PMB and the management of patients on oral anticoagulants

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Special Conference
Il Patient Blood Management: non solo una questione di ferro e anemia
Roma, 15 ottobre 2015

Il/La sottoscritto/a, in qualità di Relatore
dichiara che

nell'esercizio della Sua funzione e per l'evento in oggetto, DI NON ESSERE in alcun modo portatore di interessi commerciali propri o di terzi; e che gli eventuali rapporti avuti negli ultimi due anni con soggetti portatori di interessi commerciali non sono tali da permettere a tali soggetti di influenzare le mie funzioni al fine di trarne vantaggio.

oppure

X negli ultimi due anni ha avuto i seguenti rapporti anche di finanziamento con i soggetti portatori di interessi commerciali in campo sanitario:

Bayer
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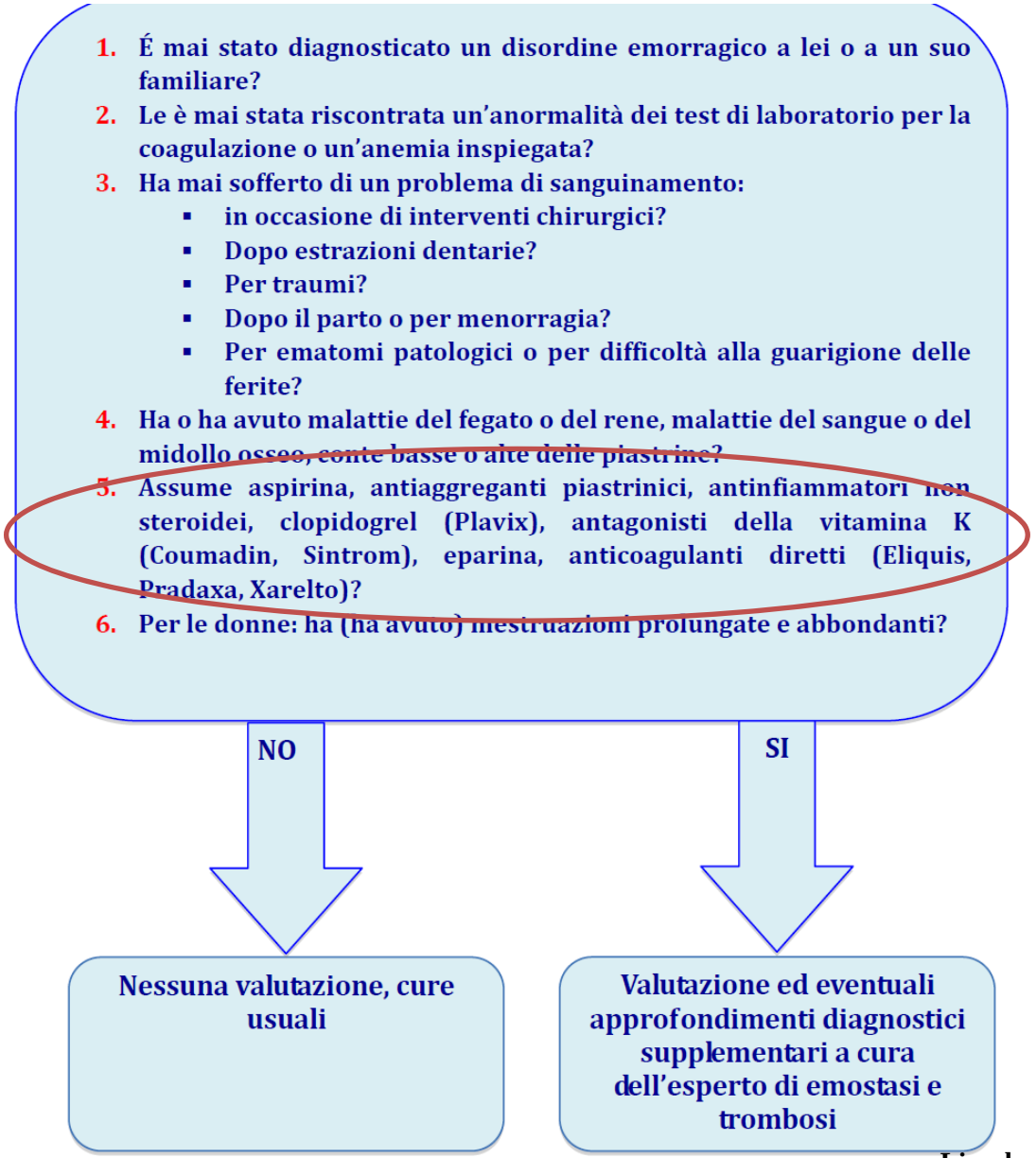

Liumbruno GM. Blood Trans 2011
Nichols WL, Haemoph 2008

The question of whether antithrombotic therapy should be suspended in a patient who will be undergoing an invasive procedure involves balancing the risk of postprocedural bleeding with continued treatment against the thrombotic risk with suspension of treatment and use of bridging anticoagulation therapy

Invasive procedures where the bleeding risk is low and oral anticoagulation can often be continued

Procedure	Comments
Minor dental, e.g. tooth extractions and endodontic (root canal)	Current UK guidance states that vitamin K antagonist therapy can safely be continued (National Patient Safety Agency, 2007; Perry *et al*, 2007). A pro-haemostatic agent (e.g. tranexamic acid (5–10%, 5 ml 3–4 times a day), starting 1 d before the procedure and for 1–2 d after the procedure, was found to be associated with a low (<5%) risk of clinically relevant non-major bleeding (Douketis *et al*, 2012))
Dermatological, e.g. excision of basal and squamous cell skin cancers, actinic keratoses and premalignant or cancerous skin nevi	The reported incidence of bleeding complications appears to be low (<5%) when oral anticoagulation is continued
Cataract	Prospective cohort studies report an incidence of clinically relevant bleeding of <3% when oral anticoagulation therapy is continued (Robinson & Nylander, 1989; Roberts *et al*, 1991; Katz *et al*, 2003)
Diagnostic oesophagogastroduodenoscopy or colonoscopies	Where there is no plan to biopsy

Patel J, Br J of Hematol 2013

ACCP risk stratification of patients treated with oral anticoagulants

Thromboembolic risk	Mechanical heart valve	Atrial fibrillation	Venous thromboembolism
High (>10% annual risk)	Any mitral valve prosthesis Any caged-ball or tilting disk aortic valve prosthesis Recent (within 6 months) stroke or TIA	$CHADS_2$ score of 5 or 6 Recent (within 3 months) stroke or TIA Rheumatic valvular heart disease	Recent (within 3 months) VTE Severe thrombophilia (e.g. PS, PC, Antithrombin deficiency, antiphosphoshoplipid antibodies, multiple abnormalities)
Moderate (5–10% annual risk)	Bi-leaflet aortic valve prosthesis and one or more of the following risk factors: AF, prior stroke or TIA, hypertension, diabetes, congestive heart failure, age >75 years	$CHADS_2$ score of 3 or 4 (assuming no prior stroke or TIA)	VTE within the past 3–12 months Non-severe thrombophilia [e.g. heterozygous *F5* R506Q (factor V Leiden) or *F2* G20210A (prothrombin gene mutation)] Recurrent VTE Active cancer (treated within 6 months or palliative)
Low (<5% annual risk)	Bi-leaflet aortic valve prosthesis without atrial fibrillation and no other risk factors for stroke	$CHADS_2$ score of 0 or 2 (assuming no prior stroke or TIA)	VTE >12 months previous and no other risk factors

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ASSESSMENT OF THROMBOTIC RISK

CHADS2 Scoring System for Assessing the Risk of Stroke among Patients with Atrial Fibrillation

$CHADS_2$ Score or Assessment	Risk of Stroke	Stroke Rate per 100 Patient-Yr *range (95% CI)*
Score of 0, 1, or 2	Low	1.9–4.0 (1.2–5.1)
Score of 3 or 4	Moderate†	5.9–8.5 (4.6–11.1)
Score of 5 or 6, stroke or TIA within previous 3 mo, or severe valvular heart disease	High	12.5–18.2 (8.2–27.4)

Baron H, N Engl J Med 2013

CHA_2DS_2VASc score and stroke rate

(b) Risk factor-based approach expressed as a point based scoring system, with the acronym CHA_2DS_2-VASc (Note: maximum score is 9 since age may contribute 0, 1, or 2 points)	
Risk factor	**Score**
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

(c) Adjusted stroke rate according to CHA_2DS_2-VASc score		
CHA_2DS_2-VASc score	**Patients (n=7329)**	**Adjusted stroke rate (%/year)[b]**
0	1	0%
1	422	1.3%
2	1230	2.2%
3	1730	3.2%
4	1718	4.0%
5	1159	6.7%
6	679	9.8%
7	294	9.6%
8	82	6.7%
9	14	15.2%

Camm J et al Eur Heart Journal 2010

Approach to Bridging Therapy

Condition	Bridging Therapy Required	No Bridging Therapy	Comments
Mechanical heart valve	Mitral-valve replacement, two or more mechanical valves, non-bileaflet aortic-valve replacement, or aortic-valve replacement with other risk factors	Aortic-valve replacement, bileaflet prosthesis, and no additional risk factors	Other risk factors include prior stroke, TIA, intracardiac thrombus, or cardioembolic event
Nonvalvular atrial fibrillation	Prior stroke or embolic event, cardiac thrombus, or $CHADS_2$ score of ≥4	No prior stroke or embolic event, absence of cardiac thrombus, or $CHADS_2$ score of <4	Prior stroke, TIA, intracardiac thrombus, or cardioembolic event increases risk
Venous thromboembolism	Venous thromboembolism within previous 3 mo or severe thrombophilia	Venous thromboembolism >3 mo previously or no additional risk factors (e.g., active cancer and nonsevere thrombophilia)	Consider inferior vena cava filter if venous thromboembolism occurred <1 mo previously, if urgent or emergency surgery is required, or if there is a contraindication to anticoagulation therapy

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Guidelines applied at King's College Hospital for oral VKA therapy

Time line	Action
10–14 d pre-procedure	Patient risk assessed for the need for bridging therapy and a specific plan formulated for patient, depending on their specific circumstances
4–5 d pre-procedure	Patient stops oral anticoagulation
Days 3–1 pre-procedure	If patient requires pre-procedure bridging, patients injects low molecular weight heparin (LMWH; either treatment or prophylactic doses) depending on thromboembolic risk. Patient specifically instructed to inject LMWH in the morning
Morning of the procedure	Omit LMWH (if injecting pre-operatively)
Evening of the procedure	If no bleeding and procedure bleeding risk low, consider re-starting oral vitamin K antagonist therapy. If high risk of thromboembolism, administration of a prophylactic dose of LMWH is considered.
Day 1 and 2 post-procedure	Twice-daily prophylactic doses of LMWH with oral anticoagulation if high risk of thromboembolism, otherwise once daily prophylactic dose of LMWH, if thromboembolism risk is moderate. If thromboembolism risk is low, then no LMWH, oral anticoagulation simply re-started
Day 3 + post-procedure	Back to treatment dose LMWH (if high risk of thromboembolism) and continue oral anticoagulation until INR therapeutic is reached

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Overview of Traditional Antithrombotic Agents

Agent	Route of Administration	Mechanism of Action	Recommended Interval between Last Dose and Procedure
Anticoagulant agents			
Warfarin (Coumadin, Bristol-Myers Squibb)	Oral	Inhibition of vitamin K–dependent factors II, VII, IX, and X for γ-carboxylation; and proteins C and S	1–8 days, depending on INR and patient characteristics; INR decreases to ≤1.5 in approximately 93% of patients within 5 days[48]
Unfractionated heparin	Intravenous or subcutaneous	Antithrombin activation (inhibition of factors IIa, IXa, Xa, XIa, and XIIa)	Intravenous, 2–6 hr, depending on dose; subcutaneous, 12–24 hr, depending on dose
Low-molecular-weight heparins (enoxaparin [Lovenox, Sanofi Aventis] and dalteparin [Fragmin, Eisai])	Subcutaneous	Antithrombin activation (inhibition of factor Xa and, to a lesser extent, factor IIa)	24 hr
Fondaparinux (Arixtra, GlaxoSmithKline)	Subcutaneous	Antithrombin activation (factor Xa inhibitor)	36–48 hr

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Adverse events suffered by patients in the REGIMEN Registry
(Observational - Spyropoulos et al, 2006)

Event	UFH (n = 164)	LMWH (n = 668)	*P-value*
Any adverse event, n (%)	28 (17·1%)	108 (16·2%)	0·81
Arterial/venous thromboembolism, major bleed, or death	13 (7·9%)	28 (4·2%)	0·07
Adverse events, n (%)			
Arterial thromboembolism	4* (2·4)	4† (0·6)	–
Venous thromboembolism	0 (0)	2‡ (0·3)	–
Major bleed	9 (5·5)	22 (3·3)	0·25
Minor bleed	15 (9·1)	80 (12·0)	0·34
Thrombocytopenia	2 (1·2)	3 (0·4)	–
Death	2 (1·2)	4 (0·6)	–

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Bridging Therapy

Vascular Medicine

Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists

Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates

Deborah Siegal, MD, MSc; Jovana Yudin, MD, BSc;
Scott Kaatz, DO, MSc; James D. Douketis, MD, FRCPC;
Wendy Lim, MD, MSc, FRCPC; Alex C. Spyropoulos, MD, FCCP, FRCPC

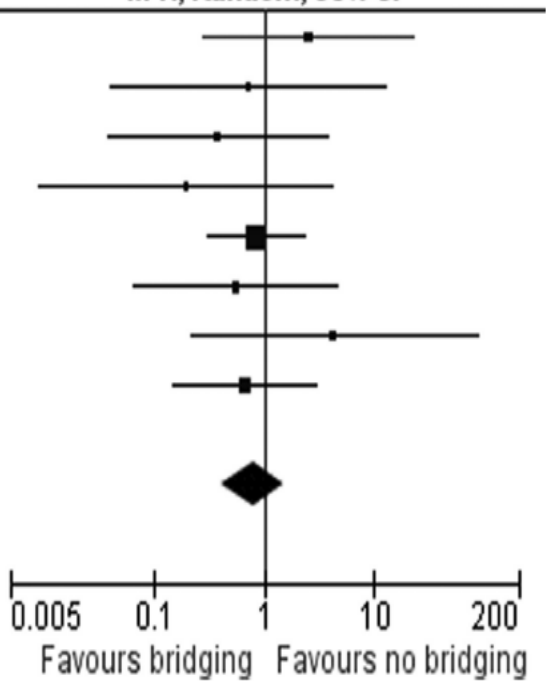
Siegal D, Circulation 2012

Forest plot of thromboembolic events

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	4	342	1	213	8.8%	2.51 [0.28, 22.60]
Garcia et al., 2008	0	108	7	1185	5.2%	0.72 [0.04, 12.76]
Jaffer et al., 2010	1	229	3	263	8.2%	0.38 [0.04, 3.68]
Marquie et al., 2006	0	114	2	114	4.6%	0.20 [0.01, 4.14]
McBane et al., 2010	10	514	6	261	40.5%	0.84 [0.30, 2.35]
Tompkins et al., 2010	1	155	6	513	9.4%	0.55 [0.07, 4.59]
Varkarakis et al., 2005	0	25	3	762	4.7%	4.25 [0.21, 84.56]
Wysokinski et al., 2008	3	204	4	182	18.6%	0.66 [0.15, 3.01]
Total (95% CI)		**1691**		**3493**	**100.0%**	**0.80 [0.42, 1.54]**
Total events	19		32			

Heterogeneity: Tau² = 0.00; Chi² = 3.68, df = 7 (P = 0.82); I² = 0%

Test for overall effect: Z = 0.67 (P = 0.50)



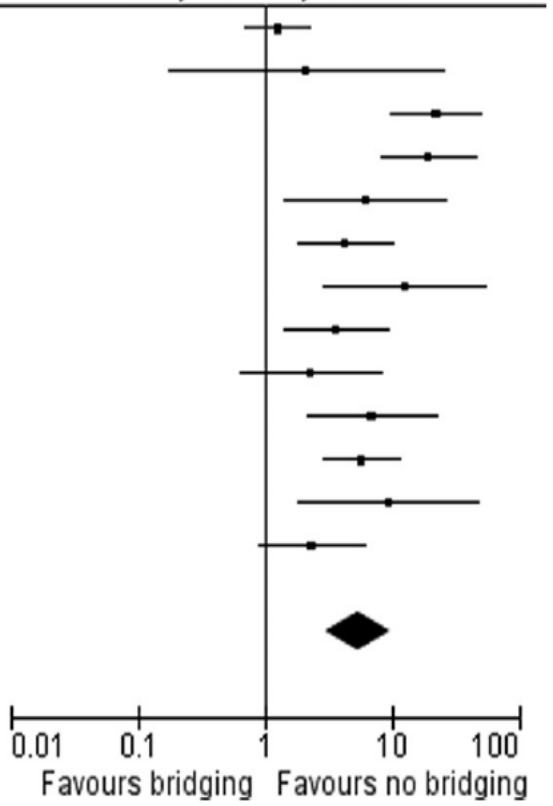
Siegal D, Circulation 2012

Forest plot of overall bleeding events

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: Tau² = 0.83; Chi² = 52.47, df = 12 (P < 0.00001); I² = 77%

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



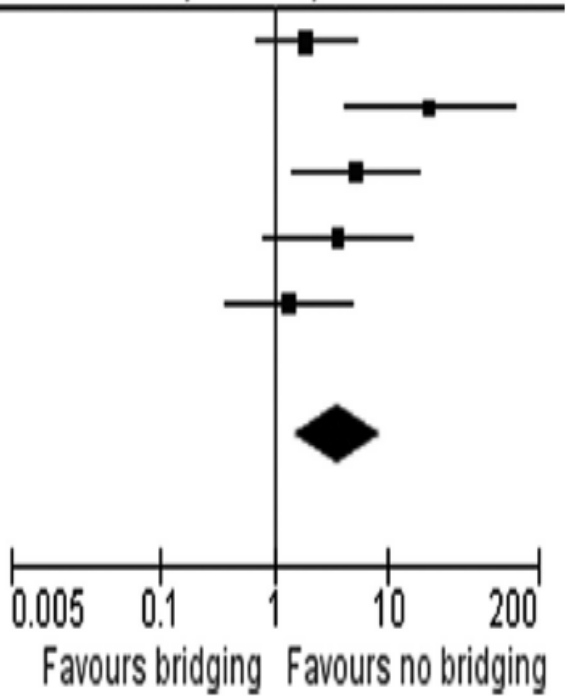
Siegal D, Circulation 2012

Forest plot of major bleeding events

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: Tau² = 0.50; Chi² = 8.41, df = 4 (P = 0.08); I² = 52%

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



Siegal D, Circulation 2012

Conclusion

We found that VKA-treated patients who require an elective surgical or invasive procedure and receive periprocedural bridging anticoagulation with LMWH appear to be at increased risk of overall and major bleeding and at similar risk of thromboembolic events compared with non bridged patients. The ACCP and other antithrombotic guidelines advocate that bridging anticoagulation should be undertaken with consideration of individual patient thromboembolic risk and procedural bleeding risk by balancing expected benefits and harms.

Siegal D, Circulation 2012

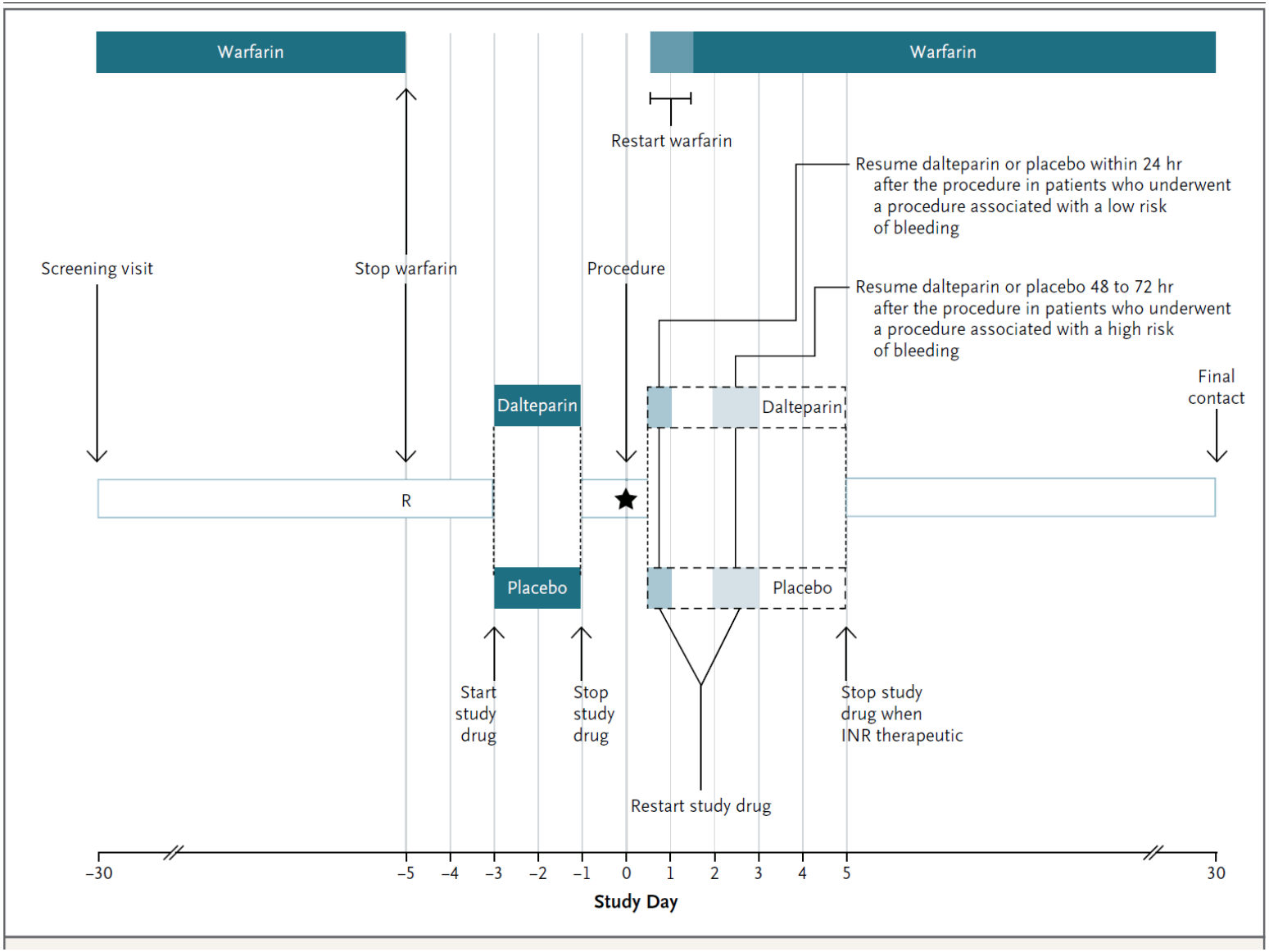
The NEW ENGLAND JOURNAL of MEDICINE

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., for the BRIDGE Investigators*

Douketis J, NEJM 2013



Douketis J, NEJM 2015

Study Outcome

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†

Douketis J, NEJM 2015

Conclusion

In the BRIDGE trial, we found that for patients with atrial fibrillation who require temporary interruption of warfarin treatment for an elective operation or other elective invasive procedure, a strategy of forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism.
The strategy of forgoing bridging treatment also decreased the risk of major bleeding

Douketis J, NEJM 2015

Vascular Medicine

Standardized Low–Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery

An Inception Cohort Management Study

V. Pengo, MD; U. Cucchini, MD; G. Denas, MD; N. Erba, MD; G. Guazzaloca, MD; L. La Rosa, MD; V. De Micheli, MD; S. Testa, MD; R. Frontoni, MD; D. Prisco, MD; G. Nante, MD; S. Iliceto, MD; for the Italian Federation of Centers for the Diagnosis of Thrombosis and Management of Antithrombotic Therapies (FCSA)

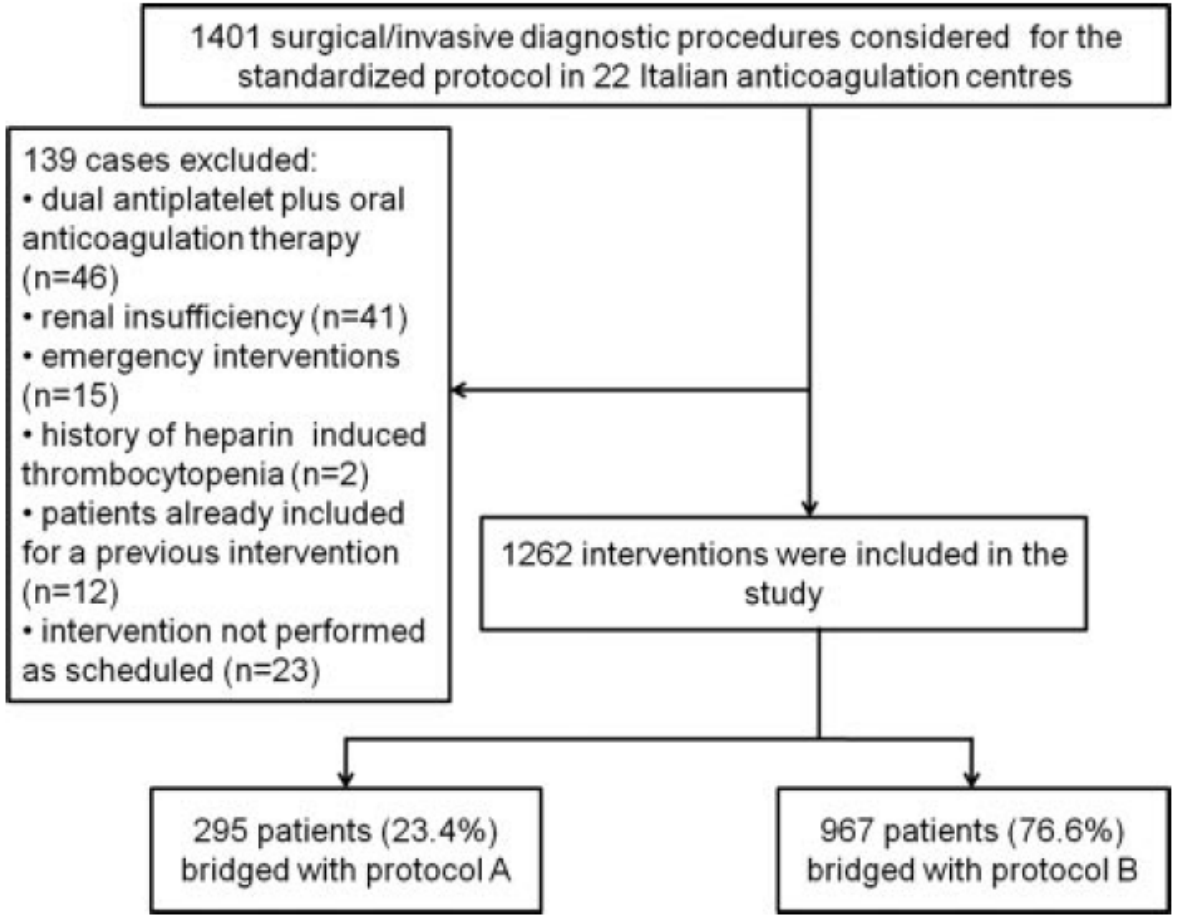
Pengo V, TH 2009

Anticoagulation Protocols Applied According to Patient Thromboembolic Risk

Weight, kg	Protocol A: Patients at High TE Risk, IU		Protocol B: Patients at Low to Intermediate TE Risk, IU	
	Nadroparin* (Twice Daily, SC)	Enoxaparin* (Twice Daily, SC)	Nadroparin* (Once Daily, SC)	Enoxaparin† (Once Daily, SC)
<50	2850	2000	2850	4000
50–69	3800	4000	3800	4000
70–89	5700	6000	5700	4000
90–110	7600	8000	5700	4000
>110	9500	10 000	5700	4000

Pengo V, TH 2009

Study Flow-Chart



Pengo V, TH 2009

Thromboembolic Event Details

Patient	Sex	Age, y	Indication	Procedure	Event	Event Day*	Comments
1	F	64	DVT	Hemicolectomy	PE	5	Thrombosis of the pulmonary artery segmental branches
2	F	63	AF+MVR	Saphenectomy	PE	0	No preoperative bridging with LMWH because day −4 INR=3.1
3	F	83	PE	Femoral osteosynthesis	PE (fatal)	6	History of PE
4	F	57	AVR+MV repair	Saphenectomy	Systemic embolism	3	No postoperative LMWH because of a considerable surgical site hematoma
5	F	70	AF+stroke+MVR	Colonoscopy	TIA	13	Day 10 INR=2.7

Pengo V, TH 2009

Conclusion

The incidence of thromboembolic events was low.
All 5 thromboembolic events occurred in high thromboembolic- risk patients resulting in an incidence 1.7%.
We also found a low incidence of bleeding events (major bleeding, 1.2%).

Pengo V, TH 2009

Interventi con rischio emorragico clinicamente non importante

- interventi di odontoiatria
  - estrazioni di 1 o 3 denti
  - chirurgia paradontale
  - incisione di ascesso
  - posizionamento di impianto
- interventi di oculistica
  - cataratta o glaucoma
- endoscopia senza chirurgia
  - chirurgia superficiale
  - incisione di ascessi
  - piccole escissioni dermatologiche

Interventi a basso rischio emorragico

- endoscopia con biopsia
- biopsia della prostata o della vescica
- ablazione per tachicardia sopra-ventricolare (inclusa singola puntura trans-settale sinistra)

Interventi ad alto rischio emorragico

- ablazione complessa
- anestesia spinale o epidurale; puntura lombare
- chirurgia toracica
- chirurgia addominale
- **chirurgia ortopedica maggiore**
- biopsia epatica
- resezione transuretrale della prostata
- biopsia renale

Modificata da Heidbuchel H et al, Europace 2013

Gestione della terapia anticoagulante
Nei pazienti a basso/medio rischio tromboembolico, **si suggerisce** di sospendere la terapia con AVK 5 giorni prima di interventi di chirurgia protesica elettiva e di impostare la *bridging therapy* (somministrando EBPM a dosaggio profilattico) secondo il seguente schema: ultima dose del farmaco al giorno – 5; prima dose sottocutanea di EBPM per una volta al giorno, a partire dal giorno – 4, se in trattamento con acenocumarolo, a partire dal giorno – 3 se, invece, in trattamento con warfarin **[2C]**.
Nei pazienti ad alto rischio tromboembolico (con FA e $CHADS_2$ *score* > 2; con TEV ricorrente trattati per meno di 3 mesi; con sostituzioni valvolari meccaniche) **si raccomanda** la *bridging therapy* (somministrando EBPM a dosaggio terapeutico) secondo il seguente schema: ultima dose del farmaco al giorno – 5; prima dose sottocutanea di EBPM per due volte al giorno a partire dal giorno – 4, se in trattamento con acenocumarolo, a partire dal giorno – 3, se in trattamento con warfarin **[1C]**.
Si suggerisce di somministrare l'ultima dose di EBPM 12 ore prima dell'intervento e/o della manovra invasiva, salvo quando sia utilizzato il dosaggio anticoagulante pieno, nel qual caso si **suggerisce** un intervallo di 24 ore **[2C]**.

Pharmacokinetic characteristics of new oral anticoagulants

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Dosing				
Non-valvular AF	150 mg BID	20 mg QD	5 mg BID	60 mg QD
DVT prophylaxis	220 mg QD	10 mg QD	2.5 mg BID	30 mg QD
DVT/PE treatment	150 mg BID	15 mg BID for 21 days, then 20 mg QD	10 mg BID for 7 days, then 5 mg BID	60 mg QD after initial therapy with heparin
Molecular weight (Da)	628	436	460	548
Target	II	Xa	Xa	Xa
Bioavailability (%)	6	63–79	66	50
T_{max} (h)	2–3	2–4	1–3	1–3
$T_{1/2}$ (h)	12–17	7–13	8–15	9–11
Protein binding (%)	35	95	87	54
Metabolism	80% renal 20% liver	1/3 renal 2/3 liver	25% renal 75% faecal	35% renal 63% liver
Interactions	P-gp inhibitors	CYP3A4 inhibitors P-gp inhibitors	CYP3A4 inhibitors P-gp inhibitors	CYP3A4 inhibitors P-gp inhibitors
Approved indications	Prevention of stroke and systemic embolism in non-valvular AF VTE prophylaxis after hip and knee replacement	Prevention of stroke and systemic embolism in non-valvular AF VTE prophylaxis after hip and knee replacement	Prevention of stroke and systemic embolism in non-valvular AF VTE prophylaxis after hip and knee replacement	In Japan for VTE prophylaxis after hip and knee replacement

Enriquez A, Europace 2015

	Dabigatran	Rivaroxaban	Apixaban
Inibitori della glicoproteina-P: amiodarone, fenotiazina, tioxanteni, acido carbossilico, antifungini azoli, verapamil, antimalarici, ciclosporina	SI	SI	SI
Induttori della glicoproteina-P: desametazone, rifampicina, iperico*	SI	SI	SI
Inibitori del citocromo CYP3A4: fenotiazina, acido carbossilico, antifungini azoli, verapamil, eritromicina, telitromicina, nefazodone, antimalarici, ciclosporina, tioxanteni	NO	SI	SI
Induttori del citocromo CYP3A4: carbamazepina, efavirenz, nevirapina, fenitoina, fenobarbital, rifabutina, rifapentina, iperico*, alcool, eucaliptolo	NO	SI	SI
Farmaci anti-infiammatori non steroidei: aspirina, naproxene, diclofenac	SI	SI	SI
Farmaci anti-piastrinici: clopidogrel	SI	SI	SI

Modificata da Pengo V, TH 2011

Approved European labels for NOACs and their dosing in CKD

	Dabigatran	Apixaban	Edoxaban	Rivaroxaban
Fraction renally excreted of absorbed dose	80%	27%[52–55]	50%[36]	35%
Bioavailability	3–7%	50%	62%[51]	66% without food Almost 100% with food
Fraction renally excreted of administered dose	4%	12–29%[52–55]	37%[36]	33%
Approved for CrCl ≥ …	≥30 mL/min	≥15 mL/min	≥15 mL/min	≥15 mL/min
Dosing recommendation	CrCl ≥ 50 mL/min: no adjustment (i.e. 150 mg BID)	Serum creatinine ≥1.5 mg/dL: no adjustment (i.e. 5 mg BID)[a]	CrCl ≥ 50 mL/min: no adjustment (i.e. 60 mg OD)[b]	CrCl ≥ 50 mL/min: no adjustment (i.e. 20 mg OD)
Dosing if CKD	When CrCl 30–49 mL/min, 150 mg BID is possible (SmPC) but 110 mg BID should be considered (as per ESC guidelines)[5] Note: 75 mg BID approved in US only[c]: if CrCl 15–30 mL/min if CrCl 30–49 mL/min and other orange factor *Table 6* (e.g. verapamil)	CrCl 15–29 mL/min: 2.5 mg BID If two-out-of-three: serum creatinine ≥ 1.5 mg/dL, age ≥80 years, weight ≤60 kg: 2.5 mg BID	30 mg OD when CrCl 15–49 mL/min	15 mg OD when CrCl 15–49 mL/min
Not recommended if	CrCl < 30 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min	CrCl < 15 mL/min

Heidbuchel H, Europace 2015

Last intake of drug before elective surgical intervention

	Dabigatran		Apixaban–edoxaban–rivaroxaban	
	No important bleeding risk and/or adequate local haemostasis possible: perform at trough level (i.e. ≥12 or 24 h after last intake)			
	Low risk	High risk	Low risk	High risk
CrCl ≥ 80 mL/min	≥24 h	≥48 h	≥24 h	≥48 h
CrCl 50–80 mL/min	**≥36 h**	**≥72 h**	≥24 h	≥48 h
CrCl 30–50 mL/min[a]	**≥48 h**	**≥96 h**	≥24 h	≥48 h
CrCl 15–30 mL/min[a]	Not indicated	Not indicated	**≥36 h**	**≥48 h**
CrCl < 15 mL/min	No official indication for use			
There is no need for bridging with LMWH/UFH				

Heidbuchel H, Europace 2015

ClCr	Nuovo anticoagulante orale					
(mL/minuto)	Dabigatran		Apixaban		Rivaroxaban	
	Rischio emorragico associato alla procedura chirurgica					
	Basso	Alto	Basso	Alto	Basso	Alto
≥ 80	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
50-80	≥ 36 h	≥ 72 h	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
30-50	≥ 48 h	≥ 96 h	≥ 24 h	≥ 48 h	≥ 24 h	≥ 48 h
15-30	NI	NI	≥ 36 h	≥ 48 h	≥ 36 h	≥ 48 h
< 15			NI			

Legenda:
ClCr: *clearance* della creatinina
h: ore.
NI: uso del farmaco non indicato.

Modificata da Heidbuchel H et al, Europace 2013

I nuovi anticoagulanti orali
Si suggerisce di non sospendere i NAO (dabigatran, rivaroxaban, apixaban) e di procedere all'intervento chirurgico dopo 12-24 ore (a seconda che il farmaco sia somministrato, rispettivamente, due o una volta/die) dall'ultima assunzione in caso di: chirurgia dermatologica, procedure odontoiatriche, gastroscopia e colonscopia (senza biopsie), interventi di oculistica (specie della camera anteriore, come la cataratta) e interventi che comportino un rischio emorragico clinicamente non importante (tabella II in appendice) **[2C]**.
Si suggerisce di sospendere i NAO 24 ore prima di procedure chirurgiche in elezione che comportino un basso rischio emorragico, in pazienti con normale funzione renale [*clearance* della creatinina (ClCr) $\geq$ 80 mL/minuto] **[2C]**.
Si suggerisce di sospendere i NAO 48 ore prima di procedure chirurgiche in elezione che comportino un alto rischio emorragico, in pazienti con normale funzione renale (ClCr $\geq$ 80 mL/minuto) **[2C]**.
Si suggerisce di sospendere rivaroxaban e apixaban 36 e 48 ore prima di interventi chirurgici, rispettivamente, a basso e alto rischio emorragico, in pazienti con ClCr compresa tra 15-30 mL/minuto; di sospendere dabigatran, in caso di interventi chirurgici a basso o alto rischio emorragico, 36 e 72 ore prima, rispettivamente, in pazienti con ClCr compresa tra 50-80 mL/minuto; di sospendere dabigatran, in caso di interventi chirurgici a basso o alto rischio emorragico, 48 e 96 ore prima, rispettivamente, in pazienti con ClCr compresa tra 30-50 mL/minuto **[2C]**.

Non si può formulare alcuna raccomandazione basata sull'evidenza per l'impiego di test di laboratorio nella valutazione pre-operatoria dell'effetto anticoagulante dei NAO.

Patients requiring an urgent surgical intervention

If an emergency intervention is required, the NOAC should be discontinued.

Surgery or intervention should be deferred, if possible, until at least 12 h and ideally 24 h after the last dose.

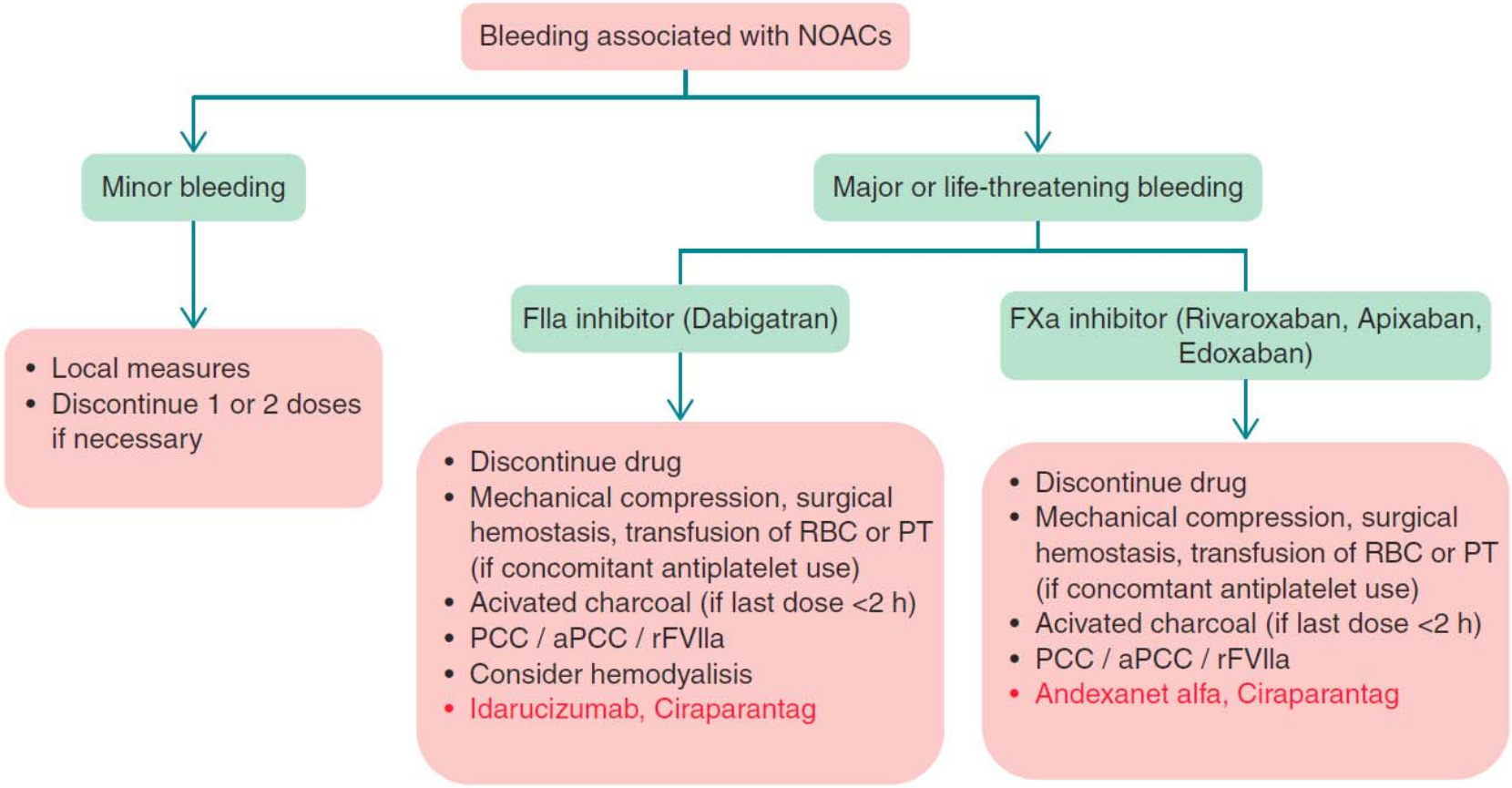
Heidbuchel H, Europace 2015

Strategies for anticoagulation reversal in bleeding associated with warfarin and new oral anticoagulants

	Warfarin	Dabigatran	Rivaroxaban, apixaban, and edoxaban
General measures	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support	Drug discontinuation, mechanical compression, surgical haemostasis, transfusional support
Activated charcoal	Consider if last dose <2 h	Consider if last dose <2 h	Consider if last dose <2 h
Haemodialysis	No benefits (highly protein bound)	Removes 62–68% of circulating drug	No benefits (highly protein bound)
Coagulation factors	PCC (25 U/kg, repeat if necessary) FFP (10–15 ml/kg) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) rFVIIa (90 ug/kg)	PCC (25 U/kg, repeat if necessary) or FEIBA (50 IE/kg, max 200 IE/day) rFVIIa (90 ug/kg)
Specific inhibitors	Vitamin K (5–10 mg IV)	Idarucizumab (Phase 1) Ciraparantag (preclinical)	Andexanet alfa (Phases 1–3) Ciraparantag (Phase 1)

Enriquez A, Europace 2015

Management of bleeding associated with NOACs



Enriquez A, Europace 2015

Comparison of specific antidotes for NOACs

Agent	Idarucizumab (Boehringer Ingelheim)	Andexanet alfa (Portola Pharmaceuticals)	Ciraparantag (Perosphere)
Target	Dabigatran	FXa inhibitors (Rivaroxaban, Apixaban, Edoxaban, Betrixaban)	Dabigatran, FXa inhibitors (Rivaroxaban, Apixaban, Edoxaban, Betrixaban), Fondaparinux, heparin
Structure	Humanized antibody fragment	Recombinant human FXa, catalytically inactive	Synthetic small molecule (512 Da)
Mechanism	Non-competitive binding to Dabigatran with 350 times greater affinity than thrombin	Binds competitively to direct FXa inhibitors	Binds to heparins and oral FXa and IIa inhibitors through hydrogen bonding
In vitro studies	Reversal of prolonged clotting time induced by Dabigatran	Complete and dose-dependent reversal of Rivaroxaban, Apixaban and Betrixaban in human plasma	Complete reversal of anti-Xa activity of Rivaroxaban, Apixaban and Edoxaban
Animal models	Reduction in blood loss and mortality in a porcine liver trauma model	Reduced blood loss induced by Rivaroxaban in 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 Dabigatran-induced anticoagulation in healthy humans Phase 3: Ongoing (RE-VERSE AD)	Phase 1: Dose-dependent reversal of Rivaroxaban in healthy volunteers Phase 2: Rapid reversal of Rivaroxaban and Apixaban. Ongoing trial with Edoxaban Phase 3: Rapid reversal of Apixaban (ANNEXA-A). Ongoing trial with Rivaroxaban (ANNEXA-R) and planned trial with Edoxaban (ANNEXA-E)	Phase 1: Rapid and sustained reversal of edoxaban

Enriquez A, Europace 2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Idarucizumab for Dabigatran Reversal

Charles V. Pollack, Jr., M.D., Paul A. Reilly, Ph.D., John Eikelboom, M.B., B.S., Stephan Glund, Ph.D., Peter Verhamme, M.D., Richard A. Bernstein, M.D., Ph.D., Robert Dubiel, Pharm.D., Menno V. Huisman, M.D., Ph.D., Elaine M. Hylek, M.D., Pieter W. Kamphuisen, M.D., Ph.D., Jörg Kreuzer, M.D., Jerrold H. Levy, M.D., Frank W. Sellke, M.D., Joachim Stangier, Ph.D., Thorsten Steiner, M.D., M.M.E., Bushi Wang, Ph.D., Chak-Wah Kam, M.D., and Jeffrey I. Weitz, M.D.

Pollack C, NEJM 2015

Comparison of specific antidotes for NOACs

Idarucizumab rapidly and completely reversed the anticoagulant activity of dabigatran in 88 to 98% of patients. There were no safety concerns among the 90 patients involved in this study — including patients who were given idarucizumab on clinical grounds but were later found to have had normal results on clotting tests at baseline — or among the more than 200 volunteers who were administered idarucizumab in previous studies

Pollack C, NEJM 2015

Targeted Anti-Anticoagulants

Kenneth A. Bauer, M.D.

…..group of patients had little or no circulating anticoagulant in their blood and would not be expected to benefit from the administration of idarucizumab. Thus, it will be useful to have activity measurements available for the various direct oral anticoagulants in real time to help guide the treatment of such patients and to prevent overutilization of what will surely be a costly medication

Bauer K, NEJM 2015

Peri-interventional management of novel oral anticoagulants in daily care: results from the prospective Dresden NOAC registry

Jan Beyer-Westendorf[1]*, Vera Gelbricht[1], Kati Förster[1], Franziska Ebertz[1], Christina Köhler[1], Sebastian Werth[1], Eberhard Kuhlisch[2], Thoralf Stange[2], Christoph Thieme[1], Katharina Daschkow[1], and Norbert Weiss[1]

Beyer-Westendorf I , Europace 2014

Effectiveness and safety outcomes of 863 interventional or surgical procedures in NOAC patients at Day 30+5 post-procedure, according to heparin bridging

Outcome at Day 30 ± 5 after procedure	Type of procedures	Procedures without heparin bridging (*N* = 606)	Procedures with heparin bridging (*N* = 257)	*P*-value no bridging vs. bridging
Major cardiovascular events, *n* (%; 95% CI)	Minimal	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	4 (0.7%; 0.2–1.7)	1 (0.4%; 0.0–2.1)	0.830
	Major	1 (0.2%; 0.0–0.9)	3 (1.2%; 0.2–3.4)	0.082
	All	5 (0.8%; 0.3–1.9)	4 (1.6%; 0.4–3.9)	0.265
Cardiovascular death, *n* (%; 95% CI)	Minimal	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	0 (0.0%; 0.0–0.6)	1 (0.4%; 0.0–2.1)	0.298
	Major	1 (0.2%; 0.0–0.9)	1 (0.4%; 0.0–2.1)	0.507
	All	1 (0.2%; 0.0–0.9)	2 (0.8%; 0.1–2.8)	0.213
Major bleeding, *n* (%; 95% CI)	Minimal	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	2 (0.3%; 0.0–1.2)	1 (0.4%; 0.0–2.1)	0.654
	Major	1 (0.2%; 0.0–0.9)	6 (2.3%; 0.9–5.0)	**0.004**
	All	3 (0.5%; 0.1–1.4)	7 (2.7%; 1.1–5.5)	**0.010**
NMCR bleeding, *n* (%; 95% CI)	Minimal	1 (0.2%; 0.0–0.9)	1 (0.4%; 0.0–2.1)	0.507
	Minor	15 (2.5%; 1.4–4.0)	5 (1.9%; 0.6–4.5)	0.759
	Major	3 (0.5%; 0.1–1.4)	4 (1.6%; 0.4–3.9)	0.122
	All	19 (3.1%; 1.9–4.9)	10 (3.9%; 1.9–7.0)	0.352
Minor bleeding, *n* (%; 95% CI)	Minimal	1 (0.2%; 0.0–0.9)	0 (0.0%; 0.0–1.4)	>0.999
	Minor	4 (0.7%; 0.2–1.7)	2 (0.8%; 0.1–2.8)	0.576
	Major	0 (0.0%; 0.0–0.6)	0 (0.0%; 0.0–1.4)	>0.999
	All	5 (0.8%; 0.3–1.9)	2 (0.8%; 0.1–2.8)	0.667
Any bleeding, *n* (%; 95% CI)	Minimal	2 (0.3%; 0.0–1.2)	1 (0.4%; 0.0–2.1)	0.654
	Minor	21 3(.5%; 0.2–5.2)	8 (3.1%; 1.3–6.0)	0.673
	Major	4 (0.7%; 0.2–1.7)	10 (3.9%; 1.9–7.0)	**0.001**
	All	27 (4.5%; 3.0–6.4)	19 (7.4%; 4.5–11.3)	0.059

Beyer-Westendorf I , Europace 2014

Uni- and multivariate analyses of potential risk factors for major bleeding events

Risk factor	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Arterial hypertension	n.a.	0–∞	0.996	–	–	–
Diabetes	1.2	0.3–4.3	0.763	–	–	–
TIA/stroke in history	0.7	0.1–5.5	0.728	–	–	–
Coronary artery disease	2.7	0.7–9.5	0.133	–	–	–
Impaired renal function (GFR < 50 mL/min)	0.67	0.1–5.2	0.687	–	–	–
Major vs. non-major procedure	22.5	5.7–88.9	**<0.001**	16.8	3.8–78.9	**<0.001**
Age >65 years vs. <65 years	0.8	0.2–4.0	0.847	–	–	–
Pre-procedural NOAC interruption >24 h vs. <24 h	n.a.	0–∞	0.955	–	–	–
Heparin bridging vs. no bridging	5.6	1.4–21.9	**0.013**	5.0	1.2–20.4	0.023
HAS-BLED ≥ 3 vs. <3	1.5	0.4–5.7	0.589	–	–	–

Beyer-Westendorf I , Europace 2014

Uni- and multivariate analyses of potential risk factors for major bleeding events

Our data indicate that interventional procedures are common in anticoagulated patients and mostly consist of minimal or minor procedures.

Rates of complications are low and fatal complications seem to be very rare, indicating that peri-interventional short-term interruption of NOAC in daily care is safe.

Bleeding complications are more common than cardiovascular complications and, in a relevant proportion, related to major procedures or to the peri-procedural heparin bridging (which is similar to VKA patients bridged for invasive procedures)

Beyer-Westendorf I , Europace 2014

Resumption of antithrombotic therapy

The reinitiation of antithrombotic therapy, particularly full-dose therapy, is a major determinant of the bleeding risk after invasive procedures. In contrast to full-dose anticoagulation therapy, prophylactic anticoagulation therapy is resumed once hemostasis is secured. In patients receiving bridging therapy, heparin at a therapeutic dose should be withheld for 48 hours after the procedure. If the risk of postprocedural bleeding is deemed acceptably low, full-dose anticoagulation therapy may be initiated after a shorter interval.

Baron T, NEJM 2013

Journal of Thrombosis and Haemostasis, **12**: 1254–1259 DOI: 10.1111/jth.12613

ORIGINAL ARTICLE

Loading dose vs. maintenance dose of warfarin for reinitiation after invasive procedures: a randomized trial

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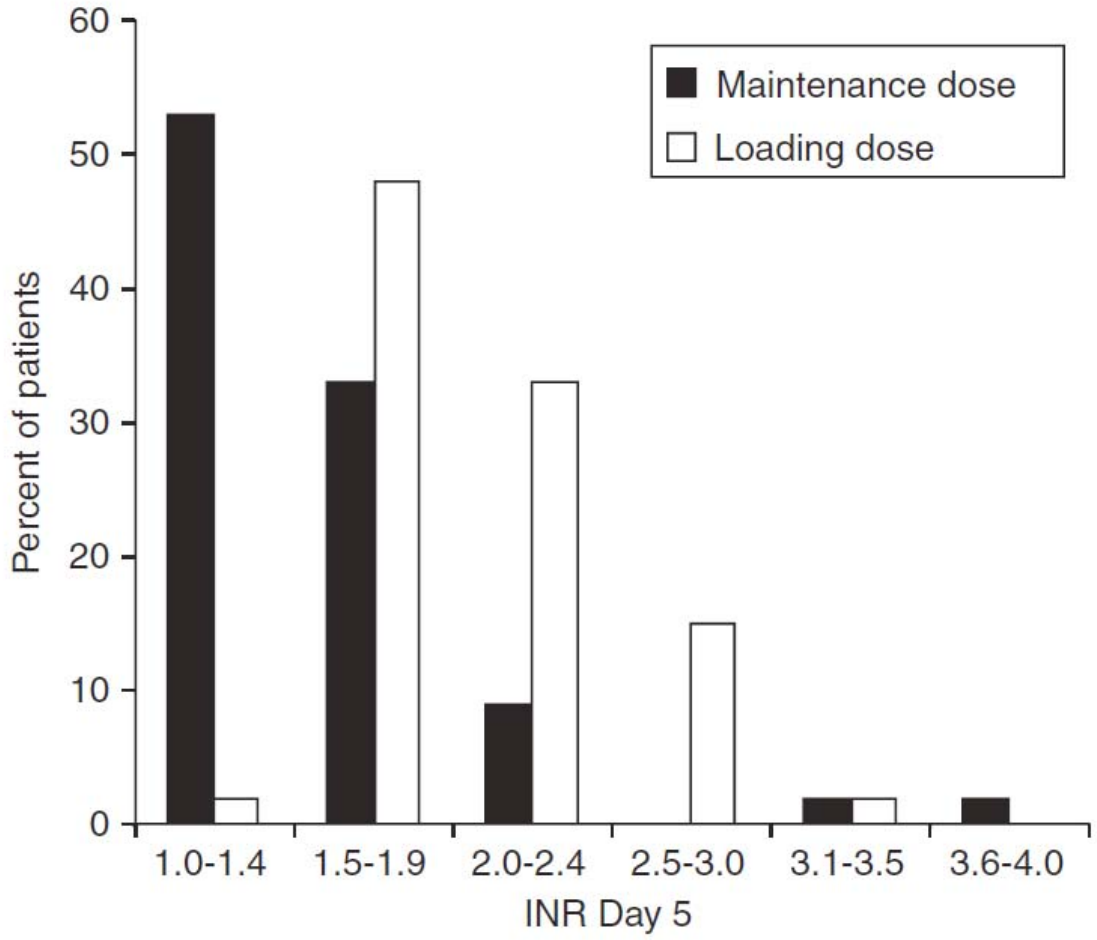
Shulman S, JTH 2014

Histogram of the primary efficacy outcome



Shulman S, JTH 2014

Conclusion

We conclude that resumption of warfarin after minor moderately invasive surgery with two initial loading doses leads to faster achievement of therapeutic INRs. For patients receiving postoperative bridging with heparin until INR becomes therapeutic, our regimen results in a shorter duration of parenteral treatment, which is inconvenient for patients and costly

Shulman S, JTH 2014

When to restart the non-vitamin K antagonist anticoagulants?

For procedures with immediate and complete haemostasis, the NOAC can be resumed 6–8 h after the intervention. The same applies after atraumatic spinal/epidural anaesthesia or clean lumbar puncture (i.e. non-bloody tap).

For many surgical interventions, however, resuming full dose anticoagulationwithin the first 48–72 h after the procedure may carry a bleeding risk that could outweigh the risk of cardio-embolism.

Heidbuchel H, Europace 2015

When to restart the non-vitamin K antagonist anticoagulants?

For procedures associated with immobilization, it is considered appropriate to initiate a reduced venous thromboprophylactic (e.g. 0.5 mg/kg/day of enoxaparin) or intermediate dose of LMWHs (e.g. 1mg/kg/day of enoxaparin) 6–8 h after surgery if adequate haemostasis has been achieved, whereas full therapeutic anticoagulation by **restarting NOACs is deferred 48–72 h after** the invasive procedure

Heidbuchel H, Europace 2015