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Anticoagulant Therapy in Patients with Atrial Fibrillation and Coronary Artery Disease

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1. Introduction

Atherosclerotic cardiovascular disease and atrial fibrillation (AF) are causes of increased mortality and morbidity all over the world. Coexistence of both leads to even higher rates of mortality and morbidity. In AF, the main reason responsible for increased mortality and morbidity is thromboembolisation and consequently the development of a stroke [1]. Among patients with atrial fibrillation, the incidence of atherosclerotic cardiovascular disease has been reported to be 20-30% [2]. Thus, development of an acute coronary syndrome (ACS) requiring percutaneous coronary intervention is very probable in patients with atrial fibrillation. Despite a 17% reduction in the incidence of stroke with aspirin compared to placebo, vitamin K antagonist (VKA) warfarin is superior to both aspirin and aspirin plus clopidogrel combinations due to its preventing AF patients from thromboemboli [3]. While triple antithrombotic therapy (VKA+aspirin+clopidogrel) lowers the risk of stroke in stent implanted patients with AF, it increases the risk of bleeding at long- term. Thus careful judgement of the risk of emboli and bleeding, the stent type (drug eluted or bare metal) to be implanted and the duration of appropriate treatment regimen is important.

2. The evaluation of embolic risk

In patients with atrial fibrillation the main goal of antithrombotic therapy is to prevent stroke. In patients with non-valvular AF, the atherosclerotic cardiovascular disease (especially a history of myocardial infarction) has been found to be associated with an increased incidence of stroke. Other important risks factors are diabetes, hypertension, previous stroke/ transient ischemic attack and age. In patients with non valvular AF $CHADS_2DS_2$-

Vasc-Score [6] derived from a European Heart Survey were found to be beneficial for estimation of the risk of stroke. This scoring system is suggested for risk stratification in both the European Society of Cardiology (ESC) [7] and the American College of Cardiology/ American Heart Association (ACC/AHA) [8] guidelines. (Table1). According to this scoring system, the patients are stratified into three risk groups as low (0), medium (1 – 2) and high (>2). While the risk of emboli is 1.3 % at score 1, the risk increases to 15.2 % at score 9. While previous embolism/TIA/stroke and age ≥75 are the major risk factors, the other clinical situations are classified as the non-major risk factors. Not only previous myocardial infarction but also complex atheroma plaques and peripheral vascular disease have also been included in the definition of vascular disease.

Letter	Clinical Condition and age	Points
C	Congestive heart failure†	1
H	Hypertension	1
A	Age≥75 years	2
D	Diabetes mellitus	1
S	Stroke/TIA/Thromboembolism	2
V	Vascular disease*	1
A	Age 65 – 74	1
S	Female sex	1
		max. 9 points

†Heart failure or moderate to severe left ventricular systolic dysfunction (e.g. LV EF < 40%)

*Prior myocardial infarction, peripheral artery disease, aortic plaque. TIA =transient ischaemic attack.

Table 1. CHA$_2$DS$_2$-Vasc-Score for determining embolic risk

3. Bleeding risk evaluation

In choosing the antithrombotic therapy regime, both the risk of bleeding and the evaluation of thromboembolic risk are important. The use of VKA causes a more meaningful decrease in embolic risk compared to aspirin alone or DAPT (dual antiplatelet therapy) in patients with a medium and high risk. However the use of VKA increases the risk of major bleeding especially when used with DAPT. Therefore, determining the risk of bleeding is important before starting the therapy. Although various risk scores evaluating the risk of bleeding have been obtained, they were all developed to estimate the risk of major bleeding and they can be classified into three groups as low, medium and advanced. ESC guidelines recommend using HAS-BLED scoring [Table 2] (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly (>65), drugs/alcohol concomi-

tantly) in the estimation of bleeding risk [9]. HAS-BLED≥3 was found to be related to high risk of bleeding. However, parameters such as a history of stroke, old age, and hypertension also affect the risk of emboli estimated by using the CHA₂DS₂-Vasc-Score,. Thus, patients with a high bleeding risk must be carefully managed.

Letter	Clinical characteristic*	Point
H	Hypertension	1
A	Abnormal renal or liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding history	1
L	Labile INR	1
E	Elderly ("/>65 years)	1
D	Drugs or alcohol comsumption (1 point each)	1 or 2
		Max 9 poits

*Hypertension' is defined as systolic blood pressure >160 mmHg. 'Abnormal kidney function' is defined as the presence of chronic dialysis or renal transplantation or serum creatinine ≥200 mmol/L. 'Abnormal liver function' is defined as chronic hepatic disease (e.g. cirrhosis) or biochemical evidence of significant hepatic derangement (e.g. bilirubin >2 x upper limit of normal, in association with aspartate aminotransferase/alanine aminotransferase/alkaline phosphatase >3 x upper limit normal, etc.). 'Bleeding' refers to previous bleeding history and/or predisposition to bleeding, e.g. bleeding diathesis, anaemia, etc. 'Labile INRs' refers to unstable/high INRs or poor time in therapeutic range (e.g., 60%). Drugs/alcohol use refers to concomitant use of drugs, such as antiplatelet agents, non-steroidal anti-inflammatory drugs, or alcohol abuse, etc. INR = international normalized ratio. Adapted from Pisters et al (9).

Table 2. HAS-BLED bleeding score

4. Choosing antithrombotic therapy

In coronary artery disease, DAPT has been found superior to aspirin plus oral anticoagulant (OAC) therapy in preventing recurrent ischemic events [10]. Although, in a long term period, OAC therapy has been found superior to DAPT in AF patients, this therapy, especially in situations when it must be combined with DAPT, has a major bleeding incidence of up to 4.7 %. This bleeding usually happens within the first month and has been fatal in almost half of the patients [11]. Therefore, the management of patients with nonvalvular AF who require PCI (percutaneous coronary intervention) is very important for many clinicians.

Nowadays, therapy guidelines include a therapy of low aspirin dose or no therapy for low risk patients, OAC or aspirin for medium risk patients, and a therapy of OAC in patients with a high risk. In medium risk patients, DAPT has been found inequivalent to VKA in studies conducted on DAPT therapy (aspirin+ clopidogrel). VKA is related to lower bleeding and stroke. Therefore, in medium and high thromboli risk patients, if the risk of hemor-

rhage is high, because of the high incidence of intracranial and extra cranial bleeding incidence, the option of DAPT should not be preferred.

In the abovementioned patients the low dose dabigatran option must be considered and if they are treated with VKA, a lower INR (1.8-2.5) target should be chosen. However according to the studies made, patients with an INR <2 have double the risk of stroke compared to patients whose INR is > 2.

5. Choosing therapy following elective percutaneous coronary intervention

In elective percutaneous coronary interventions (PCI), if there is no obligatory indication (long lesion, small vessel, diabetes, etc.) the intervention must be limited to a bare metal stent (BMS). Because after the implantation of a drug eluting stent (DES), there is a requirement for a triple antiplatelet for a longer time (3 months for sirolimus, 6 months for paclitaxel) and this may lead to a higher mortality rate associated with increased bleeding risk. While the post BMS triple anti platelet therapy is limited to a 4 week period, it has to be used longer following DES. In patients with low-medium bleeding risk but low embolic risk, during the first four weeks after BMS, triple anti platelet therapy is suggested. After 4 weeks, lifelong OAC (INR=2-3) should be preferred. As an approach, there is a difference between ESC guidelines and USA clinical practice [12]. In patients with low-medium hemorrhagic risk both the ESC and the USA approaches suggest triple anti platelet therapy for BMS and DES, but in the USA approach, only DAPT is suggested in patients with a high bleeding risk. However, in ESC guidelines, despite the high bleeding risk, during the 2-4 week interval after BMS elective implantation, triple anti platelet therapy is advised.
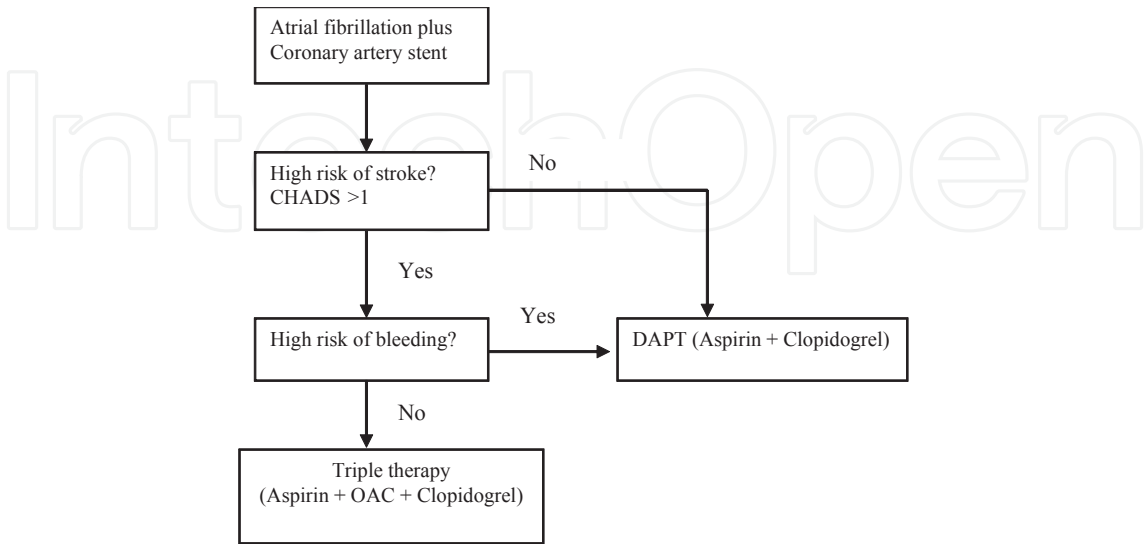

Figure 1. US Approach-Adapted from Paikin et al [12]

As a therapy regime, OAC (INR=2 – 2.5), aspirin daily ≤100 mg and clopidogrel 75 mg daily is included. In patients with a high risk of bleeding, it has been stressed in both guidelines that DES should be avoided and if possible BMS should be implanted. Among patients having a low and medium bleeding risk, for those who have been implanted BMS, 1 month of triple anti platelet therapy is advised. Among those patients who are DES implanted, for the limus group, 3 months of triple antiplatelet therapy is advised while for the paclitaxel group, 6 months of DAPT is advised. Furthermore, in DES implanted patients, a dual therapy of OAC plus aspirin up to 1 year or OAC plus clopidogrel is advised and after 1 year only OAC mono therapy is advised. Therefore, DES implantation should be avoided because it requires long term dual and triple therapy (Table3).

Hemorrhagic risk	Clinic	Stent type	Anticoagulation regime
Low-Medium HAS-BLED (0 – 2)	Elective	BMS	1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day Lifelong: warfarin (INR 2.0–3.0) alone
	Elective	DES	3 (-olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)* Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	DES/BMS	6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day)* Lifelong: warfarin (INR 2.0–3.0) alone
High HAS-BLED (≥3)	Elective	BMS	2–4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	BMS	4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day + clopidogrel 75 mg/day Up to 12 months: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day (or aspirin 100 mg/day); mg/day)* Lifelong: warfarin (INR 2.0–3.0) alone

ACS=Acute coronary syndrome, BMS=Bare metal stent, DES=Drug eluted stent, INR=International normalized ratio

*Combination of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/day may be considered as an alternative.

Drug-eluting stents should be avoided.Adapted from Lip et al

Table 3. ESC suggestions for anticoagulation in patients with coronary stent who have medium and high emboli risk

6. Acute coronary syndrome

In patients with non-valvular AF who have acute coronary syndrome (ACS), the puncture site for PCI is important. In anti- coagulated patients, how the therapy will be conducted in the hospital and choosing the right type of stent bears an importance. As for those patients who are not anti coagulated, the antithrombotic therapy during discharge is important. In anticoagulated patients, femoral intervention is an independent predictor for major hemorrhage and other vascular complications and therefore in those patients radial intervention is preferred because it causes less bleeding and better results [13,14].

In patients with ACS, especially those in whom primary PCI have been applied, BMS should be preferred because it requires a shorter duration triple antithrombotic therapy. OAC should be given to non-STEMI patients when they are hospitalized and DAPT and heparin should be given to those patients who have no therapy. If the thromboembolic risk is too high, OAC therapy might as well be started in those patients during in-hospital period. There are two approaches for patients who receive OAC during hospitalization. The first and mostly used approach in clinical practice is the bridge therapy which involves stopping OAC therapy and starting heparin. The second approach is to continue OAC therapy so that INR will be in the 2-2.5 interval. The main drawback of the bridge therapy is when the therapy is stopped and then restarted, Protein –C and –S are not suppressed, and they increase embolic complications paradoxically in patients with a very high emboli risk [15]. Therefore, in patients with ACS having a very high embolic risk, it is advised that DAPT should be added to the therapy without stopping OAC and without adding heparin (if the INR <2, then heparin may be added) [16,17]. In STEMI patients for whom P-PCI is applied, if the INR is within the interval of 2 – 3, then a similar approach is applicable. However, glycoprotein (GP) IIb/IIIa inhibitors may have to be used due to the high thrombus burden. In those patients with a high thrombus burden, if the INR>2, then GP IIb/IIIa inhibitor must not be started, and, if possible thrombectomy should be considered instead. Alternatively, in patients with INR<2, bivaluridin might be considered for use instead of GP IIb/IIIa inhibitor + heparin. Due to high hemorrhagic risks, in patients using OAC and having optimal INR, additional heparin should not be used. In patients whose bleeding risk is high, triple therapy should not be used for more than 1 month. Due to the need for short triple therapy, BMS should always be preferred. Following ACS, triple therapy should be given for 1 month, dual therapy including OAC should be given up to 12 months, and after 12 months only OAC should be given lifelong. The short and long term antithrombotic therapy regimen of the ACS patients is summarized in table 3.

Advice On Decreasing Hemorrhagic Risk:

1. The balance between hemorrhagic risk and embolic risk should be maintained very well.

2. No therapy may be given to patients who are under 65 years of age having a low embolic risk.

3. In combined therapies, the dose of aspirin should be kept low (75 – 100 mg).

4. In patients having a high bleeding risk hypertension should be treated aggressively.

5. Hepatic and renal functions should be followed closely in patients who take OAC.

6. In case of stent requirement, BMS should be preferred as much as possible.

7. During ACS, additional heparin, GP IIb/IIIa inhibitor or bivaluridin should not be given to those patients who have an effective INR and who take OAC.

8. Radial intervention should be applied to patients who take OAC and who are intervened with STEMI.

9. Triple antiplatelet therapy should not be used for more than 1 month in patients whose bleeding risk is high.

10. DAPT should not be given for a long time, instead only OAC should be given in long term therapy.

11. Proton pump inhibitors may be added to the therapy.

12. In long term therapy, dabigatran 110 mg twice a day or rivaroxaban once a day should be considered for use (compared to VKA lower bleeding incidence, equal stroke rates) in patients whose bleeding risk is high (especially in the presence of INR labile).

7. New anticoagulant drugs

In AF patients, oral anticoagulation is traditionally done with VKA. However, due to personal differences in responses, the need for a balance in dose, labile INR and bleeding risk; studies have been made on new drugs which do not require follow-up. With these new drugs such as direct thrombin inhibitor dabigatran, factor Xa inhibitors apixaban and rivaroxaban, the incidence of major bleeding is significantly lower compared to VKA. When Dabigatran 110 mg twice a day is compared with VKA, nonvalvular AF stroke prevention in the RELY study (Randomized Evaluation of Long-term Anticoagulant Therapy) there is no difference between stroke and systemic embolism, but the rate of major hemorrhage is meaningfully less in 110 mg Dabigatran than it is in VKA [18]. In the dose of 150 mg, the rates of major bleeding and stroke were determined to be similar. In patients with non valvular AF whose INR values were labile, if they cannot be followed closely and if they do not have an advanced hepatic and renal problem, dabigatran is an alternative to warfarin. In non- valvular AF patients, in the ARISTOTLE study done with Apixaban, apixaban is related to lower hemorrhage complication and lower mortality compared to warfarin [19]. In the ROCKET-AF [20] study, while there was no difference between the major hemorrhage rates of patients using rivaroxaban and warfarin, the fatal and intracranial hemorrhage rates were lower in patients using rivaroxaban than in those patients using warfarin. The systemic emboli and stroke prevention rates between the two were equal.

The results of this study are hopeful for long term anticoagulation regimes. There is no sufficient clinical evidence regarding the fact that these drugs are appropriate for a combination

therapy (DAPT plus OAC). However, regarding these three studies (RELY, ROCKET-AF, and ARISTOTLE), when the dual therapy using VKA is compared with dual therapy using new anticoagulant drugs (apixaban, rivaroxaban, dabigatran), there is no additional difference in terms of hemorrhage rate. Thus, when the combination of DAPT with new drugs is compared to the combination of VKA and DAPT, there is no additional increase in hemorrhage. Nevertheless, in the monotherapy with OAC, the risk of hemorrhage is at its lowest. However, regarding the safety of the combined use of the new anticoagulant drugs with dual antiplatelet therapy, there is no sufficient evidence regarding long-term use and there is a need for further studies.

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