it/], nostra elaborazione.

Perioperative management of antiplatelet therapy

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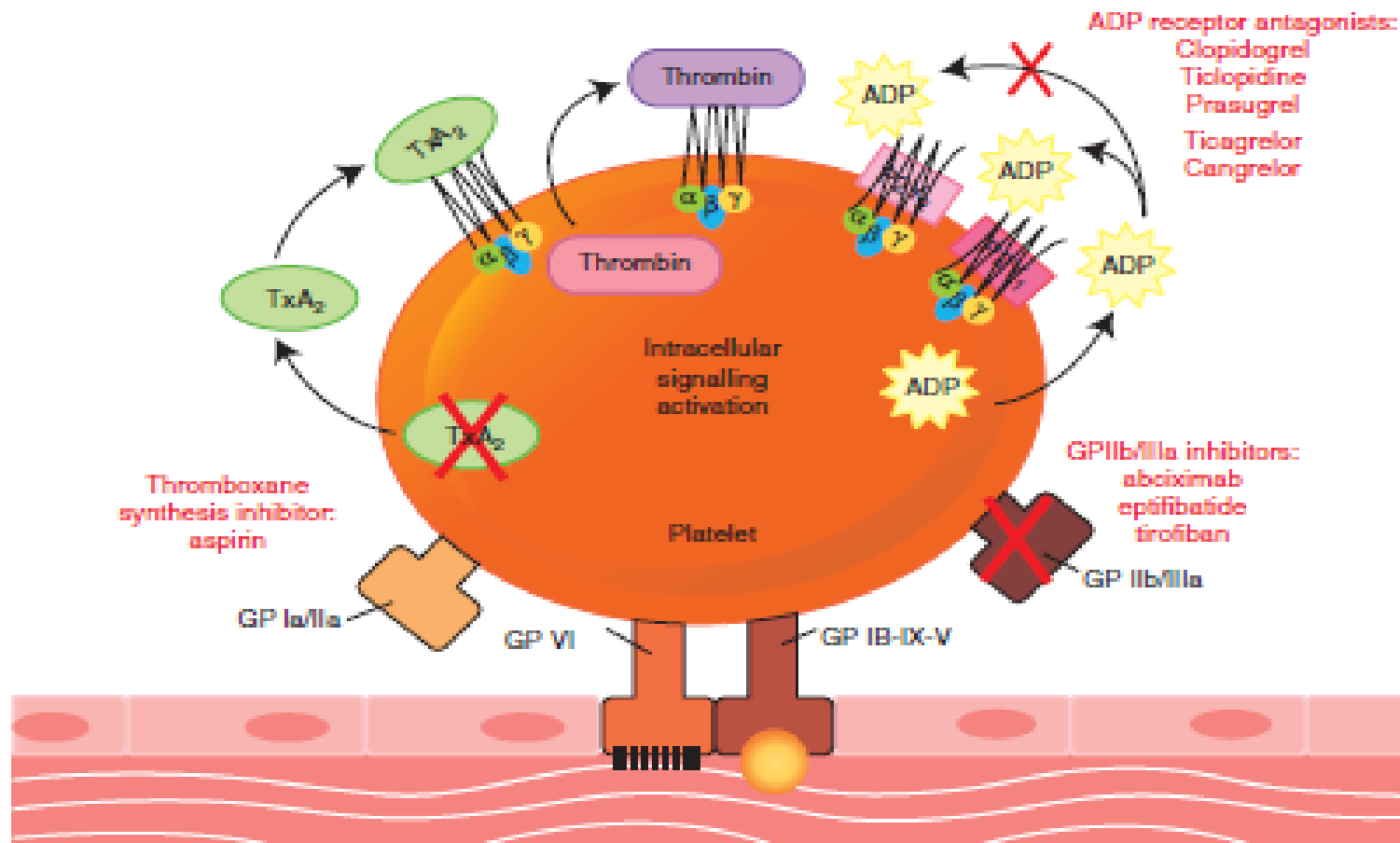


Fig 1 Therapies targeted at inhibiting various platelet receptors. These include the thromboxane inhibitors, ADP receptor antagonists, and GPIIb/IIIa inhibitors. Adapted from Meadows and Bhatt,⁴ with permission. TxA₂, thromboxane A₂; GP Ia/IIa, glycoprotein Ia/IIa; GPVI, glycoprotein VI; GP Ib-IX-V, glycoprotein Ib-IX-V; ADP, adenosine diphosphate; GPIIb/IIIa, glycoprotein IIb/IIIa.

New antiplatelet drugs and new oral anticoagulants

V. Koenig-Oberhuber^{1,2} and M. Filipovic¹

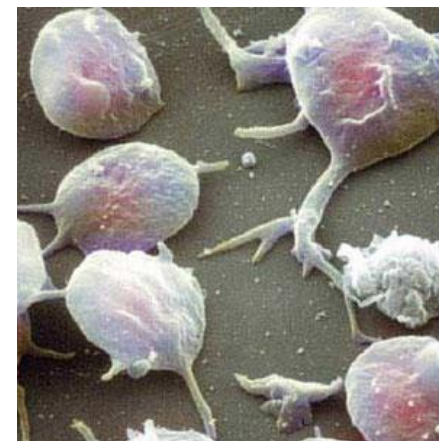


Table 1 Summary of the characteristics of currently available antiplatelet drugs

Characteristic	Aspirin	Clopidogrel	Prasugrel	Ticagrelor	Gangrelor	Abciximab	Eptifibatide	Tirofiban
Route of administration	Oral once daily, (i.v.)	Oral once daily, (i.v. under investigation)	Oral once daily	Oral twice daily	i.v.	i.v.	i.v.	i.v.
Bioavailability	68%	50%	80%	36%				
Plasma peak concentration	30–40 min	1 h	30 min	1.5 h	Seconds	Dose dependent	Dose dependent	Dose dependent
Time to plasma steady state		2–8 h	30 min to 4 h	30 min to 2 h	Seconds	Initial bolus and continuous application	Initial bolus and continuous application 4–6 h	Initial bolus and continuous application 10 min
Plasma half-life	15–30 min	8 h	7 h	7 h	2–5 min	10–15 min	2.5 h	2 h
Plasma protein binding	Strong	Strong	Strong	Strong				
Time from last dose to offset	7–10 days	7–10 days	7–10 days	5 days	60 min	12 h	2–4 h	2–4 h
Reversibility of platelet inhibition	No	No	No	Yes	Yes	Yes	Yes	Yes
Recommended period of discontinuation before surgical intervention (see Fig. 2)	0–5 days	7 days	10 days	7 days	1–6 h	48 h	8 h	8 h

Bleeding Disorders in Orthopedic Surgery



DECEMBER 2012 | Volume 35 • Number 12

JUDITH MANDOLAK, D.O.; KENNETH GRAF, MD; PAUL LAFFERTY, MD

Table 1

Antiplatelet Agents

Variable	Aspirin	NSAIDs	ADP Receptor Antagonists	GP IIb-IIIa Receptor Antagonists
Action	Inhibits platelet function via irreversible acetylation of platelet COX-1, indirectly inhibits TXA2 synthesis	Inhibits platelet function via reversible acetylation of platelet COX-1, indirectly inhibits TXA2 synthesis	Inhibits platelet activation	Inhibits platelet aggregation
Cessation preoperatively	7-10 d	24-48 h	7-10 d (clopidogrel, prasugrel); 14 d (ticlopidine)	24-48 h (abciximab); 10 h (eptifibatid); 2-4 h (tirofiban)

Abbreviations: ADP, adenosine diphosphate; COX-1, cyclooxygenase-1; GP, glycoprotein; NSAIDs, nonsteroidal anti-inflammatory drugs; TXA2, thromboxane A2.

Table 2

Herbal Medications

Variable	Garlic	Ginger	Ginseng	Ginkgo Biloba	Kava Kava	Fish Oil	Vitamin E
Action	Dose-dependent irreversible inhibition of platelet aggregation	Prolonged bleeding time	Inhibits in vitro platelet aggregation and prolongs coagulation times	May inhibit platelet-activating factor and alter platelet function	Platelet dysfunction; hepatotoxicity	Increased bleeding risk at high doses	Antioxidant; may increase effects of anticoagulants and antiplatelets
Cessation preoperatively	7 d	2 wk	7 d	36 h	2 wk		



Tab. 5: Emivite e Intervallo di tempo raccomandati tra somministrazione del FANS e puntura spinale

FANS	$T_{1/2\beta}$	Intervallo di tempo tra ultima somministrazione e puntura spinale
Diklofenac	1-2 h	12 h
Ibuprofen	2 h	12 h
Ketoprofen	2 h	12 h
Indomethacin	4.5 h	24 h
Ketorolac	4-6 h	24 h
Naproxen	10-17h	48 h
Lornoxicam	4 h	24 h
Piroxicam	10-70 h	2 settimane
Tenoxicam	72 h	2 settimane
COX-2-specific inhibitors		Nessun effetto sulle piastrine

Perioperative management of antiplatelet therapy

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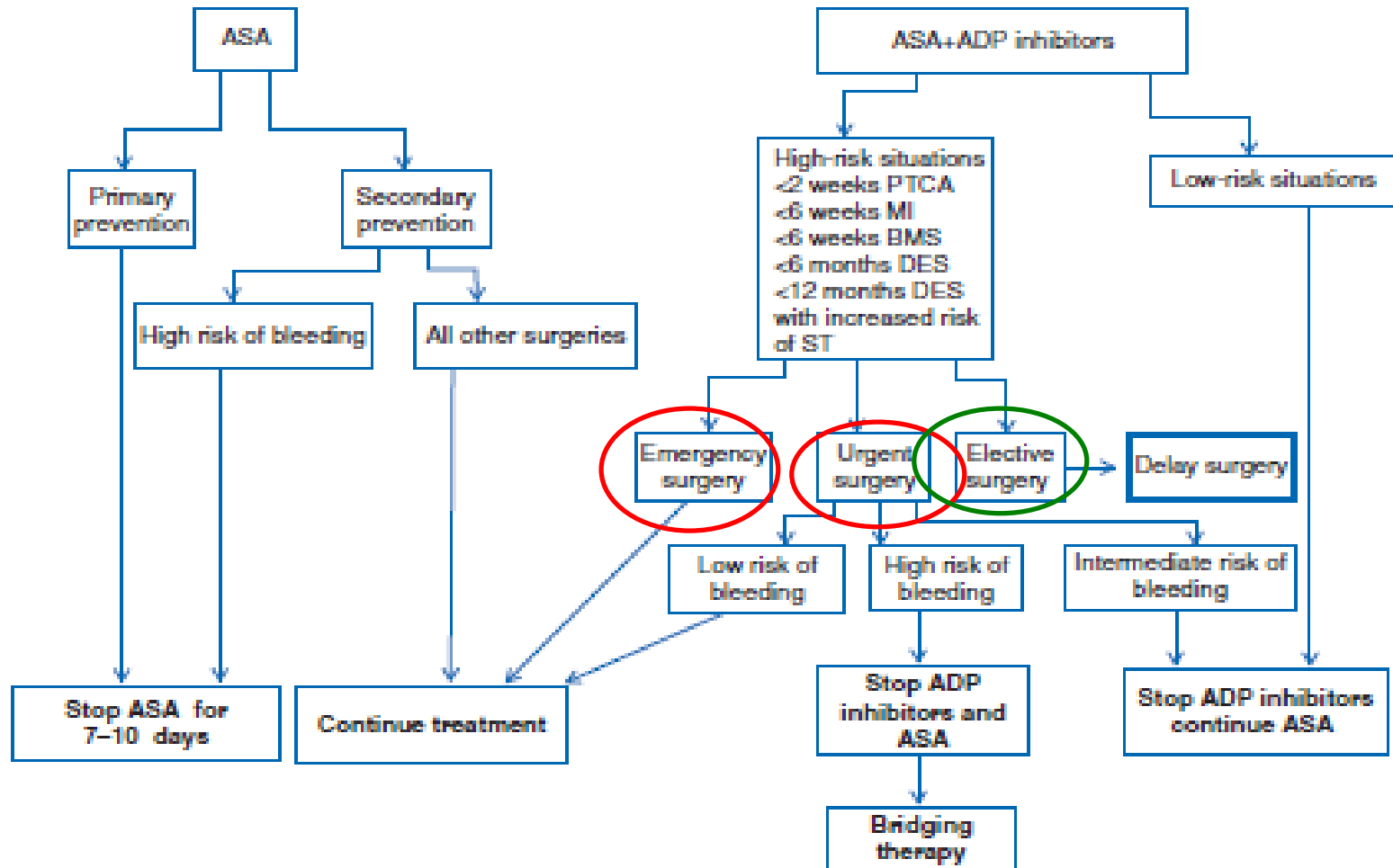


Fig 2 Algorithm for perioperative management of antiplatelet therapy. Adapted from Di Minno and colleagues,²⁰ with permission. ADP, a diphosphate; ASA, aspirin; PTCA, percutaneous transluminal coronary angioplasty; BMS, bare metal stent; DES, drug-eluting stent; MI, myocardial infarction; ST, stent thrombosis.

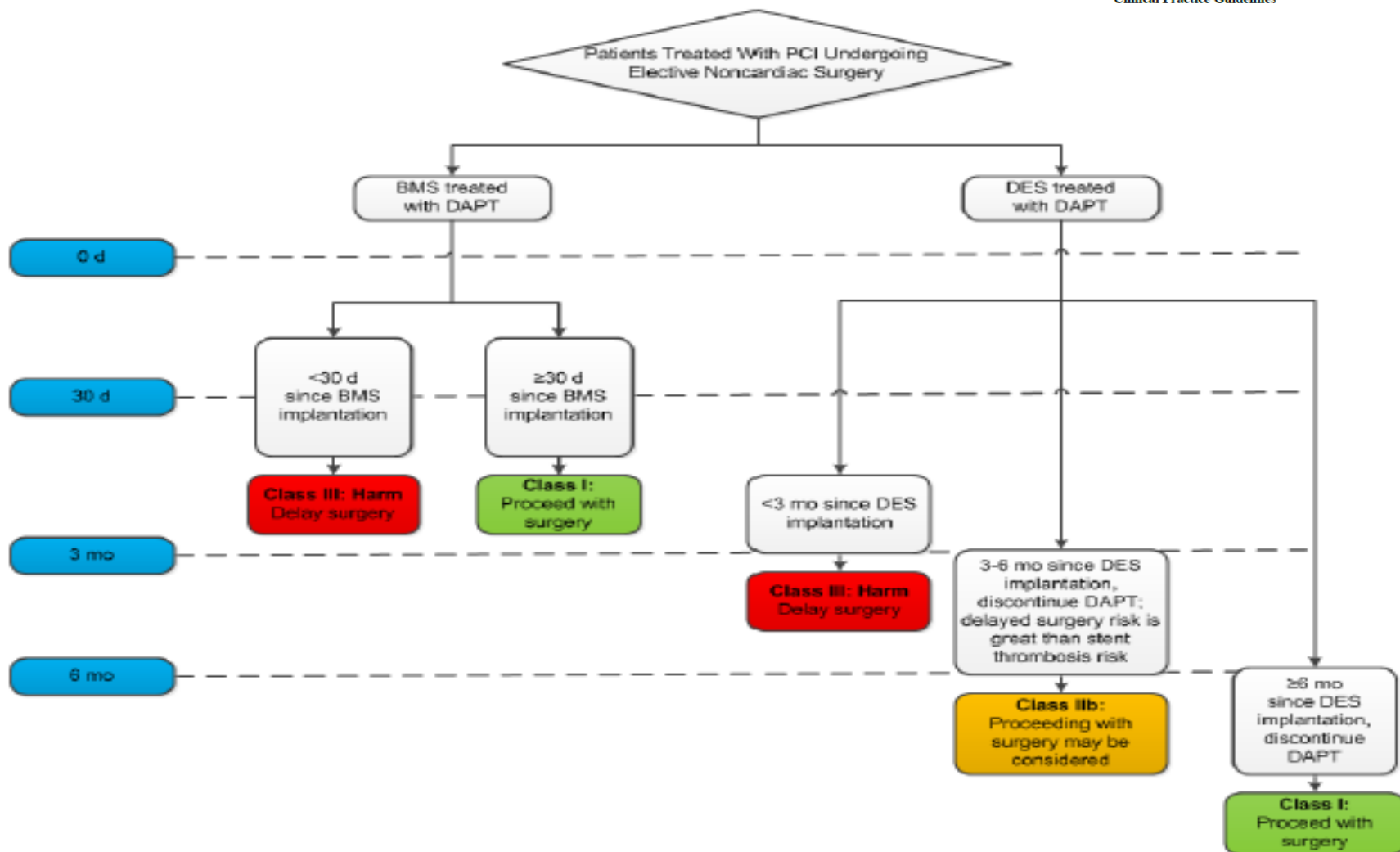


Figure 6. Treatment Algorithm for the Timing of Elective Noncardiac Surgery in Patients With Coronary Stents

Colors correspond to Class of Recommendation in Table 1.

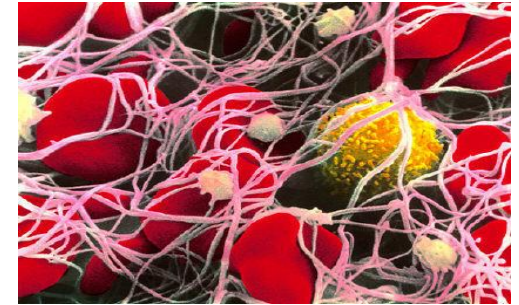
BMS indicates bare metal stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; and PCI, percutaneous coronary intervention.



Peri-operative management of anticoagulation and antiplatelet therapy

David Keeling,¹ R. Campbell Tait,² and Henry Watson³ on behalf of the British Committee for Standards in Haematology

¹Oxford University Hospitals NHS Foundation Trust, Oxford, ²Glasgow Royal Infirmary, Glasgow, and ³Aberdeen Royal Infirmary, Aberdeen, UK



- Between **4% and 8%** of PCI (percutaneous intervention) patients will require surgery within 1 year of stenting.
- The risk of peri-operative major adverse cardiac events is greatest within the **first month** after PCI with gradually lessening risk at 2-6 month, 6-12 month and > 1 year.

DOCUMENTO DI CONSENSO

Stent coronarico e chirurgia: la gestione perioperatoria della terapia antiaggregante nel paziente portatore di stent coronarico candidato a intervento chirurgico

Roberta Rossini¹, Ezio Bramucci², Battistina Castiglioni³, Stefano De Servi⁴, Corrado Lettieri⁵,
Maddalena Lettino⁶, Giuseppe Musumeci¹, Luigi Oltrona Visconti², Emanuela Piccaluga⁷,
Stefano Savonitto⁸, Daniela Trabattoni⁹, Francesca Buffoli⁵, Dominick J. Angiolillo¹⁰,
Francesco Bovenzi¹¹, Alberto Cremonesi¹², Marino Scherillo¹³, Giulio Guagliumi¹,
a nome della Società Italiana di Cardiologia Invasiva (GISE)
e dell'Associazione Nazionale Medici Cardiologi Ospedalieri (ANMCO)

In paziente con alto rischio di trombosi dello STENT considerare bridging therapy con inibitori glicoproteina quali **EPTIFIBATIDE** (da sospendere 8 ore preop) o **TIROFIBAN** (da sospendere 4 ore preop), in ambiente monitorizzato (es. Terapia intensiva o sub intensiva).

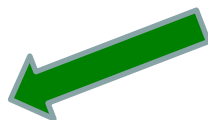


Tabella 1. Definizione del rischio trombotico.

Rischio basso	Rischio Intermedio	Rischio alto
<ul style="list-style-type: none"> • >6 mesi dopo PCI con BMS • >12 mesi dopo PCI con DES 	<ul style="list-style-type: none"> • >1 mese <6 mesi dopo PCI con BMS • >6 mesi <12 mesi dopo DES • >12 mesi dopo DES a rischio elevato (stent lunghi, multipil, in overlapping, piccoli vasi, biforcazioni, tronco comune, last remaining vessel) 	<ul style="list-style-type: none"> • <1 mese dopo PCI con BMS • <6 mesi dopo DES • <12 mesi dopo DES a rischio elevato (stent lunghi, multipil, in overlapping, piccoli vasi, biforcazioni, tronco comune, last remaining vessel)

La presenza di sindrome coronarica acuta in occasione della PCI, pregressa trombosi di stent, frazione di elezione <35%, insufficienza renale cronica, diabete mellito aumentano il rischio di trombosi intrastent. I pazienti sottoposti a bypass aortocoronarico ed i pazienti con sindrome coronarica acuta non sottoposti a PCI vengono considerati ad alto rischio entro il primo mese, rischio intermedio tra 1 e 6 mesi, basso rischio oltre i 6 mesi. I pazienti sottoposti a PCI con il solo palloncino sono ritenuti ad alto rischio entro 2 settimane, a rischio intermedio tra 2 e 4 settimane, a basso rischio oltre le 4 settimane.

ASA, aspirina; BMS, stent metallico; DES, stent medicato; PCI, angioplastica coronarica.

- 4 weeks following bare metal stent
- 12 months following drug-eluting stent (shorter with the newer bioabsorbable polymer drug-eluting stent)
- Hip fracture surgery can take place early in patients on clopidogrel
- Given the uncertain net benefit of platelet transfusion, consider the use of pre-operative *intravenous tranexamic acid*
- ...if excessive peri or post op bleeding or if the bleeding risk is very high ..consider infusion of 2 pools of platelets but....if given 2 h after the last dose of aspirin and 12-24h after the last dose of clopidogrel to avoid being inhibited by circulating drugs or active metabolite.



<u>NOME DEL FARMACO</u>	<u>TEMPI DI SOSPENSIONE</u>
<u>Tiklid</u> (ticlopidina)	14 gg
<u>Clopidogrel</u> cp 75 mg	5 gg
<u>Clopinovo</u> cp 75 mg (Clopidogrel)	5 gg
<u>Duoplavin</u> 75/100mg (Clopidogrel+ASA)	5 gg
<u>Nogreg</u> cp 75 mg (Clopidogrel)	5 gg
<u>Plavix</u> cp 75mg (Clopidogrel)	5 gg
<u>Revlis</u> cp 75 mg (Clopidogrel)	5 gg
<u>Zyllt</u> cp 75 mg (Clopidogrel)	5 gg
<u>Brilique</u> (Ticagrelor) cp 90 mg	5 gg
<u>Efient</u> (Prasugrel) cp 10 mg	7 gg



ORIGINAL ARTICLE

Aspirin in Patients Undergoing Noncardiac Surgery



CONCLUSIONS

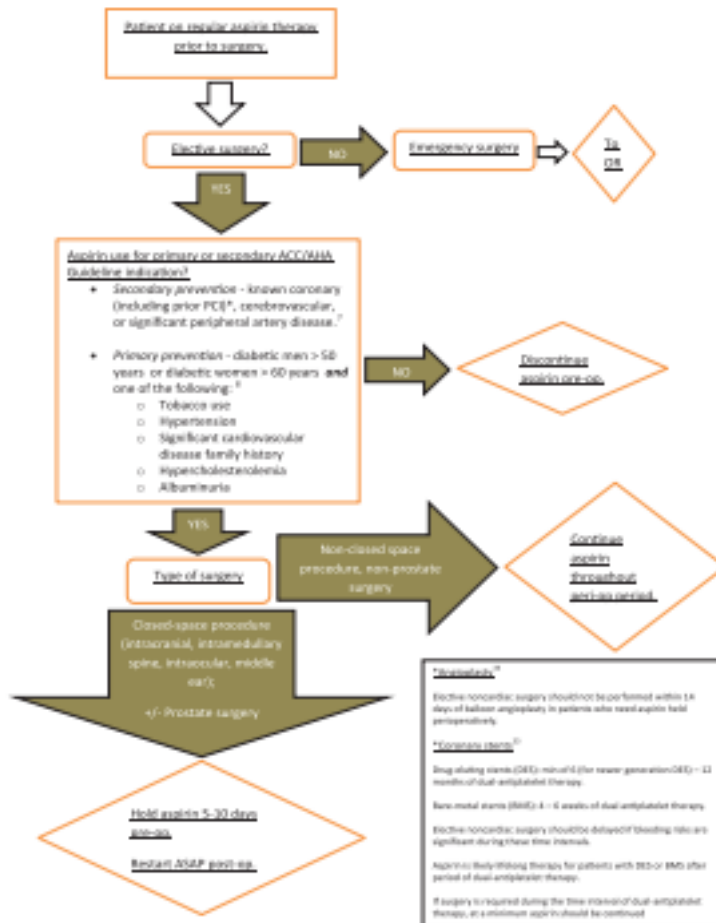
Administration of aspirin before surgery and throughout the early postsurgical period had no significant effect on the rate of a composite of death or nonfatal myocardial infarction but increased the risk of major bleeding. (Funded by the Canadian Institutes of Health Research and others; POISE-2 ClinicalTrials.gov number, NCT01082874.)

N ENGL J MED 370:16 NEJM.ORG APRIL 17, 2014

*Qual è l'indicazione alla terapia con
aspirina?*

Perioperative Aspirin Management After POISE-2: Some Answers, but Questions Remain

Neal Stuart Gerstein, MD, FASE,* Michael Christopher Carey, MD,* Joaquin E. Cigarroa, MD,† and Peter M. Schulman, MD‡



Aspirin use for primary or secondary ACC/AHA Guideline indication?

- **Secondary prevention** - known coronary (including prior PCI)*, cerebrovascular, or significant peripheral artery disease.⁷
- **Primary prevention** - diabetic men > 50 years or diabetic women > 60 years and one of the following:⁸
 - Tobacco use
 - Hypertension
 - Significant cardiovascular disease family history
 - Hypercholesterolemia
 - Albuminuria

Figure 2. Algorithm for the management of patients presenting for surgery while receiving aspirin therapy. OR = operating room; ACC = American College of Cardiology; AHA = American Heart Association; PCI = percutaneous coronary intervention.



EVITARE EBPM come sostituzione della doppia antiaggregazione.

- Reinserire terapia completa di antiaggregazione **48h** dopo l'intervento e dopo adeguata valutazione dell'emostasi chirurgica



CLINICAL PERSPECTIVES

New oral anticoagulants: a practical guide on prescription, laboratory testing and peri-procedural/bleeding management

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Anticoagulants



Perioperative Management of Patients Receiving New Oral Anticoagulants
An International Survey

Ieko et al. *Journal of Intensive Care Medicine* 2015, 30(1), 1-7
DOI 10.1186/s40560-016-0144-5

Journal of Intensive Care

REVIEW

Open Access

Profiles of direct oral anticoagulants and clinical usage—dosage and dose regimen differences

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Circulation

2015

Please follow your local copyright law

P15-04700

DOI: 10.1161/CIRCULATIONAHA.115.015688



HTRS Review Article

Direct Oral Anticoagulants (DOACs) in the Laboratory: 2015 Review

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ABSTRACT

Direct oral anticoagulant therapies, including direct anti-Xa and thrombin inhibitors have recently been introduced and may have advantages over vitamin K antagonists such as warfarin. This review describes briefly the clinical utility and mechanism of action of these agents. Detailed information is provided on effect of these agents on routine assays including the APTT and PT as well as their impact on specialty laboratory assays. Also included are the use of drug specific assays and a discussion of alternative methods to determine relative drug concentration, such as evaluating drug calibrators in APTT and PT assays and using heparin calibrated anti-Xa assays to measure direct Xa inhibitors.

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European Heart Journal – Cardiovascular Pharmacotherapy (2015) 1, 134–145
doi:10.1093/ehjcp/ptv002

REVIEW

New oral anticoagulants: a practical guide for physicians

Rocio Hinojar*, Jose Julio Jiménez-Natcher, Covadonga Fernández-Golfín, and Jose Luis Zamorano

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Received 21 January 2015; accepted 22 January 2015; online published ahead of print 25 February 2015

New oral anticoagulants (NOACs) are an alternative for vitamin K antagonists (VKAs) to prevent stroke in patients with non-valvular atrial fibrillation (AF). Unlike VKAs, these anticoagulants do not require routine INR monitoring and possess favorable pharmacological properties. The lack of an effective antidote, use of these new drugs will be practical and easy-to-use algorithms.

AHA SCIENTIFIC STATEMENT

Management of Patients on Non-Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Perioperative Setting

A Scientific Statement From the American Heart Association

Perioperative Management of Dabigatran: A Prospective Cohort Study

Running title: Schulman et al.; Perioperative dabigatran management



Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting

Circulation. 2017;

A Scientific Statement From the American Heart Association

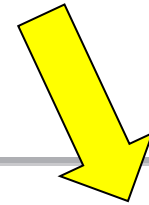


Table 1. Comparison Among NOACs

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Approved indications	Nonvalvular AF ↓ Risk of stroke and systemic embolism	Nonvalvular AF ↓ Risk of stroke and systemic embolism	Nonvalvular AF ↓ Risk of stroke and systemic embolism	Nonvalvular AF ↓ Risk of stroke and systemic embolism. Limitation: should not use in patients with CrCl >95 mL/min as a result of ↑ risk of ischemic stroke compared with warfarin at 60 mg
	DVT, PE Treatment after 5–10 d parenteral AC ↓ Recurrence Prophylaxis after hip replacement	DVT, PE Treatment ↓ Recurrence Prophylaxis after hip or knee replacement	DVT, PE Treatment ↓ Recurrence Prophylaxis after hip replacement	DVT, PE ↓ Recurrence Treatment after 5–10 d initial parenteral AC
Mechanism of action	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor

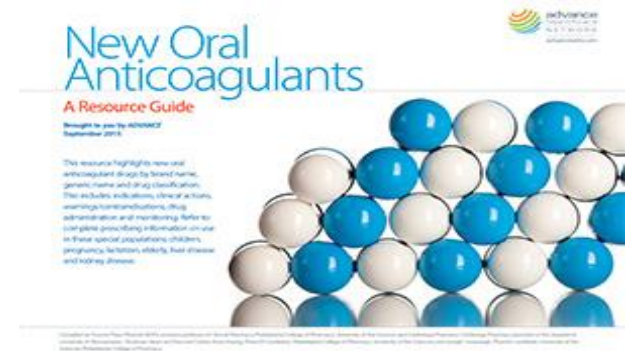
The perioperative management of new direct oral anticoagulants: a question without answers

Thromb Haemost 2013; 110: 515–522

Ogni anno il 10% dei
pazienti che
assumono
anticoagulanti orali
devono interrompere
il trattamento per
sottoporsi ad
interventi chirurgici
o procedure invasive

New oral anticoagulants offer
potentially improved safety
profiles over traditional agents;
however, their optimal
management in the
perioperative
period **remains unknown.**

Curr Opin Anesthesiol 2014, 27:344–352



Dipartimento di Medicina e delle Specialistiche Mediche Direttore Dr Giancarlo Landini

Dipartimento di Chirurgia Direttore Dr Stefano Michelagnoli

Dipartimento di Emergenza e Medicina Critica Direttore Dr Luciano Bagnoli

Dipartimento Aziendale dei Servizi Direttore Dr Roberto Carpi

CONSENSUS INTERDIPARTIMENTALE/MULTIDISCIPLINARE SUL MANAGEMENT PERI-OPERATORIO DEI NUOVI ANTICOAGULANTI ORALI (NAO) IN EMERGENZA/URGENZA ED ELEZIONE

SCOPO DEL PRESENTE DOCUMENTO E' LA STESURA DI LINEE DI INDIRIZZO PER LA GESTIONE PERI-OPERATORIA DEL PAZIENTE IN TRATTAMENTO CON NUOVI FARMACI ANTICOAGULANTI

Il documento si rivolge al Personale Medico ed Infermieristico di:

DEA, Medicina Interna, Cardiologia, Anestesia/Rianimazione, Chirurgia Generale e Specialistiche, , Ortopedia, Medicina di Laboratorio, Medicina Trasfusionale, Radiologia ed altre Specialistiche interessate

INTERVENTI CHE RICHIEDONO SOSPENSIONE

ALLEGATO 2. Rischio di sanguinamento. Tipologia di intervento. Da LINEE GUIDA ACCP, EHRA e Douketis, Blood 2012.

Alto rischio di sanguinamento
2-4% emorragia peri-procedurale

- Ablazione trans-catetere complessa (isolamento vena polmonare)
- **Anestesia spinale/epidurale**
- Biopsia renale
- Cardiocirurgia
- Ch addominale, mammaria, testa/collo, neoplastica
- Ch ortopedica protesica
- Ch toracica
- Ch urologica (anche TURP)
- Ch Vascolare
- Endoscopia operativa (Polipectomia, mucosectomia, dissezione sottomucosa, ERCP, intervento su varici esofagee, sfinterotomia biliare, dilatazione pneumatica su esofago, vie biliari, papillotomia, EUS operativa, debulking lesioni neoplastiche)
- Estrazioni >2 denti o particolari interventi anche su unico dente (VIII dente) che prevedano manovre cruente (a giudizio del chirurgo odontoiatra)
- Neurochirurgia
- PEG
- Qualsiasi intervento che dura > 45 minuti
- Rachicentesi

Basso rischio di sanguinamento
<2% emorragia peri-procedurale

- Angiografia
- Biopsia prostatica/vescicale
- Chir cataratta
- Chirurgia cutanea di superficie
- Endoscopia digerente non operativa ± biopsia, tatuaggio, stenting delle vie digerenti senza dilatazione, enteroscopia device-assisted, EUS diagnostica, videocapsula
- Endoscopia urologica
- Impianto PM-ICD
- Studio EF con ablazione

VALUTAZIONE FUNZIONALITA' RENALE

- Clearance creatinina:

Formula di **COCKROFT-GAULT**

- eGFR (secondo CKD-EPI)

Il 40% dei pz. con frattura di femore hanno GFR $\leq 60\text{ml/min/1,73m}^2$

QUANDO

- Non più di 10 giorni prima dell'intervento
- Nei pazienti particolarmente a rischio nuovo controllo della creatinina al momento del ricovero

Rischio Tromboembolico

ALLEGATO 5. Definizione del rischio tromboembolico nei pazienti in NAO. DA LINEE GUIDA ESC/ESA 2014

	FANV	TEV
Alto rischio	CHA ₂ DS ₂ -VASc ≥ 4 Recente TIA o stroke Valvulopatia reumatica	Episodio di TEV negli ultimi 3 mesi Trombofilia severa
Rischio intermedio	CHA ₂ DS ₂ -VASc 2-3	Episodio di TEV 3-12 mesi Recidiva di TEV Trombofilia non severa Neoplasia
Basso rischio	CHA ₂ DS ₂ -VASc 0-1	Singolo episodio di TEV > 12 mesi non idiopatico e nessuna altro fattore di rischio

Peri-Procedural Thromboembolic Risk

Low	Moderate to High
CHA ₂ DS ₂ -VASc ≤ 1	CHA ₂ DS ₂ -VASc > 2
No Stroke/TIA, VTE within 3 months	Stroke/TIA, VTE within 3 months
Heterozygous Factor V Leiden Heterozygous PT gene mutation	Protein C or S Deficiency Antithrombin Deficiency Antiphospholipid Syndrome

Rischio emorragico individuale

Management of Patients on Non-Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Peri-procedural Setting
A Scientific Statement From the American Heart Association

Table 2 Items of the perioperative checklist

THE PERIOPERATIVE CHECKLIST

- The thrombo-embolic risk of the patient
- The bleeding risk of the patient
- Timing of stopping DOAC before an invasive procedure:
 - The bleeding risk of the invasive procedure
 - The elimination half-life of the DOAC used depending on the patient's
 - * renal function, liver function, and co-medication
- Specific considerations for some invasive procedures:
 - * Neuraxial anesthesia
 - * Atrial fibrillation ablation
- When should bridging therapy with heparin be suggested?
- Resuming a DOAC after an invasive procedure or surgery



Dubois et al. *Thrombosis Journal* 2017;15:14
DOI: 10.1186/s12959-017-0121-1

Thrombosis Journal

REVIEW

Open Access

Perioperative management of patients on direct oral anticoagulants

Virginie Dubois^{1*}, Anne-Sophie Dincq^{1,2*}, Jonathan Dourfi^{3,2}, Brigitte Icks⁴, Charles-Marc Samama⁵, Jean-Michel Dogne^{6,3}, Maximilien Gourdin^{3,2}, Bernard Chatelain^{1,6}, François Mullier^{1,6*} and Sarah Leslie^{1,2*}



Timing della sospensione dei NAO

SOSPENSIONE PREOPERATORIA:

Caratteristiche paziente
 Caratteristiche intervento

	Alto rischio di sanguinamento
≥80 ml/min	
80-50 ml/min	
50-30 ml/min	48 ore prima
<30 ml/min	Controindicazione all'impiego

RIVAROXABAN E APIXABAN EDOXABAN

≥80 ml/min	24 ore prima	48 ore prima
80-50 ml/min	24 ore prima	48 ore prima
50-30 ml/min	24 ore prima	48 ore prima
30-15 ml/min	36 prima	48 ore prima
<15 ml/min	Controindicazione all'impiego	



ATTIVITA' ANTICOAGULANTE NAO ASSENTE

~~❖ Dabigatran: aPTT ratio ≤ 1.2 TT ratio ≤ 1.2~~

~~❖ Rivaroxaban: PT ratio ≤ 1.2~~

❖ Concentrazione dabigatran ≤ 30 ng/ml

❖ Concentrazione rivaroxaban ≤ 30 ng/ml

❖ Concentrazione apixaban ≤ 30 ng/ml



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Plasma levels of direct oral anticoagulants in real life patients with atrial fibrillation: Results observed in four anticoagulation clinics



Sophie Testa^a, Armando Tripodi^b, Cristina Legnani^c, Vittorio Pengo^d, Rosanna Abbate^e, Claudia Dellanoce^f, Paolo Carraro^g, Lujsa Salomone^h, Rita Panicciaⁱ, Oriana Paoletti^j, Daniela Poli^k, Gualtiero Palareti^l, for the START-Laboratory Register

^a Haemostasis and Thrombosis Center, Department of Laboratory Medicine, AO Istituti Ospitalieri, Cremona, Italy
^b Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Department of Clinical Sciences and Community Health, Università degli Studi di Milano, IRCCS Cà Granda Maggiore Hospital Foundation, Milano, Italy
^c Angiology and Blood Coagulation, University Hospital of Bologna, Italy
^d Department of Cardiothoracic and Vascular Sciences, University Hospital of Padua, Padua, Italy
^e Thrombosis Centre, Department of Heart and Vessels, University Hospital of Florence, Florence, Italy
^f Department of Laboratory Medicine, ULSS 16 and University-Hospital of Padova
^g Cardiovascular Diseases, University of Bologna, Bologna, Italy

- Clearance creatinina
- Hepatic function
- Gender
- Body mass index
- ecc

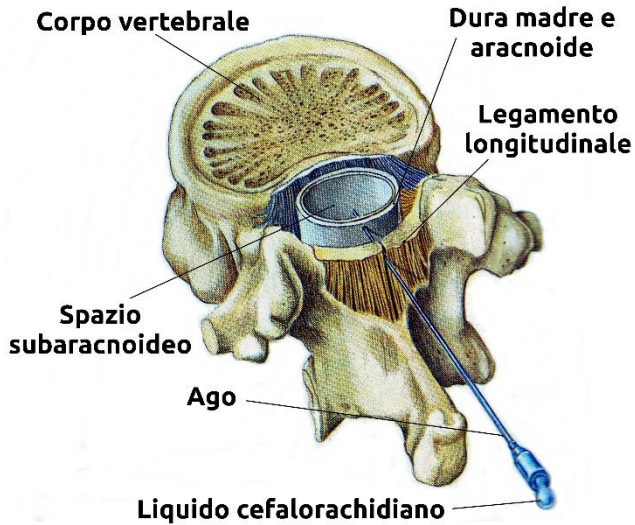
Quale è la tua realtà?

Conclusion: ... variability that cannot be explained by ... the rate of renal ... the correlation with CrCl was relatively ... poor. This poor ... the laboratory parameter to indirectly evaluate ... residual ...

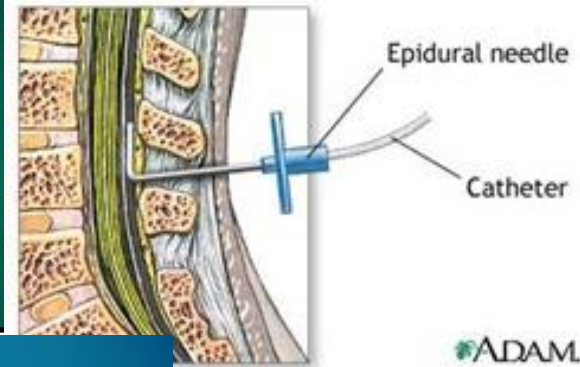
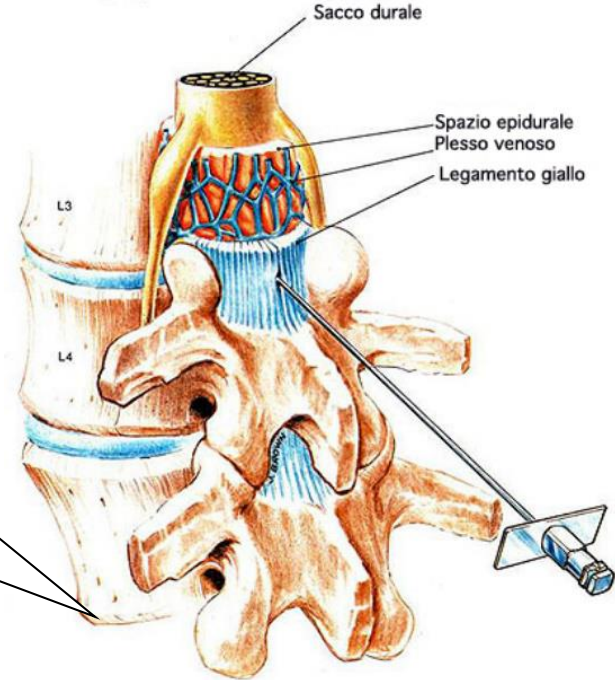
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Grande variabilità inter-individuale!!!!!!!

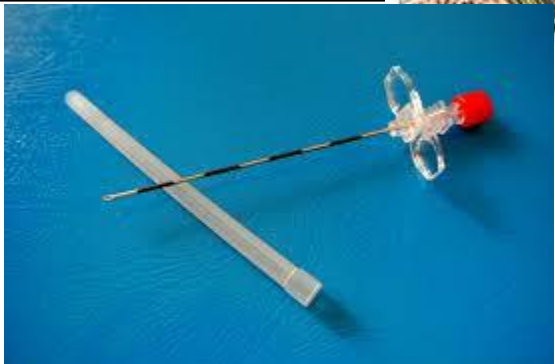
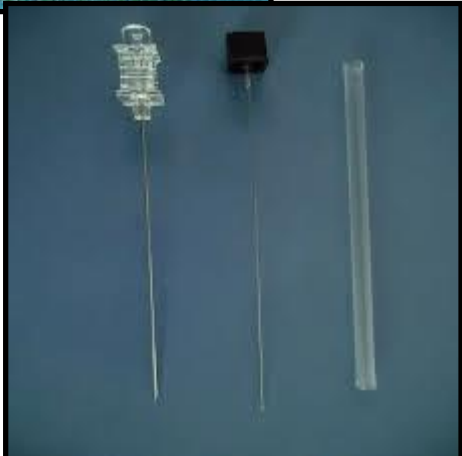




ANESTESIA PERIDURALE



ADAM



EMATOMA

Anestesia spinale 1:220.000
Anestesia epidurale 1:150.000

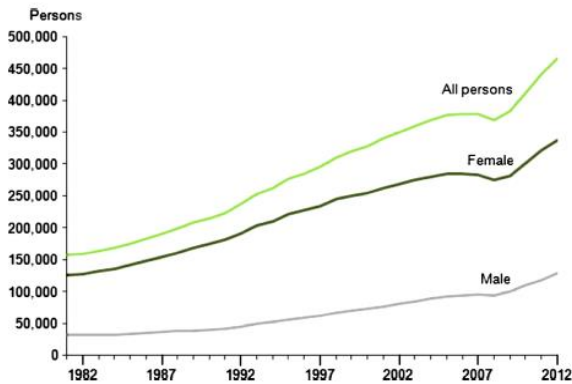


Figure 1 Population aged 90 years and over in England and Wales 1981–2012. Graph reproduced from the Office for National Statistics (see <http://www.ons.gov.uk/ons/rel/mortality-ageing/estimates-of-the-very-old—including-centenarians-/2002-2012/stbevo2012.html?format=print> under the Open Government Licence v2.0).

Anestesia in
chirurgia
nell'anziano:
rischio
ematoma
spinale
1:3000 se
età maggiore
di 75 aa

Table 1 Risk factors associated with spinal epidural hematoma during central neuraxial block [33]

Patient related

- Elderly
- Female sex
- Inherited coagulopathy
- Acquired coagulopathies (liver/renal failure, malignancy, HELLP syndrome, DIC etc)
- Thrombocytopenia
- Spinal abnormalities (spinal bifida/stenosis, spinal tumors, ankylosing spondylitis, and osteoporosis)

Drug related

- Anticoagulation/antiplatelet/fibrinolytic
- Immediate (pre- and post-CNB) anticoagulant administration
- Dual anticoagulant/antiplatelet therapies

Procedure related

- Catheter insertion/removal
- Traumatic procedure (multiple attempts)
- Presence of blood in the catheter during insertion/removal
- Indwelling epidural catheter > single-shot epidural block > single-shot spinal block

CNB = central neuraxial block; DIC = disseminated intravascular coagulation; HELLP = hemolysis, elevated liver enzymes, low platelet count.

1:1000 - 1:10000 se tromboprolifassi preop con EBPM in pz frattura di femore

Peri-operative Care of the Elderly 2014

Type of anaesthesia

The choice of anaesthesia – regional or general – appears to be of less importance than how sympathetically it is administered with regard to the patient's pathophysiological status. Observational studies and



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Email: info@aagbi.org

www.aagbi.org

January 2014

Intuitively, sympathetically administered regional anaesthesia, particularly with minimal/no sedation, would appear to offer some benefit in terms of avoiding short-term morbidities, including hypotension, delirium, cardiorespiratory complications and the need for opioid analgesia [60–62]. However, patients with cognitive dysfunction may not be able to comply with regional anaesthesia without heavy sedation, negating the benefits of avoiding the postoperative cognitive effects of general anaesthesia [63].

onset time longer [55]. Depth of anaesthesia monitoring is recommended.

Perioperative Management of Dabigatran: A Prospective Cohort Study

Running title: Schulman et al.; Perioperative dabigatran management

The guidelines from the American Society of Regional Anesthesia recommend stopping dabigatran 5 days before surgery with neuraxial block.¹⁷ This is not based on clinical evidence but based on concern for the potential risk of epidural hematoma after neuraxial anesthesia. In our population we had 13 cases with surgery performed under neuraxial anesthesia or with epidural or spinal injection as the main procedure and no bleeding complications related to this;

Eight patients had neuraxial anesthesia for their surgery and another 5 had epidural injections as the qualifying procedure, all of which were uncomplicated.

SU 552
PAZIENTI!!!

Table 3. Number of invasive procedures and surgeries by bleeding risk.

Procedure	Bleeding risk		Total
	Standard	High	
Abdominal surgery	7	21	28
Ankle/knee/hip/shoulder surgery	10	19	29
Biopsy	8	16	24
Brain surgery	0	3	3
Cardiac catheterization	67	0	67
Dental	7	2	9
EPS and ablation therapy	78	1	79
Ear surgery	4	1	5
Endoscopy, bronchoscopy*	84	34	118
Epidural/spinal injection	1	4	5
Eye surgery	20	1	21
Gynecologic surgery	4	2	6
Hand or wrist surgery	6	1	7
ICD or pacemaker insertion†	0	52	52
Kidney surgery	0	5	5
Lung surgery	0	7	7
Neck surgery	1	6	7
Skin surgery	13	3	16
TURP/TURBT	2	15	17
Vascular surgery	6	13	19
Other‡	6	11	16
Total, n (%)	324 (60)	217 (40)	541

EPS – electrophysiological study; ICD – implantable cardioverter-defibrillator; TURP/TURBT – transurethral resection of prostate or bladder tumor.

*High risk endoscopy was typically when combined with polyp removal or multiple biopsies.

†Considered high risk for pocket hematoma.

‡The standard risk procedures were thoracocentesis (2), cyst removal, joint injection, unspecified analgesic injection, and insertion of artificial urinary sphincter. The high risk procedures were rhizotomy (2), wide resection of myxosarcoma with free flap rotation, lumbar decompression laminectomy, trans-apical aortic valve replacement, radical prostatectomy, breast lumpectomy, cystoscopy, perineal cancer excision, scapular tumor removal, and amputation of 2 toes.



Interventional Spine and Pain Procedures in Patients on
Antiplatelet and Anticoagulant Medications
Guidelines From the American Society of Regional Anesthesia and Pain
Medicine, the European Society of Regional Anaesthesia and Pain Therapy,
the American Academy of Pain Medicine, the International
Neuromodulation Society, the North American Neuromodulation
Society, and the World Institute of Pain

Samer Narouze, MD, PhD,* Honorio T. Benzon, MD,† David A. Provenzano, MD,‡ Asokumar Buvanendran, MD,§
José De Andres, MD, PhD,|| Timothy R. Deer, MD,# Richard Rauck, MD,** and Marc A. Huntoon, MD††

TABLE 4. Recommended Intervals Between Discontinuation of the New Anticoagulants and Interventional Pain Procedure and Between the Procedure and Resumption of the New Anticoagulants

Drug	Half-life	Recommended Interval Between Discontinuation of Drug and Interventional Pain Procedure* (5 Half-lives)†‡	Recommended Interval Between Procedure and Resumption of Drug
Dabigatran	12–17 h 28 h (renal disease)	4–5 d 6 d (renal disease)	24 h
Rivaroxaban	9–13 h	3 d	24 h
Apixaban	15.2 ± 8.5 h	3–5 d‡	24 h

*The procedures include medium- and high-risk interventional pain procedures. For low-risk procedures, a shared decision making should be followed, a 2 half-life interval may be considered.

†Because of the lack of published studies and in view of the added risks involved in patients with spine abnormalities, we took the upper limit of the half-life of each drug in calculating the 5 half-lives.

‡The potency and the wide variability in the pharmacokinetics of these drugs make us recommend a longer interval.

....discontinuation periods of ≥ 4 days are inconsistent with the return to hemostasis time of these agents which may expose patients to excess thromboembolic risk

EXPERTS' OPINION

Regional anesthesia and antithrombotic agents: instructions for use

Gennaro SCIBELLI¹, Lucia MAIO¹, Gennaro SAVOIA^{2*}

TABLE III.—Simplified scheme of suggested times when neuraxial blocks are planned during NOACs administration.

NOAC	Drug used for postoperative neurophylaxys (low doses)		Drug used for AFIB (high doses)
	Time before puncture/catheter manipulation or removal	Time after puncture/catheter manipulation or removal	Drug withdrawal if neuraxial blocks are performed for surgery
Dabigatran	1-1.5 days	2 to 12 hours	3.5-4 days ←
Rivaroxaban	22-26 hours [¶] 18 hours [§]	4-6 hours [¶] 6 hours [§]	2-3 days
Apixaban	26-30 hours [¶] No data [§]	4-6 hours [¶] 6 hours [§]	3-4 days ←
Edoxaban	12 hours	2 hours	2 days

NOAC: new oral anticoagulant; AFIB: nonvalvular atrial fibrillation.
[¶] European guidelines; [§] Scandinavian guidelines.

....the comparison of the guidelines of the main Society shows very strong differences.... particularly concerning the time of intervals to be respected in carrying out regional anaesthesia procedures

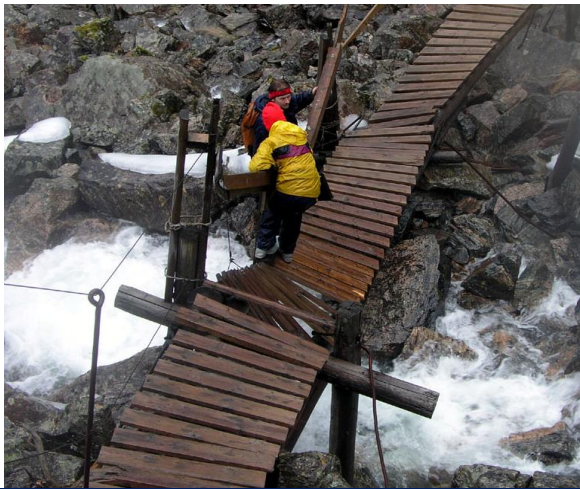
....the decision for or against regional anaesthesia always requires a careful risk-benefit analysis

When the anesthesiologist decides not to comply with this guidelines, the reason should be noted in patient's chart





BRIDGING THERAPY



There is sparse evidence on which to base specific recommendations on the use of bridging of oral anticoagulants among patients with nonvalvular AF with adjusted-dose heparin or LMWH

2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation *Circulation*. published online March 28, 2014

Management of severe perioperative Bleeding *Eur J Anaesthesiol* 2013;30:270-382

La **determina AIFA**, pubblicata sulla Gazzetta Ufficiale del 6 agosto scorso, prevede l'utilizzo delle eparine a basso pm (EBPM) in due condizioni importanti: 1) le donne in gravidanza a rischio tromboembolico o con storia clinica positiva per aborti ripetuti e 2) la sospensione della terapia con farmaci Anti-Vitamina K (AVK) in occasione di interventi chirurgici o procedure invasive (bridging therapy).



Ma anche le LMWH hanno una farmacocinetica poco prevedibile nell'insufficienza renale e non sono monitorizzabili!



How I treat anticoagulated patients undergoing an elective procedure or surgery

Alex C. Spyropoulos and James D. Douketis



Reverse Antidoti specifici

- Vitamina K + CPP per i VKA

Table 3. Perioperative anticoagulation and bridging protocol

Day	Intervention
Preprocedural intervention	
-7 to -10	Assess for perioperative bridging anticoagulation; classify patients as undergoing high-bleeding risk or low-bleeding risk procedure; check baseline labs (Hgb, platelet count, creatinine, INR)
-7	Stop aspirin (or other antiplatelet drugs)
-5 or -6	Stop warfarin
-3	Start LMWH at therapeutic or intermediate dose*
-1	Last preprocedural dose of LMWH administered no less than 24 h before start of surgery at half the total daily dose; assess INR before the procedure; proceed with surgery if INR < 1.5; if INR > 1.5 and < 1.8, consider low-dose oral vitamin K reversal (1-2.5 mg)
Day of procedural intervention	
0 or +1	Resume maintenance dose of warfarin on evening of or morning after procedure†
Postprocedural intervention	
+1	Low-bleeding risk: restart LMWH at previous dose; resume warfarin therapy High-bleeding risk: no LMWH administration; resume warfarin therapy
+2 or +3	Low-bleeding risk: LMWH administration continued High-bleeding risk: restart LMWH at previous dose
+4	Low-bleeding risk: INR testing (discontinue LMWH if INR > 1.9) High-bleeding risk: INR testing (discontinue LMWH if INR > 1.9)
+7 to +10	Low-bleeding risk: INR testing High-bleeding risk: INR testing

*LMWH regimens include enoxaparin 1.5 mg/kg once daily or 1.0 mg/kg twice daily subcutaneously; dalteparin 200 IU/kg once daily or 100 IU/kg twice daily subcutaneously; and tinzaparin 175 IU/kg once daily subcutaneously. Intermediate-dose LMWH (ie, nadroparin 2850-5700 U twice daily subcutaneously; enoxaparin 40 mg twice daily subcutaneously) has been less studied in this setting

†Loading doses (ie, 2 times the daily maintenance dose) of warfarin have also been used.

BRIDGING THERAPY



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation

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

CONCLUSIONS

In patients with atrial fibrillation who had **warfarin** treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding. (Funded by the National Heart, Lung, and Blood Institute of the National Institutes of Health; BRIDGE ClinicalTrials.gov number, NCT00786474.)

Dubois et al. *Thrombosis Journal* (2017) 15:14
DOI 10.1186/s12959-017-0137-1

Thrombosis Journal

REVIEW

Open Access

Perioperative management of patients on direct oral anticoagulants



Virginie Dubois^{1†}, Anne-Sophie Dincq^{1,2†}, Jonathan Douxfils^{2,3}, Brigitte Ickx⁴, Charles-Marc Samama⁵, Jean-Michel Dogné^{2,3}, Maximilien Gourdin^{1,2}, Bernard Chatelain^{2,6}, François Mullier^{2,6†} and Sarah Lessire^{1,2†*}

JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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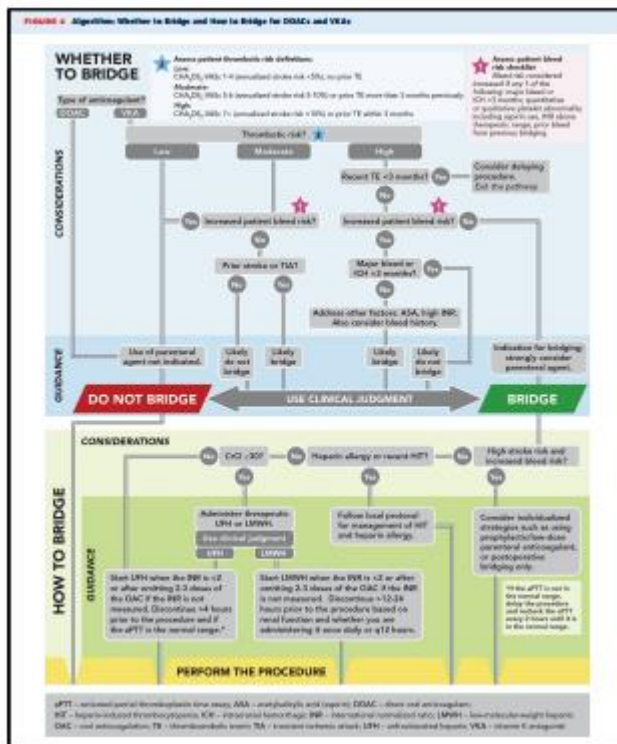
VOL. ■, NO. ■, 2017
ISSN 0735-1057/1516.00
<http://dx.doi.org/10.1016/j.jacc.2017.08.010>

EXPERT CONSENSUS DECISION PATHWAY

2017 ACC Expert Consensus Decision Pathway for Perioperative Management of Anticoagulation in Patients With Nonvalvular Atrial Fibrillation

A Report of the American College of Cardiology Clinical Expert Consensus Document Task Force

FIGURE 4 Algorithm Whether to Bridge and How to Bridge for DOACs and VKAs



Peri-operative management of anticoagulation and antiplatelet therapy

David Keeling,¹ R. Campbell Tait,² and Henry Watson³ on behalf of the British Committee for Standards in Haematology
¹Oxford University Hospitals NHS Foundation Trust, Oxford, ²Glasgow Royal Infirmary, Glasgow, and ³Aberdeen Royal Infirmary, Aberdeen, UK

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British Journal of Haematology, 2016, **175**, 602–613

Table 1. When to consider bridging with treatment dose heparin in patients who stop warfarin if thrombotic risk is especially high.

	Consider bridging with treatment dose heparin in
VTE	Patients with a VTE within previous 3 months. Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3–5.
AF	Patients with a previous stroke/TIA in last 3 months. Patients with a previous stroke/TIA and three or more of the following risk factors: <ul style="list-style-type: none"> • Congestive cardiac failure • Hypertension (>140/90 mmHg or on medication) • Age >75 years • Diabetes mellitus CHADS₂ ≥ 4
MHV	MHV patients other than those with a bileaflet aortic valve and no other risk factors

VTE, venous thromboembolism; INR, International Normalized Ratio; AF, atrial fibrillation; TIA, transient ischaemic attack; MHV, mechanical heart valve.

In who receiving bridging with LMWH, the last dose should be at least 24h before surgery and if on a once day regimen, some recommend the last dose is halved for high risk surgery

We recommend that post-operative bridging is not started until at least 48h after high bleeding risk surgery (1C)

REINSERIMENTO

Tabella 8. Indicazioni sulla ripresa post-operatoria dei NOAC

	Ripresa ottimale del NOAC*
Intervento ad alto rischio di sanguinamento	
Alto/moderato rischio tromboembolico	48 ore
Basso rischio tromboembolico	72 ore
Intervento a basso rischio di sanguinamento	
Alto/moderato rischio tromboembolico	24 ore
Basso rischio tromboembolico	24 ore

*salvo complicazioni nel post-operatorio



Pharmacological prevention of venous thromboembolism in orthopaedic surgery

Domenico Prisco
Caterina Cenci
Elena Silvestri
Giacomo Emmi
Lucia Ciucciarelli

Clinical Cases in Mineral and Bone Metabolism 2014; 11(2): 192-195



www.mammaebambini.it

Table 2 - Timing and dosages of available prophylactic strategies in major orthopaedic surgery (modified from Dign J, et al. 2013).

Active principle	Brand name	Dosage and time of administration	Duration of prophylaxis
Enoxaparin	Clexane®	4000 IU 12 h before surgery, then 4000 IU/day	a minimum of 10 days in all patients, with a strong recommendation to protract prophylaxis for 35 days after HR and FNF surgery (*)
Nadroparin	Fraxiparine® Selaparine®	38 IU/kg 12 h before surgery and 12 h after, 38 IU/kg every 24 h during the 3 days following surgery, thereafter increasing the dose to 57 IU/kg/day	a minimum of 10 days in all patients, with a strong recommendation to protract prophylaxis for 35 days after HR and FNF surgery
Dalteparin	Fragmin®	5000 IU 8-12 h before surgery, then 5000 IU/day. Alternatively 2 h, 500 IU 1-2 before surgery and 2500 IU 8-12 h after, thereafter either 5000 IU/day or (only in hip surgery) 2500 IU 4-8 h after surgery then 5000 IU/day	a minimum of 10 days in all patients, with a strong recommendation to protract prophylaxis for 35 days after HR and FNF surgery
Bemiparin	Ivor®	3500 IU 6 h after surgery, then 3500 IU/day. Alternatively 3500 IU 2 h before surgery, then 3500 IU/day	a minimum of 10 days in all patients, with a strong recommendation to protract prophylaxis for 35 days after HR and FNF surgery
Pamaparin	Fluxum®	0.4 ml (4250 anti-Xa IU) 12 h before surgery, then 0.4 ml (4250 anti-Xa IU)/day	a minimum of 10 days in all patients, with a strong recommendation to protract prophylaxis for 35 days after HR and FNF surgery
Rivaroxaban	Glaxo®	0.4 ml (4200 anti-Xa IU) 12 h before surgery, then 0.4 ml (4200 anti-Xa IU)/day	a minimum of 10 days in all patients, with a strong recommendation to protract prophylaxis for 35 days after HR and FNF surgery
Fondaparinux	Arixtra®	2.5 mg at least 6 h after surgery, then 2.5 mg/day If creatinine clearance 30-50 ml/min 1.5 mg	a minimum of 10 days in all patients, with a strong recommendation to protract prophylaxis for 35 days after HR and FNF surgery
Apixaban	Eliquel®	2.5 mg twice a day, 12-24 h after surgery	35-38 days for HR, 10-14 days for KR
Dabigatran	Pradaxa®	110 mg 1-4 h after surgery, then 220 mg/day If age >75 years or creatinine clearance 30-50 ml/min or amiodarone intake, 75 mg 1-4 h after surgery, then 150 mg/day	4-5 weeks for HR, 10 days for KR
Rivaroxaban	Xarelto®	10 mg 6-10 h after surgery, then 10 mg/day	5 weeks for HR, 2 weeks for KR

(*) It is suggested to protract treatment similarly in patients undergoing KR surgery (1)



Management of Patients on Non–Vitamin K Antagonist Oral Anticoagulants in the Acute Care and Periprocedural Setting

A Scientific Statement From the American Heart Association

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
DVT, PE prophylaxis after hip or knee replacement	<p>After hip replacement surgery:</p> <p>CrCl >30 mL/min after achievement of hemostasis: If given day of surgery, 110 mg 1–4 h postop; after day of surgery 220 mg once daily x 28–35 d</p> <p>CrCl ≤30 mL/min or on dialysis: Not recommended</p> <p>CrCl <50 mL/min with concomitant P-gp inhibitors: Avoid coadministration</p>	<p>Initial dose 6–10 h after surgery provided hemostasis established</p> <p>10 mg daily with or without food x 35 d for hip replacement, x 12 d for knee replacement</p>	<p>2.5 mg BID x 35 d after hip replacement surgery or x 12 d after knee replacement surgery</p>	



Perioperative Stroke in Noncardiac, Nonneurosurgical Surgery

Julie L. W. Ng, M.B.B.S.,* Matthew T. V. Chan, M.B.B.S.,† Adrian W. Gelb, M.B.Ch.B.‡



- 0,05%-7% of patients
- Predisposition factors
- Intraoperative hypotension
- The majority of perioperative stroke occur after the second perioperative day

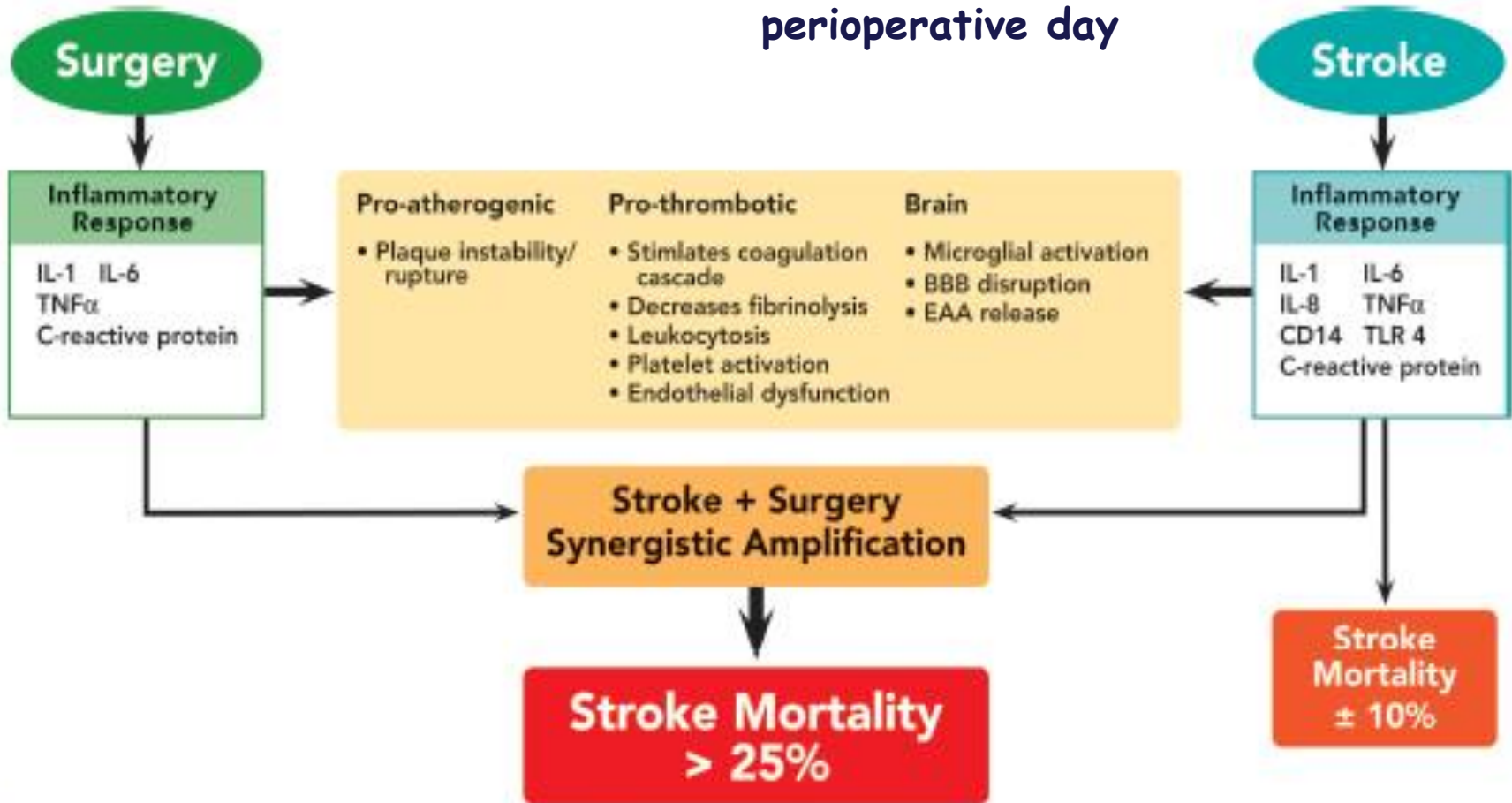


Fig. 1. Pathophysiology of perioperative stroke. BBB = blood brain barrier; CD = cluster of differentiation; EAA = excitatory amino acids; IL = interleukin; TLR = Toll-like receptor; TNF α = tumor necrosis factor α .

..in conclusione.....



- Informare il paziente e il medico curante che questa è la migliore strategia ma non annulla né il rischio emorragico né il rischio trombotico
- Programmare sospensione e reinserimento dei farmaci antiaggreganti, NAO e antiVitK
- Concordare con "gli attori" la strategia - importanza della *multidisciplinarietà*
- Richiedere attività/dosaggio NAO solo in casi molto selezionati quali la necessità di eseguire un blocco neuroassiale

Grazie per l'attenzione.....e grazie al gruppo multidisciplinare.....

