

## REVIEW

# Antithrombotic treatment in acute coronary syndrome in elderly patients

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**Abstract:** The management of antithrombotic treatment in elderly patients represents a great challenge in every day medical practice, taking into account both increased ischemic events risk as well as high bleeding risk as characteristics of this particular subset of patients. The great number of physiopathological changes that are found in elderly people in multiple organs and systems, mostly liver and kidneys, lead to an increase in the individual variability of therapeutic response, as well as to an augmented drug toxicity and potential decreased therapeutic benefit.

**Keywords:** elderly patient, ischemic risk, bleeding risk, antithrombotic treatment

**Rezumat:** Administrarea tratamentului antitrombotic la pacientul vârstnic reprezintă o mare provocare în practica de zi cu zi, atât riscul crescut de evenimente ischemice cât și riscul crescut de sângerare fiind caracteristicile acestei categorii particulare de pacienți. Multitudinea de modificări fiziopatologice care survin odată cu înaintarea în vârstă la nivelul a numeroase organe și sisteme, preponderent hepatic și renal, determină creșterea variabilității individuale a răspunsului terapeutic, putându-se de asemenea înregistra creșterea toxicității medicamentoase și potențiala atenuare a beneficiilor terapeutice.

**Cuvinte cheie:** pacient vârstnic, risc ischemic, risc hemoragic, tratament antitrombotic.

## INTRODUCTION

Since the increase of the medium life expectancy time has been established as a modern society characteristic, the number of people over 60 years of life in the general population is constantly growing, with an estimated prevalence of over 2 billion until 2050<sup>1</sup>. Regarding age, there is a general tendency of considering as “elderly” the people aged over 75 years, although, in a number of studies that have led to the elaboration of multiple risk scores, the value taken into consideration was 65 years of age<sup>2</sup>.

On the other hand, the prevalence of acute coronary syndromes in this particular category of patients is a significant one, and, according to recent statistics, more than one third of acute myocardial infarction diagnosed patients and approximately two thirds of the deceased following this pathology were over 75 years of age<sup>3</sup>.

The great challenge concerning the management of antithrombotic treatment in elderly patients is generated by numerous factors that are common in these particular patients: multiple organ damage, increased

bleeding as well as ischemic events risk, comorbidities and concomitant medical therapy and last, but not least, low medical treatment adherence.

## ELDERLY PATIENT: BETWEEN ISCHEMIC AND BLEEDING RISK

Antithrombotic treatment, including antiplatelet, anticoagulant and fibrinolytic treatment, is used in order to prevent or to ameliorate the severity of embolic events – stroke, acute myocardial infarction, systemic embolism, deep vein thrombosis or pulmonary embolism, as well as to ameliorate cardiovascular and any cause mortality, of course, with an associated increased bleeding risk.

The great challenge for the medical practitioner is to establish if, in the elderly patient, the benefit of antithrombotic treatment surpasses the bleeding risk, risk that can generate an increased mortality by itself<sup>4</sup>.

The connection between advanced age and vascular pathology is illustrated by the increase of cardiovascular risk when aging. Thus, elderly people are characterized by a number of modified haemostatic factors,

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such as the rise of procoagulants factors (fibrinogen, factor VII, factor VIII), the rise of fibrinolytic system factors such as plasminogen activating inhibitor in women and the rise in antithrombotic factors in women (C protein, antithrombin, tissue factor inhibitor), all of these having as consequence the formation of an antithrombotic status<sup>5</sup>. This antithrombotic status, associated with modified aged related blood rheology, with the increased plasmatic viscosity and erythrocytes rigidity, is contributing, along with endothelial dysfunction, inflammation and the imbalance between oxidative stress and antioxidant factors in the development of elderly patient atherosclerosis<sup>6</sup>.

The administration of antithrombotic treatment in elderly is also complicated by a number of modifications related to multiple systems and organs. Related to the liver function, the decrease of hepatic blood flow and the modified structure and dimensions are contributing to the decrease of the activity of P450 (CYP) I, 2C4 and 2D6 cytochromes. In a similar way, concerning the kidneys activity, blood flow and the kidneys function are reduced. Constant renal function reduction associated with frequent intercurrent illnesses (heart failure decompensations, intercurrent respiratory infections) may lead to the decrease of creatinine clearance, with direct impact on the antithrombotic molecules that have a predominant renal filtration rate (low molecular weight heparines—LMWH, fondaparinux, bivalirudine, dabigatran, eptifibatide and tirofiban). Moreover, it is recommended to evaluate the renal function using calculation formulas that are taking into account the age and the weight, beyond the simple serum creatinine value that might overestimate the renal function in this particular subgroup of patients<sup>8</sup>.

## INDIVIDUALIZING ANTITHROMBOTIC TREATMENT IN THE SETTING OF ACUTE CORONARY SYNDROME

### Aspirine

Aspirine is acting by the irreversible inhibition of cyclooxygenase-I, thus decreasing the thromboxane A2 production and the benefits of its administration in primary prevention of athero-thrombotic cardiovascular disease are well documented by numerous studies and meta-analyses<sup>8</sup>. These extended research has demonstrated a decreased vascular event rate in elderly in compare to younger patients, following aspirine administration (1.53% vs. 0.40% per year)<sup>8</sup>. A recent Japanese study, Japanese Primary Prevention Project, has demonstrated that in hypertensive, dyslipidemic or di-

abetic patients aged between 60-85 years randomized to aspirine 100 mg/day versus placebo, the administration of aspirine has halved the rate of myocardial infarction or transient ischemic attack, but has also doubled the risk of extracranial major bleeding<sup>9</sup>. The benefit of aspirine administration is also found, without doubt, in secondary athero-thrombotic disease secondary prevention. It is also important to notice that the bleeding risk associated with low dose aspirine administration (75-100 mg/d) is 2-3 fold higher in elderly in compare to younger population, for both genders and that the risk of upper gastro-intestinal tract bleeding is considerably increased after 70 years of age<sup>10</sup>.

Thus, the current guidelines are recommending low dose aspirine administration (75-100 mg/day) in elderly patients with overt athero-thrombotic cardiovascular disease, in the absence of contraindications represented by allergies, active bleeding or intracranial hemorrhage<sup>11</sup>.

### Thienopyridines: clopidogrel and prasugrel

Thienopyridines (Clopidogrel and Prasugrel) are prodrugs with active metabolites that irreversibly inhibit platelet activity by interfering with the P2Y<sub>12</sub> receptor. Trials such as CURE (primary PCI in acute coronary syndromes), COMMIT and CLARITY-TIMI 28 (STEMI patients treated with aspirine and fibrinolytic therapy) have demonstrated the benefits of clopidogrel administration in a loading dose of 300 mg followed by a maintenance dose of 75 mg/day<sup>12-14</sup>. To notice that trials that have included patients treated with thrombolytic therapy did not include patients over 75 years of age, and thus, not knowing the effect of administering loading clopidogrel dose, guidelines only recommend the administration of maintenance 75 mg/day dose.

The duration of dual antiplatelet therapy after acute coronary syndromes is still a matter of great debate. The DAPT trial, that included 40% of patients in the proximity of an acute coronary syndrome, compared a duration of 12 months of dual antiplatelet therapy versus an extended 30 months period of time and reported a smaller ischemic event rate in the extended dual antiplatelet therapy group, but with increased bleeding complications<sup>15</sup>.

The TRITON-TIMI-38 trial, that included acute coronary syndrome patients treated with Primary PCI, aspirine and prasugrel or clopidogrel, demonstrated the superiority of prasugrel (60 mg loading dose, then 10 mg/day) vs. Clopidogrel, but with an increased rate of bleeding complications in the group of patients over 75 years of age<sup>16</sup>.

For the moment, the recommendation for elderly patients with acute coronary syndromes is to be treated preferably with clopidogrel rather than prasugrel or ticagrelor, if they have a high bleeding risk<sup>11</sup>. The administration of prasugrel in patients over 75 years and under 60 kilograms should be cautioned and is contraindicated in patients with previous stroke or ischemic transient attack. In acute coronary syndromes without ST segment elevation (NSTEMI), it is not recommended to administer prasugrel before angiography<sup>11</sup>.

### Ticagrelor

Ticagrelor, reversibly inhibits platelet aggregation by binding with the P2Y<sub>12</sub> receptor and is recommended in dual antiplatelet therapy along aspirine, in the treatment of NSTEMI acute coronary syndromes regardless of the management and in STEMI patients referred to primary PCI, with a recommended lowing dose of 180 mg followed by 2x90 mg/day. The main trial that demonstrated the superiority of ticagrelor vs. Clopidogrel is the PLATO trial, trial that included 15% of patients over 75 years of age<sup>17</sup>.

That is why, in the situations mentioned above, we recommend the administration of ticagrelor associated with aspirine in elderly patients with acute coronary syndromes, in the absence of contraindications represented by active bleeding or intracranial bleeding and carefully administration in patients with history of asthma/COPD or sino-atrial advanced disease without pacemaker implantation<sup>11</sup>. We consider important to mention that there are no evidences regarding ticagrelor administration in patients receiving thrombolytic therapy.

## DUAL ANTIPLATELET THERAPY: HOW LONG?

As we have already mentioned, the duration of dual antiplatelet therapy after interventionally revascularized acute coronary syndrome is still a matter of great debate. It is now recommended to maintain dual antiplatelet therapy for up to one year and to exactly establish the duration of therapy after considering the type of stent used for revascularization (bare metal vs. drug eluting stent) and the risk of bleeding, that is increased by using prasugrel or ticagrelor in compare to clopidogrel<sup>11</sup>. One of the studies that have evaluated the extended dual antiplatelet therapy administration is the DAPT trial, trial that included patients without adverse cardio-vascular events during the first year after primary PCI and that were randomized to either extended to additional 18 months of dual antiplatelet therapy with aspirine and clopidogrel or to prasugrel vs aspirine alone. The results demonstrated that extended dual antiplatelet therapy determined the decrease of intra-stent thrombosis rate and adverse cardio-vascular events but with a significant increase in the bleeding complications rate<sup>18</sup>.

## PARENTERAL ANTIGOAGULANTS: UNFRACTIONATED HEPARIN AND LMWH

Since it is not eliminated through the kidneys, unfractionated heparin may be administered even in situations when creatinine clearance is under 30 ml/minute. Even so, in elderly patients frequent bioavailability changes

Molecule	Dose for ACS	Dose adjustment in elderly	Dose adjustment in renal function impairment
<b>ASPIRINE</b>	75-100 mg/day Maintenance dose	No	No
<b>CLOPIDOGREL</b>	Primar PCI: 600 mg lowing dose, then 150 mg/day for 2 weeks, then 75 mg/day Fibrinolytic treatment: 300 mg lowing dose, then 75 mg/day	Fibrinolytic treatment: no lowing dose required after 75 years of age	No
<b>PRASUGREL</b>	60 mg, lowing dose, then 10 mg/day maintenance dose	Not recommended after 75 years	Contraindicated for values of ClCr<15 ml/minute
<b>TICAGRELOR</b>	180 mg, lowing dose, then 2x90 mg/day maintenance dose		Contraindicated for values of ClCr<15 ml/minute
<b>UNFRACTIONATED HEPARINE</b>	Dose adjustment according to aPTT value	No	No
<b>LMWH</b>	Dose varies by molecule	For. Enoxaparine, In elderly over 75 years of age, 2x0.75 mg/kg /day every 12 hours subcutaneous	For Enoxaparine and for values of ClCr<30 ml/minute 1x1 mg/kg/day
<b>FONDAPARINUX</b>	2.5 mg/day subcutaneous	No	Contraindicated for values of ClCr<20 ml/min

may appear, as well as changes in the inflammatory status, cardiac output or body weight. Because a number of trials have established the superiority of LMWH in compare to unfractionated heparin concerning bioavailability and efficiency in acute coronary syndromes treated with trombolitic therapy or primary PCI, with a similar bleeding complications rate, LMWH are preferred to unfractionated heparine.

One of the major disadvantages of LMWH is represented by the mainly renal elimination rate, with the need of adjusting the administered dose related to creatinine clearance (CrCl) in patients with impaired renal function. Concerning enoxaparine, it is recommended to administer 1x1mg/kg/day for values of the CrCl<30 ml/minute and above 75 years of age the administration of 2x0.75 mg/kg/day and no i.v. bolus for trombolitic therapy (Table 1)<sup>19</sup>.

### Fondaparinux

Fondaparinux is represented by a synthetic pentasaccharide, an inhibitor of factor Xa, mainly eliminated on renal level and thus contraindicated for values of CrCl under 20 ml/minute. Since a number of studies, including OASIS-5 have demonstrated a similar ischemic events rate in NSTEMI patients treated with Fondaparinux 1x2,5 mg/day subcutaneous vs. enoxaparine 2x1mg/day for a maximum of 8 days, with a bleeding rate significantly lower after fondaparinux administration, it is recommended to administer fondaparinux in NSTEMI and STEMI patients that are not undergoing primary PCI<sup>19-21</sup>. In the case of an invasive management, bivalirudine or unfractionated heparine administration is recommended in order to prevent periprocedural thrombotic complications (catheter thrombosis).

## TRIPLE ANTITHROMBOTIC THERAPY IN ELDERLY PATIENTS - THE GREAT CHALLENGE

Since atrial fibrillation has a great risk of mortality and morbidity due to stroke and thrombo-embolic events and taking into consideration the fact that this rhythm disturbance is having a high prevalence and is representing an important health issue world wide, one of the most important indications of anticoagulant oral treatment is represented by the prevention of thrombo-embolic accidents in patients with non-valvular atrial fibrillation that are associating at least one risk factor for stroke<sup>22,23</sup>.

That is why the current guidelines of the *European Society of Cardiology* for the management of atrial non-valvular fibrillation as well as the most recent focus

update on the same field from 2012 recommend the use of CHA<sub>2</sub>D<sub>2</sub>S-VASc score for stratifying embolic risk of these patients and identifying those at „low” risk, that is the ones with CHA<sub>2</sub>D<sub>2</sub>S-VASc score=0 (men) or 1 (women)<sup>22</sup>. Taking these data into consideration, the majority of patients diagnosed with atrial fibrillation (>80%) will require oral anticoagulation.

On the other hand, elderly patients often present with acute coronary syndromes in the setting of another pathology that requires anticoagulation, as usual atrial fibrillation and thus, the management of antithrombotic treatment in these conditions may be a true challenge.

The latest guideline of the European Society of Cardiology for the management of patients with acute coronary syndromes without ST segment elevation that are undergoing PCI is giving a straight answer to that problem<sup>21</sup>. According to that guideline, for the patients with non-valvular atrial fibrillation and NSTEMI with a low and intermediate HAS-BLED risk (0-2), triple therapy with aspirine, clopidogrel and oral anticoagulant – antivitamin K or novel oral anticoagulant, is recommended for 6 months followed by dual therapy with anticoagulant and aspirine or clopidogrel for up to one year and then oral anticoagulation for lifetime. For the patients that are having a high bleeding risk (HAS-BLED score≥3), triple therapy is recommended for up to 4 weeks, then dual therapy with anticoagulant and aspirine and clopidogrel for up to one year, then oral anticoagulation for lifetime. For the patient with medical management only the guideline is recommending dual therapy with anticoagulant and aspirine or clopidogrel. <sup>21</sup> Nevertheless, administering triple antithrombotic therapy in elderly patients may have a number of risks, especially concerning bleeding complications.

One of the options taken into consideration in order to minimize bleeding risk, emerged after the WOEST trial, is the one that is recommending dual antithrombotic therapy with clopidogrel and anticoagulant as an alternative to triple antithrombotic therapy in patients with great hemoragic risk<sup>24</sup>.

Other strategies recommended in order to minimize bleeding risk in elderly patients that require triple therapy are the use of radial vs. femoral approach, the use of bare-metal stents vs. drug eluting ones and the use of proton pump inhibitors with low inhibition of CYP19 capacity (ex. Pantoprazol)<sup>1</sup>.

Since oral anticoagulation with vitamin K antagonists has a number of limitations such as late therapeutic effect, great interindividual variability of the therapeu-

tic response and multiple drug interactions, the use of new oral anticoagulants in patients with non-valvular atrial fibrillation is nowadays well documented<sup>25,26</sup>.

The use of new oral anticoagulants in the setting of acute coronary syndromes can be a great challenge, especially while treating elderly patients. Among these, three anticoagulant agents are currently available: dabigatran etexilate, a new direct thrombin inhibitor and rivaroxaban and apixaban, both inhibitors of factor Xa (Table 2). A number of clinical trials have evaluated the efficacy of these agents in the prevention of stroke and systemic embolism in patients with non valvular atrial fibrillation, all these trials demonstrating the non-inferiority of these new anticoagulant agents versus warfarine: dabigatran etexilate – the RE-LY trial (*Randomized Evaluation of Long Term Anticoagulant Therapy*), rivaroxaban - the ROCKET-AF trial (*An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation*) and apixaban - the ARISTOTLE trial (*Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation*)<sup>27-29</sup>.

On the other hand, since factor Xa plays a central role in thrombosis, the study ATLAS ACS 2–TIMI 51 (*Rivaroxaban in Combination With Aspirin Alone or With Aspirin and a Thienopyridine in Patients With Acute Coronary Syndromes*) has evaluated the efficacy of rivaroxaban administered in small dose (2x2.5 mg/day and 2x5 mg/day) in patients with acute coronary syndrome, in addition to standard therapy. Best results in reducing the rate of cardiovascular death were found with the 2x2.5 mg/day dose, but however the therapy with rivaroxaban was associated with an increased rate of hemorrhage<sup>30</sup>.

## CONCLUSIONS

Elderly patients, always between ischemic and hemorragic risk, are requiring a special management of antithrombotic therapy in the setting of acute coronary

syndromes, with the need of individualization of therapy for each patient, with close evaluation of the clinical condition.

**Conflict of interest:** none declared.

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**Table 2. New oral anticoagulants**

New Oral Anticoagulants	Mechanism of action	Renal excretion	Dose	Clinical trials	Reference
Dabigatran etexilat	Direct thrombin inhibitor	85%	2x150 mg/day 2x110 mg/day over 80 years of age, with close monitoring of renal function	RE-LY	27
Rivaroxaban	Inhibitor of factor Xa	66%	1x20 mg/day 1x15 mg/day in patients with ClCr=30-49ml/min	ROCKET-AF ATLAS ACS 2–TIMI 51	28 30
Apixaban	Inhibitor of factor Xa	27%	2x5 mg/day 2x2,5 mg/day	ARISTOTLE	29

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