

**TRIPLE THERAPY - WALKING ON A TIGHT ROPE!**Mohammad Hafizullah<sup>1</sup>, Wahaj Aman<sup>2</sup>

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Managing patients with atrial fibrillation (AF) requiring percutaneous intervention or those on anticoagulant therapy needing an intervention is an act of great balancing like walking on a tight rope. The premise revolves around three basic considerations - the risk of embolism and stroke due to AF, the possibility of thrombosis due to underlying coronary obstructive disease and interventions and more importantly the hazard of bleeding in combining different therapeutic agents.

AF is the commonest arrhythmia recorded in 1-2% of population and the prevalence increases with advancing age.<sup>1,2</sup> Oral anticoagulants are the mainstay of treatment in patients with higher risk of cardio-embolism and have been shown to reduce the occurrence of stroke/TIA.<sup>3,4</sup> The prevalence of coronary artery disease is on the rise in developing countries, it increases with age and coexists in one third of patients with AF.<sup>5,6</sup> In patients being subjected to percutaneous coronary intervention (PCI), who should be treated with dual antiplatelet therapy (DAPT) as per current guidelines, roughly 6% may be on oral anticoagulants therapy either for AF or some other indication.<sup>7-9</sup> This special group of patients requiring triple therapy may increase in the times to come as longevity increases in developing and developed nations.<sup>10,11</sup>

ACC/AHA guidelines of 2016 recommend at least 12 months of DAPT duration in patients with acute coronary syndrome (ACS) with Aspirin and P2Y12 inhibitors like clopidogrel, prasugrel or ticagrelor irrespective of type of stent as class 1 indication. In patients with stable CAD DAPT with clopidogrel is recommended for at least one month in case of bare metal stent (BMS) and six months for drug eluting stent (DES) implantation as class 1 indication. Prolongation of DAPT after 1 year is considered as class II b indication.<sup>12</sup> Earlier, Canadian Cardiovascular Society (CCS) Antiplatelet guidelines offered similar recommendations in patients with ACS and stable CAD.<sup>13</sup> However both guidelines take cognizance of patients with enhanced ischaemic or bleeding risk and allowance is made to either prolong or shorten the duration of DAPT and switching from DAPT to SAPT as deemed appropriate.

Bleeding remains the biggest threat in such a cohort of patients. Contrary to the previous understanding and belief, major bleeding besides being an ominous risk has been incriminated to be responsible for increase in adverse cardiovascular outcomes like stroke, MI and cardiovascular death by 2-10 folds.<sup>14,15</sup> Major bleeding rates have been recorded 5-15% in different studies depending on the

demographics of patient, choice of anticoagulant and antithrombotic agents.<sup>16-20</sup> The risk of bleeding is directly related to the intensity of antithrombotic regimen. Patients treated with single antiplatelet regimen - aspirin versus clopidogrel have similar risks of bleeding.<sup>21</sup> However more potent P2Y12 antagonists like prasugrel, ticagrelor are reported to have higher risk of bleeding.<sup>22,23</sup> Newer oral anticoagulants like dabigatran, rivoraxaban and apixaban have lower risk of bleeding as compared to traditional warfarin.<sup>24-26</sup> DAPT offers higher risk of bleeding as against SAPT and combination of DAPT with oral anticoagulant further enhances the risk of bleeding.<sup>27,28</sup>

Risk of thromboembolic stroke is determined by a host of factors. CHA<sub>2</sub>DS<sub>2</sub>VASC score is well-validated risk score based on age, gender and comorbidities. It identifies patients at higher risk of thromboembolism who require anticoagulants to prevent stroke.<sup>29,30</sup> HASBLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile international normalized ratio [INR], elderly [ $>65$  years], drugs/alcohol concomitantly) has been recommended as a bleeding risk score for patients with AF, with scores  $\geq 3$  considered high risk.<sup>31,32</sup> Both scores have to be used with a grain of common sense and considering patient as a whole, though the HAS-BLED score has been credited to predict bleeding significantly; the discriminating value is overall limited and similar to CHA<sub>2</sub>DS<sub>2</sub>VASC score.<sup>33,34</sup>

What is the recent evidence in this perspective? To date, only 2 randomized clinical trials have been completed. WOEST study (What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting) compared OAC (warfarin) with single antiplatelet therapy (SAPT -clopidogrel) versus OAC and DAPT (aspirin and clopidogrel) among patients undergoing stent implantation. A total of 573 patients were randomized and followed for 1 year. All patients received aspirin during hospitalization. The warfarin-clopidogrel arm was associated with less total bleeding without statistically significant differences in major bleeds. The number of ischemic events including MI, stent thrombosis, stroke, or target vessel revascularization did not differ significantly, although it was numerically less in the warfarin plus clopidogrel only arm. Although the study was underpowered for this end point but it reported a reduction in mortality, which needs to be interpreted with caution. The limitations of the WOEST trial is that these results cannot be applied to patients at higher ischemic/thrombotic risk, such as patients with ACS or highly complex coronary anatomy.<sup>35</sup>

ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug-Eluting Stent Implantation) explored the question about triple therapy duration in patients undergoing DES implantation. A total of 614 patients, two-thirds with stable CAD, were randomized to 6 weeks or 6 months of clopidogrel in addition to aspirin and warfarin to assess the composite of definite stent thrombosis, MI, death, stroke, or TIMI major bleeding at 9 months. The primary endpoint was same in two arms of 6-week versus the 6-month triple therapy (9.8% versus 8.8%; 95% confidence interval 0.68-1.91;  $P=0.63$ ). No significant differences in ischemic or bleeding end points were observed between the 2 durations. Total bleeding and Bleeding Academic Research Consortium (BARC)  $\geq 2$  bleeding tended to be higher in the group receiving longer-duration clopidogrel. Although this represents the only randomized trial of duration of triple therapy in PCI, the small sample size and the limited number of ACS patients should be taken into consideration.<sup>36</sup>

What should be the clinical approach in handling this special group of patients? Recently published expert consensus panel makes following recommendations broadly divided as before procedure, intra-procedure and post procedure.<sup>37</sup> Before the procedure, 'appropriate criteria' should be applied rigorously considering chronology of symptoms, severity of symptoms, stability of disease ACS vs SCAD, extent of disease, and therapeutic regimen as to the number of anti-anginal agents.<sup>38</sup> Risk stratification based on thrombotic risk and bleeding as determined by CHA<sub>2</sub>DS<sub>2</sub>VASC and HAS-BLED scores may be meticulously calculated for decision-making. During the procedure radial approach may be preferred to femoral access.<sup>39</sup> Usually patients with AF have more complex coronary artery disease and BMS should only be considered for simple short length and large lumen lesions. Newer generation of DES may be preferred in such challenging patients, which have better safety profile regarding stent thrombosis.<sup>40,41</sup>

A brief period of washout from the anticoagulant effect of OAC is preferable whenever possible in elective and non-emergent procedures. In patients on Vit K antagonists, those being subjected to radial approach, INR should be preferably  $\leq 2.0$  and if femoral approach is used INR has to be  $\leq 1.5$ . In patients on NOAC, irrespective of vascular access site, treatment may be withheld for 24 hours (or 48 hours for patients with impaired renal function with dabigatran). Although in stable CAD patients bridging with parenteral anticoagulation can be omitted yet this should be considered for patients presenting with an ACS.<sup>38</sup>

Post procedure, the choice of oral anticoagulant may be VKA or NOAC and this is at the discretion of the treating physician, with patients informed on the risk-benefit profiles of both agents. Continuing with the same OAC after PCI may be reasonable, more so if the patient has been compliant and has not experienced any complications. If a VKA is chosen, INR should be in the 2.0-3.0 range. A NOAC at the lowest therapeutic dose effective for stroke prevention should be preferred over a VKA in patients unable to have their INR routinely monitored or are unable to maintain INR in the therapeutic range.

The expert consensus recommended that the duration of DAPT in AF patients treated with stents and on OAC should not extend to a full 12 months. The cardiologist may consider SAPT starting within the first 6-months post-stenting depending on the ischemic/thrombotic and bleeding risk profile. In the scenario of newer generation stents with lower stent thrombosis, recent guidelines provide an opportunity to shorten DAPT with higher bleeding risk and discontinuation of DAPT may be reasonable in patients with stable CAD after three months and inpatients with ACS after six months.<sup>12</sup>

Clopidogrel may be preferred in such patients over prasugrel or ticagrelor. DAPT duration may be minimized with early start of SAPT. Aspirin as against a P2Y12 receptor inhibitor may be dropped in SAPT, choosing clopidogrel over aspirin because of the essential role of P2Y12 mediated signaling in thrombotic and inflammatory processes and established clinical efficacy of P2Y12 inhibitors to reduce stent thrombosis. Although bleeding risk with OAC plus clopidogrel is higher than OAC plus aspirin, the combination of OAC plus clopidogrel is comparable to triple therapy in respect to the prevention of ischemic stroke, with a trend towards benefit of MI/coronary death. Moreover, the risk of all-cause mortality is similar between OAC plus clopidogrel and triple therapy but markedly increased for OAC plus aspirin.<sup>38,42,43</sup>

To conclude, treating patients with triple therapy in the setting of AF and PCI is like walking on a tight rope. Three important considerations for all decisions making are risk of thrombo-embolism and stroke, risk for thrombotic complications and risk of bleeding. Meticulous management is recommended pre, intra and post procedure. This entails selecting patients using appropriate criteria, employing radial approach, using latest generation DES, starting triple therapy and then changing over to SAPT earlier or later balancing thrombotic versus bleeding risks.

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