Gestione peri-operatoria del paziente in terapia con antagonisti della vitamina K

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Overview

- Background and general framework to manage vitamin K antagonists (VKA) in the peri-operative setting
- 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

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

- 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: balancing the competing risks

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

2-
Risk of bleeding after restarting VKA
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%	
Heart valve replacement Coronary artery bypass Abdominal aortic aneurysm repair Neurosurgical, urologic, head and neck, abdominal, or breast cancer surgery Bilateral knee replacement Laminectomy Transurethral prostate resection Kidney biopsy	Polypectomy, variceal treatment, biliary sphincterotomy, pneumatic dilatation Placement of a percutaneous endoscopic gastrostomy tube Endoscopically guided fine needle aspiration Multiple tooth extractions Vascular and general surgery Any major operation (duration >45 minutes)

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	Dilatation and curettage Skin cancer excision Abdominal hernia repair Hemorrhoidal surgery Axillary node dissection Hydrocele repair Cataract and non-cataract eye surgery Non-coronary angiography Bronchoscopy with or without biopsy Removal of a central venous catheter Skin, bladder, prostate, thyroid, breast, and lymph node biopsies ***Daniels PR, BMJ 2015;351:2391***

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** ***Daniels PR, BMJ 2015;351:2391***	**Venous thromboembolism >12 months, reversible risk factors**

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

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**

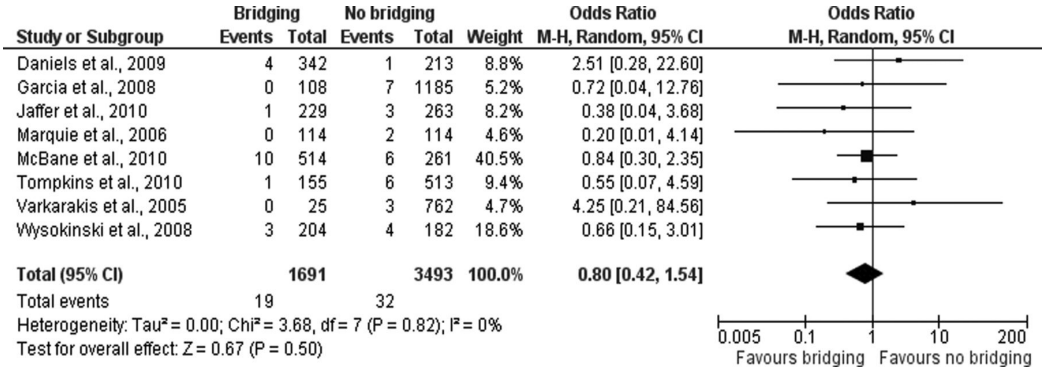
- **RCTs :**
- ***Bruise Control 2013***

- ***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

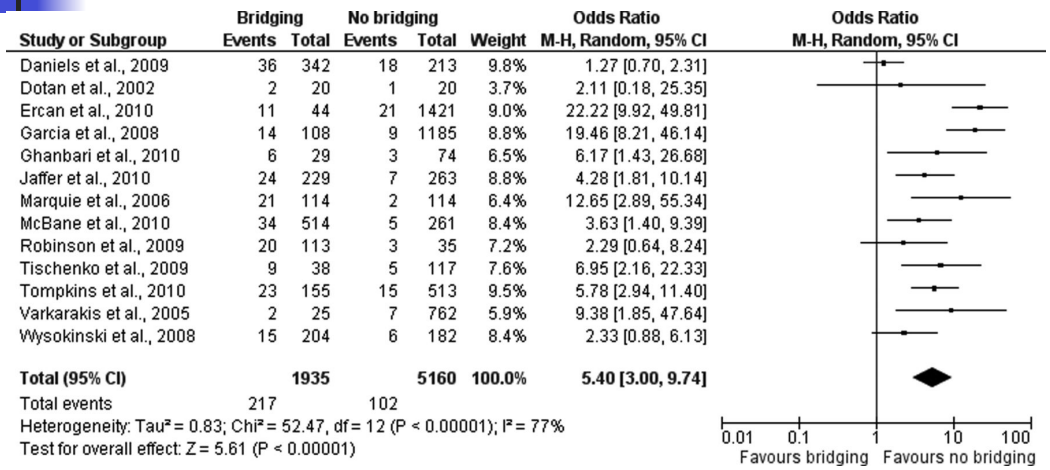
Overall: 73 of 7118 bridged patients (pooled incidence, 0.9%; 95%CI: 0–3.4)
vs
32 of 5160 non bridged patients (pooled incidence, 0.6%; 95%CI:0.0–1.2).



Forest plot of thromboembolic events.

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

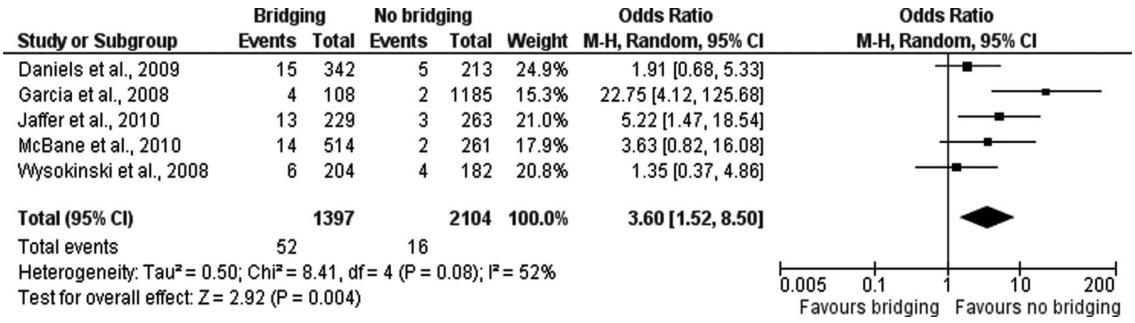
Periprocedural Heparin Bridging in Patients Receiving Vitamin K Antagonists: Systematic Review and Meta-Analysis of Bleeding and Thromboembolic Rates



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



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)
Birnie et al. N Engl J Med 2013;368:2084-93

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Heparin Bridging (N=338)	Continued Warfarin (N=343)
Age — yr	71.4±10.6	71.8±9.9
Male sex — no. (%)	247 (73.1)	248 (72.3)
Body-mass index†	28.4±6.4	28.3±5.4
Medical history — no. (%)		
Rheumatic heart disease	28 (8.3)	30 (8.7)
Embolic transient ischemic attack	63 (18.6)	62 (18.1)
Embolic stroke	60 (17.8)	65 (19.0)
Non-CNS embolism	13 (3.8)	8 (2.3)
Hypertension	237 (70.1)	247 (72.0)
Diabetes mellitus	133 (39.3)	133 (38.8)
Cardiomyopathy	217 (64.2)	233 (67.9)
Coronary-artery bypass surgery	87 (25.7)	96 (28.0)
Indication for anticoagulation therapy — no. (%)		
Mechanical heart-valve replacement‡	108 (32.0)	95 (27.7)
Mechanical mitral-valve replacement	56 (16.6)	48 (14.0)
Caged-ball or tilting-disk aortic valve	13 (3.8)	9 (2.6)
Bileaflet aortic-valve prosthesis	56 (16.6)	51 (14.9)
Atrial fibrillation or atrial flutter	298 (88.2)	305 (88.9)
Deep-vein thrombosis or pulmonary embolus	16 (4.7)	21 (6.1)
Protein C or S deficiency or antiphospholipid antibodies§	3 (0.9)	7 (2.0)
$CHADS_2$ score¶	3.4±1.0	3.4±0.9
Medications — no. (%)		
Aspirin	129 (38.2)	139 (40.5)
Clopidogrel	21 (6.2)	21 (6.1)
Clopidogrel continued perioperatively	16 (4.7)	17 (5.0)

Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISE CONTROL)
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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 Anticoagulation in Patients with Atrial Fibrillation The BRIDGE Investigators

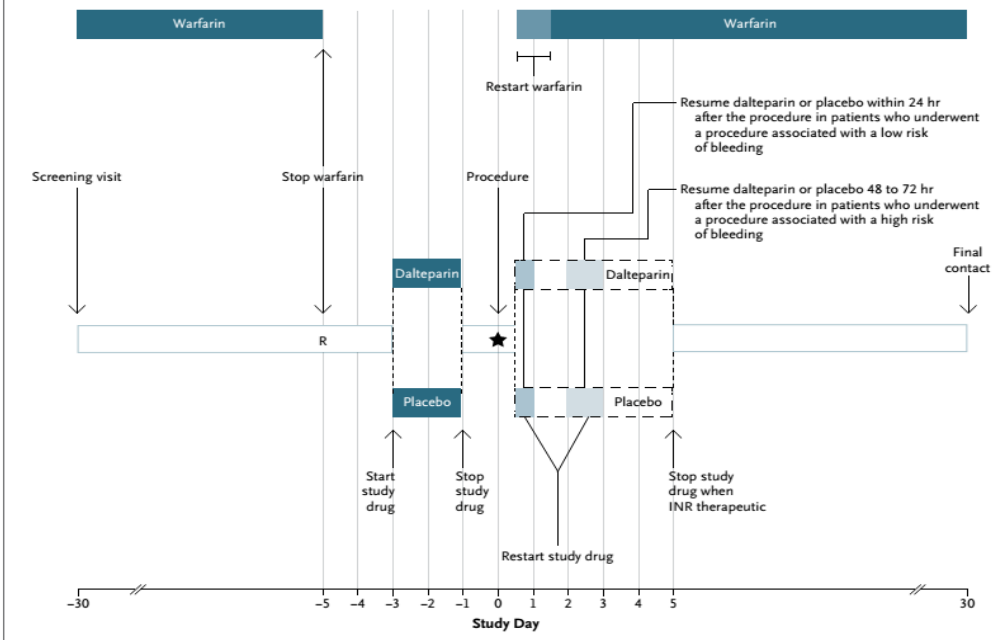

Figure 1. BRIDGE Study Design.

Douketis et al.NEJM 2015

Perioperative Bridging Anticoagulation in Patients with Atrial Fibrillation The 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 1. Baseline Characteristics of the Patients.*

Characteristic	No Bridging (N=950)	Bridging (N=934)
Age — yr	71.8±8.74	71.6±8.88
Male sex — no. (%)	696 (73.3)	686 (73.4)
Race — no. (%)†		
White	860 (90.5)	849 (90.9)
Nonwhite	88 (9.3)	82 (8.8)
Unknown	2 (0.2)	3 (0.3)
Weight — kg	96.2±24.87	95.4±23.50
$CHADS_2$ score‡		
Mean	2.3±1.03	2.4±1.07

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 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 (ongoing)

- prospective multicentre randomized double-blind controlled trial in 11 teaching hospitals in Canada.
- 1773 patients with
- prosthetic heart valves receiving warfarin or
- patients with atrial fibrillation/flutter and a major risk factor

- Dalteparin, a LMWH, at 200 IU/kg sc **early in the morning for the 3 days prior to, but not including the day of, the procedure except on the day prior to surgery the dose will be 100 I.U./kg given 24 hours preoperatively. Warfarin will be resumed the evening of the procedure**. vs placebo
- Primary outcomes: major thromboembolism over a 90-day follow-up.
- Secondary outcomes: major bleeding and overall survival.

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

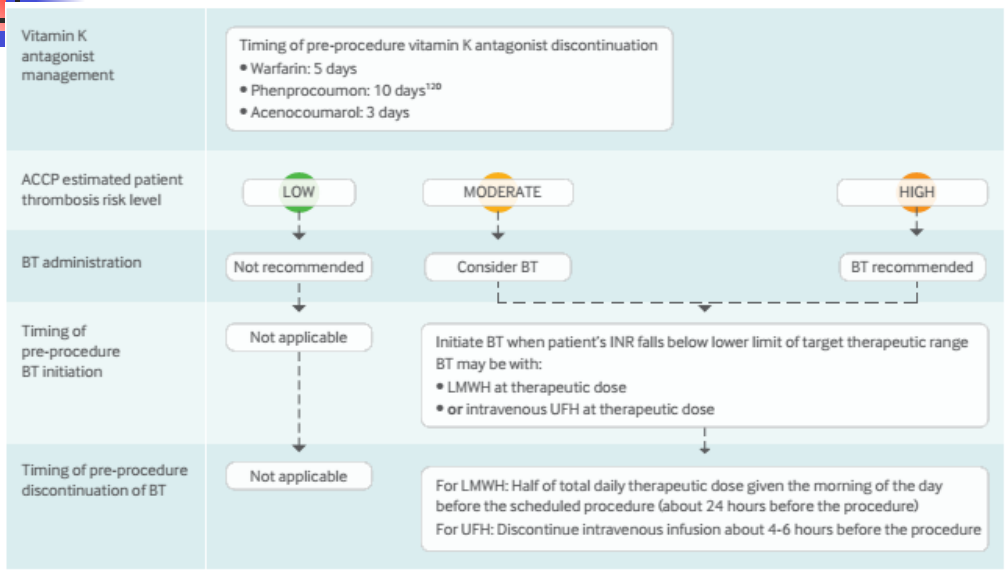

Fig 6 | Suggested approach to elective pre-procedure management of vitamin K antagonists. ACCP=American College of Chest Physicians; BT=bridging therapy; INR=international normalized ratio; LMWH=low molecular weight heparin; UFH=unfractionated heparin[21 118]

Daniels PR, BMJ 2015;351:2391

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

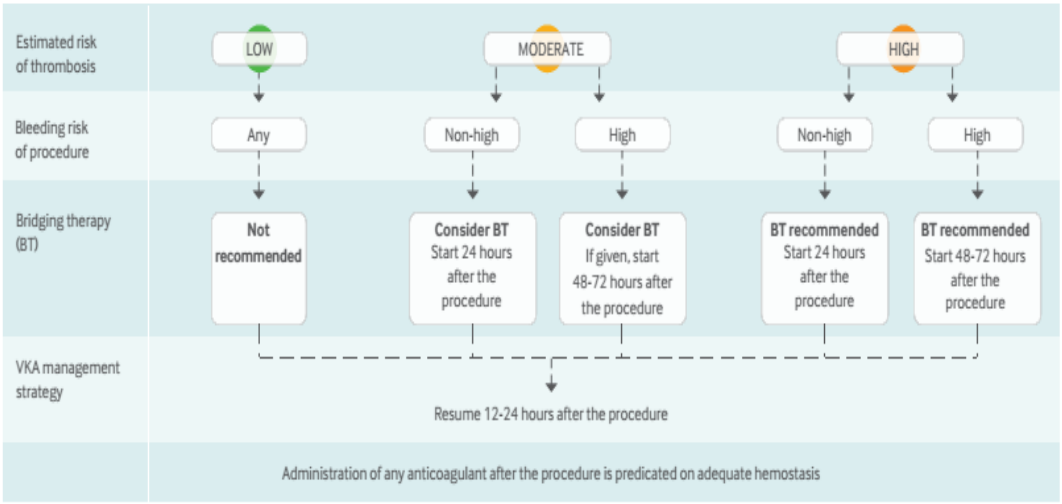

Fig 7 | American College of Chest Physicians' suggested approach to elective post-procedure management of vitamin K antagonists (VKAs)[21]

Daniels PR, BMJ 2015;351:2391

Major guidelines

- American College of Cardiology and American Heart Association (ACC/AHA) guideline (2014) : in general agreement with those from the ACCP
- no bridging therapy in one bileaflet aortic mechanical valve only who have none of the following risk factors:
AF, previous thromboembolism, “hypercoagulable condition,” older generation-type prosthesis, or LVEF 30% or less.
- Bridging therapy recommended in patients with a mitral, tricuspid, or aortic mechanical heart valve who have any of the risk factors listed above.
- If LMWH is used as bridging therapy, then twice daily dosing and last dose 12 hours before surgery is recommended

Major guidelines

- **ESC 2014 : recommends interrupting warfarin 5 days before and recommends considering bridging therapy in patients with a mechanical heart valve or AF who are at high risk of thromboembolism**

- **BCSH 2011: potential harm of postoperative bridging therapy and states that for procedures with a high risk of bleeding, bridging therapy should be given only 48 hours or more after the procedure.**

- **For patients who have had a VTE more than three months earlier the BCSH recommends prophylactic doses of LMWH rather than therapeutic dose bridging therapy.**
- **No bridging therapy for patients with AF and no history of stroke or a transient ischemic attack or for patients with a bileaflet aortic mechanical valve and “no other risk factors.”**

Standardized Low–Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery An Inception Cohort Management Study

Pengo V et al, FCSA.Circulation 2009

- high thromboembolic risk:
- mechanical mitral valve prostheses, monoleaflet mechanical aortic prostheses or bileaflet aortic prostheses associated with AF or previous arterial embolism,
- AF associated with previous arterial thromboembolism or mitral valve disease, previous cardiogenic or unexplained systemic embolism, and venous thromboembolism in the previous 3 months.

- All other cases were considered low to intermediate thromboembolic risk.

Standardized Low–Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery An Inception Cohort Management Study

Pengo V et al FCSA .Circulation 2009

Table 1. 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

TE indicates thromboembolic.
*Dosages (units of anti–factor Xa) varying according to body weight.
†Prophylactic dosage that is independent of body weight.

70 anti–factor Xa U/kg twice daily

Day -5 (prior to procedure):
Stop OAT

Day -4 /-3 (prior to procedure):
Start LMWH according to Protocol A or B, on day -4 if the OA is acenocoumarol, on day -3 if it is warfarin.

Day -1 (prior to procedure):
Administer last dose of LMWH at least 12 hours before the procedure

Day 0 (day of procedure):
• Check INR; if INR>1.5 consider postponing the procedure

Day +1 / +2 (post procedure):
Resume OAT at pre-procedure dose + 50% boost dose;
Resume LMWH at pre-procedure dose on *day +1* (at least 12h after the procedure) or *day +2* according to haemostasis adequacy

Day +3 / +5 (post procedure):
If haemostasis is adequate continue OAT at the usual pre-procedure dose
Continue LMWH

Day +6 (post procedure):
Check INR and stop LMWH if INR is therapeutic
Continue OAT at usual pre-procedure dose

Standardized Low–Molecular-Weight Heparin Bridging Regimen in Outpatients on Oral Anticoagulants Undergoing Invasive Procedure or Surgery An Inception Cohort Management Study

Pengo V et al FCSA .Circulation 2009

- Five thromboembolic events (0.4%; 95% CI, 0.1 to 0.9), 3 venous and 2 arterial, were recorded during follow-up
- All events occurred in high-thromboembolic-risk patients,1 fatal.

- 15 episodes of major bleeding (1.2%; 95% CI, 0.7 to 2.0)
- All events were postprocedural, and none was fatal. Most of the bleeding episodes (11 of 15) were overt surgical site bleeding, and 9 required the transfusion of ≥2 U packed red blood cells.

- 8 occurred in the 295 cases bridged with protocol A (2.7%) and 7 in the 967 cases bridged with protocol B (0.7%; *P*= 0.011)
- Major bleeding was associated with twice-daily LMWH administration (high-risk patients) but not with the bleeding risk of the procedure

Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation

Table 10 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				

Bold values deviate from the common stopping rule of ≥24 h low risk, ≥48 h high risk.
Low risk: with a low frequency of bleeding and/or minor impact of a bleeding; high risk with a high frequency of bleeding and/or important clinical impact. See also *Table 11*.
CrCl, creatinine clearance.
[a]Many of these patients may be on the lower dose of dabigatran (i.e. 110 mg BID) or apixaban (i.e. 2.5 mg BID), or have to be on the lower dose of rivaroxaban (i.e. 15 mg OD) or edoxaban (i.e. 30 mg OD).

DOACs may be restarted 6 to 8 after a procedure if immediate and complete hemostasis, but it notes that resumption of therapeutic dose anticoagulation in the first 48-72 hours after a procedure may increase the risk of bleeding. For patients who are immobile after a procedure, EHRA recommends considering prophylactic LMWH until DOACs restarted.

Heidbuchel H et al, Europace 2015