Patient Blood Management strategies in obstetrics and in the peri-operative period

PATIENT BLOOD MANAGEMENT ITALY

Terapia anticoagulante - Quando sospendere e quando attivare la terapia di bridging? / Antithrombotics - when to stop and whom to bridge?

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La sottoscritta **Daniela Rafanelli** 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.

1. É mai stato diagnosticato un disordine emorragico a lei o a un suo familiare?
2. Le è mai stata riscontrata un'anormalità dei test di laboratorio per la coagulazione o un'anemia inspiegata?
3. Ha mai sofferto di un problema di sanguinamento:
   - in occasione di interventi chirurgici?
   - Dopo estrazioni dentarie?
   - Per traumi?
   - Dopo il parto o per menorragia?
   - Per ematomi patologici o per difficoltà alla guarigione delle ferite?
4. Ha o ha avuto malattie del fegato o del rene, malattie del sangue o del midollo osseo, conte basse o alte delle piastrine?
5. Assume aspirina, antiaggreganti piastrinici, antinfiammatori non steroidei, clopidogrel (Plavix), antagonisti della vitamina K (Coumadin, Sintrom), eparina, anticoagulanti diretti (Eliquis, Pradaxa, Xarelto)?
6. Per le donne: ha (ha avuto) mestruazioni prolungate e abbondanti?

NO

Nessuna valutazione, cure usuali

SI

Valutazione ed eventuali approfondimenti diagnostici supplementari a cura dell'esperto di emostasi e trombosi

PATIENT BLOOD MANAGEMENT ITALY

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

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

ACCP risk stratification of patients treated with oral anticoagulant

(Douketis, 2012)

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

Perioperative Management of Antithrombotic Therapy

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

James D. Douketis, MD, FCCP; Alex C. Spyropoulos, MD, FCCP; Frederick A. Spencer, MD; Michael Mayr, MD; Amir K. Jaffer, MD, FHM; Mark H. Eckman, MD; Andrew S. Dunn, MD; and Regina Kunz, MD, MSc (Epi)

CHEST 2012; 141(2)(Suppl):e326S–e350S

2.4. In patients with a mechanical heart valve, atrial fibrillation, or VTE at high risk for thromboembolism, we suggest bridging anticoagulation *instead of* no bridging during interruption of VKA therapy (Grade 2C).

Remarks: Patients who place a higher value on avoiding perioperative bleeding than on avoiding perioperative thromboembolism are likely to decline heparin bridging.

In patients with a mechanical heart valve, atrial fibrillation, or VTE at low risk for thromboembolism, we suggest no-bridging instead of bridging anticoagulation during interruption of VKA therapy (Grade 2C).

In patients with a mechanical heart valve, atrial fibrillation, or VTE at moderate risk for thromboembolism, the bridging or no-bridging approach chosen is, as in the higher- and lower-risk patients, based on an assessment of individual patient- and surgery-related factors.

High ≠ Moderate ≠ Low risk

C Samama NATA 2016

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

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

Adverse 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)	–

LMWH, low-molecular-weight heparin; UFH, unfractionated heparin.

*One cardiac valvular or mural thrombosis, one intracranial event, one transient ischemic attack, one peripheral arterial event.

†Two intracranial events and two transient ischemic attacks.

‡Two deep vein thromboses.

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

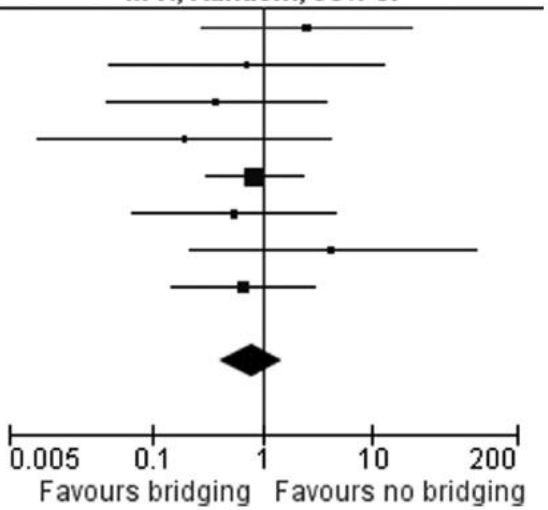
Siegal D, Circulation 2012

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: $Tau^2 = 0.00$; $Chi^2 = 3.68$, df = 7 (P = 0.82); $I^2 = 0\%$

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



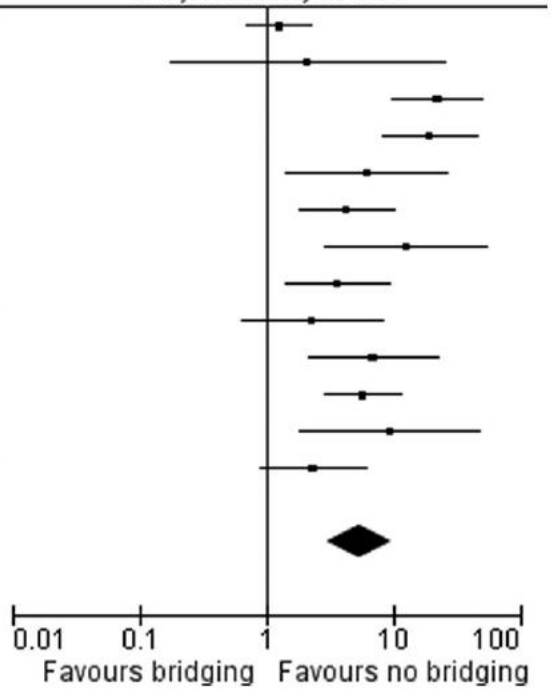
Siegal D, Circulation 2012

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

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



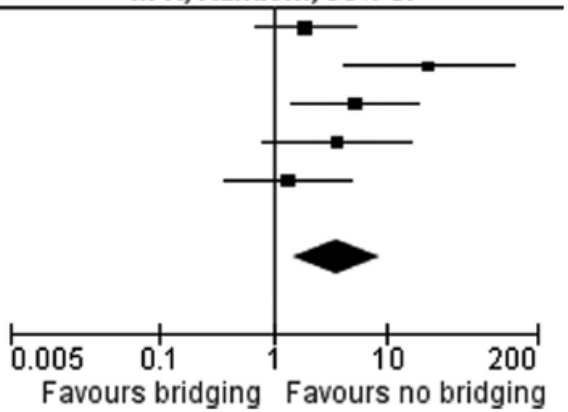
Siegal D, Circulation 2012

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

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



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 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, Cirulation 2009

Anticoagulation Protocols Applied According to Patient Thromboembolic Risk

	Protocol A: Patients at High TE Risk, IU		Protocol B: Patients at Low to Intermediate TE Risk, IU	
Weight, kg	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, Circulation 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 Circulation 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 Circulation 2009

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]**.

Oral anticoagulant agents

- ✓ **Direct Oral Anticoagulants**

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	Prevention of stroke and systemic embolism in non-valvular AF	Prevention of stroke and systemic embolism in non-valvular AF	In Japan for VTE prophylaxis after hip and knee replacement
	VTE prophylaxis after hip and knee replacement	VTE prophylaxis after hip and knee replacement	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 pre-operative 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) ≥ 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 ≥ 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.

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

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

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)

…. bridging anticoagulation, especially in therapeutic-dose regimens and in patients not at high thromboembolic risk undergoing high bleed-risk procedures, should be avoided in the peri-procedural setting'.

Beyer-Westendorf I , Europace 2014

	Low bleeding risk	Moderate and high bleeding risk		
Before	No oral intake the day before, or the morning of the procedure	rivaroxaban apixaban edoxaban	Cockcroft ≥ 30 ml/mn	Last intake at D-3
		dabigatran	Cockcroft ≥ 50 ml/mn	Last intake at D-4
			Cockcroft 30-49 ml/mn	Last intake at D-5
	No bridging No biology			

C Samama NATA 2016

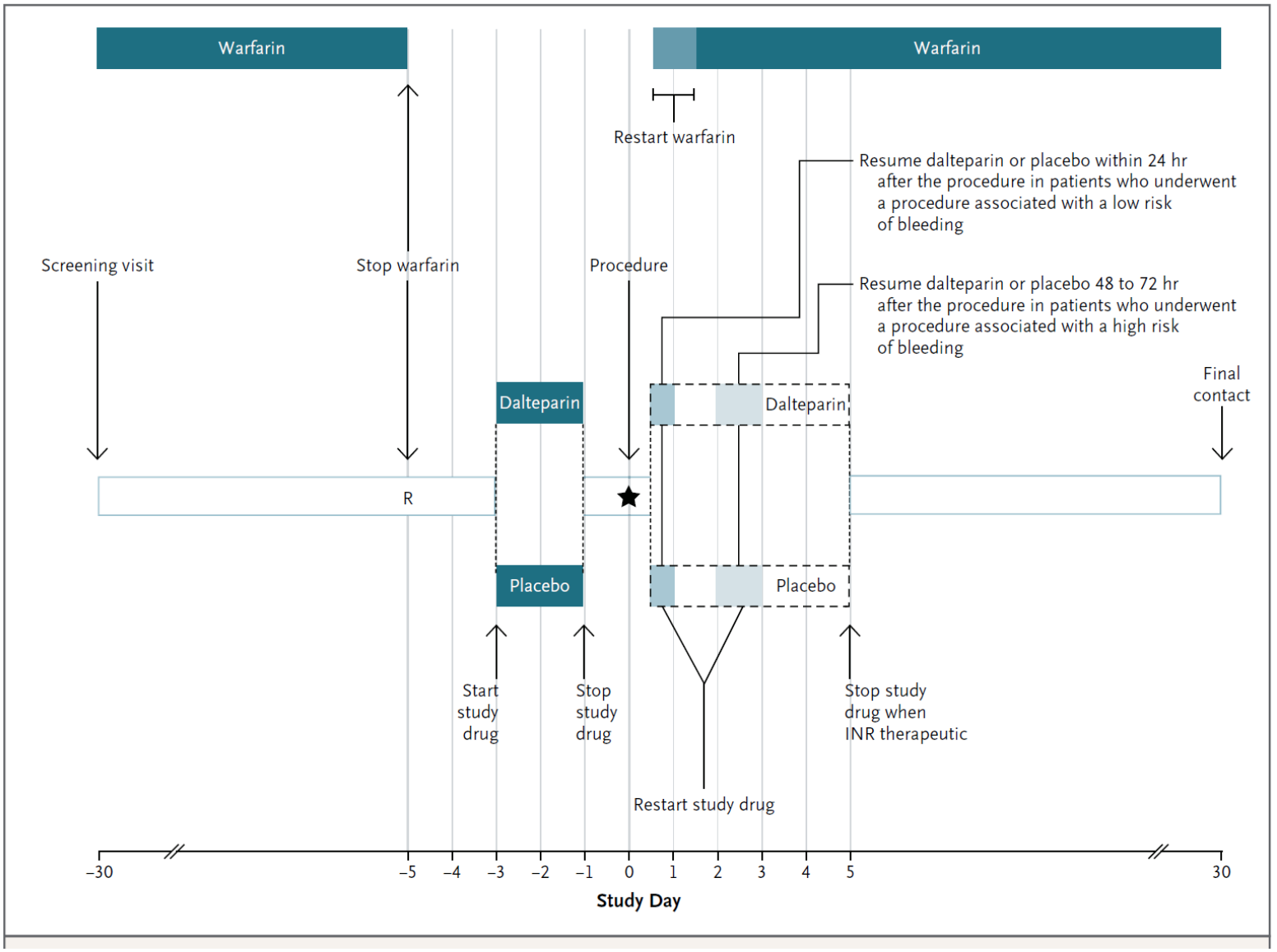
Antithrombotics: when to re-start?

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.

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

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



Douketis J, NEJM 2015

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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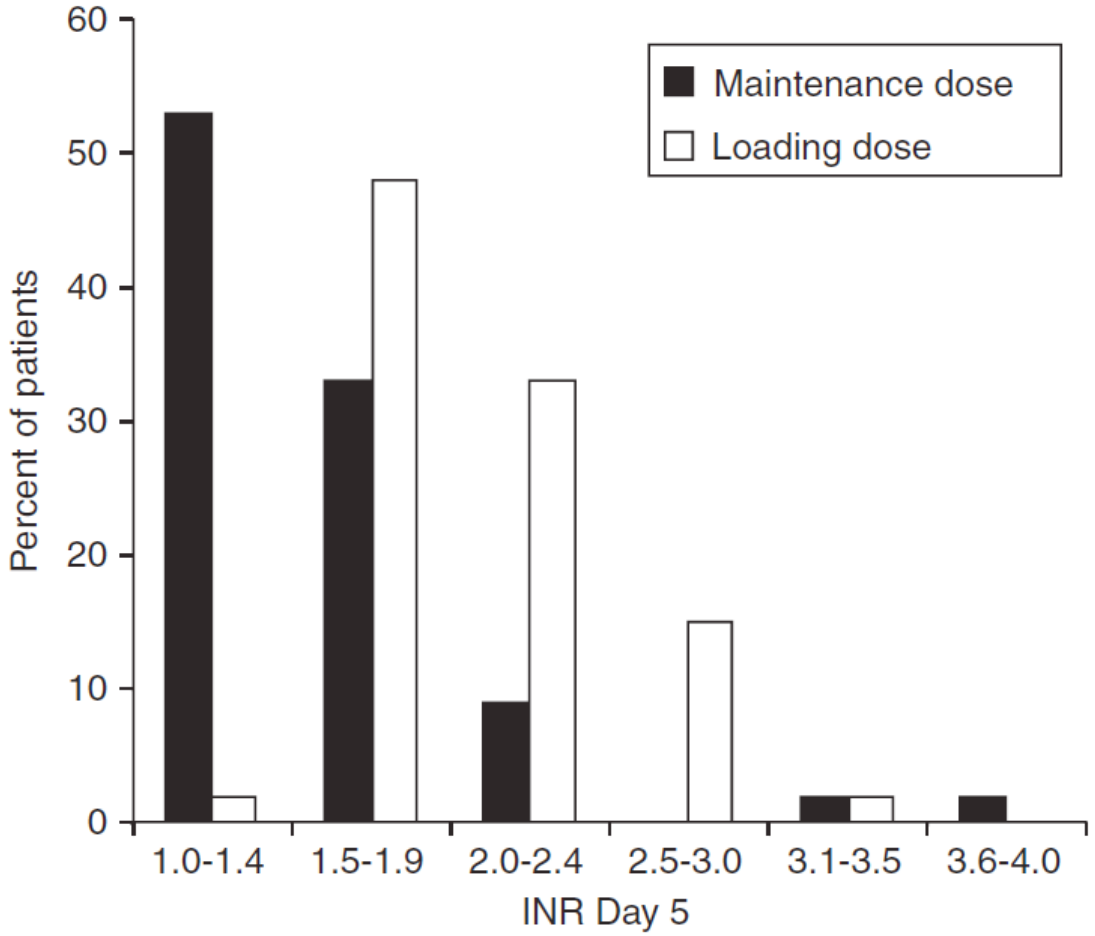
Schulman S, JTH 2014

Histogram of the primary efficacy outcome



Schulman 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
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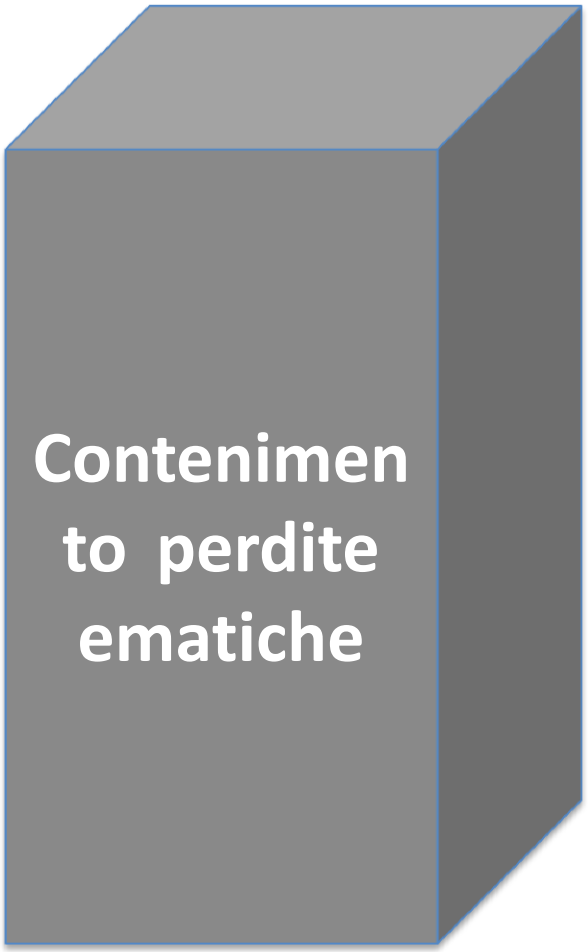
Heidbuchel H, Europace 2015

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. 1 mg/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



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Grazie per l'attenzione