2021

Progetto Ematologia Romagna

EMORRAGIE E PROCEDURE INVASIVE NEL PAZIENTE ANTICOAGULATO

B.COSMI

UO Angiologia e Malattie della Coagulazione, Azienda Ospedaliero Universitaria S.Orsola Malpighi-IRCCS Università di Bologna, Bologna, Italia

Disclosures

Employment	No conflict of interest to disclose
Research support	No conflict of interest to disclose
Scientific advisory board	Techdow
Consultancy	No conflict of interest to disclose
Speakers bureau	Daiichi Sankyo, Sanofi. IL, Techdow
Major stockholder	No conflict of interest to disclose
Patents	No conflict of interest to disclose
Honoraria	No conflict of interest to disclose
Travel support	No conflict of interest to disclose
Other	No conflict of interest to disclose

Come gestire la terapia anticoagulante (eparina, antagonisti della vitamin K -VKA, anticoagulanti orali diretti-DOACS):

emorragia

setting peri-procedurale/operatorio

Balancing the benefits and risks in the management of bleeding during antithrombotic treatment

1-
severity of bleeding
Stratification on the basis of:
-hemodynamic stability
-source of bleeding
-degree of blood loss

2-
thromboembolic risk without anticoagulants (AC):
depending on
indication for treatment

3-
enact strategies to stop bleeding as rapidly as possibly,
minimizing the thrombotic risk.
(e.g. urgent referral)

Severity of bleeding

- **Major bleeding** in non-surgical patients:
- 1- **Fatal bleeding**,

and/or

- 2- **Symptomatic bleeding in a critical area or organ**, such as
- intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome,

and/or

- 3- **Bleeding causing a fall in hemoglobin level of 20 g/L** (1.24 mmol/L) or more, or leading to transfusion of >2 units of whole blood or red cells.

- **Minor bleeds**: all the others

Shulman S et al, JTH 2005-ISTH

Thromboembolic risk without anticoagulants

High > 10% / year	Moderate 5-10% / year	Low < 4% / year
Prosthetic heart valve: • Any mitral valve type Older type aortic valve (caged ball, tilting disk) • Recent stroke/TIA (<6 months)	Bi-leaflet aortic valve and any of the following: atrial fibrillation, prior stroke, age > 75,diabetes mellitus,hypertension, congestive heart failure	Bi-leaflet aortic valve without atrial fibrillation or other risk factors for stroke
Atrial fibrillation: • CHADS2 score 5-6 • Recent stroke/TIA (<3 months) • Rheumatic valve disease	Atrial fibrillation: • CHADS2 score 3-4	Atrial fibrillation: • CHADS2 score 0-2 no previous stroke or TIA
Recent venous thrombo-embolism (<3 months), severe thrombophilia	VTE within 3-12 months, recurrent VTE, non severe thrombophilia , active cancer	Venous thromboembolism >12 months, reversible risk factors

Daniels PR, BMJ 2015;351:2391

Strategies to stop bleeding

1- treatment interruption

2- measurement of the anticoagulant effect

3- anticoagulation reversal

4- non specific haemostatic measures

local mechanical hemostasis
haemodynamic support
coagulation factors infusion (concentrates or fresh frozen plasma)
antifibrinolytic (tranexamic acid)
desmopressin

How to manage major/life-threatening bleeding?

Consensus:

treatment interruption
and

reversal,
regardless of the thromboembolic risk

Measurement of the anticoagulant effect

- YES, if possible :
- to establish that:

1- bleeding depends from anticoagulants

2- indication to the reversal of the anticoagulant effect

Reversal of anticoagulants

1- agents which can neutralize directly the anticoagulant effect

specific agents (antidotes), if available

2- coagulation factors

What to do in case of minor bleedings?

- Consider treatment interruption only if the thrombotic risk is low
- look for and treat local causes (especially if the anticoagulant effect is subtherapeutic or in range)
- Reversal in case of urgent surgery or invasive procedures

Reversal agents for VKAs and heparin

	Time until restoration of hemostasis after cessation of therapeutic dose Vs drug T/2	Laboratory tests to measure drug effect	Antidote- Reversing agent
Warfarin	60–80 h vs 36-42 h	Prothrombin time (widely available)	Antidote : YES *Vitamin K* i.v.: reversal in 12–24 h
Acenocoumarol	18–24 h Vs 9 h		*Clotting factors*: Prothrombin complex concentrates (PCCs): immediate reversal : 1h
Phenprocoumon	8–10 days Vs 120 h		Dose of vitamin K or PCCs depend on INR and bodyweight Fresh Frozen Plasma (FFP) > 5 h
Heparin ev	1-2 hours (dose-dependent) =T/2	PTT	Antidote:YES protamine 1 mg neutralizes 100 UI
Low molecular weight Heparin	2-6 hours = T/2	anti-Factor Xa	1 mg per 1 mg enoxaparin)

- In presence of persisting risk of major bleeding, vit K + PCC are necessary to avoid a rebound rise of INR

Modified from Levi et al J Thromb Haemost 2011; 9: 1703–12.

Use of FFP, PCC, aPCC, rFVII for urgent VKA reversal: Pros and Cons

	Pros	Cons
FFP	All factors in normal concentration Limited thrombotic risk Lower cost	Volume overload (especially in the elderly) Delayed use due to thawing Only partial correction of F IX level (not >20%, not reflected by INR) Required AB0 compatibility Possible allergic reactions and transmission of infectious agents Transfusion-related acute lung injury (TRALI); time to effect: hours
4F-PCC aPCC (FEIBA)	all deficient vit K dependent clotting factors (FII; FVII; FIX; FX; + prot C and S), small volume, rapidly infused, FVIIa in FEIBA (no prot C ans S) Time to effect: 10-30 minutes	small volume (liophiiyzed 20 ml, double viral inactivation non volume overload) rapid infusion (20-30 min) immediate effect informed consent Risk of thrombotic complications risk greatest with activated factors
3F-PCC	little factor VII and less effective in correcting the INR and the coagulopathy of patients on VKA	
rFVIIa	Directly activates thrombin on platelets; rapid; small volume; recombinantproduct without infection risk	Higher cost

Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists

Thromb Haemost 2011

A meta-analysis

Francesco Dentali[1]; Chiara Marchesi[1]; Matteo Giorgi Pierfranceschi[2]; Mark Crowther[3]; David Garcia[4]; Elaine Hylek[5]; Daniel M. Witt[6,7]; Nathan P. Clark[6]; Alessandro Squizzato[1]; Davide Imberti[8]; Walter Ageno[1]

7 studies used 3-factor and 20 4-factor PCCs.

Rate of complications.

	Rate (95% CI)
TE events	1.4% (0.8–2.1)
Death for all causes	10.6% (5.9–16.6)
TE events in pts treated for bleeding	1.9% (1.0–3.1)
TE events in pts treated before urgent surgery or invasive procedures	0.8% (0.1–2.0)
TE events in pts treated with 4-factor PCCs	1.8% (1.0–3.0)
TE events in pts treated with 3-factor PCCs	0.7% (0.0–2.4)
TE events in high quality studies	2.3% (0.5–5.4)
Viral transmission after PCC administration	1.9% (0.3–4.9)

Recombinant factor VIIa for the prevention and treatment of bleeding in patients without haemophilia.

Cochrane Database of Systematic Reviews 2012, Issue 3. Art. No.: CD005011

- Thirteen trials involving 2929 pts examined the therapeutic use of rFVIIa; 1878 received rFVIIa.

- no outcomes where any observed advantage or disadvantage of rFVIIa over placebo could not have been observed by chance alone.

- trend in favour of rFVIIa for reducing mortality
- (RR 0.91; 95% CI 0.78 to 1.06).

- trend against rFVIIa for increased thromboembolic adverse events
- (RR 1.14; 95% CI 0.89 to 1.47).

- When all trials were pooled together to examine the risk of thromboembolic events, significant increase in total arterial events
- (RR 1.45; 95% CI 1.02 to 2.05).

Come gestire emorragie maggiori in VKA (Guida alla terapia antitrombotica, FCSA 2021)

(anche in chirurgia d'urgenza con o senza emorragia maggiore)
Obiettivo rapido ripristino di normale attività emostatica INR < 1.5

Procedura:
1- Sospendere TAO
2- Infondere CCP

INR	UI/KG
1.5- 2	20
2.1-3.9	30
4- 5.9	40
>6	50

3-Controllare INR dopo 5-10 min
4-Nell'attesa di controllo INR, somministrare vit K 10 mg diluita in 100 cc SF ed infusa in 30min
Se INR < 1.5: reversal completato
Se INR > 1.5 infondere CCP al dosaggio corrispondente all'INR residuo
Se emorragia intracranica: senza attendere INR, subito PCC 20 UI /Kg e via K

ASH Guidelines 2018

Recommendation

In patients with **life-threatening bleeding** during VKA treatment for VTE who have an elevated INR, the panel **suggests using 4-factor PCC rather than FFP**, in addition to cessation of VKA and intravenous vitamin K *(conditional recommendation, very low certainty)*

PCC compared with **FFP**, in addition to intravenous vitamin K cessation of VKA:

Outcomes (Quality of Evidence)	Relative effect (95% CI)	Anticipated absolute effects (95% CI)	
		Risk with FFP	*Risk difference with PCC*
● Mortality	**RR 0.92** (0.37 to 2.28)	18 of 145 (12.4%)	**10 fewer deaths per 1,000** (78 fewer to 159 more)
● PE	**RR 7.71** (0.44 to 136.11)	0 of 23 (0.0%)	**15 more PE per 1,000** (0 fewer to 0 fewer)
● Symp. Prox DVT	**RR 2.57** (0.11 to 60.24)	0 of 23 (0.0%)	**4 more DVT per 1,000** (2 fewer to 13 more)
● Major bleeding	**RR 1.34** (0.78 to 2.29)	12 of 132 (9.1%)	**31 more bleed per 1,000** (20 fewer to 117 more)

Given low certainty of effects, other driving factors for PCC recommendation:

- PCC: less volume overload, faster reduction of INR compared with FFP
- PCC easier to administer

Quality of Evidence (GRADE): Low ● Moderate ● Strong ●

Witt et al, ASH 2018

How to manage major bleeding during DOACS

- Initially introduced without specific reversal agents

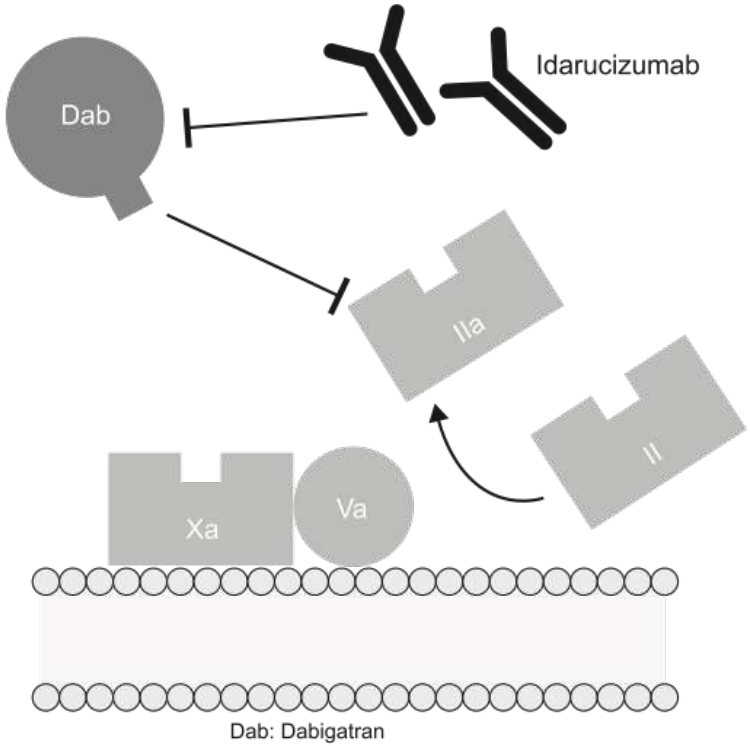
- Advantage : short half life (few hours)

- Treatment interruption may not be sufficient in case of major/life threatening bleeding

Strategies currently available for reversal of DOACs

	Time until restoration of hemostasis after cessation of therapeutic dose	Laboratory tests to measure drug effect	Activated Charcoal **	Protein binding Dialysis**	Antidote
Dabigatran	Half life: 12-17 h	dTT, ECT Anti-IIa activity Specific assay	Not mentioned	35% yes	Antidote:YES idarucizumab
Rivaroxaban	Half life: 7-13 h	Anti-Xa activity specific assay (not widely available)	May be considered to reduce absorption in case of overdose	95% no	Antidote: YES andexanet
Apixaban	Half life: 8-15 h	Anti-Xa activity specific assay (not widely available)	2 and 6 hours after ingestion of a 20-mg dose of apixaban reduced mean apixaban AUC by 50% and 27%,respectively	87% no	Antidote: YES andexanet
Edoxaban	Half life : 9-11 h	Anti-Xa activity specific assay (not widely available)	Not mentioned	54% no	Antidote: ?? andexanet

Reversal Agents in DOACS

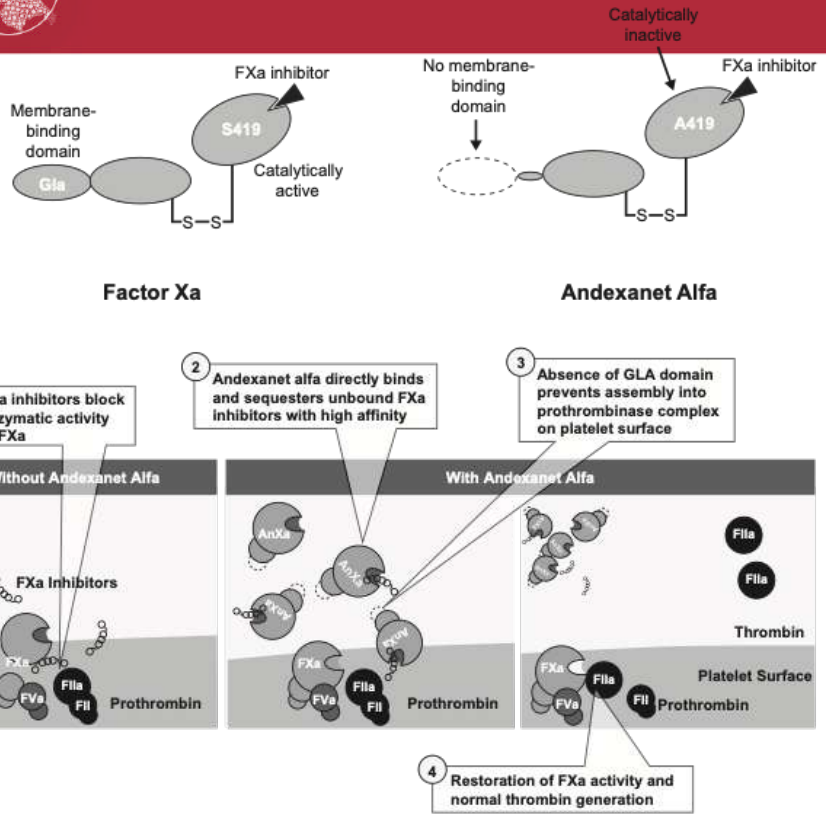


Dab: Dabigatran

Kaide et al The Journal of Emergency Medicine, Vol. 58, No. 2, pp. 217–233, 2020

	Idarucizumab
Structure	Fully humanized Fab
Target	Dabigatran only
Mechanism	Non-competitive binding to Dabigatran with 350 times greater affinity than thrombin binds dabigatran with high affinity preferentially over thrombin, and readily displaces dabigatran, a lowing fibrin formation to occur normally

Reversal Agents for DOACS



Andexanet alfa binds lacks the membrane-binding g-carboxyglutamic acid domain.

By binding and sequestering FXa inhibitors, andexanet alfa reverses FXa inhibition and restores that capacity of prothrombinase to generate thrombin and to effect hemo-stasis

	Andexanet alfa	Ciraparantag PER 977
Structure	Recombinant, modified human inactive Factor Xa	Di-arginine piperazine
Target	Factor Xa Inhibitors (Riva; Apix; Edox)	All NOACs (Dabi; Riva; Apix; Edox) UFH, LMWH, fondaparinux
Mechanism	Binds competitively to direct FXa inhibitors	Binds to heparins and oral FXa and IIa inhibitors through hydrogen Bonding

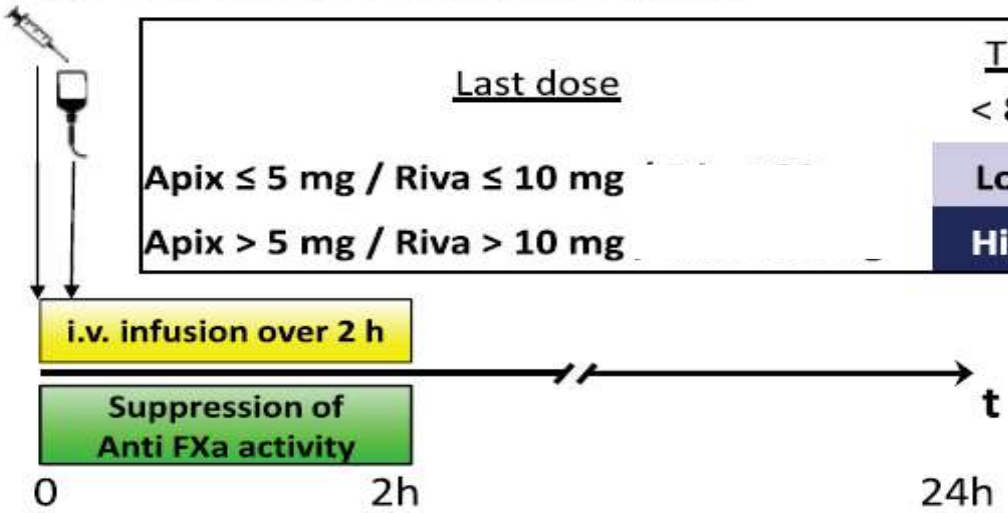
Kaide et al The Journal of Emergency Medicine, Vol. 58, No. 2, pp. 217–233, 2020

	Idarucizumab	Andexanet alfa	Ciraparantag
In vitro studies	Reversal of prolonged clotting time induced by Dabigatran	Complete and dose-dependent reversal of Riva, Apix and Betrix in human plasma	Complete reversal of anti-Xa activity of Riva, Apix and Edox
Animal models	Reduction in blood loss and mortality in a porcine liver trauma model	Reduced blood loss induced by Rivar mouse (tail transection) and rabbit (liver laceration) models	Decreased bleeding in a rat-tail transaction model
Clinical trials	Phase 1: Immediate, complete and sustained reversal of Dabi-induced anticoagulation in healthy humans: 1 split dose of 5 gr ev **Phase 3: RE-VERSE AD in dabigatran related major bleeding**	Phase 1: Dose-dependent reversal of Riva in healthy volunteers Phase 2: Rapid reversal of Riva and Apix. Ongoing trial with Edox **Phase 3: Rapid reversal of Apix (ANNEXA-A).** **trial with Riva (ANNEXA-R) and planned trial with Edox (ANNEXA-E)**	Phase 1: Rapid and sustained reversal of edoxaban

Application of Idarucizumab

5g i.v. in two consecutive infusions of
2.5g i.v. over 5-10 minutes each (or as a bolus)

Application of Andexanet Alpha



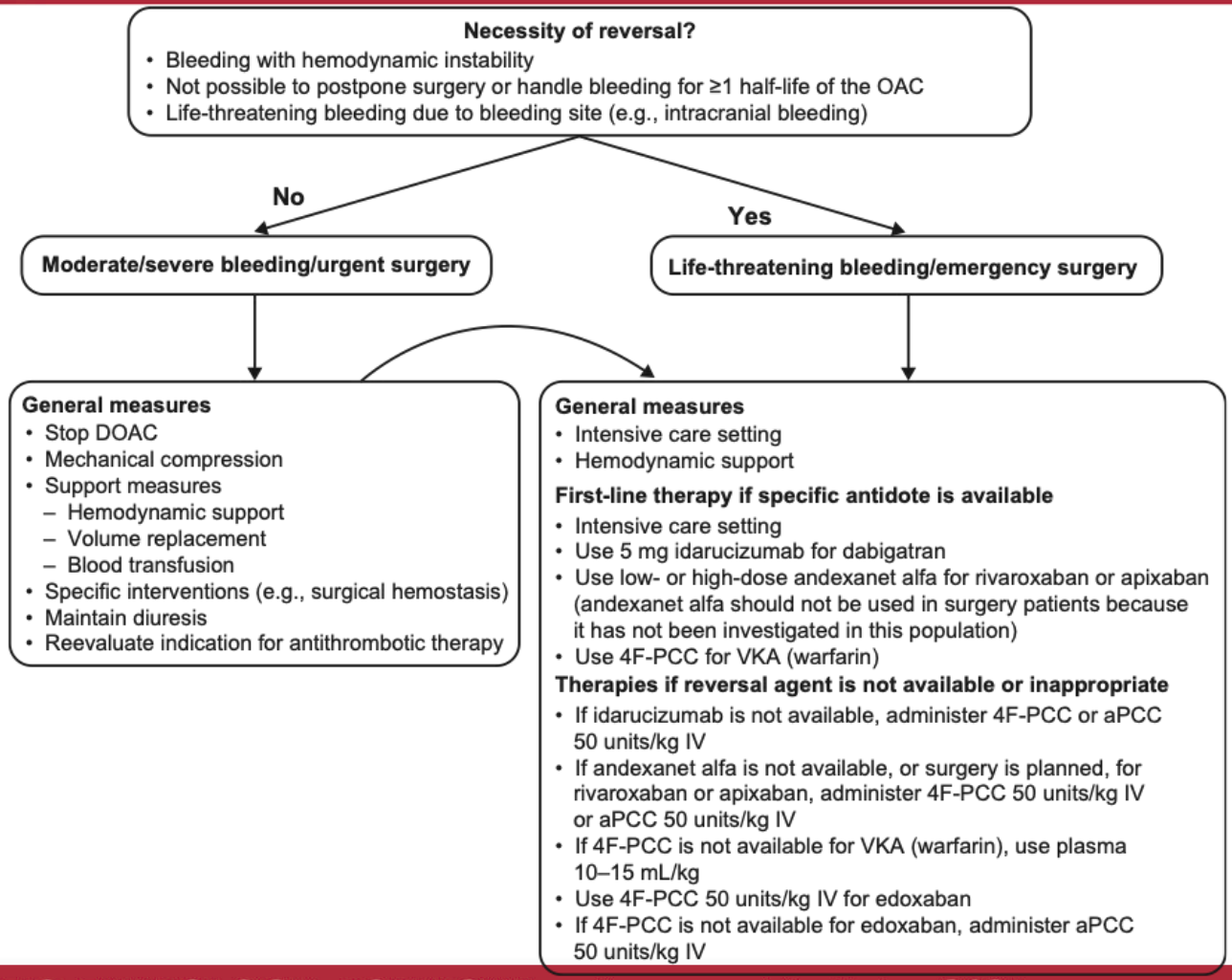
Low dose:
- Bolus: 400mg (at 30 mg/min)
- Infusion: 4 mg/min (=480 mg)

High dose:
- Bolus: 800mg (at 30 mg/min)
- Infusion: 8 mg/min (=960 mg)

Steffel et al Europace (2021)

Recommendation for anticoagulation reversal

(American College of Cardiology and European Society of Cardiology).



Kaide et al The Journal of Emergency Medicine, Vol. 58, No. 2, pp. 217–233, 2020

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

Idarucizumab è un inattivatore specifico per dabigatran ed è indicato nei pazienti adulti trattati con

Pradaxa (dabigatran etexilato) nei casi in cui si rende necessaria l'inattivazione rapida dei suoi effetti anticoagular

- negli interventi chirurgici di emergenza/nelle procedure urgenti;
- nel sanguinamento potenzialmente fatale o non controllato.

4.2 Posologia e modo di somministrazione Limitato esclusivamente all'uso ospedaliero. Posologia

La dose raccomandata è di 5 g di idarucizumab (2 flaconcini da 2,5 g/50 mL).

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

Per pazienti adulti trattati con un inibitore diretto del fattore Xa (FXa) (apixaban o rivaroxaban),

quando è richiesta l'inversione della terapia anticoagulante a causa di emorragie potenzialmente fatali o incontrollat

4.2 Posologia e modo di somministrazione

Uso esclusivamente ospedaliero.

Posologia
Andexanet alfa viene somministrato sotto forma di bolo endovenoso a una velocità target di circa 30 mg/min in

15 minuti (dose bassa) o 30 minuti (dose elevata), seguito da un'infusione continua di 4 mg/min (dose bassa) o

8 mg/min (dose elevata) per 120 minuti (vedere tabella 1).

- Bridging anticoagulation:
- definition, aim, and dose regimens

- Literature evidence on efficacy and safety of bridging

- Guideline recommendations

Rationale for peri-operative bridging of VKAs

- VKAs have a slow offset and onset, when stopped and then restarted around the time of a procedure
- There is a period during which therapeutic anticoagulation is not achieved.
- To minimize this time, bridging therapy is often used.

Perioperative Management of Antithrombotic Therapy

- No universally accepted definition
- bridging anticoagulation = administration of a short-acting anticoagulant, consisting of SC LMWH or IV UFH, for a ~ 10- to 12-day period during interruption of VKA therapy when INR is not within a therapeutic range.
- Bridging therapy itself must also be interrupted during the time of the procedure, but the shorter half lives of the drugs used for bridging treatment enable the time off all anticoagulation to be minimized.

Douketis JD et al, CHEST 2012; 141(Suppl):e326S

Peri-operative management of VKA/DOACS: balancing the competing risks

1-
thromboembolic risk without AC:
depending on:
indication for treatment

2-
Risk of bleeding after restarting AC
Stratification on the basis of:
-type of procedure

3-
basis for determining whether antithrombotic therapy is interrupted and, if so,whether bridging anticoagulation is considered

Procedural bleeding risk

High risk two day risk of major bleed 2-4%	

Daniels PR, BMJ 2015;351:2391

Procedural bleeding risk

Low Two day risk of major bleed 0-2%	
Cholecystectomy Abdominal hysterectomy Gastrointestinal endoscopy with or without biopsy, enteroscopy, biliary or pancreatic stent without sphincterotomy, endosonography without fine needle aspiration Insertion of a pacemaker or cardiac defibrillator and electrophysiologic testing Simple dental extractions Carpal tunnel repair Knee or hip replacement and shoulder, foot, or hand surgery Arthroscopy	

Daniels PR, BMJ 2015;351:2391

Bridging dose regimens

- Therapeutic dose : similar to that used for the treatment of acute VTE or ACS (eg, enoxaparin 1 mg/kg bid or 1.5 mg/kg daily, IV UFH to attain an aPTT 1.5 to 2 times the control aPTT: greatest therapeutic benefit with the potential of greatest harm

- A low-dose (prophylactic-dose) heparin regimen: administering a dose that is used, typically, to prevent postoperative VTE

- An intermediate-dose regimen: intermediate in anticoagulant intensity between high- and low-dose regimens (eg, enoxaparin 40 mg/kg bid)

Douketis JD et al, CHEST 2012; 141(Suppl):e326S

Perioperative Management of Antithrombotic Therapy

Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

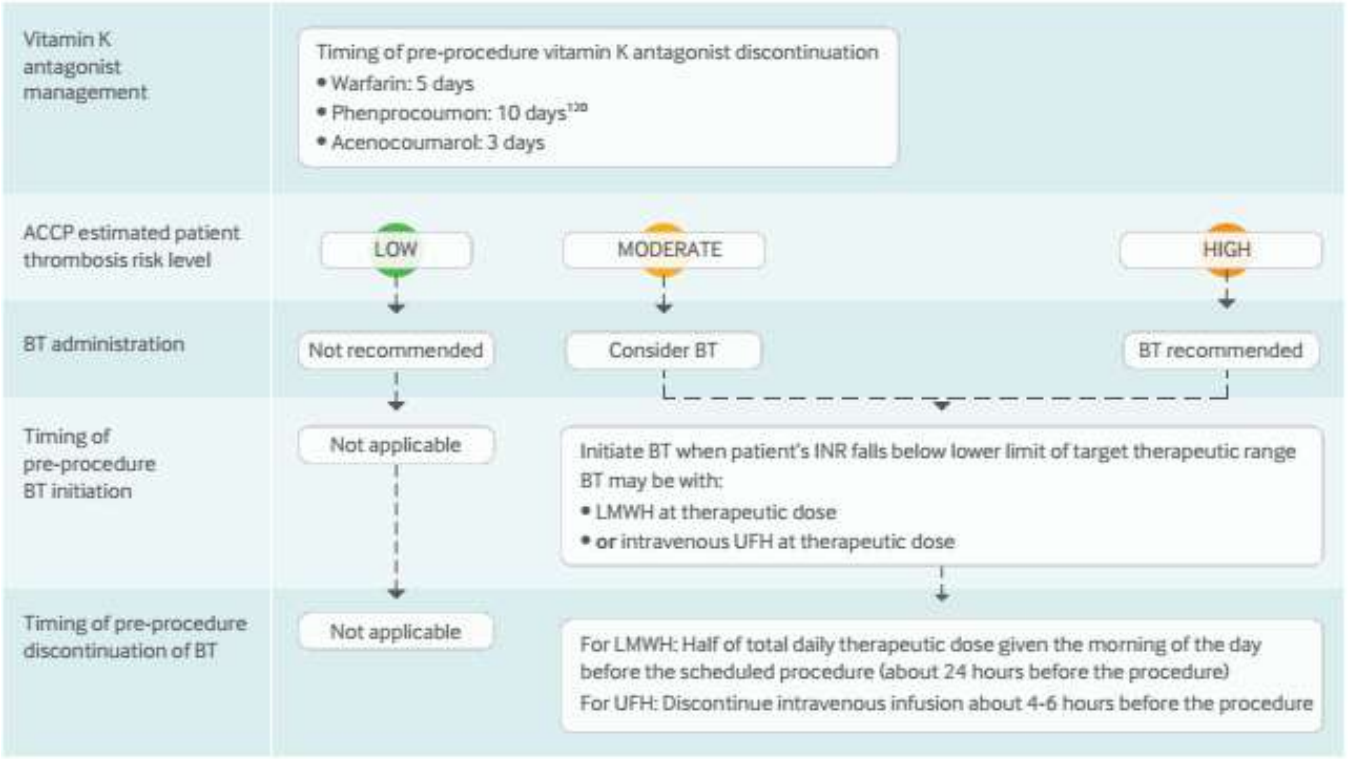


Fig 6| Suggested approach to elective pre-procedure management of vitamin K antagonists. ACCP=American College of Chest Physicians; BT=bridging therapy; INR=international normalized ratio; LMWH=low molecular weight heparin; UFH=unfractionated heparin[21 118]

Daniels PR, BMJ 2015;351:2391

Evidence on bridging

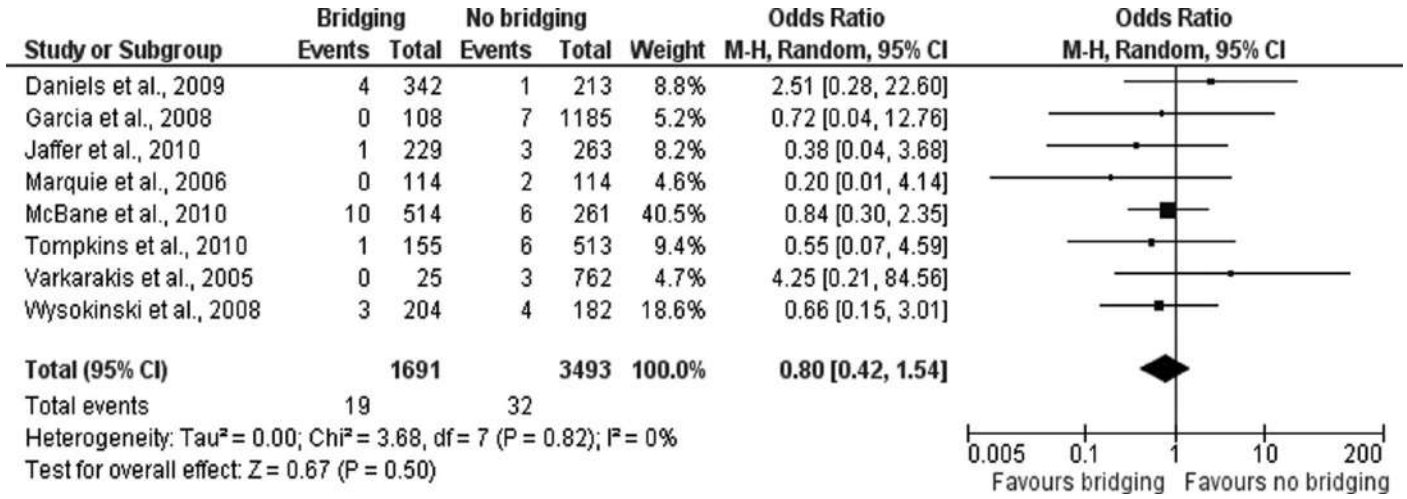
- Most of the data from observational studies of limited quality with variable outcome definitions, bridging therapy regimens, procedure types, and patient characteristics.
- Systematic reviews

- RCTs :
- *Bruise Control 2013*
-
- *Bridging Anticoagulation for Surgery (BRIDGE) (NEJM 2015)*

- *A Safety and Effectiveness Study of LMWH Bridging Therapy Versus Placebo Bridging Therapy for Patients on Long Term Warfarin and Require Temporary Interruption of Their Warfarin (PERIOP-2)*

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists: Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

Overall: 73 of 7118 bridged patients (pooled incidence, 0.9%; 95%CI: 0–3.4) vs 32 of 5160 non bridged patients (pooled incidence, 0.6%; 95%CI:0.0–1.2).



Forest plot of thromboembolic events.

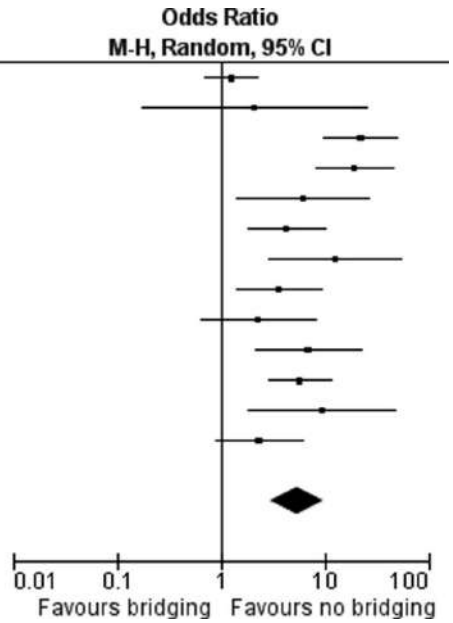
Siegal D et al. Circulation. 2012;126:1630

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists: Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

Study or Subgroup	Bridging Events	Bridging Total	No bridging Events	No bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	36	342	18	213	9.8%	1.27 [0.70, 2.31]
Dotan et al., 2002	2	20	1	20	3.7%	2.11 [0.18, 25.35]
Ercan et al., 2010	11	44	21	1421	9.0%	22.22 [9.92, 49.81]
Garcia et al., 2008	14	108	9	1185	8.8%	19.46 [8.21, 46.14]
Ghanbari et al., 2010	6	29	3	74	6.5%	6.17 [1.43, 26.68]
Jaffer et al., 2010	24	229	7	263	8.8%	4.28 [1.81, 10.14]
Marquie et al., 2006	21	114	2	114	6.4%	12.65 [2.89, 55.34]
McBane et al., 2010	34	514	5	261	8.4%	3.63 [1.40, 9.39]
Robinson et al., 2009	20	113	3	35	7.2%	2.29 [0.64, 8.24]
Tischenko et al., 2009	9	38	5	117	7.6%	6.95 [2.16, 22.33]
Tompkins et al., 2010	23	155	15	513	9.5%	5.78 [2.94, 11.40]
Varkarakis et al., 2005	2	25	7	762	5.9%	9.38 [1.85, 47.64]
Wysokinski et al., 2008	15	204	6	182	8.4%	2.33 [0.88, 6.13]
Total (95% CI)		**1935**		**5160**	**100.0%**	**5.40 [3.00, 9.74]**
Total events	217		102			

Heterogeneity: $Tau^2 = 0.83$; $Chi^2 = 52.47$, df = 12 ($P < 0.00001$); $I^2 = 77\%$

Test for overall effect: $Z = 5.61$ ($P < 0.00001$)



Forest plot of overall bleeding events.

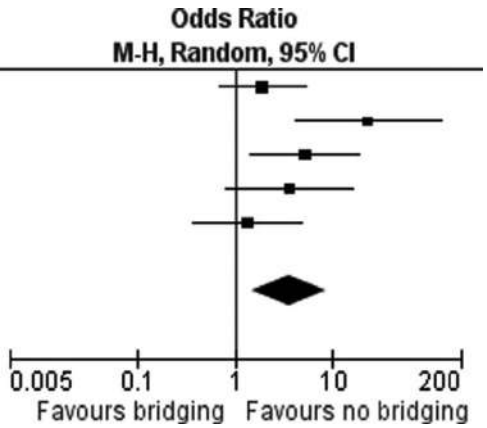
Siegal D et al. Circulation. 2012;126:1630

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists: Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

Study or Subgroup	Bridging Events	Bridging Total	No bridging Events	No bridging Total	Weight	Odds Ratio M-H, Random, 95% CI
Daniels et al., 2009	15	342	5	213	24.9%	1.91 [0.68, 5.33]
Garcia et al., 2008	4	108	2	1185	15.3%	22.75 [4.12, 125.68]
Jaffer et al., 2010	13	229	3	263	21.0%	5.22 [1.47, 18.54]
McBane et al., 2010	14	514	2	261	17.9%	3.63 [0.82, 16.08]
Wysokinski et al., 2008	6	204	4	182	20.8%	1.35 [0.37, 4.86]
Total (95% CI)		**1397**		**2104**	**100.0%**	**3.60 [1.52, 8.50]**
Total events	52		16			

Heterogeneity: $Tau^2 = 0.50$; $Chi^2 = 8.41$, $df = 4$ ($P = 0.08$); $I^2 = 52\%$

Test for overall effect: $Z = 2.92$ ($P = 0.004$)



Forest plot of major bleeding events.

Siegal D et al. Circulation. 2012;126:1630

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists: Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

Table 4. Pooled Incidence Rates of Thromboembolic and Bleeding Events in Studies With and Without Bridging Comparator Groups

Group	TE Events, % (95% CI), and Events/Patients at Risk	ATE Events, % (95% CI), and Events/Patients at Risk	VTE Events, % (95% CI), and Events/Patients at Risk	Major Bleeding, % (95% CI), and Events/Patients at Risk	Overall Bleeding, % (95% CI), and Events/Patients at Risk	Mortality, % (95% CI), and Events/Patients at Risk
Total bridged cohort	0.9 (0.0–3.4)	1.0 (0.0–2.8)	0.2 (0.0–0.6)	4.2 (0.0–11.3)	13.1 (0.0–45.2)	0.3 (0.0–1.0)
	73/7118	50/6426	21/4632	211/6404	833/7188	31/6079
LMWH						
Full dose	0.4 (0.0–0.9)	1.7 (1.2–2.1)	0.4 (0.0–1.0)	3.2 (1.3–5.2)	13.6 (2.9–24.3)	0.0 (0.0–0.2)
	17/2314	17/2002	1/734	69/2126	334/2314	5/1836
Prophylactic/ intermediate dose	0.2 (0.0–0.6)	0.2 (0.0–0.6)	0.2 (0.0–0.5)	3.4 (0.0–8.7)	8.5 (2.9–14.2)	0.1 (0.0–0.3)
	14/1956	7/1824	6/1688	35/1900	133/1956	5/1800
Total nonbridged cohort	0.6 (0.0–1.2)	0.5 (0.1–0.9)	0.3 (0.0–0.7)	0.9 (0.2–1.6)	3.4 (1.1–5.8)	0.1 (0.0–0.3)
	32/5160	15/2468	11/2141	18/2104	100/5160	4/2393

TE indicates thromboembolic; CI, confidence interval; ATE, arterial thromboembolic; VTE, venous thromboembolic; and LMWH, low-molecular-weight heparin. Results shown are pooled incidence rates. The number of events in patients at risk is also shown.

increased risk of overall bleeding (OR, 2.28; 95% CI, 1.27–4.08) with full versus prophylactic/intermediate-dose low-molecular-weight heparin bridging

Siegal D et al. Circulation. 2012;126:1630

Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL)

Table 3. Primary and Secondary Outcomes.*

Outcome	Heparin Bridging (N=338)	Continued Warfarin (N=343)	Relative Risk (95% CI)	P Value
Primary outcome				
Clinically significant hematoma — no. (%)	54 (16.0)	12 (3.5)	0.19 (0.10–0.36)	<0.001
Components of primary outcome				
Hematoma prolonging hospitalization — no. (%)	16 (4.7)	4 (1.2)	0.24 (0.08–0.72)	0.006
Hematoma requiring interruption of anticoagulation — no. (%)	48 (14.2)	11 (3.2)	0.20 (0.10–0.39)	<0.001
Hematoma requiring evacuation — no. (%)	9 (2.7)	2 (0.6)	0.21 (0.05–1.00)	0.03
Secondary outcomes				
Death from any cause — no. (%)	0	4 (1.2)		0.12

Perioperative Bridging Anticoagulationin Patients with Atrial FibrillationThe BRIDGE Investigators

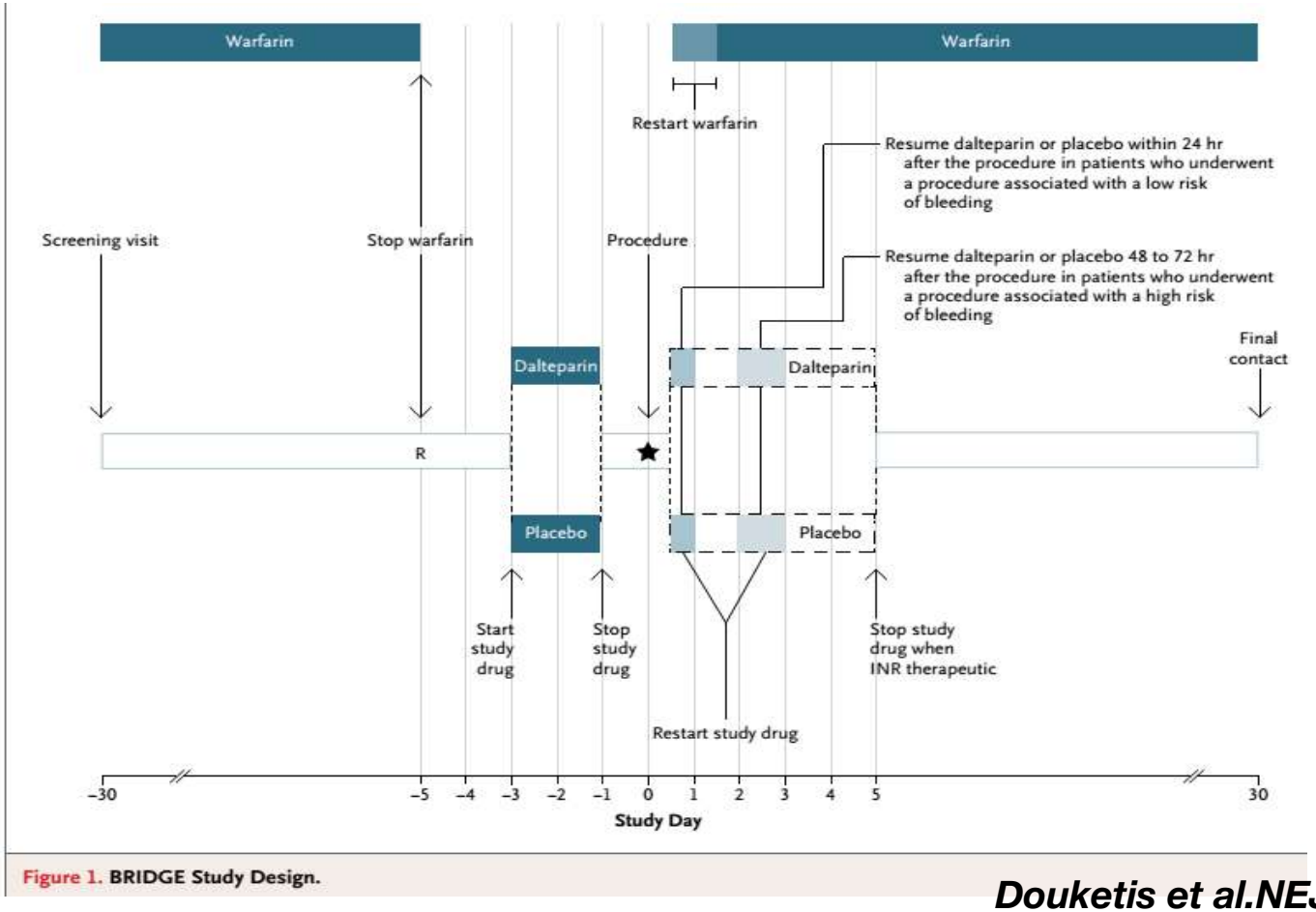


Figure 1. **BRIDGE Study Design.**

Douketis et al.NEJM 2015

Perioperative Bridging Anticoagulationin Patients with Atrial FibrillationThe BRIDGE Investigators

randomized, double-blind, placebo-controlled trial after perioperative interruption of warfarin therapy,

pts randomly assigned to receive bridging anticoagulation with LMWH (100 IU of dalteparin per kilogram of body weight)
vs matching placebo administered SC bid

from 3 days before the procedure until 24 hours before and then for 5 to 10 days after the procedure.
Warfarin treatment was stopped 5 days before the procedure and was resumed within 24 hours after the procedure.
Follow-up: 30 days after the procedure.
The primary outcome: arterial thromboembolism (stroke, systemic embolism or transient ischemic attack) and major bleeding.

Douketis et al.NEJM 2015

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation The BRIDGE Investigators

Table 3. Study Outcomes.

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

* P value for noninferiority.
† P value for superiority.

Douketis et al.NEJM 2015

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation: *The Bridge Investigators*

- Few patients with CHADS2 score of 5 or 6, mean score of 2.3
- mechanical heart valves excluded
- major surgical procedures associated with high rates of arterial thromboembolism and bleeding (e.g., carotid endarterectomy, major cancer surgery, cardiac surgery, or neurosurgery) not represented
- overall rate of arterial thromboembolism (0.4%) lower than expected
- observed rate of major bleeding in the bridging group (3.2%, with no instances of fatal bleeding) may be considered to be modest
- the reduction in the study sample size may raise concerns

PERIOP-2

a multicenter randomized double-blind controlled trial of patients with atrial fibrillation or a mechanical heart valve who require interruption of warfarin for a planned procedure

All patients received pre-procedure bridging therapy with dalteparin 200 IU/kg (max 18,000 IU) subcutaneously in the morning day-3 and day-2 then dalteparin 100 IU /kg (max 18,000 IU) subcutaneously 24 hours pre-procedure.
Warfarin was resumed in the evening of the procedure at twice the usual dose for the first two days and then titrated according to INR

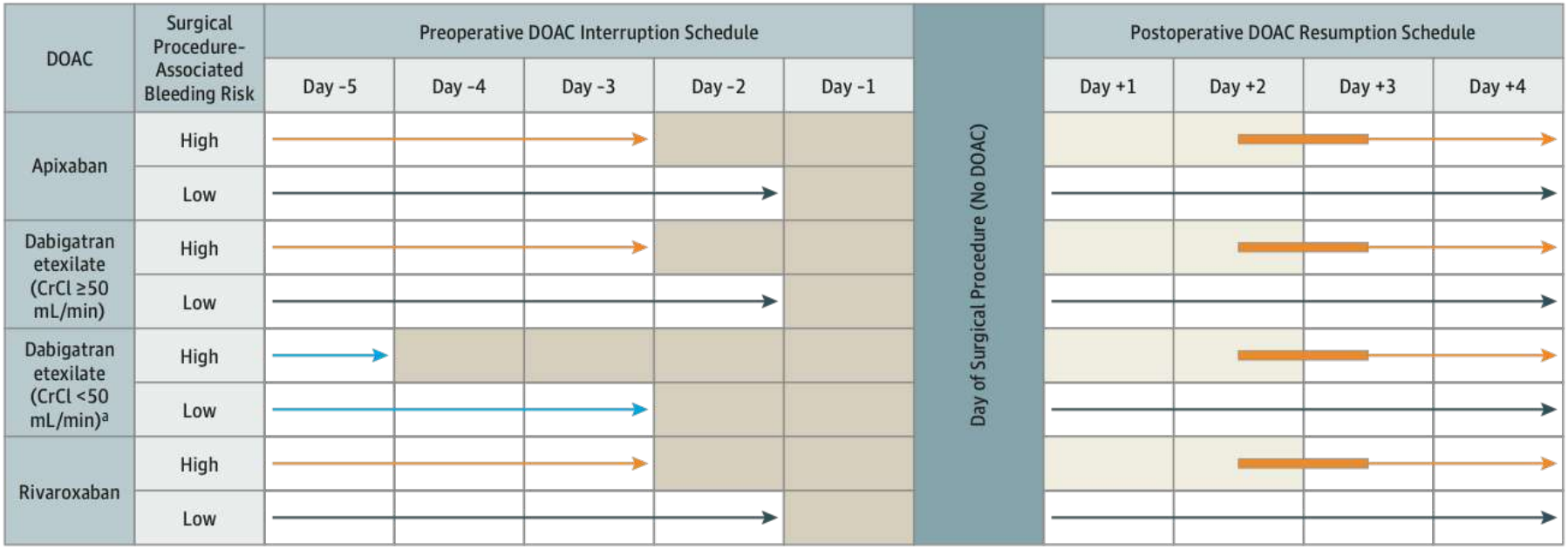
Major thromboembolism : 6/820 (0.71%) dalteparin vs 7/650 (1.11%) placebo
Major post-procedure bleeding: 12 (1.46%) dalteparin vs16 (2.46%) placebo

Findings were similar in patients with atrial fibrillation alone and in patients with mechanical heart valves (with or without atrial fibrillation).

Kovacs et al, Blood 2018

2021 Perioperative Management of Patients With Atrial Fibrillation Receiving a Direct Oral Anticoagulant-PAUSE trial

Figure. Perioperative Direct Oral Anticoagulant (DOAC) Management Protocol



3007 patients using apixaban, dabigatran, or rivaroxaban, DOAC stopped and resumed before and/or after elective surgery or procedure using standardized protocols without heparin bridging.

Douketis et al, Jama Internal Medicine,2019

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

30-day postoperative rates of major bleeding < 2%, and the rates of stroke <1%.

Preoperative DOAC treatment levels were measured for 2541 patients (84.5%)

The pro- portion of patients with a level less than 50 ng/mL was 90.5% in the apixaban cohort, 95.1% in the dabigatran cohort, and 96.8% in the rivaroxaban cohort

Douketis et al, Jama Internal Medicine,2019

	Dabigatran		Apixaban - Edoxaban - Rivaroxaban	
No perioperative bridging with LMWH / UFH				
Minor risk procedures: - Perform procedure at NOAC trough level (i.e., 12 h / 24 h after last intake). - Resume same day or latest next day.				
	Low risk	**High risk**	**Low risk**	**High risk**
CrCl ≥80 ml/min	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
CrCl 50-79 ml/min	**≥ 36 h**	**≥ 72 h**		
CrCl 30-49 ml/min	**≥ 48 h**	**≥ 96 h**		
CrCl 15-29 ml/min	Not indicated	Not indicated	**≥ 36 h**	
CrCl <15 ml/min	No official indication for use			

Important:

- Timing of interruption may require adaptation based on individual patient characteristics (Fig. 13)
- In patients / situations with risk of NOAC accumulation (renal insufficiency, older age, concomitant medication, see Fig. 6) pausing the NOAC 12-24 hours earlier may be considered.[207,208]
- Resume full dose of NOAC 24h after low-risk- and 48 (-72) h after high-risk interventions

Steffel et al Europace (2021)