Editorial

Paradigm shift in anticoagulation therapy, fueling the pump and preventing rhythm crisis

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Synchronism in paddling both sides is prerequisite to winning a Dragon boat race.

——Anonymous

The outcome of the study by Gibson *et al*. [2016] (1) entitled "Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI" suggests titrating either low-dose rivaroxaban plus P2Y12 inhibitor or very low-dose rivaroxaban plus dual antiplatelet therapy (DAPT) "blood thinning" regimen may result in bleeding reduction among individuals with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) and coronary artery stenting (CAST) compared with the standard regimen. Accomplishing an optimal anticoagulation therapy (ACT) in AF patients who have received stents requires meticulous planning and careful calculation of accurate titer values of the anticoagulant components. These, combined with factoring in individual patient's physiological peculiarities, should create a therapeutic window wide enough to cover the risks of stent thrombosis and ischemic stroke without bleeding mishaps. The use of ACT in balancing hemorrhagic and thromboembolic factors in the management of patients with the coexistence of AF and CAST has been a hot clinical topic, and this publication presents a step towards solving the puzzle.

Traditionally, AF patients who have undergone CAST are managed with triple anticoagulation therapy (TRACT). TRACT was created from the combination of the anticoagulation agents from the DAPT with a P2Y12 inhibitor plus aspirin and oral anticoagulation with warfarin a vitamin K antagonist (VKA). The rationale for the TRACT is based on the fact that these agents have their specialized advantages in reducing risks of thrombosis in patients undergoing placement of a first-generation drug eluting stent (DES) and ischemic stroke in patients with AF (2,3). Studies also reported exponential increase of risks of intracranial hemorrhage (ICH) with the VKA based TRACT within the first year of initiation (4). Indirect and multiple inhibition of factors (II, VII, IX, X, proteins S and C etc.) of the coagulation cascade partly explain the clinical hemorrhagic events and influence dose response of VKA mediated therapy. Monitoring patients on warfarin based ACT using the international normalized ratio (INR) for prothrombin time (PTT) not only adds to cost of treatment, but also affects patient compliance to treatment. Therefore, finding an alternative that achieves satisfactory hemostatic results with comparatively lower risks of bleeding, most importantly ICH, is essential.

In Gibson *et al*. [2016], the researchers randomized 2124 non-valvular AF patients who had undergone CAST to receive, in a 1:1:1 ratio, low-dose rivaroxaban (15 mg once daily) plus a P2Y12 inhibitor for 12 months (group 1), very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT for 1, 6, or 12 months (group 2), or standard therapy with a dose adjusted VKA (once daily) plus DAPT for 1, 6, or 12 months (group 3). Note that the course and the P2Y12

inhibitor (clopidogrel, prasugrel, or ticagrelor) type were the basis of the stratification. Following a baseline INR of 2.5 or lower, participants were randomized within 72 hours after sheath removal. At the end of the 12-month follow-up, primary safety end point (clinically significant bleeding or bleeding requiring medical attention, which was explained to be bleeding observed anytime between the first administration of a trial drug to 2 days after the trial drugs were discontinued, through 12 months of therapy) favored the two groups receiving rivaroxaban compared to the group receiving standard therapy (DAPT plus VKA) with lower rates of clinically significant bleeding registered using Kaplan-Meier estimates (16.8%, 18.0% and 26.7% of the participants in groups 1, 2, and 3 respectively). Between group hazard ratios were: [group 1 *vs.* group 3, 0.59, 95% confidence interval (CI): 0.47 to 0.76, P<0.001; group 2 *vs.* group 3, 0.63, 95% CI: 0.50 to 0.80; P<0.001]. There was however, no statistical significance in terms of mortality rate from cardiovascular causes, myocardial infarction, or stroke between the three groups. For the efficacy end point, a major adverse cardiovascular event (a composite of death from cardiovascular causes, myocardial infarction, or stroke) in groups 1, 2, and 3 was 6.5%, 5.6% and 6.0% respectively (P>0.05). There was no significant difference among the three treatment groups rates for each component of the end point. There were also low and similar rates of stent thrombosis among the three groups.

Rivaroxaban yielded lower risks of stroke and systemic embolism, significantly lower rates of ICH and fatal bleeding when applied in patients with non-valvular AF a result which was non-inferior to the standard (5). Rivaroxaban significantly reduced the risk of death from cardiovascular causes, myocardial infarction, and stroke when administered to subjects in the ATLAS ACS 2–TIMI 51 trial for secondary prevention after acute coronary syndrome (6). The low-dose rivaroxaban (15 mg once daily) plus a single P2Y12 inhibitor and very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT, and standard triple therapy with a VKA plus DAPT used in this current study were derived from the WOEST and the ATLAS ACS 2-TIMI 51 respectively.

Practical advantages of rivaroxaban over the warfarin based regimen include eliminating the need for periodic INR monitoring, it has until now not been demonstrated to be affected by behavioral factors (diet, alcohol intake, body mass, etc.), as well as it being non-teratogenic. The selective and specific inhibition of only factor Xa by rivaroxaban could also explain its advantages over warfarin in reducing bleeding of clinical significance in this group of patients.

Before the results of this study can be universally applied, there are some factors that should be further investigated. First of all, the test subjects in some of the sub-groups were predominantly male and Caucasian (more than 60% and 90% in all the groups), so further investigation will be required to ensure suitable dose adjustment in other ethnic and demographic groups. Secondly, availability is an important factor to be considered in determining how much impact a therapeutic regimen can make. Unfortunately, the very-low-dose rivaroxaban (2.5 mg twice daily) plus DAPT is predominantly used only in some European countries for the prevention of cardiovascular events in patients with an acute coronary syndrome. Moreover, the 15 mg once daily (or 10 mg once daily in those with moderate renal impairment) is not currently approved for the management of acute coronary syndrome or AF. Rivaroxaban is also associated with some degree of bleeding, especially when used concomitantly with DAPT in the management of the coexistence of AF and CAST. Also, a rivaroxaban antidote, for the management of bleeding, other than drug withdrawal is an important element missing for the regimen to be more successful. ACT in patients with permanent AF (failure to retain sinus rhythm after repeated radiofrequency catheter ablation) is lifelong and therefore cost is an important question.

Clinician experience, and the application of tools (CHA2DS2-VASc, HAS-BLED, GRACE, TIMI scores etc.) for the estimation of pre-therapeutic thromboembolic and hemorrhagic events in both CAD-CAST and in AF may contribute tangible values in reducing significant bleeding in these patients. Assessing adherence to the use of these NOACs agents will help direct the management of any reported event(s) of bleeding, periodic review of evidence of bleeding and symptoms of thromboembolic events, checking for prescriptions that may interact with the regimen (7).

In administering anticoagulating agents, it is prudent to employ periodic follow ups and bleeding assessments, making patient-health professional team building and cooperation a priority, and patient education and re-education to reduce the occurrence of hemorrhagic and thromboembolic events. The dose adjustments of rivaroxaban and the careful combination of the anticoagulation agents involved in this trial speak volumes of the challenges encountered in clinical practice when safety and efficacy is to be achieved. Achieving perfect efficacy and safety with a therapeutic regimen without the occurrence of adverse events is the goal, though it is probably only theoretically possible. It is also undeniable fact that

being clinicians in this information age of large data clinical trials and randomized clinical trials (RCTs) (8) piling up therapeutic merits and superiorities of various combinations of pharmaceutical products, we run the risk of being "dampened" with countless alternatives of achieving efficacy in the ACT. It is too early to say how much the outcome of this study will affect the treatment guidelines, and whether or not aspirin will be removed from the titration equation in the management of patients with AF and baseline CAD.

Gibson *et al.*'s publication may shift the paradigm of the drug administration for patients with AF undergoing CAST depending on the outcomes of follow-up studies, but for now, there is more to be learned before anything definitive can be gleamed.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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