I pazienti anziani sono a maggior rischio di tromboembolia a causa della presenza di comorbidità, di polifarmacoterapia e dell’invecchiamento. Gli anziani presentano un aumentato rischio sia tromboembolico, arterioso e venoso, che emorragico per tale motivo risulta difficile la scelta della miglior terapia da parte del medico. Negli ultimi anni sono stati creati dei sistemi di punteggio per la valutazione del rischio di stroke e di quello emorragico che potessero aiutare il medico nella scelta della miglior terapia anticoagulante. Le evidenze scientifiche indicano che i nuovi anticoagulanti orali (NAO) non sono associati ad un maggiore sanguinamento rispetto alla terapia convenzionale negli anziani. Viceversa i NAO riducono significativamente il rischio di ictus e di embolia sistemica negli anziani con fibrillazione atriale e sono anche più efficaci della terapia convenzionale per la riduzione del rischio di tromboembolismo venoso o di morte correlata a tromboembolismo venoso. Tuttavia, sebbene numerose evidenze scientifiche abbiano chiaramente affermato che i pazienti anziani con scompenso cardiaco hanno un elevato rischio intrinseco di eventi trombotici, le linee guida non suggeriscono l’utilizzo routinario di anticoagulanti, se non nei pazienti con fibrillazione atriale e/o portatori di valvola protesica e/o storia di tromboembolismo. La relazione tra scompenso cardiaco, fibrillazione atriale e asse sistema nervoso simpatico-emostasi dovrebbe essere approfondita in studi che focalizzano ed integrano l’approccio clinico con le nuove conoscenze biochimiche e biologiche degli anticoagulanti.

**Parole chiave:** Anticoagulazione, Anziano, Nuovi anticoagulanti orali, Insufficienza cardiaca, Fibrillazione atriale e tromboembolismo venoso

Older adults have an increased risk of thromboembolism, due to the presence of many comorbidities, polypharmacotherapies and of the age process itself. Both venous and arterial thromboembolic diseases have an high impact in elderly patients. Aging is regarded as one of the strongest and most prevalent risk factors for venous thromboembolism (VTE). Previous studies have showed that conventional risk factors, malignant disease, and the presence of comorbidities in elderly adults increase the risk of VTE and bleeding and might complicate anticoagulation treatment. For arterial thrombosis, one of the main causes, for individuals aged 80 to 90, is atrial fibrillation (AF). AF related stroke also increases with age; in the Framingham Study, 23.5% of strokes in individuals aged 80 and older were attributable to AF. Age 75 and older is considered a risk factor in stroke risk stratification scores and contributes 1 point toward a maximum risk score of 6 in the cardiac failure, hypertension, age, diabetes, stroke (CHADS2) score. In the CHA2DS2-VASc score, aged 75 and older contributes 2 points toward a maxi-
In addition, other risk factors, such as hypertension, prior stroke, diabetes mellitus and heart failure have an higher prevalence in older adults. Anticoagulants such as heparin and vitamin K antagonists remain the mainstay for the treatment of arterial and venous thromboembolic diseases, although they have potential limitations. Recently, new oral anticoagulants (NOACs) such as dabigatran, rivaroxaban, apixaban and edoxaban have been developed as an alternative to conventional anticoagulants, but the efficacy and safety profiles of NOACs have not been established in elderly adults and there are particular concerns regarding bleeding with NOACs in elderly adults. The suggested predisposing factors are low body mass index in frail and in adults over 85 years, altered body composition of muscle and fatty tissue and high frequency of renal impairment.

Recent reports suggest an higher potential risk of bleeding with NOACs in older individuals. No randomized trial has specifically randomized elderly adults to compare NOACs with vitamin K antagonists (VKA), or low-molecular-weight heparin (LMWH) as the population of primary interest.

This review has focused on a proposed physiopathological link between coagulation and the ageing process in order to analyze the role of anticoagulation in HF without AF and the role of NOACs in elderly adults for stroke prevention in individuals with AF and for VTE in acutely medically ill patients.

**Physiopathological Link Between Coagulation and Ageing**

Hemostatic processes contribute to gradual fibrin deposition within atherosclerotic plaques and over thrombus formation subsequent to plaque disruption. It is still debated whether hypercoagulability indicates an underlying atherosclerotic process or is cause of atherosclerosis and thrombosis. Stimulation of sympathetic nervous system (SNS) increases blood clotting (by V, VIII, and Von Willebrand factors) and platelet activation with raised risk for atherothrombotic events and major cardiovascular events after coronary revascularization procedures. In addition, the phenomena may be exacerbated in the elderly since the well recognized age-related autonomic dysfunction. The SNS regulates several homeostatic functions (e.g. cardiac, respiratory, digestion, urination and sexual arousal) and induces physiological changes during the “fight-or-flight response” (also called the acute stress response), that is a physiological reaction occurring in response to a perceived harmful event, attack, or threat to survival. During acute stress response or prolonged exercise, catecholamines (adrenaline and noradrenaline) facilitate immediate physical reactions associated with a preparation for violent muscular action and increased strength and speed in anticipation of fighting or running. These physiological changes include: increased blood flow to the muscles, raised blood pressure, heart rate, blood sugars and fats, increased muscle tension, dilation of pupil, enhanced perspiration, increased the blood clotting function of the body speeds up, and changes of circulating biomarkers. Although hastened blood coagulation the impact of SNS activation on hemostasis is not still clearly understood. Given the significance of increased hemostatic activity in atherosclerosis and the important role of the SNS in cardiovascular disease, SNS activation might contribute to arterial thrombus formation. Several studies have demonstrated that SNS activation induced procoagulant responses in patients with atherosclerotic plaques and endothelial dysfunction. Adrenaline infusion induces platelet activity and it is higher in hypertensive individuals than in normotensive controls. Moreover behavioral stressors, such as mental arithmetic and cold test, led to increase in fibrinogen and platelet activity as well as to impaired fibrinolysis in hypertensive individuals compared with normotensive controls. In patients with heart failure, there is an higher platelet activity with acute mental stress than normal controls. Chronic stimulation of the SNS and concomitant hypercoagulable changes could contribute to gradual fibrin deposition at sites of atherosclerotic lesions. Once hemodynamic stress for instance emotional arousal has triggered rupture of an atherosclerotic plaque, hypercoagulability due to catecholamine spillover with both activation of the hypothalamic-pituitary-adrenal axis and myocardial ischemia may promote coronary thrombus growth. These evidence raise the hypothesis that targeting the beta-adrenergic receptor system might be advantageous also for the control of blood coagulation. Also, hypercoagulable changes with morning surge in catecholamine levels due to both circadian
variation in catecholamine activity and postural change may be related to increased morning frequencies of thrombotic vascular events. In conclusion, future studies on the effects of SNS function on hemostasis mechanisms may further help integrating arduously achieved biochemical and biological knowledge for understanding the regulation of the SNS-hemostasis axis.

**NOACS IN ELDERLY PEOPLE WITH AF/VTE**

A recent meta-analysis of Lip G showed that NOACs did not cause greater major or clinically relevant bleeding than conventional therapy in individuals aged 75 and older (6.4% with NOACs vs 6.3% with conventional anticoagulants). Similar results were observed with NOACs and pharmacologically active agents (6.4% vs 6.3%). NOACs also did not cause extra bleeding for treatment of acute VTE or pulmonary embolism, extended treatment of VTE, or AF except thromboprophylaxis for acutely ill medical individuals. Risk of stroke and systemic embolism was significantly lower with NOACs than conventional therapy or pharmacologically active agents (3.3% vs 4.7%; absolute risk reduction = 1.4%). NOACs also resulted in a significantly lower risk of VTE or VTE-related death than conventional therapy (3.7% vs 7.0%) and pharmacologically active agents (3.9% vs 6.6%). In particular, regarding each NOACs: rivaroxaban did not cause greater major or clinically relevant bleeding than conventional therapy in elderly adults (4.5% vs 4.5%). Rivaroxaban was noninferior to or more effective than conventional therapy in prevention of stroke or systemic embolism and VTE or VTE-related death. The risk of major or clinically relevant bleeding was not higher with apixaban (5.1% vs 7.3%). Risk of stroke or systemic embolism and VTE or VTE-related death with apixaban was equal to or lower than conventional therapy. Safety data on dabigatran were more limited. Major or clinically relevant bleeding was similar with dabigatran and conventional therapy (9.3% vs 8.7%). Dabigatran was more effective than conventional agents in the prevention stroke or systemic embolism (3.2% vs 4.3%). NOACs did not cause greater bleeding than warfarin (6.5% vs 7.1%) or LMWH or LMWH followed by VKA (6.9% vs 5.3%).

These data suggest that NOACs did not lead to greater major or clinically relevant bleeding than conventional therapy and pharmacologically active agents in elderly adults. NOACs significantly reduced the risk of stroke or systemic embolism in elderly adults with AF. NOACs were also more effective than conventional therapy for the reduction of the risk of VTE or VTE-related death. A similar profile was also found for the effectiveness of the individual NOACs. Dabigatran, rivaroxaban and apixaban were more or as effective and safe as conventional therapy or pharmacologically active agents. However, the main concerns of geriatricians are about the bleeding risk. Several recent reports have raised concerns regarding the safety profile of NOACs in the elderly population. Reports initially suggested that NOACs may cause more bleeding events, including life-threatening or fatal bleeding in elderly adults. A 2 months audit conducted by the Haematology Society of Australia and New Zealand identified 78 episodes of bleeding in dabigatran treated individuals and participant age was one of the four major factors that contributed to these episodes. Two thirds of the participants were aged 80 and older and 58% had moderate or severe renal impairment. One of the major arguments for the findings was that the mean age of the trial population (RE-LY trial) was lower, and data from that trial may not be extrapolated into clinical practice in this case, but the current analysis for individuals aged 75 and older, including data from ten randomized controlled trials (RCTs), did not show excess bleeding with NOACs or with dabigatran specifically (data pooled from 2 RCTs). The data also showed that NOACs are significantly more effective than conventional therapy in this population.

Recent detailed analysis of bleeding related to apixaban and rivaroxaban in elderly adults in two large randomized trials also did not show excess bleeding with these drugs. The reasons frequently suggested for the greater risk of bleeding in elderly adults are renal function impairment, low body weight, drug interactions, and unavailability of reliable coagulation tests to monitor blood level of NOACs. Almost all previous articles reporting greater bleeding in elderly adults included individuals who had comorbidities, mainly coexisting renal failure, but all of the reports were from small observational studies or case reports and no randomized data are available. A possible explanation for the contrasting results of the current study might be that the chances of bleeding with NOACs are more related to associated comorbidi-
ties than the age of the individual per se. At the moment for edoxaban there are no publication about elderly patients.

The key message for clinicians is that the benefit of antithrombotic therapy is well established in elderly adults, including those who are at high risk of falling or bleeding. The Lip study suggests that NOACs are more effective than conventional anticoagulants in elderly adults. Old age per se should not be a criterion for withholding anticoagulation with NOACs. The recommended dose of apixaban is lower (2.5 vs 5 mg) in elderly adults with at least one comorbidity in addition to older age (i.e., a lower dose is recommended in those with ≥ 2 of aged ≥ 80, body weight ≤ 60 kg or serum creatinine ≥ 1.5 mg/dL). For individuals with AF, 110 mg of dabigatran twice a day is recommended for aged 80 and older in the European Union, rather than a 150 mg twice a day regular dose, although the Food and Drug Administration (FDA) does not recommend a routine dose modification for dabigatran in elderly adults. Dose modification for rivaroxaban is also not recommended for elderly adults, but a lower dose of dabigatran and rivaroxaban is recommended in individuals with moderate renal impairment.

A recent FDA postmarketing report of bleeding with dabigatran did not identify any unrecognized risk factors for bleeding. A large propensity score matched nationwide cohort study from Denmark supports the FDA report (which does not adjust for comorbidities). Another report showed no greater risk of bleeding with dabigatran in VKA-naive individuals. These arguments do not contradict the fact that caution should still be taken with NOACs in elderly adults with other comorbidities (mainly renal impairment) and very low body weight. Lack of a reversal agent for the anticoagulant effects of NOACs should also be kept in mind while prescribing these agents. Thus, an individualized case by case approach might be best for elderly adults, with proper judgment of risk of bleeding and associated comorbidities rather than a generalized “one drug fits all” approach.

**ANTICOAGULATION IN HF WITHOUT AF**

Although it has been a topic of investigation for more than 50 years, the use of anticoagulants in patients with heart failure (HF) in sinus rhythm remains an argument of controversy and clinical debate. Increased risk of thromboembolism, cardioembolic stroke and sudden death due to coronary occlusion occurs in about one third of HF patients, contributing to the high mortality and morbidity rates of the disease. A Cochrane systematic review compared anti-platelet treatment versus oral anticoagulation therapies (OATs) in HF patients without AF and included three RCTs. The rates of death, myocardial infarction (MI) and stroke were similar across OATs versus antiplatelet treatment. In pooled analyses there was no difference between warfarin and aspirin in all cause deaths or cardiovascular deaths. Although aspirin is of proven benefit in post-MI patients, there is inadequate evidence from long term studies to recommend its routine use in HF patients. Again, there is also no evidence to indicate superior beneficial effects from oral anticoagulation, when compared to aspirin, in HF patients, and there was some evidence of greater risk of bleeding events in warfarin as compared to aspirin. In conclusion, anticoagulation/antiplatelet therapy should be reserved for HF patients with other comorbidities (such as AF or underlying coronary artery disease) who may further benefit from these therapies. A recent meta-analysis has explored the potential role of anticoagulation for HF in sinus rhythm, showing that OATs might reduce the entire cardiovascular thromboembolic risk also in HF patients without AF. This meta-analysis included four randomized controlled studies of oral anticoagulation (the same three of Cochrane systematic review and WARCEF trial) involving overall 1825 HF patients treated with warfarin who were compared to 1838 HF patients treated with aspirin. There was no significant difference in mortality between OATs group and antiplatelet drug group. OATs have reduced ischemic stroke risk, but have increased major bleeding risk compared to antiplatelet
treatment. In all trials included, the primary outcome was cardiovascular death (stroke, MI, pulmonary embolism, peripheral arterial embolism) and sudden death. The WASH pilot study randomized 279 HF patients to treatment with either aspirin, warfarin or no antithrombotic therapy and showed no difference in mortality among these interventions. However, compared to the other two groups, more patients randomized to aspirin were hospitalized for worsening HF. The HELAS trial separated 197 patients according to the etiology of their HF. Only patients in the ischemic cardiomyopathy group (n = 115) were randomized to receive warfarin (target INR 2-3) or aspirin (325 mg), while patients in the non-ischemic group (n = 82) were randomized to receive warfarin or placebo. The incidence of the primary endpoint (composite endpoint of non fatal stroke, peripheral or pulmonary embolism, MI, re-hospitalization, exacerbation of heart failure or death from any cause) was not different between the groups. Major bleeding only occurred in the warfarin groups and was usually due to over anticoagulation but no case led to death. The WATCH trial included 1587 HF patients receiving aspirin (162 mg), clopidogrel (75 mg) or warfarin (target INR 2-3.5). Unfortunately, this trial was terminated early due to poor recruitment and was therefore underpowered to make any firm conclusion on antithrombotic therapy. Furthermore, this study did not have a placebo arm to show the effectiveness of antithrombotic therapy compared with no treatment. There was no difference among the three treatment groups for the primary endpoint (all cause mortality, non fatal MI or non fatal stroke). However, the data show a significant decrease in hospitalization rate in the warfarin group compared to aspirin and suggest that up to one third of all hospitalizations for HF could be attributed to the use of aspirin, which is consistent with the findings of the WASH study. Deaths and vascular events were similar on aspirin and clopidogrel. There were fewer hospitalizations for HF in the clopidogrel group. The safety data showed, as expected, a greater incidence of bleeding complications in the warfarin group. The WARCET trial randomized 2305 HF patients to receive aspirin (325 mg) or warfarin (target INR 2.5-3.5). The rates of the primary endpoint (composite endpoint of ischemic stroke, intracerebral hemorrhage or death from any cause) were 7.47 events per 100 patient-years in the warfarin group and 7.93 per 100 patient-years in the aspirin group, with no significant difference between the two groups. The rates of MI and hospitalization for heart failure did not differ significantly between the two groups, although there was a trend toward a higher rate of hospitalization for heart failure in the warfarin group. Major bleeding was significantly higher with warfarin than with aspirin (1.78 events with warfarin versus 0.87 with aspirin per 100 patient-years). However, intracerebral and intracranial bleeding did not differ significantly according to treatment group (0.27 events in the warfarin group and 0.22 in the aspirin group per 100 patient-years). Despite the reduction in stroke events observed with anticoagulants compared to control, this evidence needs to be interpreted with caution. In fact, nowadays OATs are indicated only in HF patients with AF, since the overall data available do not support its use in HF patients who are in sinus rhythm because, despite the reduction of stroke, increased bleeding is observed. The main cause of death in HF patients is attributed to refractory HF or sudden cardiac death and the latter is frequently due to new coronary (thrombotic) occlusion causing arrhythmic events. Systemic thromboembolism is common in HF patients, even in the absence of AF. Moreover, several studies indicate that patients with previous stroke or peripheral thromboembolism have depressed left ventricular (LV) function. In an analysis of > 600 deaths in a community long-term study comparing HF patients with depressed LV function versus those with preserved LV function, sudden death occurred in 21% and 16% respectively. New coronary occlusions (as reflected by MI) occurred in 50% of the patients within the first month during follow-up of 1.5 year in the depressed LV group. In fact, it is well established that patients with HF in sinus rhythm are burdened with a moderate risk of thromboembolism and frequent comorbid conditions such as AF, valvular disease and atherosclerotic vascular disease that predispose to thrombosis only add to intrinsic thromboembolic risk. Moreover, a recent study demonstrated similar levels of platelet activation in both AF and non-AF patients with cardiovascular comorbidities, suggesting that platelet activation in AF may be caused by underlying cardiovascular disease rather than AF itself. Thus, the increased risk of thromboembolism in HF may be related to the fulfillment of Virchow's triad for thrombogenesis in HF and its pathogenesis is multifactorial: low cardiac
output through dilated cavities of poor contractility, regional wall motion abnormalities and atrial fibrillation are the main factors. Abnormal endocardial surface after MI or inflammatory/infiltilative cardiomyopathy may also favor the formation of clots. It has also been recently suggested that patients with HF may be in a hypercoagulable state. Indeed, the pathophysiology of thrombosis in HF is complex and the underlying mechanisms are only partially known. Despite several evidence demonstrating the increased thromboembolic risk in HF patients, current guidelines from the American Heart Association and American College of Cardiology, the American College of Chest Physicians, and the European Society of Cardiology (ESC) do not support the routine use of warfarin in cardiomyopathy in sinus rhythm. In ESC Guidelines for the diagnosis and treatment of acute and chronic HF, warfarin (or an alternative anticoagulant) is recommended in patients with HF and permanent, persistent or paroxysmal AF without contraindications to anticoagulation (Class of recommendation I, level of evidence A). It is also recommended in patients with intracardiac thrombus detected by imaging or evidence of systemic embolism (Class of recommendation I, level of evidence C). The key evidence reports that warfarin is more effective in reducing the risk of stroke with respect to antiplatelet therapy and is preferred over antiplatelet therapy in patients at high risk for stroke. The same issue is addressed in the American Guide to Warfarin Therapy indicating that "warfarin is used frequently in patients with dilated cardiomyopathy, although no randomized trial has confirmed the benefit of anticoagulation." A Consensus Document from the ESC Heart Failure Association and the ESC Working Group on Thrombosis, which reviewed the published evidence, summarized ‘best practice’ and put forward consensus statements that may assist management decisions in clinical practice. This Consensus Document states “Given no overall benefit of warfarin on rates of death and stroke, with an increase in major bleeding – despite the potential for a reduction in ischemic stroke – there is currently no compelling reason to routinely use warfarin for all HF patients in sinus rhythm.” Thus, whilst there is no doubt about whether HF patients in AF should receive OATs, the routine use of OATs cannot be recommended in those patients in sinus rhythm without any previous AF.

NOACs

Recently, the therapeutic armamentarium for anticoagulation has been expanded thanks to the evidence arising from RE-LY, ROCKET-AF, ARISTOTLE and ENGAGE AF studies. These trials have evaluated the non inferiority of new anticoagulant molecules compared to warfarin in patients with AF. For more than 50 years, warfarin has been the primary medication used to reduce the thromboembolic risk events in patients with AF. Despite its clinical efficacy, warfarin has several limitations, including interactions with other drugs and food, a narrow therapeutic range, the need for frequent laboratory monitoring and frequent bleeding. Therefore, it is often not used and when it is, rates of discontinuation are high. Moreover, many patients receiving warfarin might still have inadequate anticoagulation. Thus, physicians and patients may favorably take new oral anticoagulants into account for the management of thromboembolic risk in AF.

In the RE-LY trial, patients with AF and high risk of stroke were randomized to receive dabigatran, a competitive inhibitor of thrombin, in blinded fashion at the doses of 110 mg or 150 mg twice daily, or adjusted-dose warfarin, in unblinded fashion. The study demonstrates that both dabigatran doses were non-inferior to warfarin with respect to the primary efficacy outcome of stroke or systemic embolism. In addition, the 150 mg dose of dabigatran was superior to warfarin with respect to stroke or systemic embolism and the 110 mg dose was superior to warfarin with respect to major bleeding. In the ROCKET-AF trial the investigators compared rivaroxaban, a direct factor Xa inhibitor, with warfarin for the prevention of stroke or systemic embolism among patients with nonvalvular atrial fibrillation who were at moderate to high risk for stroke. The study shows that rivaroxaban was non inferior to warfarin in the prevention of subsequent stroke or systemic embolism. Although there were no significant differences in rates of major and clinically relevant non major bleeding between the two study groups, intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. In the ARISTOTLE trial, the authors compared apixaban, a direct oral factor Xa inhibitor, with warfarin for the prevention of stroke or systemic embolism in patients with atrial fibrillation and at least one additional risk factor for stroke. The use of apixaban, as compared with warfarin, significantly reduced...
the risk of stroke or systemic embolism by 21%, major bleeding by 31%, and death by 11% in patients enrolled in the study. In the ENGAGE-AF TIMI 48 trial, the efficacy and safety of edoxaban, a direct oral factor Xa inhibitor, was compared with warfarin in patients with moderate to high risk atrial fibrillation for the prevention of stroke or systemic embolism. Both once a day regimens of edoxaban (60 mg and 30 mg) were non inferior to warfarin with respect to the prevention of stroke or systemic embolism and were associated with significantly lower rates of bleeding (significantly reduced risk of major bleeding by 20% with edoxaban 60 mg and 53% with edoxaban 30 mg) and death from cardiovascular causes 123.

These trials have similar conclusions: dabigatran, rivaroxaban, apixaban and edoxaban compared with warfarin, all significantly reduce the risk of hemorrhagic stroke. However, there are also some differences among the four trials, regarding patients' risk profile, modalities of drug administration and the study design especially for statistical analysis plans and power. However, head-to-head trials (superiority trial) are needed to further assess the therapeutic potential of this novel compounds and, possibly, test their use in pathologic conditions other than AF, such as in HF patients in sinus rhythm. In conclusion, at present, there are no guidelines indicating the use of prophylactic anticoagulation in elderly adults. NOACs significantly reduce the risk of stroke or systemic embolism in elderly adults with AF. NOACs are also more effective than conventional therapy for the reduction of the risk of VTE or VTE-related death. However, while numerous evidence have clearly stated that elderly patients with HF have an intrinsic risk of thrombotic events, no guidelines indicating the use of prophylactic anticoagulation in HF, a severe clinical condition whose mortality rates are still high.

CONCLUSIONS

Evidence suggests that NOACs do not lead to greater major or clinically relevant bleeding than conventional therapy and pharmacologically active agents in elderly adults. NOACs significantly reduce the risk of stroke or systemic embolism in elderly adults with AF. NOACs are also more effective than conventional therapy for the reduction of the risk of VTE or VTE related death. While numerous evidence have clearly stated that elderly patients with HF have an intrinsic risk of thrombotic events, no guidelines indicating the use of prophylactic anticoagulation in HF except in those affected by AF and/or carriers of prosthetic valve and/or history of thromboembolism. The SNS-hemostasis axis should be investigated better in further studies integrating biochemical and biological knowledge.

Older adults have an increased risk of thromboembolism, due to many comorbidities, polypharmacotherapies and the aging. Both venous and arterial thromboembolic risk have a high impact in elderly patients but they also have an increased risk of bleeding so for the physicians it is difficult to choose the best anticoagulation treatment. Over the last years some scores for risk stratification of stroke and bleeding have been created to help physicians, since new oral anticoagulants (NOACs) were introduced. Evidence suggests that NOACs do not lead to greater major or clinically relevant bleeding than conventional therapy in elderly patients. NOACs significantly reduce the risk of stroke or systemic embolism in elderly adults with AF and are also more effective than conventional therapy for the reduction of the risk of venous thromboembolism (VTE) or VTE-related death. However, while numerous evidence have clearly stated that elderly patients with heart failure (HF) have an intrinsic risk of thrombotic events, no guidelines indicating the use of prophylactic anticoagulation in HF except in those affected by atrial fibrillation (AF) and/or carriers of prosthetic valve and/or history of thromboembolism.
sympathetic nervous system-hemostasis axis should be investigated deeply in further studies integrating clinical approach with the novel biochemical and biological knowledge.

**Key words:** Anticoagulation, Elderly, NOACs, Heart failure, Atrial fibrillation and venous thromboembolism

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