CHAPTER

198 Combined Oral Anticoagulation and Antiplatelet Therapy - Management of a Difficult Situation

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The combination of atrial fibrillation (AF) and coronary artery disease (CAD), is not only an uncommon clinical setting, but also a complex setting associated with significantly higher mortality rates[1] that requires doctors to deal with using a combination of anticoagulation (OAC) and antiplatelet therapy. The benefit of the combination has to be balanced with the increased bleeding risk.

A common clinical dilemma regarding treatment of patients with AF is the need to use concomitant antiplatelet agents for a variety of reasons including, primary prevention of CAD, or for secondary prevention after a diagnosis of coronary disease, or for maintenance therapy after percutaneous coronary intervention (PCI). In some of these situations, dual antiplatelet therapy may be utilized, for example after an acute myocardial infarction or after PCI. While the combination of OAC and antiplatelet therapy carry the potential of additive benefits, they also carry the danger of increased risk of bleeding.[2]

Fortunately, we have subgroup data available from the various novel oral anticoagulant (NOAC) trials looking at concomitant antiplatelet use with NOACs. In ARISTOTLE trial, concomitant aspirin was used in around 20–25% of patients with AF treated with an anticoagulant and was associated with a higher risk of bleeding. Similar effects of apixaban, compared with warfarin, on stroke or systemic embolism, major bleeding, or mortality were observed irrespective of concomitant aspirin use. Clopidogrel use was an exclusion criterion at randomization and only started in a small proportion of patients included in the ARISTOTLE trial thus limiting ability to assess the outcomes associated with concomitant apixaban or warfarin and either clopidogrel or dual antiplatelet therapy.[3]

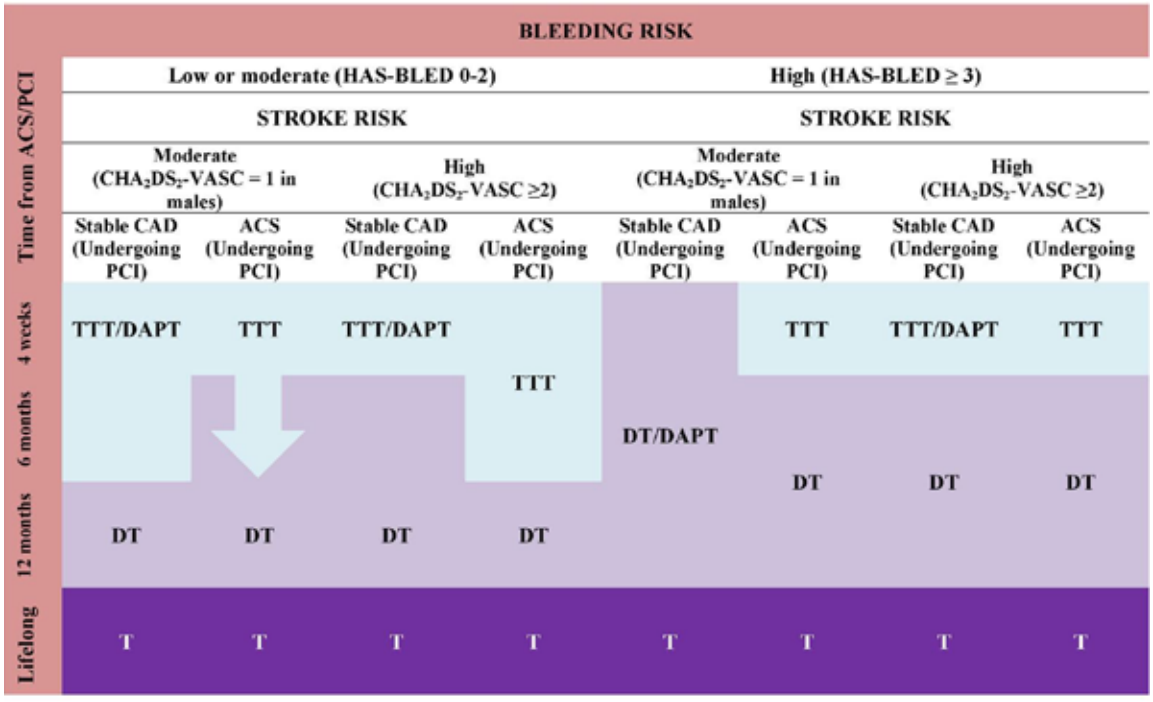
In RE-LY trial, concomitant antiplatelet use led to a significant rise in the overall risk of major bleeding when dabigatran was combined with any OAC. The risk appeared to increase by 50% with a single antiplatelet, and doubled when dual antiplatelet was used at any time. The relative increase in risk was similar with dabigatran 110mg, 150mg or warfarin.[2]

In ENGAGE AF-TIMI 48 trial, the addition of a single antiplatelet drug to an anticoagulant (warfarin or edoxaban) was associated with a significantly greater risk of bleeding. However, the addition of a single drug did not modify the relative efficacy and safety of edoxaban as compared to warfarin. Notably, when compared to warfarin, both edoxaban regimens resulted in a significant reduction in all forms of bleeding, including intracranial hemorrhage and life-threatening bleeding, both in patients who were as well as those who were not, receiving a single antiplatelet therapy.[4]

There is no randomized study comparing vitamin K antagonist (VKA) and NOACs in patients with AF undergoing PCI for acute coronary syndromes (ACS) or for stable CAD, i.e. patients who have an indication to receive single or DAPT.[1] There are no large-scale randomized studies published evaluating the newer antiplatelet agents in patients with AF receiving either VKAs or NOACs, adding to the uncertainty on how to use these antithrombotic agents in combination when both CAD (ACS or stable disease) and AF converge in a given patient.[1]

There are currently three ongoing large-scale outcome studies evaluating combinations of NOAC or VKA and antiplatelets in patients with AF that undergo a PCI with stenting (elective or due to an ACS), providing hope that within the next few years there will be more evidence in this field.

1. The PIONEER AF PCI study (NCT01830543) evaluates the safety of two different rivaroxaban treatment strategies vs. VKA: (i) 15 mg rivaroxaban OD plus clopidogrel; (ii) 2.5 mg BID plus low-dose aspirin 75–100 mg plus clopidogrel, prasugrel or ticagrelor, followed by rivaroxaban 15 mg OD (or 10 mg for subjects with moderate renal impairment) plus aspirin for 12 months; or (iii) VKA treatment strategy utilizing similar combinations of antiplatelet therapy.
2. The RE-DUAL PCI study (NCT02164864) evaluates dual antithrombotic therapy regimens of (i) 110 mg dabigatran BID plus clopidogrel or ticagrelor, or (ii) 150 mg dabigatran BID plus clopidogrel or ticagrelor, with (iii) a triple antithrombotic therapy combination of warfarin plus clopidogrel or ticagrelor plus low-dose aspirin for 1–3 months.
3. The AUGUSTUS trial (NCT02415400), apixaban will be evaluated vs. VKA in AF patients with a recent ACS. All patients will be receiving a P2Y12 inhibitor and will be randomized in a 2 × 2 factorial design to 6 months of apixaban 5 mg BID vs. VKA, and aspirin vs. placebo.



TTT- triple therapy of OAC + aspirin 75–100 mg/day + clopidogrel 75 mg/day
DT- OAC and clopidogrel 75 mg/day (or alternatively, aspirin 75–100 mg/day)
T- Monotherapy with oral anticoagulants
DAPT - Dual antiplatelet therapy consisting of aspirin 75 mg/day and clopidogrel 75 mg/day

Fig. 1: Management of acute coronary syndrome in atrial fibrillation (Dalal et al IHJ; 67, 2015, s13-34)

The optimal combination, or duration of combination antithrombotic therapy for AF patients undergoing percutaneous coronary intervention is not known, but the increased bleeding risk suggests all efforts must be made to keep the duration short. Expert consensus, reviewed and reconsidered by the ESC 2016 Guidelines Task Force, suggests the following principles:[5]

AF patients at risk for stroke, patients with mechanical valves, and patients with recent or recurrent deep vein thrombosis or pulmonary embolism should continue OAC during and after stenting. In general, a short period of triple therapy (OAC, aspirin and clopidogrel) for six weeks to three months only is recommended, especially for those with less thrombotic and high bleeding risk, followed by a period of dual therapy (OAC plus a single antiplatelet) upto one year. For those with less bleeding and high thrombotic profile, triple therapy may be continued for six months and changed to single antiplatelet pus OAC for one year. At the end of one year, antiplatelet therapy may be stopped and only OAC continued. A review of the combination therapy of AF and ACS is shown in Figure 1.[7] There is data to show that VKA plus clopidogrel is preferred to VKA plus aspirin to reduce bleeding complications,[6] however no data is available whether aspirin or clopidogrel combination is better with NOACs. Newer antiplatelet agents such as prasugrel and ticagrelor are presently not recommended with NOACS or VKAs. When a NOAC is used, the consensus recommendation is that the lowest dose effective for stroke prevention in AF should be considered. Dose reduction beyond the approved dosing tested in phase III trials is not currently recommended, and awaits assessment in ongoing controlled trials.

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