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A Bridge Too Far? Findings of Bridging Anticoagulation Use and Outcomes in the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF)

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In the current issue of *Circulation,* Steinberg et al. describe use and outcomes associated with bridging anticoagulation (AC) in patients with atrial fibrillation (AF) in the contemporary Outcomes Registry for Better Informed Treatment of AF (ORBIT-AF)[1]. Chronic oral anticoagulation (OAC) significantly reduces the risk of stroke or thromboembolism in patients with atrial fibrillation (AF). Despite the growing population burden of AF[2], increasing use of OAC, and frequent need for cardiac and non-cardiac procedures in this population, remarkably little contemporary data exist to help guide the clinician with respect to peri-procedural AC decision-making. Although guidelines exist on the topic, they are based on limited and largely observational data[3,4]. Current guideline-supported peri-procedural AC management supports discontinuation of OAC and the use of short-acting AC, most commonly low-molecular weight heparin or unfractionated heparin, to 'bridge' AF patients at high risk for thromboembolic complications during the immediate pre- and post-procedure period (ACCP Grade 2C; AHA Grade 1C)[3,4].

"To bridge or not to bridge," is a question often asked in clinical practice, with an estimated 250,000 patients on OAC undergoing cardiac and non-cardiac procedures annually in North America[3]. The authors are therefore to be congratulated for examining the topic of use and outcomes of bridging AC in an effort to better inform us and enhance the safety of our AF patients. Currently, the peri-procedural management of patients who are receiving OAC is

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often informed by a clinician's (i) assessment of patient risk for thromboembolism, (ii) assessment of risk for peri-operative bleeding, and the (iii) type of procedure. Although CHADS2, CHA2DS2-VASc, HAS-BLED, and ATRIA scores are used in clinical practice to assess the risks of thromboembolism and bleeding, respectively[5], there are no validated risk stratification schemes specific to peri-procedural AC decision-making. Hence, management of peri-procedural AC among AF patients varies widely, as is evidenced by the findings of the present investigation[3]. Further complicating the situation is the fact that timing of OAC discontinuation, timing of resumption of OAC, and differences in type of short-acting AC agent used for bridging are areas where considerable uncertainty and practice variation remains.

Recent data, including from clinical trials of AF patients undergoing catheter ablation and cardiac device implantation suggest that uninterrupted OAC therapies may be associated with lower likelihood of bleeding than discontinuation of OAC with bridging[6-8]. Consistent with the findings of these smaller studies, a recent meta-analysis including more than 12,000 patients undergoing an elective invasive procedure or surgery in 34 studies (however, only 1 randomized-controlled trial) showed that bridging therapy in patients with AF using OACs increased the risk of bleeding events with a similar risk of thromboembolic events[9]. Nevertheless, few studies have examined current practices in peri-procedural AC management in a large, contemporary cohort of real-world AF patients treated with novel and traditional OAC agents and undergoing a diverse array of cardiovascular and non-cardiovascular procedures. Therefore, the findings of the present analysis, while consistent with prior studies, are of great importance and provide valuable new insights to the field.

Among ORBIT-AF participants, a bridging strategy was employed in 1 out of 4 AF patients who had interruption of OAC for a procedure[1]. Not surprisingly given the fact that clinicians often use stroke risk prediction instruments to guide peri-procedural AC management, bridged AF patients generally had higher average CHADS2 and CHA2DS2-VASc scores or had history of mechanical heart valve replacement. Despite their higher predicted risk for stroke based on AF risk prediction instruments, bridged patients in ORBIT-AF did not have higher risk for thromboembolism over the 30-days following their procedure. This finding suggests that traditional thromboembolic risk prediction scores validated for ambulatory AF populations may not have merit as predictors of short-term peri-procedural stroke/thromboembolism risk.

In contrast to thromboembolic events, bleeding events were much more common among ORBIT-AF participants who were bridged with a short-acting AC than among patients who were not bridged (5.0% vs. 1.3%), even after adjustment for factors affecting risk for bleeding (OR 3.8, $p < 0.0001$). Although one might have expected higher bleeding risks among patients undergoing more invasive surgeries, in a stratified analysis, procedure type did not significantly influence risk for bleeding. It is notable, however, that a significant minority (approximately 1 in 10) of patients in ORBIT-AF were bridged for low-risk procedures (e.g., dental procedures) not recommended for bridging based on current ACCP guidelines[3]. This emphasizes that opportunities exist for improved education around current peri-procedural AC guidelines.

This study by Steinberg et al. is well positioned to examine the safety and efficacy of contemporary peri-operative AC bridging practices and guidelines, but it does have several limitations that warrant consideration when interpreting its findings. Besides the fact that the observational study design precludes causal inference and introduces the possibility that unmeasured confounding may explain the observed differences between study groups, the study does not provide important information about why a decision was made to interrupt AC in some cases and not in others. Although this question was not the primary focus of the present investigation (which focused instead on bridging vs. not among those with interrupted OAC), the question as to whether or not uninterrupted OAC is superior to interrupted OAC without bridging with respect to thromboembolic and bleeding complications in patients undergoing cardiac and non-cardiac procedures remains a critical unanswered question. Many cardiac electrophysiologists have already shifted practice away from OAC interruption for catheter-based procedures, including AF ablation, in light of recent data showing fewer bleeding complications with uninterrupted OAC[6]. Further study in this area is needed.

Another limitation of Steinberg's analysis is that it does not indicate whether or not OAC reversal agents (e.g., vitamin K, fresh frozen plasma) were used for reversal of AC effect, nor do the authors present data on timing of initiation and discontinuation of bridging AC agents, factors known to contribute to peri-procedural bleeding complications[10,11]. Moreover, the absolute number of ORBIT-AF participants with interrupted OAC, when grouped by procedure type, was relatively small (e.g., cardiac surgery, n=109). Therefore the results of secondary analyses showing similar rates of adverse events across all procedure types (e.g., dental procedures and cardiac surgery) should be interpreted with some caution. We do not believe this analysis is adequately powered and suggest that providers should, until data from larger samples are available, continue to utilize the 3-tier risk stratification system proposed by ACCP, which includes procedure type and duration as important contributors to peri-procedural bleeding risk[3,11].

Time to achievement of therapeutic OAC after procedure was significantly shorter among patients bridged with a short-acting AC as compared to those who were not bridged[1]. Whether earlier achievement of a therapeutic INR led to higher risk for bleeding in the bridged group remains unclear, especially since the timing of bridging AC discontinuation is not reported. One can imagine that patients on both bridging agents and therapeutic OAC would be at considerably higher risk than other patient subgroups.

Although this analysis would be of considerable importance, the authors were unable to compare rates of bleeding complications by type of OAC (novel vs. warfarin) based on the limited number of patients treated with dabigatran who had OAC interrupted. In contrast, a recent RE-LY secondary data analysis was able to examine the topic and concluded that dabigatran-treated AF patients had increased risk of major bleeding without any significant difference for the risk of thromboembolism when a bridging strategy was employed as compared to patients who were not bridged[12]. A recent multi-center study of 290 AF patients undergoing catheter ablation showed that peri-procedural dabigatran use without interruption was associated with higher risk of adverse events as compared to uninterrupted warfarin therapy[6]. In light of the increasing number of AF patients treated with novel OACs,

further study is clearly needed to compare risks for bleeding among AF patients treated with novel OAC vs. warfarin who undergo a procedure, further stratified by whether or not a bridging strategy is employed.

In this important study, Steinberg et al.[1] show that: 1) OAC interruption was common (approximately half of AF patients over a 2-year follow-up), 2) a bridging strategy was employed in a significant minority (1 in 4) of ORBIT-AF participants with interrupted OAC, and 3) bridging was associated with higher rates of bleeding and overall adverse event rates. These findings fly somewhat in the face of conventional dogma and may begin a paradigm shift away from the routine use of a bridging strategy for AF patients undergoing procedures.

We agree strongly with Steinberg et al.[1] that the results of randomized studies are needed to build on their foundational work. Randomized studies should not only examine whether or not AC is discontinued and bridging AC employed, but should also examine whether or not outcomes differ by type of short-acting AC (heparin vs. low-molecular weight heparin), type of OAC (novel vs. warfarin), or based on timing of initiation and discontinuation of bridging AC[9]. Fortunately, two large randomized, placebo-controlled trials (Effectiveness of Bridging Anticoagulation for Surgery [BRIDGE][13] and 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])[14] are underway to better inform peri-procedural AC decision-making. For the time being, however, this investigation calls into serious question whether or not, in our efforts to reduce peri-procedural thromboembolic complications from AF, we are in fact exposing patients to increased risk of harm from bleeding. To borrow the words of the British Lieutenant General Frederick Browning before the over-reaching and unsuccessful Allied Market Garden campaign, “I think we may be going a bridge too far.”[15]

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