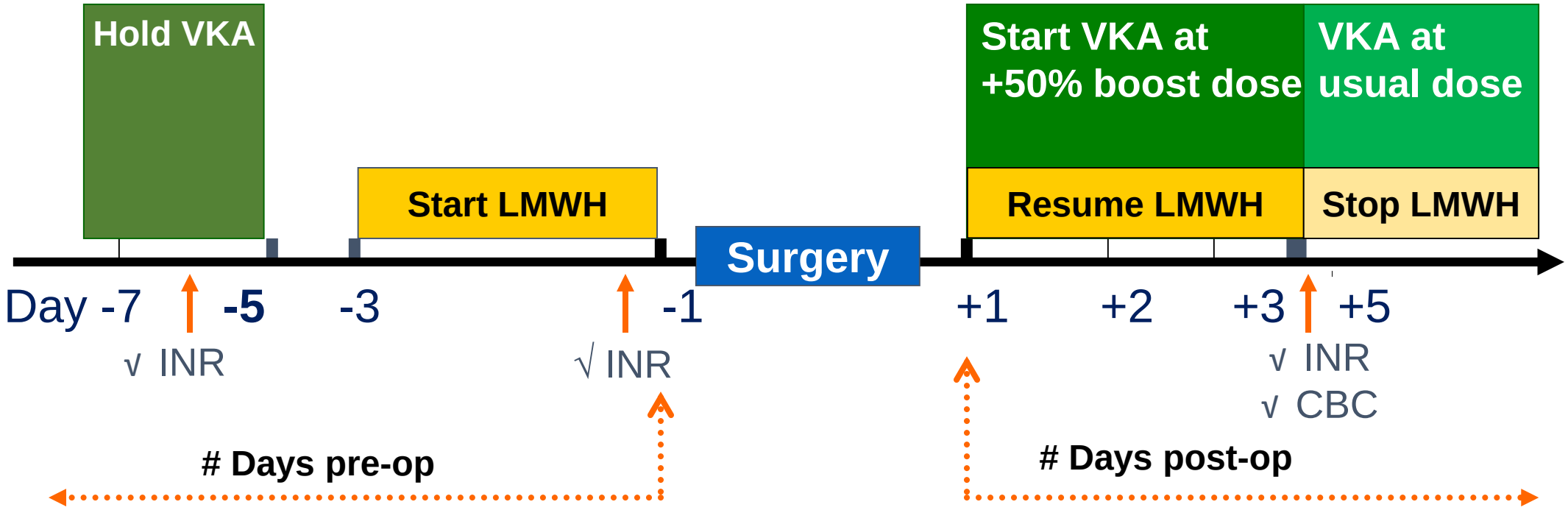
Bridging anticoagulation definition

Giving a short-acting anticoagulant, consisting of sc LMWH or ev UFH for 10 to 12 day period during interruption of VKA therapy when the INR is not within therapeutic range to minimize risk of thromboembolism

- *Although the term encompasses a variety of conditions, it has become a synonym for perioperative bridging*
- *The use of any bridging anticoagulant is "off label"*

How to perform Bridging



Pengo et al Circulation 2009

FCSA

Gestione dei pazienti in terapia con anticoagulanti orali
che devono sottoporsi ad intervento chirurgico
(escluse estrazioni dentarie, cataratta o biopsie in cui il sanguinamento sia controllabile visivamente

Paziente _____ Età Sesso Peso corporeo
Assume anticoagulanti orali (warfarina ☐ acenocumarolo ☐) per:

In vista dell'intervento/indagine_____ del_____ ha seguito/iniziato lo schema seguente
Eseguire profilassi dell'endocardite NO ☐ SI ☐ _____ (eseguita ☐)

		Data	INR	COUMADIN (Sintrom)	Eparina a basso peso molecolare sc §
-5				NIENTE	
-4				NIENTE	
-3				NIENTE	SI
-2				NIENTE	SI
-1			NIENTE	NIENTE	SI
0	INTERVENTO o PROCEDURA	x	x +Piastrine	NIENTE	NO
+1				Dose usuale + 50%	SI*
+2				Dose usuale + 50%	SI**
+3				Dose usuale	SI
+4				Dose usuale	SI
+5				Dose usuale	SI
+6				Dose	Considera INR
+7				Dose	Considera INR

*Chirurgia maggiore in elezione ed altre manovre invasive
(Tutta la chirurgia in elezione eccetto quella ad alto rischio emorragico, biopsie a cielo coperto)
**A giudizio del chirurgo in caso di chirurgia maggiore ad alto rischio emorragico (Neurochirurgia, Prostatectomia, Chirurgia in laparoscopia, Interventi sulla retina)

§dosaggi consigliati (si inizia a 2 gg dalla sospensione di Coumadin, ad 1g dalla sospensione di Sintrom):

-Rischio tromboembolico alto (protesi meccanica mitralica o protesi aortica +FA o pregresso TE arterioso, FA+pregresso TE arterioso o valvulopatia mitralica, Tromboembolismo venoso nel mese precedente)

EBPM ogni 12 o 24 ore alla dose sotto riportata:

	Nadroparina	Enoxaparina
< 50 kg	2850 U x 2 =0.3 ml x 2/die sottocute	2000 U x 2=0.2 ml x 2/die sottocute
50-69 kg	3800 U x 2 =0.4 ml x 2/die sottocute	4000 U x 2=0.4 ml x 2/die sottocute
70-89 kg	5700 U x 2 =0.6 ml x 2/die sottocute	6000 U x 2 =0.6 ml x 2/die sottocute
90-110 kg	7600 U x 2 =0.8 ml x 2/die sottocute	8000 U x 2=0.8 ml x 2/die sottocute
> 110 kg	9500 U x 2 =1 ml x 2/die sottocute	10000 U x 2=1 ml x 2/die sottocute

	Dalteparina (NB x1/die)	Reviparina	Parnaparina	Bemiparina (NB x1/die)
< 50 kg	----------	----------	3200 U x 2/die	3500 U x 1/die
50-69 kg	7500 U x 1/die	4200 U x 2/die	4250 U x 2/die	5000 U x 1/die
70-89 kg	10000 U x 1/die	----------	6400 U x 2/die	----------
90-110 kg	12500 Ux 1/die	6300 U x 2/die	----------	7500 U x 1/die
> 110 kg	15000 U x 1/die	6300 U x 2/die	----------	----------

-Rischio tromboembolico medio-basso (tutte le altre condizioni non ad alto rischio):
nadroparina : < 50 Kg: 2850 U (= 0.3 ml x 1 al dì sottocute), 50-70 Kg: 3800 U (= 0.4 ml x 1 al dì sottocute), > 70 Kg: 5700 U (= 0.6 ml x 1 al dì sottocute)
enoxaparina 4000 U (= 0.4 ml x 1 al dì sottocute)
dalteparina 5000 U, reviparina < 50 Kg 1750 U, ≥ 50 Kg 4200 U, parnaparina 4250 U, bemiparina 3500 U al dì tutte in unica somministrazione.
Giorni successivi all'intervento o manovra:

- Anticoagulante alla dose usuale maggiorata del 50% nei primi due giorni non appena il paziente è in grado di assumere farmaci per os
- Eparina sottocutanea fino a che INR>2.0 per due giorni consecutivi (> 2.5 per pazienti a target ≥ 3)

Il medico:

Parte riservata al chirurgo (operatore nel caso di manovre invasive)
Reparto/Ambulatorio/Laboratorio:_____
Data e ora intervento/indagine:_____
Tipo di intervento/indagine:_____
INR giorno intervento: _____
Data e ora inizio eparina sottocute post intervento:_____
Tipo e dosaggio di eparina:_____

Complicanze post-intervento/indagine:

- Emorragia maggiore (=se avviene a livello cerebrale, retroperitoneale, retinico, articolare, oppure in altre sedi se comporta un calo di Hb>2gr o la trasfusione di 2 o più unità di sangue o un nuovo intervento per arrestare l'emorragia)
  □ NO □ SI: _____
- Tromboembolismo(=venoso con diagnosi oggettiva, arterioso con sintomi tipici e documentato alla TAC o RNM o arteriografia o dimostrato chirurgicamente)
  □ NO □ SI: _____
- Altre complicanze
- Note:

Il chirurgo/operatore

NB. Modalità di Partecipazione allo Studio

Thromboembolic risk stratification

- High thromboembolic risk
  - mechanical mitral valve prostheses
  - monoleaflet mechanical aortic prostheses or bileaflet aortic prostheses associated with AF or previous arterial embolism
  - AF associated to previous arterial thromboembolism or mitral valve disease
  - previous cardiogenic or unexplained systemic embolism
  - venous thromboembolism in the previous 3 months

- Low-Intermediate thromboembolic risk
  - The remaining scenarios

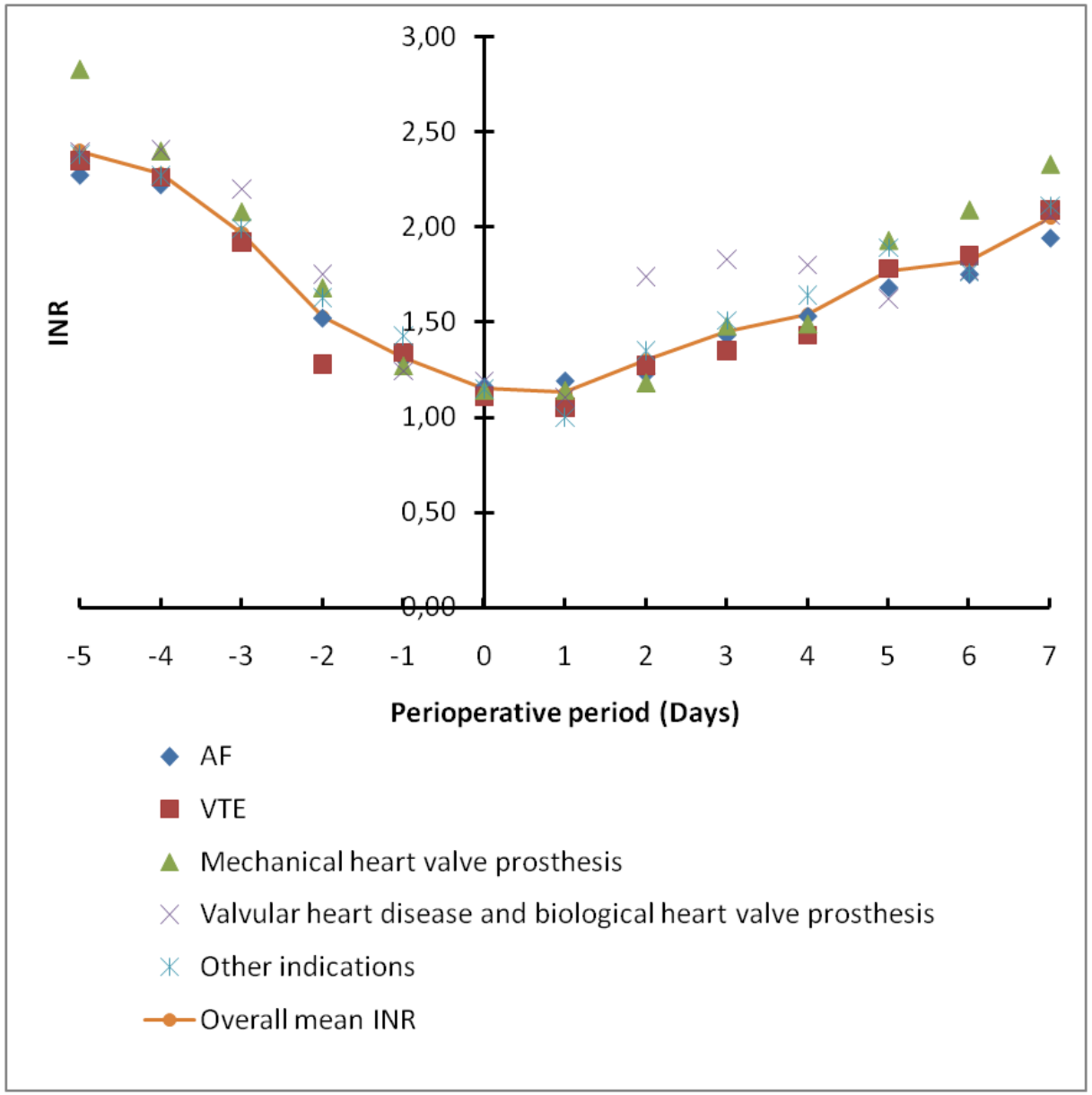
The Bridging Regimen

- **Protocol A High thromboembolic risk**
  - Sub-therapeutic **(70 anti–Xa U/kg b.i.d)** doses of LMWH

Baudo *et al. J Thromb Haemost. 2005;3:537*

- **Protocol B Low-intermediate risk**
  - Prophylactic **(57 anti–Xa U/Kg o.d)** doses of LMWH in low-intermediate TE risk patients (weight-adjusted for nadroparin)

Geerts *et al. Chest. 2001; 119: 132S–175S*



Results – INR trend

- *day -5:*
  - Mean INR 2.4 (±0.6)
- *day 0:*
  - Mean INR 1.2 (±0.2)
- day +6:
  - Mean INR 1.8 (±0.5)

Conclusions

- The incidence of thromboembolic (0.4%) and major bleeding (1.2%) events was low
- The use of sub-therapeutic doses of LMWH seems feasible and safe in high TE risk patients
- Tailoring bridging therapy to the patients' TE risk (high and low-intermediate) appears to be reasonable
- This protocol although general needs to be applied to the patient's clinical context. TEAM-work between anticoagulation physicians, cardiologists and surgeons/interventionists is greatly encouraged in complex cases

BRUISE

- Patients with a thromboembolic risk of more than 5%/y treated with warfarin and undergoing Pace Maker or ICD implantation were randomly assigned to continue warfarin or to briging strategy with **full therapeutic dose of LMWH or intravenous heparin** starting 3 days before the procedure.

- The **primary outcome was clinically significant device-pocket hematoma**, defined as a hematoma requiring further surgery, resulting in prolongation of hospitalization, or requiring interruption of oral anticoagulation therapy.

N Engl J Med 2013

BRUISE

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

N Engl J Med 2013

BRUISE-conclusions

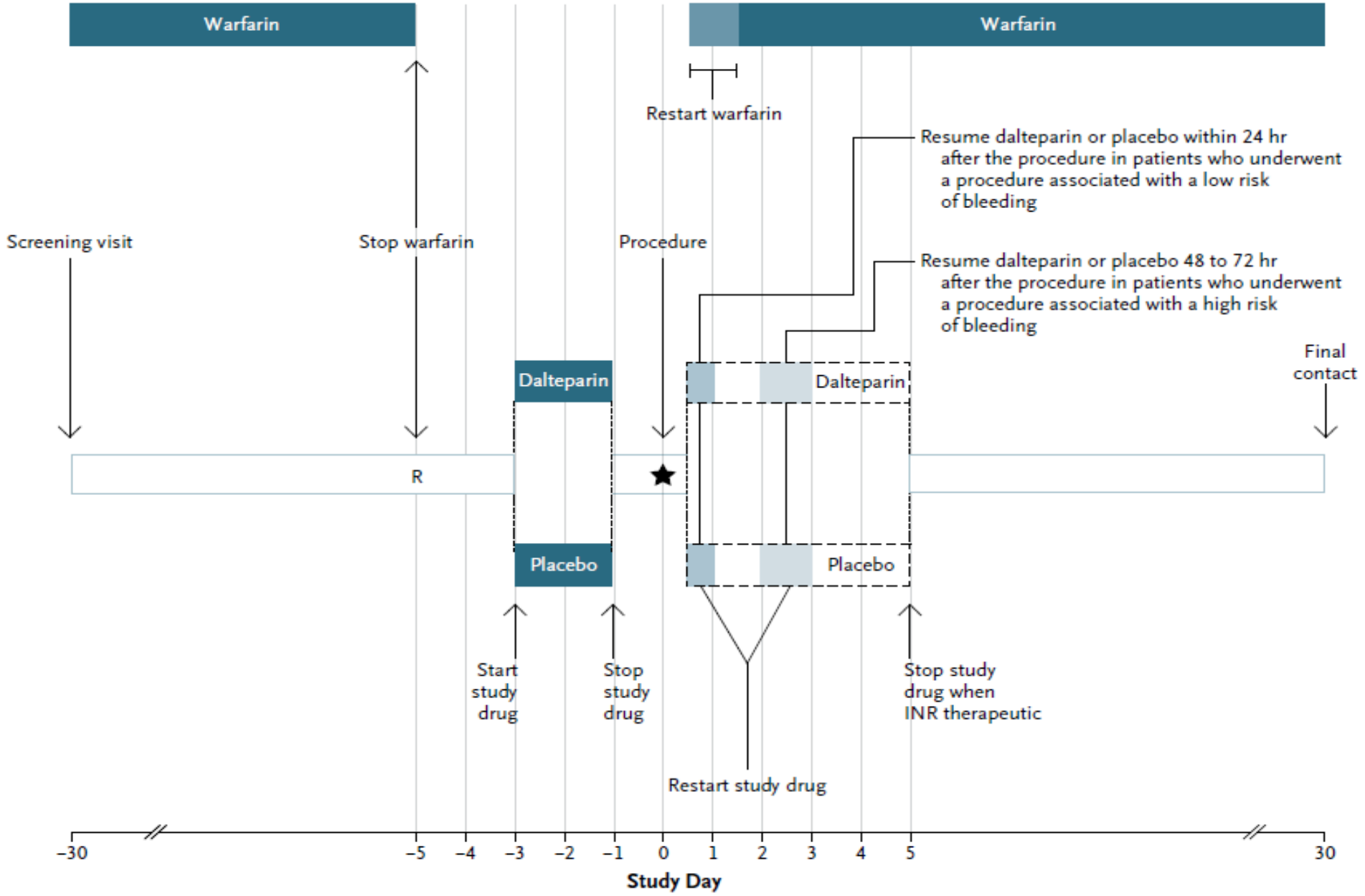
- As compared with bridging therapy with heparin, a strategy of continued warfarin treatment at the time of pacemaker or ICD surgery markedly reduced the incidence of clinically significant device-pocket hematoma.

Bridge study

- Patients with nonvalvular atrial fibrillation undergoing elective surgery or procedures, only 29 of 1884 (1.5%) with mitral stenosis
- Excluded if bearing a mechanical heart valve; recent cerebral ischemia; recent major bleeding; creatinine clearance < 30 ml/min; platelet count <100×103 mmc; planned cardiac, intracranial, or intraspinal surgery.
- 934 pts bridging and 950 no bridging
- Dalteparin 100 IU per kilogram of body weight or placebo twice daily
- 62.9% of patients had a CHAD2 score of 1-2
- 35% of patients were on apirin, >50% of whom did not interrupt aspirin in the perioperative period
- Outcomes assessed by 37 days after procedure

N Engl J Med 2015

Bridge: Douketis NEJM 2015



Bridge study: outcomes

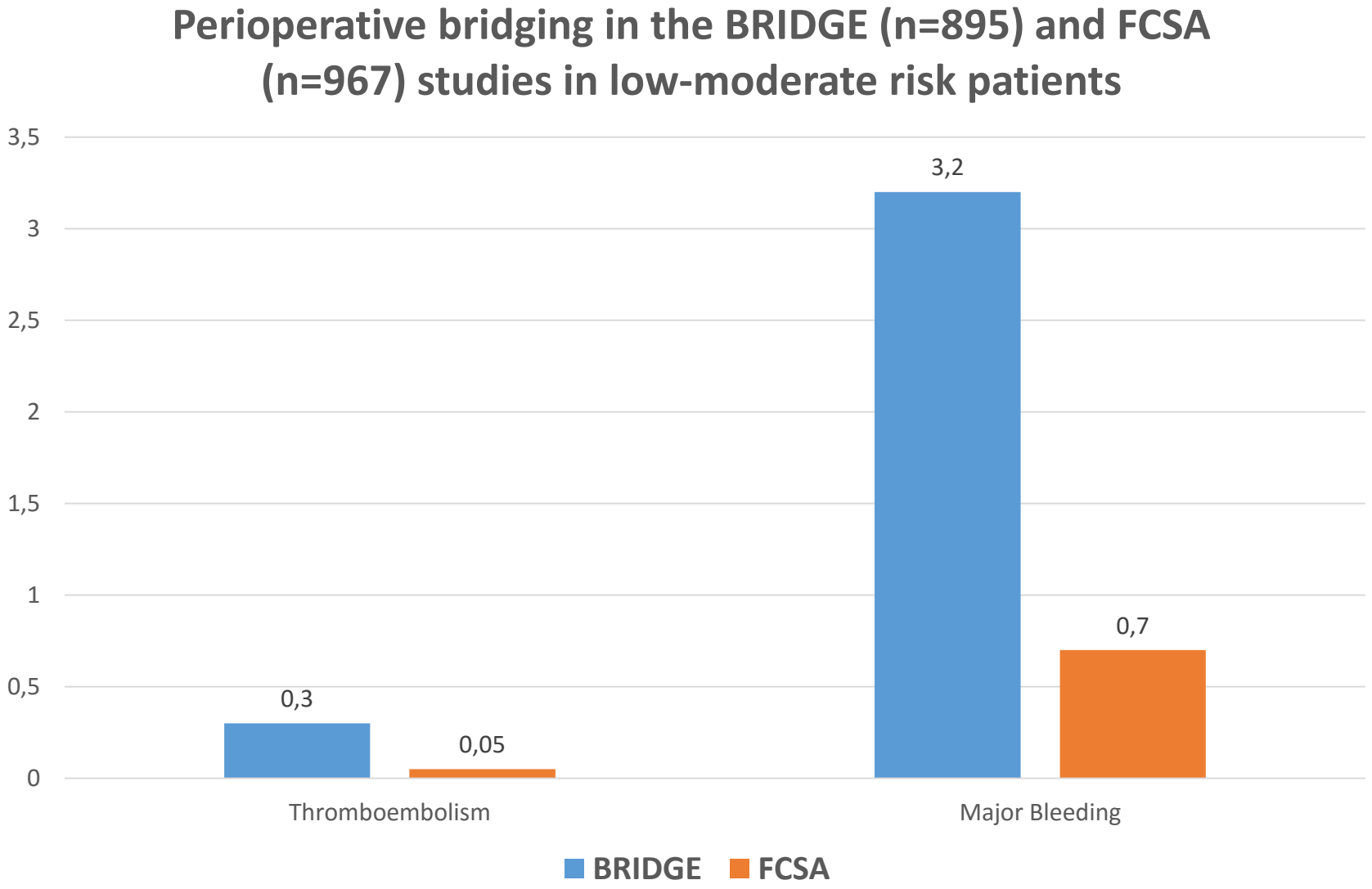
Outcome	No Bridging (N=918)	Bridging (N=895)	P Value
	number of patients (percent)		
Primary			
Arterial thromboembolism	4 (0.4)	3 (0.3)	0.01*, 0.73†
Stroke	2 (0.2)	3 (0.3)	
Transient ischemic attack	2 (0.2)	0	
Systemic embolism	0	0	
Major bleeding	12 (1.3)	29 (3.2)	0.005†
Secondary			
Death	5 (0.5)	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.

Bridge-conclusions

- In patients with atrial fibrillation who had warfarin treatment interrupted for an elective operation or other elective invasive procedure, forgoing bridging anticoagulation was noninferior to perioperative bridging with low-molecular-weight heparin for the prevention of arterial thromboembolism and decreased the risk of major bleeding.

N Engl J Med 2015



BRIDGE: Dalteparin 100U twice daily; **Placebo TE 0.4%, Major Bleed 1.2%** FCSA LMWH once daily prophylactic dose

Not all procedures are born the same:
Bleeding risk

High Bleeding risk	Low Bleeding risk
• All cardiac and neurosurgeries • Kidney/Liver biopsy • Chest tube placement • Joint replacement • Hysterectomy • Hickman and tunneled dialysis catheter placement	• Endoscopy (+/- mucosal biopsy) • Cataract surgery • Bone marrow biopsy • Dental extractions • Dermatologic surgery • Joint aspiration

Baron et al. N Engl J Med. 2013.

- Patients' Characteristics (history of bleeding, diathesis etc)
- Integrity of the hemostasis/coagulation system

Not all procedures are born the same: Thrombotic risk

- Procedure-related thrombotic risk
  - For example, heart valve replacement, carotid endarterectomy, or other major vascular surgeries automatically stratify patients in the high-risk category, regardless of underlying medication condition

DOACs and bridging

- Rapid onset of action thus **do not need bridging** with heparin
- **Pay attention** concentration may vary
- Consider use of LMWH or UFH in patients unable to restart **oral** DOAC following surgery
- No evidence to suggest use of these agents for bridging protocols **instead** of heparin

	Rivaroxaban (Xarelto®)	Apixaban (Eliquis®)	Dabigatran (Pradaxa®)
Time to Onset	2 - 4 hours	3 - 4 hours	1 - 2 hours
Half Life	5 - 9 hours	12 hours	15 hours

Perioperative management of DOACs

	Dabigatran		Rivaroxaban		Apixaban	
	Procedure bleeding risk					
CrCl ml/min	Low	High	Low	High	Low	High
>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	Not indicated		**≥36 h**	**≥48 h**	**≥36 h**	**≥48 h**

In case of no need for OAT interruption, perform intervention at trough level

Adapted from Europace 2013;15(5):625-651

Conclusions

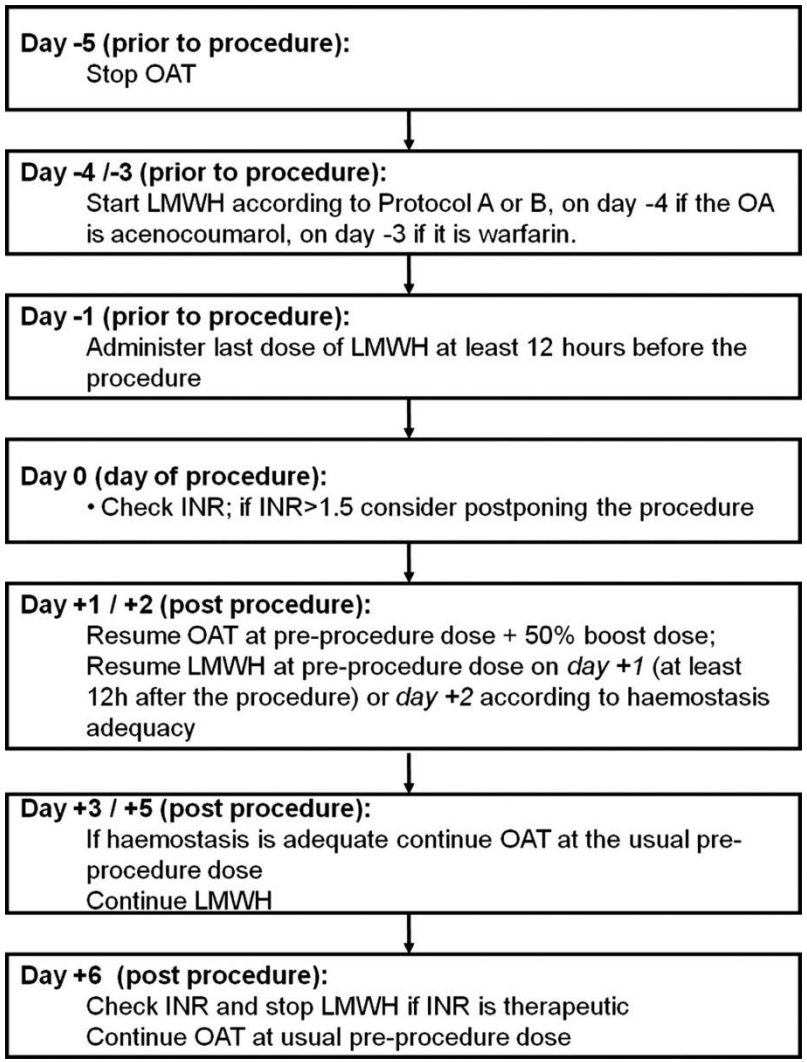
- Bridging or not bridging should be guided by the assessment of individual patient- and surgery-related factors
- Guidelines are based largely on observational data, and lack specific recommendations
- Data from prospective trials show that in selected patients and interventions receiving bridging exposes to higher risk of bleeding
- In patients with AFib without a MHV and considered at low-moderate risk of TE, **bridging anticoagulation may not be used**
- In high TE risk patients bridging should be used
- When bridging is used, sub-therapeutic dosage LMWH is safer
- DOACs usually do not require bridging

Comments

- In Bruise and Bridge studies full doses LMWH in low moderate risk patients lead to an excess of bleeding

- Bridging therapy should be always performed in high thromboembolic risk patients and in surgery at high risk of thromboembolic events

Bridging Protocol



- Day -5 stop OA
- Day -4/-3 start LMWH
- Day -1 stop LMWH
- Day 0 check INR
- Day +1/+2 restart LMWH; start OA custom dose+50%
- Day +3/+5 continue LMWH; OA custom dose
- Day +6 stop LMWH for therapeutic INR; OA custom dose

CLINICA CARDIOLOGICA di PADOVA