

Periprocedural Bridging Management of Anticoagulation

Waldemar E. Wysokinski and Robert D. McBane II

Circulation. 2012;126:486-490

doi: 10.1161/CIRCULATIONAHA.112.092833

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2012 American Heart Association, Inc. All rights reserved.

Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://circ.ahajournals.org/content/126/4/486>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Circulation* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:
<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Circulation* is online at:
<http://circ.ahajournals.org/subscriptions/>

Periprocedural Bridging Management of Anticoagulation

Waldemar E. Wysokinski, MD, PhD; Robert D. McBane II, MD

More than 2.5 million Americans are chronically anticoagulated for indications including venous thromboembolism (VTE), mechanical heart valve(s), or atrial fibrillation (AF).¹ Each year, ≈10% of these patients require temporary interruption of anticoagulation for an invasive procedure. Defining the most appropriate management strategy for these patients requires an assessment of the periprocedural risk of thromboembolism and major hemorrhage. Bridging therapy is a recent term used to describe the application of a parenteral, short-acting anticoagulant during the interruption of warfarin. In this Clinician Update, we outline a systematic approach to defining the appropriate periprocedural strategy for anticoagulation management.

Case 1

A 78-year-old man is scheduled for elective colonoscopy with polypectomy next week. He is receiving chronic warfarin for stroke prevention in paroxysmal AF. He has no prior history of stroke, diabetes mellitus, or heart failure. He is treated with metoprolol both for hypertension and rate control. His international normalized ratio (INR) is well controlled on a

stable warfarin dose, and he has no history of major bleeding.

Case 2

A 66-year-old woman was diagnosed with a first life-time right femoral-popliteal DVT 6 weeks ago. She is currently fully anticoagulated with warfarin. As part of her general medical examination, she is found to have ovarian cancer limited to her right ovary without obvious metastases. She is scheduled for total abdominal hysterectomy with bilateral oophorectomy in 5 days. Her INR is 2.2, and her creatinine clearance is 60 mL/min.

Systematic Approach to Anticoagulants

There is no universal strategy for periprocedural anticoagulation for patients on chronic warfarin therapy. However, a stepwise approach can be useful (Figure 1). In urgent/emergent settings, there is neither time nor opportunity for “bridging” therapy. Warfarin can be reversed with fresh-frozen plasma and parenteral vitamin K.

If the procedure is deemed elective, then the next step is to determine whether anticoagulant discontinuation is necessary. A growing list of procedures may be safely performed without anticoagulation interruption (Table 1).

For these procedures, the intensity of warfarin anticoagulation is usually reduced to the lower limit of the therapeutic range.

If oral anticoagulants must be stopped, then the patient-specific thrombotic risk should be assessed to determine whether bridging therapy is required. Low-risk patients not requiring bridging therapy include the following: AF with CHADS-2 score ≤2 and no previous thromboembolism or intracardiac thrombus; bileaflet mechanical aortic valve prosthesis in sinus rhythm with no previous thromboembolism; and VTE occurring beyond 3 months in the absence of active cancer. For these patients, warfarin is stopped 4 to 5 days before the anticipated procedure. Normalization of the INR is confirmed on the morning of the procedure. Postprocedural warfarin is reinitiated on postoperative day 0 as long as hemostasis has been achieved and the patient is able to take oral medications. Postoperative variables to consider when reinitiating warfarin include the need and timing of additional surgery, administration of interacting drugs including antibiotics, and reduced nutritional intake. Consider increasing the frequency of INR monitoring. In addition, appropriate mechanical and pharmacological VTE prophylaxis should be

From the Division of Cardiovascular Medicine, Section of Hematology Research, Mayo Clinic, Rochester, MN.

Correspondence to Robert D. McBane II, MD, Mayo Clinic, Rochester, MN, 55905. E-mail mcbane.robert@mayo.edu

(*Circulation*. 2012;126:486-490.)

© 2012 American Heart Association, Inc.

Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.112.092833

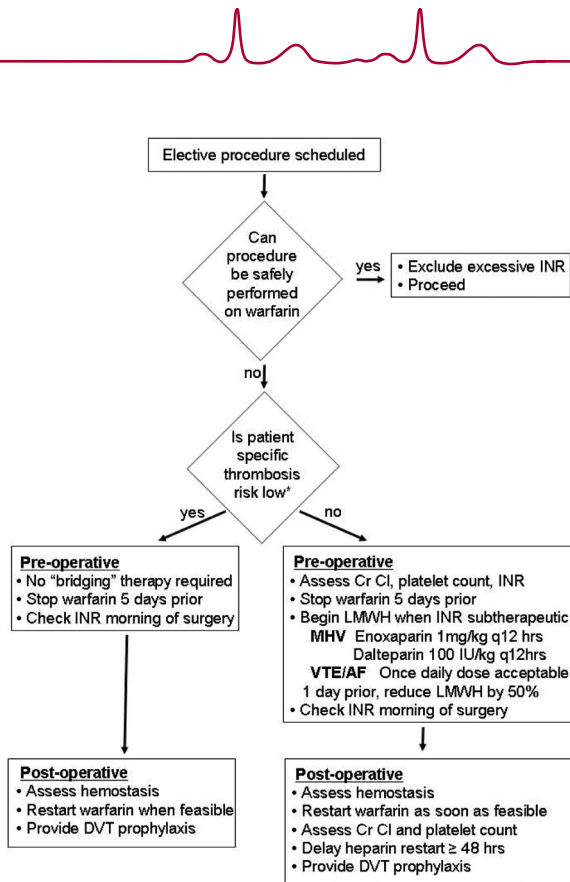


Figure 1. Bridging algorithm for warfarin. Patients with low thrombosis risk include those with aortic bileaflet MHV in sinus rhythm and no previous thromboembolism; AF without previous thromboembolism, intracardiac thrombus, and CHADS2 score ≤ 2 ; VTE ≥ 3 month previously without active cancer. INR indicates international normalized ratio; CrCl, creatinine clearance; LMWH, low molecular weight heparin; MHV, mechanical heart valve; VTE, venous thromboembolism; AF, atrial fibrillation; and DVT, deep vein thrombosis.

implemented until the patient is fully reanticoagulated.

The ongoing National Institutes of Health-funded Bridge Trial will assess the safety and efficacy of bridging therapy with low molecular weight heparin (LMWH) in the setting of atrial fibrillation.² This trial is poised to enroll 3626 patients with an anticipated completion date in 2014 or 2015. It is anticipated

that this trial will answer the question whether AF patients with CHADS-2 score of 3 to 4, but no previous stroke or thromboembolism, require bridging therapy.

When the thromboembolic risk is deemed to be moderate to high, bridging therapy with parenteral anticoagulants is justified. If feasible, LMWH given subcutaneously in the outpatient setting is preferred for patient convenience, safety, and cost.^{3,4} In patients with severe renal impairment (creatinine clearance 15–30 mL/min; stage IV chronic kidney disease), LMWH dose reduction and anti-Xa monitoring should be performed.⁵ For patients with stage V chronic kidney disease, intravenous unfractionated heparin should be used for this purpose. After warfarin discontinuation, a daily therapeutic dose of LMWH is initiated once the INR falls below the therapeutic range.^{6–8} In

keeping with the guidelines, it is our practice to provide twice daily dosing of LMWH in high-risk patients with mechanical heart valve(s).^{9,10} For all other indications, once daily therapeutic LMWH is given. To avoid a residual LMWH effect on the day of surgery, 50% of the calculated daily dose is provided on the morning of the day before the procedure.¹¹ Postoperatively, warfarin should be cautiously restarted as soon as feasible. Therapeutic heparin should be delayed for 48 hours to reduce the risk of major hemorrhage, and conservative dosing should be considered.^{6–8,12} Following surgeries with a high risk of major bleeding, heparin could initially be restricted to prophylactic dosing if used at all. Intravenous unfractionated heparin without a bolus has the advantage of rapid clearance and ease of reversal with protamine and may be preferable under these circumstances. For patients with VTE indications, prophylactic LMWH dosing postoperatively is appropriate. Warfarin and heparin should be overlapped for at least 5 days or until a therapeutic INR is achieved, whichever is longer. Depending on the indication and procedure, aspirin may be stopped 1 week before the procedure.

There is a general tendency to incorporate inferior vena cava filters as part of the bridging strategy for patients with previous VTE.⁸ In our experience of 775 patients anticoagulated for VTE undergoing an invasive procedure, only 4 inferior vena cava filters were placed as part of the bridging recommendations. In patients with acute or subacute VTE, elective surgery should be delayed until the patient has received 3 months of anticoagulant therapy. Inferior vena cava filter placement should only be recommended for patients requiring urgent surgery within 1 month of VTE diagnosis. Retrievable filters are preferred and should be promptly removed when no longer needed.

In patients with a history of heparin-induced thrombocytopenia, heparin products should be avoided. Alternatives

Table 1. Procedures That May Be Safely Performed Without Warfarin Interruption

Dental extraction
Bone marrow biopsy
Endoscopy ($\pm$ mucosal biopsy)
Cataract surgery
Pacemaker placement
Venography
Dermatologic surgery
Joint aspiration

Table 2. Periprocedural Risk of Thromboembolism and Bleeding in Mechanical Heart Valves

Author	n	Aortic	Mitral	Both	Thromb, %	Bleed, %
Douketis ¹³	215	143	46	26	0.9	0.5
Pengo ¹⁴	190	114	76	?	1.6	1.2
Kovacs ¹⁵	112	?	?	?	4.5	7.1
Hammerstingl ¹⁶	116	76	31	9	0	0.9
Daniels ⁶	556	372	136	48	0.7	3.6
Total	1189				1.2	2.7

include short-acting direct thrombin inhibitor therapy such as argatroban, lepirudin, or bivalirudin. Desirudin might be particularly attractive because it can be given subcutaneously and allows outpatient management. Fondaparinux is frequently used for patients with heparin-induced thrombocytopenia but is problematic as a bridging agent given its long elimination half-life (17–21 hours).

In general, the periprocedural rate of bleeding is 2-fold higher than the risk of thrombosis (Tables 2 and 3). Bleed MAP is a recently developed risk assessment tool for defining periprocedural bleeding rates.¹² This tool assigns 1 point for each risk factor: history of previous bleeding (Bleed), mechanical

heart valve (M), active cancer (A), and low platelets (P; $\leq 150\,000/\mu\text{L}$). Although not yet prospectively validated, this tool offers an estimate of bleeding risk based on clinical variables and is the only score system currently available for periprocedural use.

Recommendations for Case 1

Warfarin is stopped 5 days before the colonoscopy with polypectomy. Given the relatively low thromboembolic risk, this patient would not be bridged with LMWH either before or after the procedure. Warfarin would be reinitiated on the same day as the procedure once hemostasis is adequately achieved. In addition, it is our practice to confer with the proceduralist to make sure that the procedure was uncomplicated and that warfarin reinitiation is safe.

Recommendations for Case 2

Given the temporal proximity of the thrombus (≤ 3 months) with the proposed cancer-related surgery, bridging therapy with LMWH would be used. An inferior vena cava filter, however, would not be indicated. Warfarin would be discontinued now (5 days before surgery), and LMWH would be started tomorrow at a therapeutic once daily dose. The last dose of LMWH would be given 24 hours before surgery at half the calculated daily dose. An INR would be obtained on the morning of surgery. Postoperatively, aggressive pharmacological and mechanical DVT prophylaxis would be initiated once hemostasis is ensured. Therapeutic heparin would be withheld for at least 48 hours postoperatively to reduce the risk of bleeding. Warfarin would be reinitiated (without a loading dose) once hemosta-

sis is achieved, provided that no potential procedures are anticipated in the near future.

Novel Anticoagulants and Bridging

Dabigatran etexilate (Pradaxa) is an oral direct thrombin inhibitor approved by the US Food and Drug Administration for stroke prevention in nonvalvular AF.¹⁹ The time to peak anticoagulant effect is ≈ 1 hour, and the drug half-life is ≈ 15 hours, with elimination principally through the kidney (80%). Rivaroxaban (Xarelto) is an oral direct factor Xa inhibitor that is also approved by the US Food and Drug Administration for stroke prevention in nonvalvular AF²⁰ and VTE prophylaxis following major joint replacement surgery. Rivaroxaban is metabolized by the liver (33%) and excreted by the kidney (66%). Elimination half-life is between 7 and 11 hours.

Our approach to the periprocedural management of patients receiving either dabigatran or rivaroxaban therapy is conservative relative to the manufacturer's recommendations for several reasons.²¹ First, the rate of periprocedural thromboembolism is low (1%). Second, the onset of both dabigatran and rivaroxaban is rapid (1–2 hours), yet the half-life is long. Third, there is no antidote for dabigatran. There is no antidote for dabigatran. Prothrombin complex concentrate has been shown to reverse rivaroxaban in healthy volunteers.²²

First, the surgery and anesthesia-specific (eg, neuraxial blockade) risk of bleeding must be defined (Figure 2). The proceduralist and anesthesiologist should be aware that the patient is taking a novel anticoagulant. The creatinine clearance should be reestablished to ensure that the dosing is correct. If the procedure is urgent or emergent, then increased bleeding rates should be anticipated and weighed against the consequences of procedure deferral. Mechanical interventions for hemostasis include suture, hemoclip, pressure application, coiling, cautery, and topical thrombin. For excessive bleeding, the use of hemostatic agents such as prothrombin com-

Table 3. Periprocedural Risk of Thromboembolism and Bleeding in Atrial Fibrillation, Venous Thromboembolism, and Vascular Bypass Grafts

Author	n	Thromb, %	Bleed, %
Atrial fibrillation			
Douketis ¹³	346	1.2	0.9
Pengo ¹⁴	653	0.2	1.2
Kovacs ¹⁵	112	2.7	6.3
Dunn ¹⁷	76	2.3	3.5
Wysokinski ⁷	345	1.1	2.7
Total	1532	0.9	2.0
Venous thromboembolism			
Pengo ¹⁴	210	2.0	1.2
Dunn ¹⁷	96	1.0	3.5
McBane ⁸	775	1.8	1.8
Total	1081	1.8	1.9
Vascular bypass grafts			
Attaya ¹⁸	78	5.1	1.3

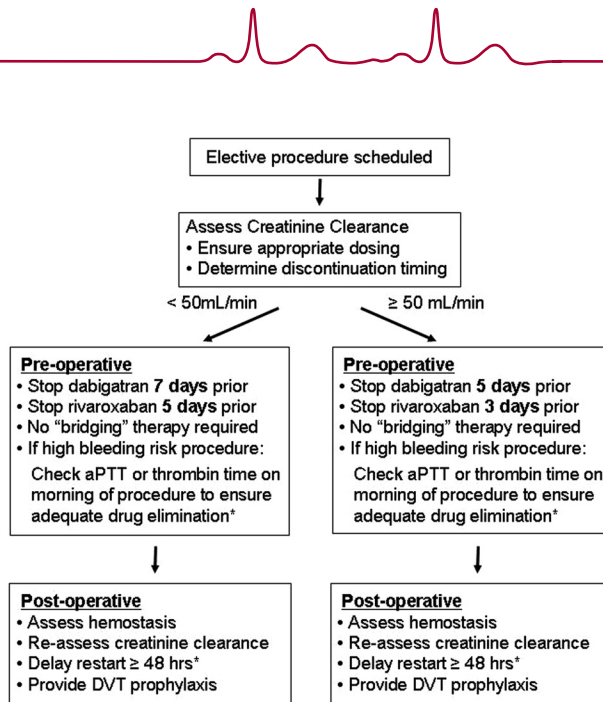


Figure 2. Bridging algorithm for dabigatran. Consider alternative anticoagulants during the postoperative period when risk of bleeding is high or if postoperative bleeding occurs. *Note, aPTT and thrombin time provide a sensitive measure of circulating dabigatran. Assays useful to assess complete rivaroxaban clearance are not yet validated. aPTT indicates activated partial thromboplastin time; DVT, deep vein thrombosis.

plex concentrate, Factor Eight Inhibitor Bypass Activity or recombinant factor VIIa must be weighed against the risk of thrombotic complications.^{21,22}

For elective procedures, the first step in managing these novel anticoagulants is to assess the creatinine clearance. In patients with creatinine clearance ≥ 50 mL/min, we recommend discontinuing anticoagulation 4 to 5 half-lives before surgery. For patients with creatinine clearance < 50 mL/min, we would extend the time of discontinuation by 2 days. For surgeries with high bleeding risk, a normal preoperative aPTT or thrombin time indicates sufficient dabigatran elimination. Currently, there is no available assay for ensuring complete rivaroxaban elimination. Bridging therapy with heparin is generally not indicated. Postoperatively, it is important to reconfirm adequate renal function. Reinitiation of these agents should be delayed ≥ 48 hours and once complete hemostasis is assured. Note, within 1 to 2 hours of either dabigatran or rivaroxaban reinitiation, the patient will be fully anticoagulated. In those patients at high risk of bleeding or if additional procedures are anticipated

in the near future, we suggest the use of a conventional anticoagulant therapy that can be reversed if necessary.

Periprocedural outcomes for 4591 patients with nonvalvular atrial fibrillation randomized to dabigatran (110 mg or 150 mg BID) or warfarin undergoing invasive procedures have recently been provided by the RELY investigators.²³ Dabigatran was discontinued on average 2 days prior to the procedure compared to 4 days for warfarin. Timing of post-procedural reinitiation was determined by the patient's care provider. Thirty day bleeding rates did not differ by anticoagulation allocation (3.8% [dabigatran 110 mg], 5.1% [dabigatran 150 mg] and 4.6% [warfarin]) but in general were 2 fold higher than previously reported data for warfarin (Table 2). Thromboembolism rates were low at approximately 1% for each group. While this is an important contribution, limitations of this manuscript include: retrospective design, alteration of management strategy mid-trial, lack of standardized approach to anticoagulation management (particularly post-procedural re-initiation) and nonstandard definition of "major" procedure. Indeed, of the procedures performed, less than 17% would be consid-

ered major by practicing clinicians. Until further data are available for patients undergoing major procedures, our approach remains conservative.

Furthermore, it is our practice to avoid dabigatran and rivaroxaban in patients with indwelling neuraxial/epidural or deep plexus catheters because of risks of associated hematomas. After removal of neuraxial or deep plexus/peripheral catheter, the first postprocedural dose of these agents should be delayed by 24 hours.

Additional Considerations: Cancer

Patients with active cancer receiving chronic anticoagulation are prone to thrombosis and bleeding complications. Chemotherapy, central line placement, cytopenias, hormone manipulation, interacting drugs, and variable dietary intake add complexity to anticoagulation management. Periprocedural VTE (1.2% versus 0.2%) and major bleeding (3.4% versus 1.7%) are significantly higher in patients with active cancer ($n=493$) in comparison with those without cancer ($n=1589$).²⁴ This difference is explained entirely by those patients receiving anticoagulation for cancer-associated VTE. For these patients, we recommend aggressive preoperative bridging therapy with LMWH. The last dose should be half of the total daily dose given 24 hours preoperatively. Postoperatively, LMWH is limited to prophylaxis dosing until complete hemostasis is assured. Therapeutic LMWH is avoided ≥ 48 hours to reduce the likelihood of major hemorrhage. Many patients with cancer-related VTE are maintained on chronic LMWH.

Disclosures

None.

References

1. Waterman AD, Banet G, Milligan PE, Frazier A, Verzino E, Walton B, Gage BF. Patient and physician satisfaction with a telephone-based anticoagulation service. *J Gen Intern Med*. 2001;16:460–463.
2. Effectiveness of Bridging Anticoagulation for Surgery (The BRIDGE Study). <http://clinicaltrials.gov/ct2/show/NCT00786474>. Accessed June 28, 2012.

3. Spyropoulos AC, Frost FJ, Hurley JS, Roberts M. Costs and clinical outcomes associated with low-molecular-weight heparin vs unfractionated heparin for perioperative bridging in patients receiving long-term oral anticoagulant therapy. *Chest*. 2004;125:1642–1650.
4. McBane RD, Attaya H, Shah N, Wysokinski WE, Van Houten H, Heit JA. Peri-procedural anticoagulation management of mechanical prosthetic heart valve patients. *J Am Coll Cardiol*. 2011;57:E1381.
5. Schmid P, Brodmann D, Fischer AG, Willemin WA. Study of bioaccumulation of dalteparin at a prophylactic dose in patients with various degrees of impaired renal function. *J Thromb Haemost*. 2009;7:552–558.
6. Daniels PR, McBane RD, Litin SC, Ward SA, Hodge DO, Dowling NF, Heit JA. Peri-procedural anticoagulation management of mechanical prosthetic heart valve patients. *Thromb Res*. 2009;124:300–305.
7. Wysokinski WE, McBane RD, Daniels PR, Litin SC, Hodge DO, Dowling NF, Heit JA. Peri-procedural anticoagulation management of patients with nonvalvular atrial fibrillation. *Mayo Clin Proc*. 2008;83:639–645.
8. McBane RD, Wysokinski WE, Daniels PR, Litin SC, Slusser J, Hodge DO, Dowling NF, Heit JA. Peri-procedural anticoagulation management of patients with venous thromboembolism. *Arterioscler Thromb Vasc Biol*. 2010;30:442–448.
9. Douketis JD, Spyropoulos AC, Spencer FA, Mayr M, Jaffer AK, Eckman MH, Dunn AS, Kunz R. Perioperative management of anti-thrombotic therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;141(suppl):e326S–e350S.
10. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, Gaasch WH, Lytle BW, Nishimura RA, O’Gara PT, O’Rourke RA, Otto CM, Shah PM, Shanewise JS; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;52:e1–e142.
11. Douketis JD, Woods K, Foster GA, Crowther MA. Bridging anticoagulation with low-molecular-weight heparin after interruption of warfarin therapy is associated with a residual anticoagulant effect prior to surgery. *Thromb Haemost*. 2005;94:528–531.
12. Tafur A, McBane R, Wysokinski WE, Slusser J, Hodge D, Heit JA. Predictors of peri-procedural bleeding among patients on chronic anticoagulation. *J Thromb Haemost*. 2012;10:261–267.
13. Douketis JD, Johnson JA, Turpie AG. Low-molecular-weight heparin as bridging anticoagulation during interruption of warfarin. *Arch Intern Med*. 2004;164:1319–1326.
14. Pengo V, Cucchini U, Denas G, Erba N, Guazzaloca G, La Rosa L, De Micheli V, Testa S, Frontoni R, Prisco D, Nante G, Iliceto S. Standardized low-molecular-weight heparin bridging regimen in outpatients on oral anticoagulants undergoing invasive procedure or surgery. *Circulation*. 2009;119:2920–2927.
15. Kovacs MJ, Kearon C, Rodger M, Anderson DR, Turpie AG, Bates SM, Desjardins CL, Douketis J, Kahn SR, Solymoss S, Wells PS. Single-arm study of bridging therapy with low-molecular-weight heparin for patients at risk of arterial embolism who require temporary interruption of warfarin. *Circulation*. 2004;110:1658–1663.
16. Hammerstingl C, Tripp C, Schmidt H, von der Recke G, Omran H. Peri-procedural bridging therapy with low-molecular-weight heparin in chronically anticoagulated patients with prosthetic mechanical heart valves: experience in 116 patients from the prospective BRAVE registry. *J Heart Valve Dis*. 2007;16:285–92.
17. Dunn AS, Spyropoulos AC, Turpie AG. Bridging therapy in patients on long-term oral anticoagulants who require surgery: the Prospective Peri-operative Enoxaparin Cohort Trial (PROSPECT). *J Thromb Haemost*. 2007;5:2211–2218.
18. Attaya H, Wysokinski WE, Bower T, Litin S, Daniels PR, Slusser J, Heit JA, McBane RD. Three-month cumulative incidence of thromboembolism and bleeding after peri-procedural anticoagulation management of arterial vascular bypass patients. *J Thromb Thrombolys*. In press.
19. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.
20. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
21. van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, Clemens A. Dabigatran etexilate: a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haem*. 2010;103:1116–1127.
22. Eerenberg ES, Kamphuisen PW, Sijkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124:1573–1579.
23. Healey JS, Eikelboom J, Douketis J, Wallentin L, Oldgren J, Yang S, Themeles E, Heidbuchle H, Avezum A, Reilly P, Connolly SJ, Yusuf S, Ezekowitz M. Peri-procedural bleeding and thromboembolic events with Dabigatran compared with Warfarin: results from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) randomized trial. *Circulation*. 2012;126:343–348.
24. Tafur AJ, Wysokinski WE, McBane R, Wolny E, Sutkowska E, Litin SC, Daniels PR, Slusser JP, Hodge DO, Heit JA. Cancer effect on peri-procedural thromboembolism and bleeding in anticoagulated patients. *Ann Onc*. April 3, 2012. doi: 10.1093/annonc/mds058.

KEY WORDS: atrial fibrillation ■ deep vein thrombosis ■ heparin ■ mechanical heart valve ■ rivaroxaban ■ warfarin ■ dabigatran