MANAGEMENT OF ATRIAL FIBRILLATION IN PATIENTS UNDERGOING PERCUTANEOUS CORONARY INTERVENTION.

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Abstract - Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1-2% of overall population, involving more than 6 millions of European people. It is associated to a reduced quality of life and an increased morbidity and mortality. The Framingham study showed the link between angina and AF. The same risk factors, such as hypertension, diabetes and obesity promote both AF and coronary artery disease (CAD). About 1/4 of AF patients develop a CAD and, in this setting, about 1/5 undergoes a percutaneous coronary intervention (PCI). In patients with both AF and CAD, the optimal medical strategy is challenging and it is still debated in cardiological community, since patients treated by dual (two antiplatelets drugs ore one antiplatelets drug and an oral anticoagulant drug) or triple therapy (two antiplatelets drugs and an oral anticoagulant drug) are exposed to divergent risk of bleeding or thromboembolic and ischemic complications.
Aim of this paper is to focus the attention on the different problems arising from the presence of AF in patients undergoing PCI, such as the risk of stroke, bleeding and stent thrombosis.

Keywords: Atrial fibrillation, Acute coronary syndromes, Dual antiplatelet therapy, Triple therapy.

I. INTRODUCTION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, occurring in 1-2% of overall population, involving more than 6 millions of European people [1]. AF is associated to a reduced quality of life and an increased morbidity and mortality, due to its not uncommon complications, such as arterial embolism [2,3]. Furthermore, AF development after an acute coronary syndrome is related with a worse prognosis [4]. The Framingham study showed the link between angina and AF, especially in males [5-7]. Both AF and coronary artery disease (CAD) are occurring in presence of similar risk factors, such as hypertension, diabetes and obesity. In AF patients the average CAD incidence is 34%, according to the different study populations, reaching more than 40% in patients older than 70 years [8]. Among all this patients about 1/5 undergoes a percutaneous coronary intervention (PCI), opening a controversy about the optimal antiplatelet medical strategy [8]. In patients with concomitant coronary artery disease and AF, the optimal medical strategy is challenging, since patients treated by dual (two antiplatelets drugs or one antiplatelets drug and an oral anticoagulant drug) or triple therapy (two antiplatelets drugs and an oral anticoagulant drug) are exposed to divergent risk of bleeding or thromboembolic and ischemic complications.
Aim of this paper is to focus the attention on the different problems arising from the presence of AF in patients undergoing PCI, such as the risk of stroke, bleeding and stent thrombosis.

II. RISK STRATIFICATION

According to the current guidelines of the European Society of Cardiology (ESC) for AF oral anticoagulation should be started after risk stratification [1]. The most commonly used stroke risk score in clinical practice is the CHA2DS2-Vasc-Score; it consists of eight different clinical and anamnestic parameters with the attribution of one point per each, with exception of age ≥ 75 years and previous stroke or thrombo-embolism (attribution of 2 points). Oral anticoagulation is indicated when the CHA2DS2-Vasc-Score is ≥ 2. The superiority of oral anticoagulation compared to antiplatelet therapy in prevention of thromboembolism in patients with atrial fibrillation has been already demonstrated [9]. Therefore, not all AF patients need to be treated by oral anticoagulation, but only those with an elevated embolic risk. The patients at low embolic risk should be treated by using aspirin alone; unfortunately the rate of this low risk patients is less than 10% [1]. On the other hand a more aggressive antiplatelet strategy correlates with an increased bleeding risk, that should be evaluated by using an haemorrhagic risk score, such as the HAS-BLED-Score. However some clinical variables are common in both embolic and haemorrhagic risk score, leading to a very challenging appropriate medical therapy.

III. ANTIPLATELET THERAPY AFTER STENT IMPLANTATION

According to ESC guidelines on myocardial revascularization, the dual antiplatelet therapy (DAPT) should be performed 1 month after bare metal stent (BMS) implantation in stable angina, 6-12 months after drug eluting stent (DES) implantation in all patients, and 12 months in all patients after acute coronary syndrome irrespectively of revascularization strategy [10]. By using risk score stratification a triple therapy consisting of a vitamin-K-antagonist, aspirin, and clopidogrel is recommended in all patients with an higher embolic risk. Depending on the clinical setting (acute coronary syndrome or stable angina), hemorrhagic and stroke risk, and the type of stent implanted, triple therapy should be prescribed for the

shortest time possible, continuing with a vitamin-K-antagonist alone administration as lifelong therapy.
Others oral antiplatelets drugs, such as Prasugrel and Ticagrelor, are now commercially available to prevent reinfarction and stent thrombosis. The comparison in terms of efficacy and adverse events between Clopidogrel vs Prasugrel and Clopidogrel vs Ticaglelor has been performed in TRITON-TIMI 38 and PLATO studies, respectively. By using Prasugrel as well as Ticagrelor the platelets activity inhibition is faster and more effective. Unfortunately the higher efficacy of Prasugrel in platelets inhibition activity correlates to an higher rate of life threatening bleedings (1.4% vs. 0.9%; p = 0.01). Conversely, in PLATO trial no statistically significant increase of major bleeding has been reported (11.6% with Ticagrelor vs 11.2% with Clopidogrel; p = n.s.) [11, 12].
Despite the superior efficacy of these new antiplatelets drugs, we do not have data on their association with vitamin-K-antagonist, available in AF patients who underwent PCI. The major risk of bleeding carried out by these new drugs makes them potentially harmful in association with vitamin-K-antagonist. Thus dedicated randomized trials and or registries are needed in order to demonstrate their efficacy and safety in this particular clinical setting.

IV. PROBLEMS IN TRIPLE ANTIPLATELET THERAPY

Stroke, bleeding and stent thrombosis are different aspects of the same phenomenon. An aggressive antiplatelet strategy (oral anticoagulation, OAC, + DAPT) leads to an increased bleeding risk, conversely a conservative antiplatelet strategy (OAC + single antiplatelet therapy, SAPT) leads to an increased embolic risk and an increased stent thrombosis rate [13]. In 239 patients treated by SAPT, comparing efficacy and safety of OAC + Aspirin vs OAC + Clopidogrel at 12 months, the first group showed a lower incidence of major bleedings and an higher incidence of stent thrombosis (6,1 vs 11,1% and 15,2 vs 0%, respectively) [14]. According to a consensus document of the European Society of Cardiology AF patients, with moderate to high stroke risk, undergoing PCI should be treated by triple therapy (TT), consisting in oral anticoagulation, aspirin and clopidogrel after stent implantation, preferably a BMS [15]. Nevertheless the major bleedings rate increase during the first 12 months, irrespective of the type of stent implanted [16].
Despite guidelines recommendations, in clinical practice the duration of DAPT after PCI depends from the type of stent used, 1 month for a BMS and 12 months for a DES, respectively [17].

V. DES AND BMS, WHICH STENT FOR WHICH PATIENT

Thus, what is the best management in AF patient undergoing PCI?

- Appropriate bleeding and embolic risk stratification should be performed.
- Radial approach should be preferred, due to its lower incidence of bleeding complications [18].
- INR therapeutic range should be lower, between 2.0-2.5 [19].
- Gastric protection with either protonic pump inhibitors, H2-receptor antagonists or antiacid drugs is recommended [15].
- TT should be performed as less as possible.

According to a consensus document of the European Society of Cardiology, in AF patients requiring a stent implantation BMS should be preferred, restricting DES implantation in few clinical and/or anatomical situations, such as age < 75 years, long lesions, small vessels, diabetes, etc, in which DES have shown a better performance than BMS [15]. In case of DES implantation, a second generation DES should be preferred, such as a tacrolimus eluting stent, a Carbostent polymer-free stent, which requires DAPT only for two months, as reported from the MATRIX study, in 572 patients [20]. Conversely, if an everolimus and zotarolimus eluting stent has been implanted, DAPT could be discontinued after 3 months without an increasing rate of stent thrombosis, as observed in more than 6800 patients and more than 2200 patients, respectively [21,22]. In case of BMS implantation a last generation of BMS should be used. The preferred stent used should be Genous stent, requiring only 15 days of DAPT, due to its anti-hCD34 coating, which allows an accelerated re-endothelization by capturing circulating CD34+ endothelial progenitor cells [23, 24]. This peculiar aspect has been reported in 384 patients enrolled in the ARGENTO study, validating the safety of this very short time of DAPT [24]. Another possibility is represented by the Avantgarde stent, which requires less than one month DAPT, due to its peculiar projected design, favoring a better endothelization. This stent was evaluated in 42 patients requiring coronary revascularization before an undeferrable major non-cardiac surgery, performed 27 ± 9 days after PCI. Only one major cardiac adverse event was observed at one month follow-up [25]. Finally, in STEMI setting with angiographic evidence of thrombus a bare metal MGuard stent should be implanted. MGuard stent has been evaluated in 150 patients undergoing primary or rescue PCI; its ability to dramatically reduce distal thrombus embolization led to a TIMI flow grade 2.85 ± 0.40 and a myocardial blush grade 3 of 90%. Furthermore, within 30 minutes after the procedure a very high rate of complete (> or = 70%) ST-segment resolution (90%) was observed [26, 27].
Independently of the implanted stent, as suggested by the current guidelines, the radial approach should be preferred in order to its lower incidence of bleeding complications, as already demonstrated by several meta-analyses [28, 29]. Romagnoli et al. in a recently published randomized controlled trial, comparing radial versus femoral approach in ST-elevated myocardial infarction patients who underwent primary

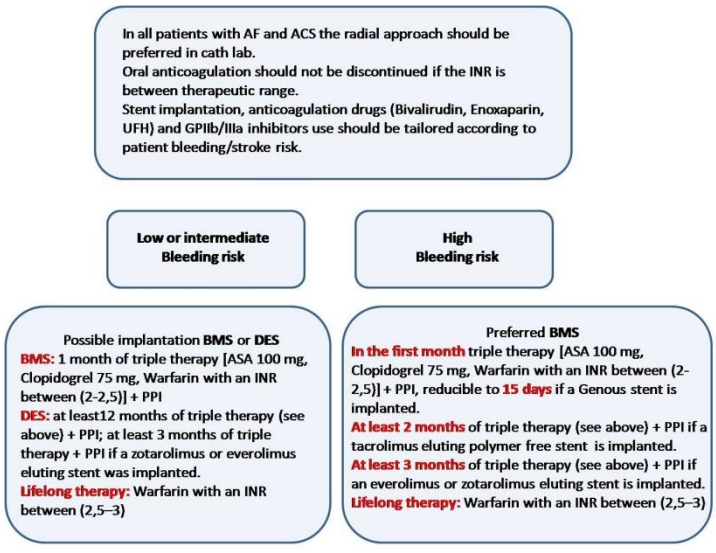
PCI, showed a significant reduction of major adverse cardiac events in the radial arm of the study [30]. However, the great enthusiasm coming from clinical trials data seems to be questioned by recent data reanalysis [31, 32]. Thus this increased enthusiasm about radial approach might be owed more to the patients and interventional cardiologist preferences, than to a true mortality rate reduction.

VI. NEW ORAL ANTICOAGULANT AGENTS

New anticoagulant drugs are safe and effective compared to warfarin in non-valvular AF patient. The use of these new anticoagulant drugs is still a matter of debate due to the controversial results observed in the different clinical trials in this particular setting. Compared with placebo, the apixaban addiction to DAPT, in treatment of non-valvular AF after acute coronary syndrome occurrence, leads to an increased rate of bleedings, with no better thromboembolic outcomes [33].
Conversely a very-low dosage of rivaroxaban, used in acute coronary patients setting, showed the reduction of thromboembolic complications with an increasing rate of nonfatal bleedings [34]. A substudy of the RE-LY trial, showed an increased bleeding risk in dabigatran addiction to DAPT compared to SAPT [35]. On this ground, further studies are strongly needed in order to evaluate the efficacy and the safety of these new drugs in association with either old and new antiplatelets drugs.

VII. CONCLUSIONS

AF and CAD are strictly related. An individualized approach with a tailored medical and interventional strategy is required in patients with concomitant AF and CAD, in order to obtain a balance between the risk of cerebrovascular events, bleeding complications and reinfarction rate. In short time TT benefits are superior to its side effects, nevertheless it should be prolonged as less as possible.



AF: atrial fibrillation; ACS: acute coronary syndrome; BMS: bare metal stent; DES: drug eluting stent; PPI: proton pump inhibitor; UHF: Unfractionated heparin.

Figure 1. Flowchart management of atrial fibrillation patients undergoing percutaneous coronary intervention.

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