A Call to Reduce the Use of Bridging Anticoagulation
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Abstract—Because of the recent publication of several important studies, there has been a major change in how we think about perioperative management of anticoagulation. Because of these changes, existing consensus guidelines are suddenly out of date and can no longer be used as-is, particularly the 2012 American College of Chest Physicians Antithrombotic Guidelines, version 9. We estimate that well over 90% of patients receiving warfarin therapy should not receive bridging anticoagulation during periprocedural interruptions of therapy, except under unusual circumstances and with appropriate justification. Accumulating evidence also suggests that bridging is not indicated among patients receiving direct-acting oral anticoagulant therapy. The large number of patients potentially affected represents an important safety concern and requires an immediate change in practice. *(Circ Cardiovasc Qual Outcomes. 2016;9:00-00. DOI: 10.1161/CIRCOUTCOMES.115.002430.)*

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The Problem: How to Treat Patients During Interruptions of Anticoagulation for Procedures
Anticoagulation, with warfarin or a direct-acting oral anticoagulant (DOAC), is extremely effective for treating and preventing thromboembolism. However, anticoagulation often must be interrupted to allow a procedure to occur safely. For years, clinicians have wrestled with the issue of how best to treat patients during such a pause in therapy. In the case of warfarin, the period during which the patient is subtherapeutic can be 2 weeks or even longer in some cases, and there is concern for increased risk of thromboembolism during this period. There is longstanding controversy over the phenomenon of rebound hypercoagulability after the cessation of anticoagulation. Although some studies do seem to confirm that there is activation of the coagulation system shortly after interruption of therapy, it is unclear if this phenomenon is clinically meaningful, or how important it would be in the context of a brief periprocedural interruption. For example, a meta-analysis of studies of patients with venous thromboembolism (VTE) found that there is a transient increase of 2% in the rate of recurrent VTE during the 2 months after cessation of anticoagulant therapy. This difference is small and likely of minimal clinical significance, and would be further eroded in the context of a briefer (10–14 days) interruption.

In any case, there is clearly a nonzero risk of thromboembolism during a brief interruption of therapy, although it may be small in absolute terms. A desire to mitigate this risk led to the practice called bridging anticoagulation, which refers to the use of parenteral anticoagulation with either low-molecular weight heparin or intravenous unfractionated heparin to bridge the patient during most of the period when the warfarin therapy is absent. Interestingly, the practice of bridging is based solely on expert opinion; no study has ever demonstrated that this practice prevents thromboembolism (ie, produces any benefit), much less that it prevents more problems than it causes (ie, produces net benefit).

Status Quo Ante: How We Practiced Until Recently
For many years, clinical practice in the area of anticoagulation has been largely guided by the highly authoritative American College of Chest Physicians guidelines, produced every 3 or 4 years, with the most recent version in 2012 (herein referred to as Antithrombotic Guidelines, version 9 [AT9]). AT9 acknowledged that the practice of bridging was based solely on expert opinion, but recommended a 3-tiered schema to decide which patients should receive bridging during interruptions of therapy. The 3 risk levels (high, moderate, and low) were based on risk scores, such as the CHADS2 score, which had been developed and validated to estimate the yearly incidence...
of thromboembolism rather than the incidence during a temporary interruption of anticoagulation. Although this schema was nonprescriptive, we think that many clinicians interpreted this schema to say that these 3 groups of patients should receive bridging usually (high risk), sometimes (moderate risk), and usually not (low risk). Some extant studies provide a snapshot of how often bridging is actually performed in modern practice, at least in academic settings. For example, in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) registry, 24% of interruptions were accompanied by bridge therapy; the mean CHADS2 score of patients who received bridge therapy was 2.53, compared with 2.34 among patients not bridged.8 In a cohort of patients receiving warfarin to treat VTE from 2006 to 2012, 31% of interruptions were accompanied by bridge therapy, with only slight differences in predicted VTE risk between those bridged and those not.9 We see from these studies that in real-world practice, bridge therapy is provided to many patients, often including those with relatively low thromboembolism risk. Although these studies do not specifically report whether the use of bridge therapy has been increasing during the past decade, it is our impression that it is.

**Brief Review of Recent Evidence**

Since the release of AT9 in 2012, multiple new, important studies have greatly changed how we look at the decision of whom to bridge.

- **2012 Meta-analysis:** This meta-analysis included 33 observational studies and 1 randomized trial.10 These studies represented a total of 7118 bridged and 5160 nonbridged patients, who were receiving anticoagulation for varied indications. Most included studies were of poor methodological quality. Thromboembolic events occurred in 0.9% of bridged patients and 0.6% of nonbridged patients. Rates of overall and major bleeding were 13.1% and 4.2% among bridged patients and 3.4% and 0.9% among nonbridged patients. Meta-analyses showed that bridging was not significantly different from nonbridging in terms of preventing thromboembolism (OR, 0.80; 0.42–1.54), but was associated with significantly higher rates of overall bleeding (OR, 5.40; 3.00–9.74) and major bleeding (OR, 3.60; 1.52–8.50).

- **ORBIT-AF Registry Study:** This study was based on a prospective registry of patients with AF in the United States.8 A total of 2803 interruptions of warfarin occurred, with bridging used in 24% of these instances. Bleeding events occurred in 5.0% of bridged versus 1.3% of nonbridged patients (P<0.001). Stroke or systemic embolism occurred in 0.6% of bridged patients and 0.3% of unbridged patients (P=0.5). The incidence of a composite end point (which included myocardial infarction, stroke, systemic embolism, major bleeding, hospitalization, or death within 30 days) was higher in bridged than nonbridged patients (13% versus 6.3%, P<0.001), mainly because of a higher rate of hospitalization. The study adjusted for covariates, although covariates were similar between groups.

- **Sub-analysis of RE-LY Study:** The RE-LY study was a randomized trial comparing warfarin with dabigatran. The authors took advantage of the detailed prospective data collection to perform this analysis.11 Anticoagulation was interrupted for 1424 warfarin patients (27.5% of whom were bridged) and 2709 dabigatran patients (15.4% of whom were bridged). In warfarin patients, bridging was associated with more major bleeding (OR, 4.62, P<0.001). In dabigatran patients, bridging was associated with more major bleeding (OR, 3.68, P<0.001). The overall rates of thromboembolism were low, with 7 events for warfarin/bridged, 3 for warfarin/not bridged, 13 for dabigatran/bridged, and 5 for dabigatran/not bridged. Thromboembolism was not reduced by bridging, and in fact bridged patients had a higher rate of thromboembolism. This difference achieved statistical significance only for the comparison of any thromboembolism among warfarin patients (more thromboembolism among those bridged, P=0.007). The authors had planned to do a propensity-matched analysis based on bleeding and thromboembolism risk scores, but patients who did and did not receive bridging were already well-matched at baseline.

- **The BRIDGE Trial:** BRIDGE enrolled 1884 patients with AF on warfarin therapy, 97% of whom had CHADS2 scores from 1 to 4.12 The mean CHADS2 score was 2.4, which is the same as the mean score in the ORBIT-AF study,8 and it is generally reflective of most real-world AF populations. Patients were randomized to receive low-molecular weight heparin bridging or no bridging during the perioperative period. Arterial thromboembolism occurred in 4 patients who were not bridged and 3 patients who were bridged (0.4% versus 0.3%), meeting the preset criterion for noninferiority. Major bleeding rates were nearly tripled among those who were bridged, occurring in 29 patients who received bridging and 12 who did not (3.2% versus 1.3%, P=0.005). Minor bleeding occurred in 187 bridging patients versus 110 nonbridging patients (P<0.001).

- **Kaiser Permanente VTE Study:** This observational study included 1178 patients receiving warfarin for long-term treatment of VTE.9 For 96% of these patients, the VTE was >1 year before study entry, with most of the remainder between 3 and 12 months before study entry. Thirty-one percent of patients received bridging. Recurrent VTE occurred in 3 nonbridged and 0 bridged patients (P=0.56). Clinically relevant bleeding occurred in 15 bridged versus 2 nonbridged patients (P=0.01).

- **Evidence About Mechanical Valves:** The published evidence about patients with mechanical valves is more limited. The most informative study to date may be a series of 556 consecutive patients treated at the Mayo Clinic, all of whom received bridge therapy with low-molecular weight heparin.13 Of these, 372 patients had an aortic valve, 136 had a mitral valve, and 48 had multiple valves. The 90-day incidence of thromboembolism was 0.9%, with no fatal events, whereas the incidence of major bleeding was 3.6%, with 0.2% fatal events. These results do not prove, but generally support the idea, that bridge therapy greatly increases the risk of bleeding, whereas the overall risk of thromboembolism is low. Similarly, the meta-analysis described above included some patients with bioprosthetic and mechanical valves, although they were not evaluated separately.10
Summary of Evidence

Within the past few years, and especially the past few months, several studies have been published which call into question the practice of bridging, at least for the majority of patients. For patients with AF, a high-quality randomized trial and a high-quality observational study both showed that the great majority of patients with AF experience net harm from bridging. A meta-analysis describing bridging outcomes in patients with mixed indications for anticoagulation, combining multiple small, low-quality studies, supports the same conclusion. For patients with VTE, a high-quality observational study showed that the great majority of patients, especially those whose event was more than a year earlier, do not receive net benefit from bridging. For patients with mechanical valves, no published study has directly addressed the issue of bridging for elective procedures, although existing studies certainly suggest that bridging is similarly unlikely to produce net benefit for these patients as well.

In all the studies we have, bridging was associated with a greatly increased risk for major bleeding—from 2.5- to 5-fold. None of these studies demonstrated any reduction in thromboembolism from bridging—let alone a reduction important enough to justify the increased bleeding. The RE-LY analysis also strongly suggests that bridging is not needed with DOAC therapy—nor would we expect it to be necessary because patients are unprotected from thromboembolism for a relatively brief and predictable period with these agents, compared with warfarin. Providers should also consider when to restart DOAC therapy after a procedure. Although it would typically take 5 to 7 days for warfarin to reach full therapeutic effect, DOAC therapy is immediately active, without a way to easily monitor anticoagulant effect. Therefore, decisions about when to restart therapy may differ from how one would manage warfarin.

Limitations of Evidence

Studies were only adequately powered to exclude a fairly large clinical benefit from bridging, in terms of preventing thromboembolism. Having sufficient power to exclude a small clinical benefit would require many thousands of patients because of a relatively low absolute risk. Studies of such a large size seem unlikely ever to occur because the BRIDGE study itself was ambitious and took almost a decade to complete. The inclusion of certain high-risk patient groups in these studies (especially BRIDGE) was not sufficient to confidently exclude the possibility that some of them could still benefit from bridging—but no study has ever demonstrated such a benefit either. To date, we still have no published data directly addressing the comparison of bridging versus nonbridging for patients with mechanical heart valves.

Interpretation/Opinion/Recommendations

Reductions in thromboembolism from bridging remain theoretical, but the increased risk of bleeding is consistent across studies and clinically important. If any group of patients would receive net benefit from bridging, their absolute risk of thromboembolism would need to be much higher than the patients represented in the studies mentioned above. However, the evidence does not suggest that our current risk stratification systems are able to identify such patients accurately. For example, in the Kaiser VTE study discussed above, the VTE risk score used did not meaningfully predict thromboembolism. Similarly, although CHADS2 and related scores are well-validated to predict long-term risk of stroke in AF patients without anticoagulation, no study has ever demonstrated their use in risk stratification in the perioperative setting; their use is based on extrapolation, and indeed may not be valid. If we could somehow identify predictors of perioperative thromboembolism, and could reliably identify patients whose risk for thromboembolism would approach 2% to 3% (ie, the risk of major bleeding), then perhaps the application of bridge therapy could be justified. However, this still presumes that bridge therapy prevents thromboembolism, which also has not been proven.

We feel confident in saying that there is an increasing body of evidence, and an increasing consensus, that the overwhelming majority of patients will receive net harm from bridging. Bridging should only be offered after careful consideration, and for highly selected patients. Patients should be informed that the practice of bridging is nonevidence-based. Although we may fear the consequences of a thromboembolic event—and justifiably so—no study has ever shown that bridging reduces this risk, and every study that has been completed to date suggests a marked increase in bleeding from bridging.

American College of Chest Physicians is not expected to update the AT9 guidelines, and we feel this recent evidence renders those guidelines obsolete on the subject of bridge therapy. There will likely be other guidelines forthcoming, but for now we would at least recommend that bridge therapy be reserved for patients interrupting warfarin therapy who have a particularly high risk of thromboembolism. Bridge therapy would seem to be unnecessary for patients receiving DOAC therapy. The high thromboembolic risk warfarin patients would probably include:

- Patients with any thromboembolism during past interruptions of anticoagulation, or while on therapeutic anticoagulation
- Patients with a cerebrovascular accident or transient ischemic attack in the past 3 months
- Patients with recent (within 1 month) evidence of mural thrombus or left atrial appendage clot
- Patients with a mitral mechanical valve
- Patients with older caged ball or tilting disc mechanical valves
- Patients with VTE in the past 3 months
- Patients with VTE and a properly diagnosed hypercoagulable state, including antiphospholipid antibody syndrome, Protein C or Protein S deficiency, or antithrombin 3 deficiency.

Together, this list encompasses far less than 10% of patients receiving warfarin. Patients not meeting these criteria should only receive bridging under unusual circumstances, after careful consideration, and with full justification. Patients remaining on this high-risk list do not have evidence of net benefit from bridging, rather, they are the groups for which
the published literature have not already shown a lack of such benefit, in most cases because of under-representation in the published studies. Although a lack of evidence cannot be construed as proof in either direction, given the general pattern of the evidence to date (that bridging does not produce net benefit), we think it is more reasonable to assume that most of these patients also will not receive a net benefit from bridging. Assuming in the other direction (ie, that they would receive net benefit) seems less likely to ultimately be borne out, although this certainly remains a question to be answered empirically.

We are not suggesting that patients on this much-reduced high-risk list should receive bridging therapy uniformly. Rather, cases should be considered individually, weighing patient-specific bleeding risk factors, providing disclosure to the patient that bridging is not evidence based, and engaging in shared decision making. For many (or even most) of these patients, it may also be in the patient’s best interest to omit bridge therapy. Until recently, we have assumed that there is a net benefit to the practice of bridging. However, the accumulating evidence would support the approach of assuming a net harm until a benefit is shown.

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References
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