More than 2 million people are currently treated with oral anticoagulation in North America alone. Indeed, chronically anticoagulated patients are expected to become more prevalent as the population ages and the incidence of conditions (for example, atrial fibrillation) requiring anticoagulation increases.

Many of these patients may undergo an invasive or operative procedure at some point, and thus their periprocedural management will be a commonly encountered problem. The challenge in periprocedural management of anticoagulated patients focuses on the need to balance risk of thromboembolism (in case of anticoagulation interruption) against the risk of bleeding during the procedure (in case of anticoagulation continuation). Thus, a crucial first step in the management of such patients is estimation of periprocedural bleeding and thrombotic risk, and balancing both.

In certain chronic conditions, such as AF, risk stratification scores assist decision making when risk of thrombosis and bleeding needs to be weighed. However, when an invasive procedure is involved, thrombosis and bleeding scores have been less well validated, and the optimal management of anticoagulated patients remains controversial.

For many years, bridging therapy has been practiced when considering an interventional procedure, and anticoagulation was continued with parenteral heparins when- ever the vitamin K antagonists (eg, warfarin) had to be interrupted (Figure). The rationale of a bridging strategy was to replace coumadins by a parenteral agent with short half-life and rapid onset of action that can be discontinued only a few hours before and commenced a few hours after the procedure. However, some argue that this empirical approach lacks robust evidence, and therefore this approach has been subject to some debate.

When considering the balance between risk and benefit, supporters of bridging therapy allege low rates of bleeding complications as the reason not to stop anticoagulation periprocedurally. In a similar way, detractors of bridging therapy put forward low rates of thromboembolism in nonbridging groups. Interestingly, both strategies are supported by some published data, but most are retrospective observational studies where heterogeneous groups of patients have undergone a variety of invasive procedures.

These uncertainties in periprocedural management are reflected in international guidelines where recommendations are usually provided with low-grade evidence.

Taking into account a 3-tiered thromboembolism risk categorization (high, moderate, low) of the most common patient groups on coumarins (eg, mechanical heart valve, atrial fibrillation, and venous thromboembolism), and a bleeding risk based on high- versus non–high-bleed-risk procedures, the recent 9th Edition American College of Chest Physicians (ACCP) Guidelines (2012) suggest continuing coumarin administration for minor dental or dermatologic procedure and cataract surgery (Grade 2C), with heparin bridging for high thromboembolic risk patient groups (Grade 2C); however, the guidelines did not qualify a recommendation for moderate thromboembolic risk groups, which requires assessment of individualized risk factors for bleeding and thrombosis.

In this issue of Circulation, Siegal et al performed a systematic review and meta-analysis to evaluate the safety and efficacy of periprocedural anticoagulation bridging. The authors reviewed 34 studies that assessed perioperative thromboembolism and bleeding events in patients undergoing elective surgical or invasive procedures. Their dataset involved >12 000 patients, a sample size 6-fold higher than the one used in a previous systematic review by Dunn and Turpie. Thromboembolic outcome data were available for all 34 studies, which included a total of 7118 patients receiving any periprocedural heparin bridging. Similarly, bleeding was included as an outcome in all 34 studies, whereas major bleeding was reported in 24 studies. The large sample size allowed the authors to calculate bleeding/thromboembolism rates based on a substantially higher absolute number of events providing the substrate for more robust conclusions. The authors concluded that heparin bridging conferred a >5-fold increased risk for overall bleeding and a >3-fold increased risk for major bleeding, whereas the risk of thromboembolic events was not significantly different between bridged and nonbridged patients. Interestingly, use of therapeutic-dose low-molecular-weight heparin bridging was associated with an increased risk of bleeding compared with prophylactic- or intermediate-dose low-molecular-weight heparin, although thromboembolic event rates did not significantly differ.

Despite the inherent limitations of a meta-analysis, the article by Siegal et al is still currently the largest source of data on the management of vitamin K antagonist–treated

The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

From the University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Birmingham, United Kingdom.

Correspondence to Gregory Y.H. Lip, MD, University of Birmingham Centre for Cardiovascular Sciences, City Hospital, Dudley Road, Birmingham, B18 7QH, United Kingdom. E-mail g.y.h.lip@bham.ac.uk

(Circulation. 2012;126:1573-1576.)
patients who require periprocedural interruption of oral anticoagulation and bridging. How should such data be interpreted and incorporated in clinical practice? A major limitation of the analysis is the heterogeneity of the data, which is a reflection of the high variation in current clinical practice. Under the term bridging, several different regimes were used, including intermediate or prophylactic doses. Moreover, a number of different procedures have been assessed with a wide range of periprocedural bleeding risk. Similarly, a variety of events were pooled under the terms bleeding and thromboembolism. Most importantly, it is unclear how the estimated baseline risk for thromboembolism or bleeding affected outcomes, because the indications for anticoagulation varied and high risk was variably defined in each study.

Also, Siegal et al \(^{11}\) assessed the outcome of bridging therapy in vitamin K antagonist–treated patients only, but the increasing availability of novel oral anticoagulants, either direct thrombin or factor Xa inhibitors, brings the question of bridging therapy with the use of these drugs. Their shorter half-life compared with coumarins suggests that the management of bleeding complications and the antithrombotic regimen during operations and invasive procedures could potentially become simpler with these drugs.\(^{13,14}\) Nevertheless, the optimal periprocedural management strategies of patients taking the novel oral anticoagulants undergoing invasive procedures need to be based on adequate quality evidence, which is not currently available.

Only randomized trials can perhaps address the remaining uncertainty in periprocedural anticoagulation. Currently, the PERIOP-2 (A Double Blind Randomized Control Trial of Post-Operative Low Molecular Weight Heparin Bridging Therapy Versus Placebo Bridging Therapy for Patients Who Are at High Risk for Arterial Thromboembolism), BRIDGE (Effectiveness of Bridging Anticoagulation for Surgery), and BRUISECONTROL (Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial), randomized trials comparing bridging with no bridging strategies in warfarin-treated patients who require elective surgery, are ongoing.\(^{15–17}\) These ongoing studies are designed to answer relevant questions on periprocedural anticoagulation in specific settings using specific regimes. Moreover, they will evaluate periprocedural bridging using clearly defined efficacy and safety end points.

BRIDGE is a prospective randomized, double-blinded study which aims to recruit >3600 patients with atrial fibrillation/flutter and a major risk factor for thromboembolism who require elective surgery or invasive procedure necessitating interruption of their oral anticoagulant therapy.\(^{16}\) Patients will be random-ized peroperatively to receive either subcutaneous dalteparin or placebo, and primary end points include arterial thrombo-
embolic events and major bleeding. PERIOP-2 has a similar study design but aims to recruit patients with prosthetic heart valves as well as patients with atrial fibrillation/flutter, whereas BRUISECONTROL compares a bridging regime with uninterrupted warfarin therapy in patients undergoing device implantation.

Until additional randomized trials provide further guidance, recent data on periprocedural risk estimation warrant a more objective and accurate estimation of periprocedural bleeding risk. Tools to assess periprocedural bleeding risk have been developed, although they are not yet prospectively validated. In the study by Tafur et al., who followed up 2182 patients between 1997 to 2007, multivariable analysis revealed that independent predictors for major bleeding included mitral mechanical heart valve, active cancer, previous bleeding history, and reinitiation of heparin therapy within 24 hours of the procedure. These authors proposed a scoring system for risk assessment of periprocedural bleeding (called the history of prior bleeding, mechanical mitral heart valve, active cancer, and low platelets [BleedMAP]) during heparin bridging therapy using the 4 identified predictors of major bleeding. More recently, Omran et al. used a prospective, observational, multicenter registry of patients undergoing invasive procedures and demonstrated that a HASBLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (≥65) and drugs/alcohol concomitantly) score ≥3 was an independent predictor of bleeding events in both atrial fibrillation and non–atrial fibrillation patients and may allow risk stratification of patients.

The Scientific and Standardization Committee of the International Society on Thrombosis and Hemostasis has recently published recommendations for standardized reporting of bridging anticoagulation regimens and outcomes, including thromboembolism and major bleeding (Spyropoulos et al). These recommendations are expected to promote homogeneity in the reported events in future observational studies and thus enable pooling of data and across-study comparisons.

In conclusion, evidence-based practice will come from randomized clinical trials that will guide our practice on periprocedural management of anticoagulated patients, whether with vitamin K antagonists or novel anticoagulants. Development and validation of risk estimation tools will eventually provide an estimate of periprocedural bleeding risk based on explicit standardized criteria instead of implicit clinical judgment, allowing better definition of high-risk patients. In anticipation of such evidence-based data, the article by Siegal et al. currently provides an excellent overview of what could be considered as practice-based evidence.

Disclosures

Dr Lip has served as a consultant for Bayer, Astellas, Merck, Sanofi, BMS/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has been on the speakers bureau for Bayer, BMS/Pfizer, Boehringer Ingelheim, and Sanofi Aventis. He serves as a DSMB committee member for the BRUISE CONTROL trial.

References


17. Canadian Institutes of Health Research. Bridge or Continue Coumadin for Device Surgery Randomized Controlled Trial (BRUISECONTROL). ClinicalTrials.gov NCT00800137.


Key Words: Editorials  ■  warfarin
Bridging Evidence-Based Practice and Practice-Based Evidence in Periprocedural Anticoagulation
Pilar Gallego, Stavros Apostolakis and Gregory Y.H. Lip

_Circulation_. 2012;126:1573-1576
doi: 10.1161/CIRCULATIONAHA.112.135681
_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/126/13/1573

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/