

	START-Eventi Walter Ageno (Varese)	
	START-Laboratorio Sophie Testa (Cremona)	
	START-Antiplatelet Rossella Marcucci (Firenze)	
	FADOI-START-VTE-DOAC Francesco Dentali (Varese), Nicola Mumoli (Livorno)	
	START-Valvole Daniela Poli (Firenze)	
12:00	<b>Letture magistrali: Errori, contraddizioni e capovolgimenti nella scienza e nella medicina</b> Sergio Coccheri (Bologna)	8:31
12:30	<b>Simposio satellite: Le decisioni cliniche per la gestione dei pazienti dopo un tromboembolismo venoso * sponsorizzato da Alfa Wassermann</b>	
	<b>Moderatori:</b> Giuseppe M. Andreozzi (Padova), Marco Cattaneo (Milano), Giovanni Davi (Chieti), Anna Falanga (Bergamo)	
	<b>La storia naturale del tromboembolismo venoso dopo la fase acuta</b> Sabina Villalta (Treviso)	
	<b>Quali scelte possibili e quali criteri</b> Walter Ageno (Varese)	10:3
	<b>Lo START-Post-VTE Registry: obiettivi e struttura</b> Gualliero Palareti (Bologna)	
14:15	<b>Quale comunicazione per pazienti e professionisti in materia di anticoagulazione. Stato e prospettive del portale <a href="http://www.anticoagulazione.it">www.anticoagulazione.it</a></b> Gualliero Palareti (Bologna), Silvia Malosio (Milano)	
15:45	<b>Panoramica degli studi clinici in corso e prossimi con i NAO</b> Giancarlo Agnelli (Perugia)	
16:00	<b>Presentazione dello studio APIDULCIS</b> Gualliero Palareti (Bologna), Paolo Prandoni (Padova)	

# Manovre invasive e periodo perioperatorio nei pazienti anticoagulati

Bologna 1,2 Febbraio 2017



**Vincenzo Toschi**  
SIMT e Centro Trombosi  
ASST Santi Paolo e Carlo  
Milano, Italy



## Disclosure

Speaker fee: Aspen, Boehringer,  
Daichii Sankio, Bayer, Pfizer

## The optimal peri-operative management of patients on chronic OAC is anchored on....

- ✓ Risk stratification of patients and procedure-related risks for thrombosis and bleeding
- ✓ Clinical consequences of thrombotic versus bleeding events
- ✓ Discontinuation and reinitiation of OAC on appropriate pharmacokinetic parameters
- ✓ Whether an aggressive management strategy such as perioperative bridging therapy has advantages for the prevention of post-operative thrombotic complications at the cost of a possible increase in bleed risk

J Thromb Hemost 2016

## Patient-related risk stratification for peri-operative thromboembolism

ACCf=American College of Chest Physicians; ATE=arterial thromboembolism; VTE=venous thromboembolism; AVR=avalv replacement; TIA=transient ischemic attack

Accepted

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CHEST 2012; 141: e326S-50S

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scienza e pratica clinica per il management dei pazienti anticoagulati • AGGIORNAMENTI 2017  
BOLOGNA, 1-2 FEBBRAIO 2017

## Stratificazione del rischio emorragico legato alla procedura

Alto rischio di sanguinamento(*)	Basso rischio di sanguinamento (^)	Minimo rischio di sanguinamento
Chirurgia maggiore con danno tissutale esteso	Artroscopia	Interventi dermatologici minori
Chirurgia dei tumori	Biopsia linfonodale o cutanea	Cataratta
Chirurgia ortopedica maggiore	Chirurgia di spalla, mano, piede	Procedure dentarie minori (estrazioni.....)
Plastica ricostruttiva	Angiografia coronarica	Impianto di PM o ICD
Chirurgia urologica o gastro-intestinale, inclusi polipi del colon	Biopsia endoscopica/ colonscopia con o senza biopsia	
Nefrectomia/biopsia renale	Colecistectomia per via laparoscopica	
Chirurgia SNC o in organi vascolarizzati	Broncoscopia con o senza biopsia	

\* Rischio a 2 gg di sanguinamento maggiore  $\geq 2\%$ ; ^ rischio di sanguinamento maggiore a 2 gg  $< 2\%$

## Clinical consequences of thrombosis

- ✓ Mechanical heart valve thrombosis is fatal in 15% patients
- ✓ Embolic stroke results in death or major disability in 70% of patients
- ✓ VTE has a case-fatality rate of 8-10%

Ann Intern Med 2010; 152: 578-89

SUMMARY OF RECOMMENDATIONS

Note on Shaded Text: Throughout this guideline, shading is used within the summary of recommendations sections to indicate recommendations that are

newly added or have been changed since the publication of Antithrombotic and Thrombolytic Therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Recommendations that remain unchanged are not shaded.

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should be weighed against the risk of str

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## Guida alla terapia antitrombotica Raccomandazioni

2016

**I pazienti vengono distinti in due categoria di rischio**

**a) Pazienti a rischio di tromboembolismo elevato**

- ✓ Protesi meccanica mitralica
- ✓ Protesi meccanica aortica non recente o associata a FA
- ✓ Protesi valvolare con pregresso TE arterioso o valvulopatia mitralica
- ✓ Precedente tromboembolismo cardiogeno o non spiegato
- ✓ Tromboembolismo venoso non recente (<3 mesi)

**b) Pazienti a rischio di tromboembolismo basso moderato**

- ✓ Tutti gli altri pazienti in terapia con AVK

## Two main questions

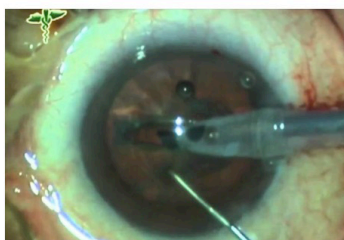


- ✓ Can OAC be safely continued for selected minor procedure or surgery?
- ✓ If a VKA needs to be temporarily interrupted, is heparin bridging necessary?

### *Can oral anticoagulants (VKA) be safely continued for selected procedures or surgeries?*



Keep VKA  
+ local  
hemostasis



Keep VKA



Keep VKA  
+ local oral  
hemostasis

CHEST 2012; 141: e326S-50S



# Guida alla terapia antitrombotica Raccomandazioni

2016

## Interventi/procedure per i quali non è necessario sospendere il trattamento con AVK

- ✓ Chirurgia cutanea
- ✓ Cataratta con anestesia topica
- ✓ Artrocentesi e iniezioni in tessuti molli e articolari
- ✓ Punture e cateterismi di vene e arterie superficiali
- ✓ Puntura sternale e biopsia osteo-midollare
- ✓ Procedure cardiologiche: Eco transesofageo
- ✓ Procedure odontoiatriche semplici: avulsioni dentarie e altre procedure

As compared with bridging therapy with treatment at the time of pacemaker or IC. of clinically significant device-pocket hem of Health Research and the Ministry of BRUISE CONTROL ClinicalTrials.gov nu

height in meters.

‡ A patient could have more than one valve.

§ Data are for the 30 patients (15 patients in each treatment group) who went testing for protein C or S deficiency or antiphospholipid antibodies.

¶ The CHADS<sub>2</sub> score is an index of the risk of stroke in patients with atrial fibrillation. Scores range from 0 to 6, with higher scores indicating a greater risk of stroke.

2088

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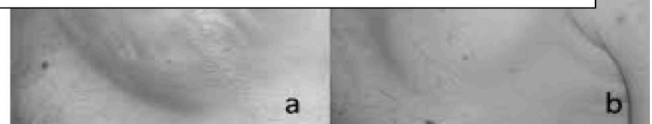
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clinicamente significativo della tasca

Bridging: stop warfarin -5gg; start LMWH/UFH -3gg e stop per 24 h





# Bridging therapy and PM implantation: the BRUISE CONTROL trial

safety of performing procedures of ICD surgery without interruption of warfarin therapy in patients requiring oral anticoagulation therapy. We found that this strategy is associated with a significantly lower rate of device-pocket hematoma, as compared with bridging therapy with heparin (3.5% vs. 16.0%). We also found that continued

tion that has been prop  
“anticoagulant stress t  
undergo surgery while  
coagulation therapy, an  
be detectable and appr  
the wound is still open

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N ENGL J MED 368;22 NEJM.ORG MAY 30, 2013

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**N Engl J Med 2013; 368: 2084-93**

# Bridging therapy and PM implantation: the BRUISE CONTROL-subgroup analysis

therapy is resumed postoperatively.<sup>9</sup>

Our results are consistent with observations on bridging therapy in other situations. Siegal et al.<sup>22</sup> recently conducted a meta-analysis of the safety and efficacy of periprocedural bridging therapy, which included more than 12,000 patients in 34 studies, with only one randomized trial. The comparison groups in these studies included mostly patients in whom oral anticoagulation therapy was discontinued without bridging, with smaller numbers of patients in whom oral anticoagulation therapy was continued during surgery. The authors concluded that bridging with heparin leads to a risk of overall bleeding that is 5 times as high, and a risk of major bleeding that is 3.6 times as high, as the respective risks associated with no bridging therapy. The risk of thromboembolic events did not differ significantly between the two treatment strategies.<sup>22</sup>

than 5%, for whom complete discontinuation of anticoagulation therapy at the time of surgery might have been too risky. The findings of this trial are not directly relevant to patients with a lower risk of thromboembolic events, but it is possible that such patients might benefit from any anticoagulation or bridging therapy during the periprocedural period. Additional large, randomized trials are needed to define the role of periprocedural bridging therapy with heparin.

Guidelines suggest that the continuation of warfarin at the time of minor device implantation, or ophthalmologic procedures, is preferred, although not directly relevant, the findings of this study are consistent with this recommendation, particularly since the bleeding risk associated with these other procedures, whereas increased with pacemaker or ICD surgery.

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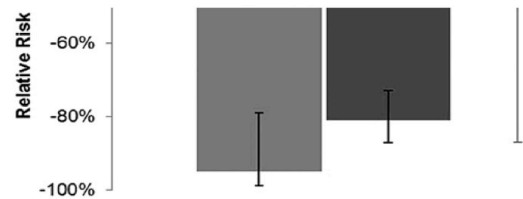
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the procedure (group 1, n=790) or to undergo the procedure with continuous warfarin (group 2, n=794; Figure 1).

The baseline characteristics and risk factors were compared between the 2 groups. In group 1, the average age was 61±10 years; 76% were male; 29% had paroxysmal AF; 49% had long-standing persistent AF; the left atrial size was 44.8±7 mm; and the left ventricular ejection fraction was 53±12%.

Patients in group 2 were 62±12 years of age; 76% were male; 25% had paroxysmal AF; 24% had persistent AF; the left atrial size was 45.1±7 mm; and the left ventricular ejection fraction was 52±13%.

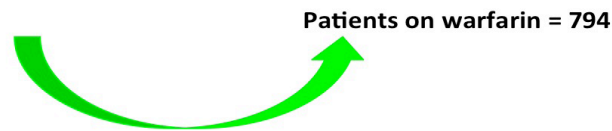
In group 1, 561 patients (71%) had a CHAD<sub>2</sub>-VASc score of 1 or less compared with 588 (74%) in group 2 (P=0.17).



**Figure 2.** Incidence of periprocedural thromboembolic or bleeding complications were more frequent in the off-warfarin population (group 1). Patients on warfarin (group 2) had a 91% relative risk reduction in stroke/transient ischemic attack (TIA), 81% relative risk reduction in minor bleeding, and 50% relative risk reduction in major bleeding compared with group 1. Error bars represent 95% confidence interval of the relative risk reduction.

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## “How to implement bridging therapy in patients who require it?”



Received October 7, 2008; accepted April 10, 2009.

From the Clinical Cardiology, Thrombosis Center, Department of Cardiothoracic and Vascular Sciences, University of Padova School of Medicine (P.V., C.U., D.G., I.S.); Merate General Hospital, Lecco (E.N.); University Hospital, Bologna (G.G.); General Hospital, Vimercate (L.L.); General Hospital, Lecco (D.V.); General Hospital, Cremona (T.S.); General Hospital, Macerata (F.R.); University of Firenze, Firenze (P.D.); and Geriatric Clinic Padova (N.G.), Italy.

The participating anticoagulation centers are listed in the Appendix.

Correspondence to Vittorio Pengo, MD, Clinical Cardiology, Thrombosis Center, Via Giustiniani 2, 35128 Padova, Italy. E-mail: vittorio.pengo@unipd.it

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## 1262 pz reclutati in 22 centri italiani; eparina a dose terapeutica nei pz ad alto rischio e a dose profilattica in quelli a rischio basso-moderato: 5 eventi TE (0.5%) e 15 emorragie maggiori (1.2%), nei pazienti ad alto rischio

interval of OAT discontinuation and resumption after the procedure, INR values throughout the perioperative and follow-up periods, type and dosage of LMWH used during the perioperative period, and adverse events with appropriate comments.

### Outcomes and Follow-Up

The primary efficacy outcome was the incidence of thromboembolism from the OAT interruption (ie, 5 days before the procedure) to 30 days after the procedure. Thromboembolic events were defined as

ical data are expressed as binomial 95% confidence intervals. Fisher exact test and Exact logistic regression were used for primary safety outcomes. Software, version 10.0 (SAS Inc, Cary, NC).

The authors have read and approved the integrity of the manuscript as written.

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## Guida alla terapia antitrombotica Raccomandazioni

2016

### **Bridging nei pazienti ad alto rischio**

Usare dosi di EBPM ogni 12 ore sec. lo schema (enoxaparina):

- ✓ < 50 kg 2000 U x 2/die s.c.
- ✓ 50-69 kg 4000 U x 2/die s.c.
- ✓ 70-89 kg 6000 U x 2/die s.c.
- ✓ 90-110 kg 8000 U x 2/die s.c.
- ✓ >110 kg 10000 U x 2/die s.c.

### **Bridging nei pazienti a rischio basso moderato**

Usare dosi di EBPM profilattiche ogni 24 ore (enoxaparina):

- ✓ In tutti i pazienti 4000 U/die s.c.



# Guida alla terapia antitrombotica Raccomandazioni

2016

## Schema di *bridging*

Usare dosi di EBPM ogni 12 ore sec. lo schema (enoxaparina):

- ✓ Giorno -5: sospensione AVK
- ✓ Giorno - 4: inizio EBPM se il pz era in acenocumarolo
- ✓ Giorno - 3: inizio EBPM se il paziente era in warfarin
- ✓ Ultima somministrazione di EBPM almeno 12-24 ore prima dell'intervento
- ✓ Controllo INR prima dell'intervento (intervento con INR>1.5)
- ✓ Riprendere EBPM alla stessa dose la mattina successiva
- ✓ Giorno + 1: riprendere AVK ad una dose >50% di quella abituale
- ✓ Giorno + 2: proseguire con AVK ad una dose >50% di quella abituale
- ✓ Giorno + 3 e successivi: proseguire con AVK alla dose abituale
- ✓ Sospendere EBPM dopo due giorni con INR superiore a 2 (o a 2.5 per pazienti in *target* 3)

## ***“Do we need to bridge?”***



## EMORRAGIE

in analyses of thromboembolic events, both arterial and venous, when assessed in patients who received bridging or no bridging and in full-dose versus prophylactic-

risk, nonbridged patients.

Our findings are relevant to patients who require temporary discontinuation

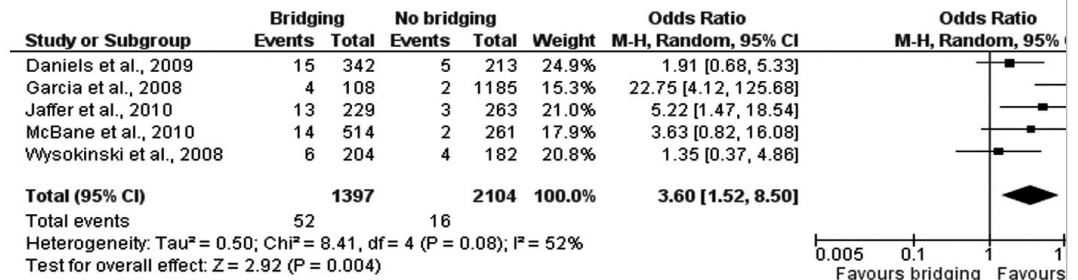


Figure 4. Forest plot of major bleeding events. M-H indicates Mantel-Haenszel; CI, confidence interval.

$P=0.004$ ) and CHA<sub>2</sub>DS<sub>2</sub>-VASc (4.25 versus 4.0; scores were higher in bridged patients, there were differences in rates of CHADS<sub>2</sub> score  $\geq 2$  (78% versus 76%) or CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  (94% versus 95%);  $P$  of additional antiplatelet therapy was similar for those on single antiplatelet (39% versus 36%) and dual antiplatelet therapy (3.0% versus 2.2%;  $P=0.2$  across antiplatelet categories).

Among patients treated with warfarin who had follow-up international normalized ratio after the procedure (n=1452), time to the achievement of the therapeutic international normalized ratio  $\geq 2$  after the procedure was significantly shorter for interruptions with bridging compared with those without bridging (median, 17 versus 23 days;

Dental work	1/166 (0.6)	0/16 (0)	0/166 (0)
Other	5/413 (1.2)	7/102 (6.9)	7/413 (1.7)

Excluding interruptions missing a date or those that occurred within 30 days of a previous interruption. PCI indicates percutaneous coronary intervention.  
\*Includes stroke, systemic embolism, myocardial infarction, or cerebrovascular hospitalization within 30 days of the procedure requiring interruption.  
†Includes major bleeding or bleeding hospitalization within 30 days of the procedure requiring interruption.

no-bridging group and 5.2% in the bridging group (relative risk, 0.4, 0.20 to 0.78; P=0.005 for superiority).

#### CONCLUSIONS

In patients with atrial fibrillation who had warfarin treatment interrupted for elective operation or other elective invasive procedure, forgoing bridging with low-molecular-weight heparin was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased major bleeding. (Funded by the National Heart, Lung, and Blood Institute; National Institutes of Health; BRIDGE ClinicalTrials.gov number, NCT01175155.)

N ENGL J MED 373;9 NEJM.ORG AUGUST 27, 2015

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Figure 1. BRIDGE Study Design.

Screening visits occurred between 30 days and 5 days before the planned procedure, and randomization (R) occurred 5 to 10 days before the procedure. Warfarin treatment was discontinued 5 days before the procedure, and administration of the study drug was started 3 days before the procedure. It was recommended that the international normalized ratio (INR) be measured 1 day before the procedure. If the INR was greater than 1.8, oral vitamin K (1.0 to 2.5 mg) was recommended; if the INR was 1.5 to 1.8, oral vitamin K was recommended. If the procedure or surgery was delayed up to 3 days, administration of the study drug was continued until 24 hours before the procedure. Warfarin treatment was restarted on the evening of or the day after the procedure, and the study drug was restarted 1 day after the procedure. LMWH denotes low-molecular-weight heparin.

#### PROCEDURES

Patients were randomly assigned to receive bridging anticoagulation therapy with dalteparin sodium (100 IU per kilogram of body weight administered subcutaneously twice daily) or to receive no bridging therapy (i.e., a matching subcutaneous placebo) from 3 days before the procedure until 24 hours before the procedure and then for 5 to 10 days after the procedure. Randomization was stratified according to study center either with the use of an interactive voice-

response system with a toll-free telephone number and access codes or through the Internet. The study drugs were provided in identical vials.

The administration of study drug followed a standardized perioperative management protocol (Fig. 1). Warfarin treatment was stopped 5 days before the procedure, and administration of the study drug (dalteparin or matching placebo) was started 3 days before the procedure. The last preprocedure dose of dalteparin or placebo was given in the morning approximately 24 hours

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**1884 pazienti con indicazione al VKA per FA arruolati e almeno un FR per stroke**

**Randomizzato, in doppio cieco. Dalteparina somministrata dal 3<sup>a</sup> g prima dell'intervento ai 5-10 gg successivi**

**Primary ED: tromboembolismo arterioso e sanguinamenti maggiori (follow up a 30 gg)**

N Engl J Med 2015; 373: 823-33

## The Bridge trial: characteristics of the patients

† Race was self-reported. The patients for whom data were unknown are those who chose not to answer.  
‡ CHADS<sub>2</sub> is a score used to estimate the risk of stroke in patients with atrial fibrillation. Two points each is assigned for congestive heart failure, hypertension, age of 75 years or older, and diabetes. One point is assigned for stroke or transient ischemic attack.

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N Engl J Med 2015; 373: 823-33

**2° CONVEGNO DI ANTICOAGULAZIONE.it**

scienza e pratica clinica per il management dei pazienti anticoagulati • AGGIORNAMENTI 2017  
BOLOGNA, 1-2 FEBBRAIO 2017

# The Bridge trial: study outcomes

bridging. There was also less minor bleeding without bridging than there was with bridging and there was no significant difference between the groups with regard to myocardial infarction, venous thromboembolism, or death. Together, these findings show that there is no clinical benefit in favor of a strategy of bridging, as compared with perioperative bridging with low-molecular-weight heparin.

The findings in our trial are consistent with those from nonrandomized comparisons of bridging strategies. A meta-analysis of observational

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\* P value for non inferiority

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**Assigned Interventions**

**Drug: Dalteparin**

5,000 iu or 200 iu/kg depending on the type of surgery injection will be given subcutaneously, once a day for a minimum of 4 days or until the INR is 2.0

Other Name: Fragmin

**Other: Placebo**

This patients will be randomized post-operative to receive either active treatment or placebo. the placebo will be given as a subcutaneous injection once a day. the amount of the placebo will be equivalent to the active treatment depending on the type of surgery. ie. 5,000 iu or 200 iu/kg

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

**Pazienti con FA e almeno un fattore di rischio maggiore per stroke o portatori di protesi valvolari meccaniche. Primary EP = tromboembolismo maggiore; secondary EP = sanguinamento maggiore. Fine dell'arruolamento prevista per marzo 2017**

**ESC/ESA Guidelines on non-cardiac surgery:  
cardiovascular assessment and management ESC/ESA  
Guidelines on non-cardiac surgery: cardiovascular  
assessment and management 2014**



Discontinuation of VKAs is hazardous:

- in pts with AF and CHA<sub>2</sub>DS<sub>2</sub> VASc score ≥ 4
- In pts with mechanical prosthetic heart valves or newly inserted biological prosthetic heart valves
- In pts with mitral valvular repair (3 months)
- In pts with recent venous thromboembolism (3 months) or thrombophilia

For bridging there is better evidence for the efficacy and safety of LMWH (twice daily or once daily in low-risk patients). In patients with mechanical prosthetic heart valves UFH is preferred.

Stop VKAs 5 dd before the procedure/intervention; start heparin 3 dd before the procedure/intervention; stay on heparin until 24-12 h before the procedure

**EXPERTS' OPINION**

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ACS	Acute coronary syndrome	IPB	Intraprocedural bleeding
ADP	Adenosine diphosphate	LMWH	Low molecular weight heparin
AF	Atrial fibrillation	MI	Myocardial infarction
APA	Antiplatelet agents	MS	Mitral stenosis
APTT	Activated partial thromboplastin time	N-STEMI	Non ST-elevation myocardial infarction
BSG	British Society of Gastroenterology	NICE	National Institute for Health Care and Excellence
CrCl	Creatinine clearance	NOAC	Non-vitamin K oral anticoagulants
DAPT	Dual antiplatelet therapy	PAR-1	Protease-activated receptor 1
DES	Drug eluting stent	PCC	Prothrombin complex concentrate
DOAC	Direct oral anticoagulant	PEG	Percutaneous endoscopic gastrostomy
eGFR	Estimated glomerular filtration rate	PPB	Post polypectomy bleeding
EMR	Endoscopic mucosal resection	PICO	Patients, Interventions, Controls, Outcomes
EPBD	Endoscopic papillary balloon dilatation	PPI	Proton pump inhibitor
ERCP	Endoscopic retrograde cholangio-pancreatography	PT	Prothrombin time
ESD	Endoscopic submucosal dissection	RCT	Randomised controlled trial
ESGE	European Society of Gastrointestinal Endoscopy	SEMS	Self-expanding metal stents
EUS	Endoscopic ultrasound		

Veitch Andrew M et al. Endoscopy in patients... Endoscopy 2016; 48: 385-40



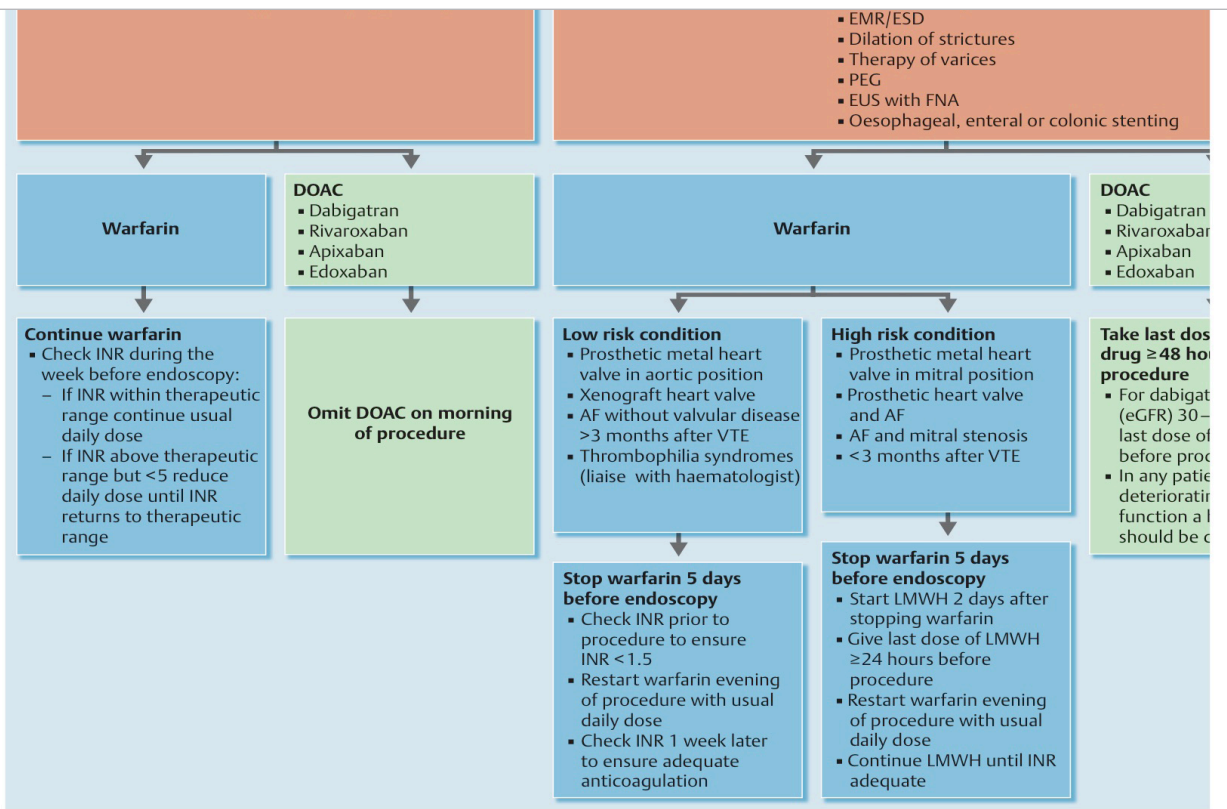


Fig. 2 Guidelines for the management of patients on warfarin or direct oral anticoagulants (DOAC) undergoing endoscopic procedures.

Veitch AM et al., Endoscopy 2016;48:385

Veitch Andrew M et al. Endoscopy in patients... Endoscopy 2016

## Conclusioni

**La definizione del rischio TE del paziente e del rischio emorragico legato all'intervento/procedura costituisce il primo passo per una corretta gestione peri-operatoria della terapia anticoagulante orale**

**Un basso rischio tromboembolico e interventi a minimo rischio emorragico non richiedono la sospensione dei VKA**

**Il bridging con "eparine" resta al momento indicato solo nei pazienti ad alto rischio TE (protesi valvolari, FA complicata da recente stroke o tromboembolismo o con CHADS<sub>2</sub> 5-6); va valutato in quelli a rischio intermedio**

**Se praticato, privilegiare l'uso di LMWH e scegliere la dose piena o quella profilattica in base al profilo di rischio emorragico della procedura**