**BARRIERS OF ANTIAGGREGANT TREATMENT**

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BARRIERS OF ANTIAGGREGANT TREATMENT (Abstract): In the present study we aimed to evaluate side effects of antiplatelet therapy in order to establish correlations with medication type, doses and association with other therapies. Material and methods: in the study we prospectively evaluated a cohort of patients who received antiplatelet therapy for different pathologies. We included patients with acute coronary syndromes, valvular disease complicated with supraventricular arrhythmias (especially atrial fibrillation), carotid critical stenosis, neurologic disease (ischemic or thrombotic), and peripheral artery disease. Results and discussions: The study included 125 patients (85 males and 40 females), aged between 45 and 85, and admitted in the 1st Cardiology Department, St Spiridon Hospital, between January 2012 and December 2013, who received antiplatelet therapy for different pathologies. All the patients included in the study received platelet antiaggregant therapy with Clopidogrel in association or not with Aspirin or low weight molecular heparin. Side effects reported (possibly correlated with antiplatelet therapy) were: macroscopic hematuria (7 cases), cutaneous ecchymosis (7 cases), purpuric lesions (9 cases), gingival bleeding (12 cases), upper gastrointestinal bleeding (6 cases), and hemoptysis (2 cases). Conclusions: Hemorrhagic events under the treatment with antiplatelet agents are rare in comparison with the large number of patients treated. Clinical manifestations are very different depending on the drug and also on the drug-associations used. Hemorrhagic accidents may sometimes be very serious, determining the specific therapeutic measures. Keywords: ANTIAGGREGANT TREATMENT, CLOPIDOGREL, ASPIRIN, HEMORRHAGE, SIDE EFFECTS.

Atherothrombosis accounts for 22.3 % of all causes of mortality worldwide as reported by the World Health Organization in 2001 (1). Cardiovascular disease (CVD) was defined as coronary heart disease (myocardial infarction (MI), angina pectoris, coronary insufficiency), cerebrovascular disease (stroke, transient ischemic attack), congestive heart failure, and intermittent claudication. This definition of CVD covers all the manifestations of athero-thrombosis. According to this analysis, more than 60% of men and women over 40 years of age will develop atherothrombotic disease at some point in their lives (1). For patients older than 50 years of age, the development of atherothrombotic disease reduces life expectancy by 8 to 12 years (1). The role of platelets in athero-thrombosis is a very important factor to be considered in...
preventing cardiovascular death, MI and stroke (2). After plaque rupture or vessel damage, platelets undergo three processes: adhesion, activation, and aggregation, and then a thrombus is formed. An agent that would inhibit these platelet processes would therefore definitely be beneficial and effective in preventing atherothrombotic events (3). Antiplatelet agents such as aspirin, triflusal, clopidogrel, and ticlopidine generally act on the platelet activation process while GIIb/IIIa inhibitors impede platelet aggregation by blocking activated fibrinogen receptors (3). They are widely used for primary and secondary prevention of cardiovascular and cerebrovascular diseases (4). However, use of either aspirin or clopidogrel is associated with bleeding adverse events (5).

Clopidogrel is a potent anti-platelet drug of the thienopyridine group that inhibits adenosine dinucleotide phosphate (ADP) receptors. It is considered superior to aspirin for secondary prevention after cardiovascular events, it is widely administered following cardiac catheterisation and stent implantation or bypass and its indications are expanding (5, 6). Combined aspirin and clopidogrel therapy is even more effective in preventing vascular events and associated mortality, but that regimen may significantly increase the risk for bleeding (7, 8).

The aim of this study was to assess the occurrence of antiplatelet therapy side effects in patients with CAD.

MATERIAL AND METHODS
We conducted a prospective cohort study in which we included 125 patients (85 males and 40 females), aged between 45 and 85, who received antiplatelet therapy for different pathologies, admitted in the 1st Cardiology Department, St Spiridon Hospital, between January 2012 and December 2013.

Patients with uncertain acute coronary syndrome criteria, those without clopidogrel therapy, patients with contraindication of platelet antiaggregant therapy (e.g., antecedents of hemorrhagic accidents or known hemorrhagic diatheses, previously known liver disease) as well as patients with psychiatric disorders, clinical severe thrombocytopenia, progressive malignancy or noncompliant ones were excluded.

Patients were initially evaluated following a complete check-up, including past history, clinical examination, blood tests, electrocardiogram and cardiac ultrasound. The final decision regarding study inclusion was taken after having a precise diagnosis and therapeutic scheme. They were followed up for one year, initially at one month and then at 3, 6 and 12 months.

All the patients included in the study received antiaggregant therapy with clopidogrel associated in some patients with aspirin or low weight molecular heparin.

After enrolment, patient age, sex, smoking and drinking habits, previous medications including antiplatelet agents (aspirin, clopidogrel), nonsteroidal anti-inflammatory drugs (NSAIDs), and gastroprotective agents, and past history of endoscopically proven peptic ulcer disease were recorded. During the follow-up period, data concerning hemoglobin, platelet levels, and evidence of bleeding were recorded.

RESULTS
We reviewed the records of 125 patients (68% men, average age 65.3 ± 10.1 years) with baseline characteristics (tab. I).

The most commonly associated comorbidities were hypertension (70.4 %), diabetes mellitus (35.5 %), congestive heart failure (26.6 %), and dyslipidemia (22.7 %).

The majority (77 patients, 61.6% of cases) were diagnosed with acute coronary syndromes (most cases with different forms
of unstable angina) that have satisfied the study inclusion criteria. Thirteen patients (10.4%) received antiaggregant treatment for acute and subacute MI, and 28% of the patients received antiplatelet therapy for other diseases such as: valvular disease (mitral or aortic) complicated with supraventricular arrhythmias (especially atrial fibrillation) (15 patients), carotidane critical stenosis (3 patients), neurologic disease (ischemic or thrombotic), peripheral artery disease (17 patients).

**TABLE I**
Baseline characteristics of study population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs (mean ±SD)</td>
<td>69.3±9.39</td>
</tr>
<tr>
<td>Male n, %</td>
<td>66 (52.8%)</td>
</tr>
<tr>
<td>Diabetes n, %</td>
<td>51 (40.8%)</td>
</tr>
<tr>
<td>Smoking n, %</td>
<td>64 (51.2%)</td>
</tr>
<tr>
<td>Blood hypertension n, %</td>
<td>79 (63.2%)</td>
</tr>
<tr>
<td>Cholesterol, mg/dl (mean ±SD)</td>
<td>229.5±45.99</td>
</tr>
<tr>
<td>Creatinine, mg/dl (mean ±SD)</td>
<td>0.98±0.39</td>
</tr>
</tbody>
</table>

All the patients included in the study received 75 mg of clopidogrel daily. In 77 patients clopidogrel was associated with aspirin 75 mg daily, and seventy-four patients (13.9%) also received low weight molecular heparin (enoxaparin). Anticoagulant treatment was associated for a medium of 7 days in patients with ACD. The majority of patients 67 (53.6%) received double antiaggregation (clopidogrel and aspirin) upon discharge (fig. 1).

**Fig. 1.** Treatment received by the patients included in the study upon discharge.

During the follow-up, we recorded 7 (5.6%) cases of hematuria, between 7 and 10 days after the treatment was begun. All the patients were males and had been treated with clopidogrel and aspirin.

Seven patients (5.6%) has developed cutaneous ecchymosis after an average period of one month, four of them had a double antiaggregation, with no platelet count. Six patients (4.8%) had purpuric lesions secondary to clopidogrel treatment. All the skin lesions were reversible after clopidogrel was stopped and replaced with aspirin (tab. II).

**TABLE II**
Side effects in patients with antiaggregant treatment

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Clopidogrel (n=45)</th>
<th>Aspirin (n=13)</th>
<th>Clopidogrel and aspirin (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macroscopic hematuria n, %</td>
<td>0</td>
<td>0</td>
<td>7 (5.6%)</td>
</tr>
<tr>
<td>Cutaneous ecchymosis n, %</td>
<td>2 (1.6%)</td>
<td>1 (0.8%)</td>
<td>4 (3.2%)</td>
</tr>
<tr>
<td>Cutaneous purpura n, %</td>
<td>5 (4%)</td>
<td>0</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Gingival bleeding n, %</td>
<td>4 (3.2%)</td>
<td>0</td>
<td>8 (6.4%)</td>
</tr>
<tr>
<td>Upper digestive hemorrhage n, %</td>
<td>0</td>
<td>0</td>
<td>7 (5.6%)</td>
</tr>
<tr>
<td>Hemoptysis n, %</td>
<td>2 (1.6%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Patients with upper digestive hemorrhages had melena and also received heparin therapy. Upper digestive endoscopy was performed in half of the cases, and acute hemorrhagic gastritis was described in all the cases. Antiaggregant treatment was stopped and a proton pump inhibitor was added as treatment.

Two smoking male patients were diagnosed with haemoptysis, all of them on clopidogrel. Bronchoscopy was normal and they did not repeat the bleeding after clopidogrel was changed to aspirin.

**DISCUSSION**

Although some studies demonstrated that clopidogrel increases the risk of bleeding (4, 6) our findings suggested that hemorrhagic adverse events are rare in patients on antiaggregant therapy. These results may have important implications in antiplatelet therapies for patients with or at risk for cardiovascular disease.

Antiplatelet therapies are effective in reducing ischemic events, yet are likely to increase bleeding risk (7). Use of more potent antiplatelet therapies is likely to further reduce the risk of ischemic events, while simultaneously increasing the risk of bleeding (6). While these agents are effective in reducing thrombotic complications of atherosclerosis (ASC), their use increases the likelihood that patients will develop a bleeding complication (8). The reported risk of bleeding during hospitalization for ACS varies between 1 and 10% and is influenced by patient co morbidities, age, sex, rates of treatment with revascularization or invasive procedures such as angiography, intra-aortic balloon pumps or coronary artery bypass grafting (CABG) and the antiplatelet/antithrombotic treatment regimen used for treatment (9).

Prior studies have consistently identified female gender, older age, lower body mass index, low creatinine clearance, and the use of percutaneous interventions as risk factors for bleeding complications (9, 10). In order to better understand an individual’s risk of bleeding, there have been several attempts to develop standardized predictive models for bleeding risk; unfortunately, the majority of these bleeding scores have had relatively poor predictive power (10).

Recently, Subherwal et al. (11) published the CRUSADE Bleeding Score using clinical criteria available at presentation such as baseline hematocrit, creatinine clearance, heart rate, sex, systolic blood pressure, diabetes, prior vascular disease, and the presence of cardiac heart failure upon presentation. Current ACC/AHA guidelines for the treatment of patients with ACS recommend dual antiplatelet therapy due to numerous studies demonstrating a reduction in ischemic complications (12). The addition of an additional antiplatelet agent does increase the incidence of bleeding, results which were also confirmed in our study.

In the CURE trial of patients with ACS randomized to clopidogrel plus aspirin versus aspirin alone, the rate of major bleeding in patients assigned to clopidogrel plus aspirin was 3.7%, while the rate in the patients assigned to aspirin alone was 2.7% (RR=1.38; p=0.001) (13). Bleeding risk was also significantly higher among patients treated with aspirin and clopidogrel who required CABG. Post hoc analysis of the CURE trial demonstrated that the bleeding risk was especially high when CABG was performed within 5 days of the last dose of clopidogrel (13).

Patients who suffer from bleeding com-
Barriers of antiaggregant treatment

Complications or require transfusions are often treated less aggressively with evidence-based medications placing them at higher risk of future ischemic events. The Prospective Registry Evaluating Myocardial Infarction: Events and Recovery (PREMIER), a registry of 2,498 patients with acute MI, found that patients with bleeding during the index MI hospitalization were less likely to be treated with antiplatelet therapy and other agents during the first 6 months after discharge (14). These findings offer insight into the current treatment of patients with bleeding complications and may help explain why patients with bleeding complications are at a significantly higher risk for ischemic events.

Bleeding events which occurred during antiplatelet therapy are relatively rare when compared to the large number of patients treated with an antiaggregant drug in monotherapy or dual therapy. Bleeding side effect can manifest in different territories and disappear with cessation of treatment. Association between double antiaggregation and heparin therapy increased the risk of upper digestive bleeding.

CONCLUSIONS
Our study did not demonstrate an increased risk of bleeding in patients treated with clopidogrel versus aspirin, but the double antiaggregation was associated with more hemorrhagic adverse events.

REFERENCES


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**A NEW ASSAY FOR PATHOGEN GENOTYPING**

A group of researchers developed a new assay for pathogen detection and amplicon genotyping, based on restriction endonuclease digestion. In the first stage, target DNA is hybridized to immobilized complementary oligonucleotide probes carrying a molecular marker (horseradish peroxidase-HRP). In the second stage, the target-probe duplex is cleaved by the restriction enzyme at the corresponding restriction site and the HRP marker released into solution is quantified colorimetrically. This assay was tested for MRSA detection, using the *mecA* gene as a target. The detection limit for the target oligonucleotide and the PCR amplicon was approximately 1 nM. The sequences of target oligonucleotides were altered in order to prove the following: mutation to the restriction site reduced the signal to zero, mutations of the sequences that flanked the restriction site reduced restriction to 50-80% of the positive control, and a minimum of 16-bp target-probe hybrid is required for a significant cleavage. The assay is able to detect the *mecA* amplicon from an unpurified PCR mixture with limits of detection similar to standard qPCR. Detection of amplicons is not affected by the presence of excess heterologous genomic DNA and because it uses two biorecognition steps, the test has a very high specificity. The study concluded that the assay is efficient, low-cost, fast (can be completed in less than 1 hour) and can also be used for analysis of different amplicons from an unpurified mixture (Smith MW, Ghindilis AL, Seoudi IA et al. A New Restriction Endonuclease-Based Method for Highly-Specific Detection of DNA Targets from Methicillin-Resistant *Staphylococcus aureus*. PLoS One. 2014;9(5):e97826. doi: 10.1371/journal.pone.0097826).

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