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COMMENTARY

Bridging Therapy: A Challenging Area in the Management of Patients with Atrial Fibrillation

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As part of the comprehensive approach to the management of atrial fibrillation (AF), improving prevention from stroke and thromboembolism (TE) has a high priority [1]. Whilst it is accepted that chronic prophylaxis is valuable, occasional interruption of oral anticoagulation (until recently, warfarin) necessitates bridging therapy with a parenteral anticoagulant, and this is where uncertainties arise [2, 3].

Bridging therapy is usually used for those patients who undergo the initiation or interruption of vitamin K antagonist (VKA) therapy, or have subtherapeutic international normalized ratio (INR) values. The decision regarding bridging therapy should be based on a careful assessment of the risks for TE and bleeding [4]. However, there are limited data about the use of bridging therapy in patients with AF.

A study published recently by Smoyer-Tomic et al. [5] found that amongst 3037 inpatients with AF for medical (70%) or surgical admissions (30%), there were 1944 (64%) patients who received bridging therapy. Given the exclusion of pulmonary embolism (PE) and cardiac surgery in this observational study, the real rate of bridging therapy could possibly be even higher among inpatients with AF. Although definite reasons for bridging are unknown given the limitations of observational data from an administrative claims dataset, most patients would likely have received bridging therapy along with initiation of warfarin as many had no evidence of warfarin use in the 6-month period before hospitalization. Also, bridged patients were more likely to have co-morbid conditions, including atrial flutter, ischemic stroke/transient ischemic attack (TIA)/cerebrovascular disease, and acute myocardial infarction (AMI). In their study, the AF patients who received bridging therapy had a mean CHA_2SD_2-VASc score of 3.5, consistent with a high risk of TE.

It was notable that length of stay (LOS) was longer for bridged than non-bridged patients. This aspect may reflect the patients' co-morbidities of such 'more complex' patients. Indeed, for the VKA-naïve patient at high risk of thromboembolism undergoing *initiation* of VKA therapy, a 'bridge' anticoagulant should be considered to minimize the delay in achieving therapeutic anticoagulation. The 'bridge' is administered parentally, thereby providing a near-immediate anticoagulant effect.

The bigger challenge for bridging anticoagulant therapy is amongst the chronically anticoagulated patients, who need to temporarily interrupt VKAs because of special situations, e.g. catheter ablation, implantation of a pacemaker or an implantable cardioverter-defibrillator (ICD), percutaneous coronary intervention (PCI), or surgery. The invasive procedure may increase the risk of bleeding, whilst on the other hand interruption of VKAs may confer an increased risk of TE.

Besides the risk for stroke, the risk for major adverse cardiac events and stent thrombosis might also increase [6–8]. Thus, clinicians would need to weigh the risk of TE

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and bleeding in deciding on bridging. Recently, bleeding risk assessment and management in AF has been comprehensively reviewed by a consensus document from the European Heart Rhythm Association and European Society of Cardiology Working Group on Thrombosis [9]. Similarly, the American College of Chest Physicians issued guidelines to address the management of patients who are receiving anticoagulant or antiplatelet therapy and require an elective surgery or procedure. The consensus was that bridging would be needed for those at high risk of thromboembolism, based on clinical criteria including the $CHADS_2$ (Congestive heart failure, Hypertension [BP >140/90 mmHg], Age ≥75 years, Diabetes mellitus, prior Stroke or TIA or thromboembolism) score [10]. However, patients with a $CHADS_2$ score 0–1 are not necessarily low risk, as even amongst a cohort of patients with a $CHADS_2$ score of 0, the rate of thromboembolism can vary between 0.8%/year (CHA_2DS_2-VASc = 0) and 3.2%/year (CHA_2DS_2-VASc = 3); indeed, use of the CHA_2DS_2-VASc score would significantly improve risk stratification of AF patients at low and intermediate risk of stroke based on the commonly used $CHADS_2$ score (score 0–1) [11].

Many patients undergoing catheter ablation do not need to interrupt oral anticoagulation if the INR is within the therapeutic range [12]. Interruption of anticoagulation preoperatively with heparin bridging in patients with ICD (or other devices) should be considered only if patients are at high risk of TE [12]. With respect to PCI, an uninterrupted strategy can be followed for patients at moderate high or very high risk of TE [6–8]. When interruption of OAC is longer than 48 hours in high-risk patients for PCI, unfractionated heparin (UFH) may be administered as a bridging anticoagulant [6–8]. In the patients requiring VKA interruption before surgery, VKA should be stopped 5 days before surgery, and bridging anticoagulation should be administered in patients at high risk of TE [11].

Nonetheless, for the patients sustaining a major bleeding event (such as intracranial hemorrhage [ICH]) secondary to anticoagulant therapy, when and how to continue anticoagulation is still a major problem, especially if the patient is at very high risk. Bridging therapy with heparin in low doses 24–72 hours after ICH for the first few days or a week is advocated to prevent TE among such patients [13].

The parenteral agents used for bridging therapy usually include subcutaneous low-molecular-weight heparin (LMWH) or intravenous UFH. The findings of Smoyer-Tomic et al [5]. also indicated that LMWH (63.1%) was the most commonly used agent, followed by UFH (54.6%), bivalirudin (1.2%), fondaparinux (0.8%), and argatroban (0.1%). LMWH may achieve a therapeutic level of anticoagulation more rapidly and consistently than UFH [14]. Bivalirudin could inhibit thrombin-induced platelet adhesion and aggregation to a similar extent to heparin, but perhaps with less risk for major bleeding [14–16].

However, bridging-dose regimens (e.g. LMWH or UFH), and whether to use a high-dose (therapeutic-dose), low-dose (prophylactic-dose), or intermediate-dose regimen, still remains controversial [10]. Moreover, new oral anticoagulants, with a fast onset of action and a predictable anticoagulant effect [17–19], provide promising alternatives for the VKAs, especially in patients with new-onset AF and warfarin initiation. Indeed, dabigatran achieves full anticoagulant activity 2 hours post-dose, and is most likely to reduce the time to achieve therapeutic anticoagulation for the patient undergoing initiation of VKA therapy. Dabigatran has been reported to be as effective as UFH and LMWH in preventing thrombus formation on mechanical heart valves in an *in vitro* investigation [20]. Until more clinical data are available, it is still advisable for dabigatran to be interrupted with bridging anticoagulation before using invasive procedures (e.g. PCI) [21, 22]. More data on other new anticoagulants, i.e. the oral factor Xa inhibitors (rivaroxaban, apixaban), are necessary to identify the optimal approach for managing patients receiving bridging therapy [23].

Just as Smoyer-Tomic et al [5]. note in their limitations, their study fails to ascertain the reason for bridging therapy and longer LOS amongst bridging than amongst non-bridging patients. Indeed, differences in efficacy or safety comparing different bridging anticoagulants and different doses used were not investigated, and more research will be needed for a greater comprehension.

In summary, to bridge or not to bridge? If the answer is 'yes', how should this be done? With the VKAs, we presumed we had some answers, but nowadays, with the new oral anticoagulants, more data are clearly required. We should be aware that classifying patients with AF as 'low risk' (and, thus, not needing bridging therapy) on the basis of a $CHADS_2$ score of 0–1 can be misleading, given the potential for a high risk of TE [11]. Things can only improve.

Conflicts of interest GYHL 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. SA and YG have no conflicts of interest to declare that might be relevant to the content of this manuscript.

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