

Featured Review



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Mechanisms And Management Of Thrombo-Embolism In Atrial Fibrillation

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Abstract

Atrial fibrillation (AF) is the most common cardiac arrhythmia in the general population and in patients with a history of cardiovascular disease. AF is becoming an outbreak particularly for the western countries as it increases with advancing age; furthermore, AF has a negative social impact because it is associated with stroke and myocardial infarction. Thrombosis generated in the left atrial appendage with ensuing embolism in the cerebral circulation is considered the most important cause of ischemic stroke. In addition to thrombo-embolism, AF is characterized by a constellation of atherosclerotic risk factors, including hypertension, dyslipidaemia and diabetes, which may predispose to serious clinical complications of atherosclerosis such myocardial infarction. Even if interventional trials with oral anticoagulants such as warfarin reduced by about 60% the risk of stroke, AF patients still disclose an elevated residual cardiovascular risk, which may severely complicate the clinical course and management of AF. Recent trials with new oral anticoagulants (NOACs) are opening a new scenario for the treatment of AF, which could improve its management, as NOACs apparently would not require monitoring. However, important caveats are emerging in the real world of AF management, which are questioning the concept that NOACs do not need monitoring. Thus, issues related to compliance and large variability in blood concentration may negatively influence the cost/effectiveness benefit of NOACs. This review will focus on pathophysiology of thrombo-embolism and athero-thrombosis and the impact of old and new anticoagulants in the real world of AF management.

Introduction

AF is becoming an outbreak particularly for the western countries as it increases with advancing age and, hence, thousands millions of subjects will suffer from AF in the next decades.¹ This will have a relevant social impact because AF is associated with high risk of cardiovascular events and increased morbidity and mortality.2 The clinical history of AF patients is complicated by ischemic events, which usually occur in cerebral circulation. Clinical characteristics of ischemic stroke from AF are increasingly severe³ and thromboembolism is considered the most important mechanism. However, in addition to thrombo-embolism, AF is characterized by a constellation of atherosclerotic risk factors which may predispose to serious clinical complications of atherosclerosis such as myocardial infarction.^{4,5} For this reason, AF is a peculiar clinical setting where ischemic events may be dependent upon either thrombo-embolism or athero-thrombosis or both.⁶ The different pathophysiology related to these two types of cardiovascular events opens a new scenario for AF management as managing clotting and platelet activation may be relevant to improve clinical outcome. This review will focus on the mechanisms that may account for thrombo-embolism and athero-

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Corresponding Author: Prof. Francesco Violi, Division I Clinica Medica, Sapienza University, Rome, Italy. thrombosis and the novel management of thrombo-embolism focusing the still unmet need to optimize anticoagulant therapy in the real word of AF.

Pathophysiology Of Thromboembolism And Athero-Thrombosis In AF

Thromboembolism

For many years, thrombosis-related clinical events have been essentially attributed to formation of thrombi in the left atrium with ensuing embolization in the cerebral and peripheral circulation. AF fulfils the criteria of Wirchow's triad, which are necessary for thrombus formation: blood stasis, endothelial dysfunction and clotting activation. Blood stasis is almost evident in the left atrium of AF patients where flow velocity is markedly reduced concomitantly with impaired contractility of left atrial appendage.7 It is still unclear, however, if remodelling-related blood stasis per se is actually implicated in favouring thrombus formation in AF. This hypothesis has been recently challenged by Nishida et al.8 who demonstrated that atrial remodelling per se does not influence clotting activation and thrombus formation. Endothelial dysfunction is another relevant component of Wirchov's triad which has been detected in patients with AF by measuring several markers of endothelial perturbation such as von Willebrand factor (vWf) and E-selectin.9,10 vWf is a glycoprotein secreted by endothelial cells in response to injury and it is usually measured to assess endothelial damage.^{9,11} Several studies consistently showed higher vWf levels in patients with AF.12 E-selectin is an adhesive molecule, which is specific of endothelial cells and is raised in the blood circulation as a consequence of



endothelial activation.¹³ Higher blood levels of E-selectin have been detected in patients with several types of AF.¹⁴ The relevance of endothelial dysfunction in the context of thrombosis-related clinical events has been investigated in 423 AF patients who were followed-up for approximately 2 years; at the end of follow-up patients with elevated levels of vWf and E-selectin were at higher risk of cardiovascular events suggesting that endothelial dysfunction may contribute to poor clinical outcomes in this setting.¹²

Clotting activation is the third component of Wirchow's triad which may contribute to thrombosis-related clinical events in AF.¹⁵ Several studies have demonstrated that AF may induce a hypercoagulation state as shown by increase of plasma levels of F1+2, D-dimer and fibrinogen.^{16,17} Different authors have investigated the relationship between clotting biomarkers and ischemic events, but results are equivocal; for instance, there are not convincing evidences that fibrinogen is associated with left thrombus or may predict vascular outcomes in AF.¹⁸ To address this issue we investigated 150 consecutive AF patients in whom plasma levels of fibrinogen was determined;¹⁸ among them 38 (25%) had an episode of ischemic stroke documented by magnetic resonance or computed tomography. The study showed a significant association between fibrinogen and ischemic stroke suggesting that coagulation system could be implicated in thrombosis-related ischemic events of AF.¹⁸

Athero-Thrombosis

Patients with AF are typically associated with different risk factors of athero-thrombosis including, overall, hypertension which may be detected in about 70-80% of the population; other risk factors are diabetes and hypercholesterolemia.⁵ AF patients disclose signs of atherosclerosis in the aortic plaque, which substantially increases the risk of stroke compared to plaque-free patients.¹⁹ Peripheral artery disease (PAD) is an established marker of systemic atherosclerosis, which depicts patients at higher risk of myocardial infarction and stroke. In an analysis of prevalence of PAD in AF an association between AF and PAD has been found ranging from 4% to 16%.²⁰ Recent data from our group showed, in >2000 patients with AF, a prevalence of low ankle/brachial index of around 20% reinforcing the concept that systemic atherosclerosis is associated with AF.²¹ Platelets play a pivotal role in the process of athero-thrombosis and

its clinical complication. The role of platelets in favouring ischemic events in AF has been also investigated by several authors; thus, P-selectin, beta-thromboglobulin and soluble CD40L (sCD40L), all markers of platelet activation, have been found elevated in AF.²² The relationship between one of these markers, i.e. sCD40L, and vascular outcomes has been investigated in 231 AF patients who were followed-up for a mean period of 28 months.²³ During the follow-up 35 patients experienced fatal and nonfatal ischemic stroke and myocardial infarction; Cox proportional hazard model showed that patients with sCD40L above the median were more likely to suffer from ischemic events suggesting a role for platelet activation in the clinical progression of AF.²³

Mechanism Of Disease

Together considered, these data indicate that an on going prothrombotic state, which encompasses clotting and platelet activation, is detectable in AF but the underlying mechanism is still undefined. An interesting hypothesis underlies on the existence of systemic inflammation and oxidative stress, which may not only confer a pro-thrombotic state via endothelium, platelet and clotting activation but may also be implicated in triggering electrical changes ultimately leading to AF.24 Elevated values of several markers of inflammation have been, in fact, detected in AF, such as C reactive protein (CRP), Tumor Necrosis Factor-alpha, interleukin 2,6 and 8 and monocyte chemoattractant protein-1.25 Some of them such as CRP and interleukin-6 has been suggested to contribute to the development of AF in different clinical models as shown by large population-based prospective studies indicating that CRP levels and other inflammatory markers are predictive of incident AF.²⁶ Of note, CRP is also associated with left atrium/left atrial appendage spontaneous echocardiographic contrast or thrombus corroborating the concept of an interplay between inflammation and thrombosis in AF.27 Furthermore, inflammatory markers have been investigated in patients undergoing cardiac surgery, which may be complicated by post-operative AF; in this clinical models elevated values of interleukin-6 and CRP have been associated with post-.operative AF suggesting inflammation as trigger of AF.25,28

As for markers of inflammation, experimental and clinical studies suggested that reactive oxidant species (ROS) might have a role as trigger of AF.^{29, 30} Experimental studies demonstrated that myeloperoxidase (MPO)-treated animals disclosed increased electrical instability and higher vulnerability for the development of AF, an effect that was not observed in animal knockout for the enzyme.³¹

Nicotinamide adenine dinucleotide phosphate oxidase (Nox) is the most important cellular producer of ROS and, as MPO, may play a crucial role for the development of AF. In several experimental and clinical studies a significant association between Nox-derived oxidase stress and AF was demonstrated.³² Nox up-regulation was also associated with nitric oxide synthase (NOS) 'uncoupling' suggesting that both Nox activation and dysfunctional NOS contribute to structural and functional remodelling.²⁹ In accordance with these findings, our group recently demonstrated that patients with paroxysmal/persistent AF had enhanced urinary excretion of isoprostanes, a marker of oxidative stress, and up-regulation of Nox2 compared with patients with permanent AF suggesting a role for Nox2 as a trigger of AF.³³

The interplay between Nox-derived oxidative stress and AF has

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Table 1: Take-home messages

-In atrial fibrillation either thrombo-embolism or athero-thrombosis may concur to the onset of ischemic complications

-In addition to the thrombo-embolic risk, patients with atrial fibrillation experience an increased rate of myocardial infarction

-Novel oral anticoagulants may represent a useful therapeutic approach, mostly for patients with low quality anticoagulation with warfarin

-Blood monitoring for novel oral anticoagulants could be appropriate for patients in which a high variability of blood levels is expected

-The association of anti-platelet drugs with oral anticoagulants increases the risk of bleeding without a clear benefit on ischemic events

been investigated in patients undergoing cardiac surgery.³⁴ Noxderived ROS were over-produced in right and left atria and were predictive of post-operative AF.^{29, 34}

The mechanisms eliciting inflammation and oxidative stress may be only a matter of speculation at the moment. AF is characterized by systemic signs of atherosclerosis, which are associated per se with inflammation. For instance, the fact that Ang-II is able to elicit MPO release from leucocytes is of particular relevance taking into account that hypertension, which is a classic atherosclerotic risk factor, is detected in the majority of AF patients. It is, therefore, arguable that hypertension may favour the occurrence of AF via an inflammatory process involving MPO release from leucocytes. Upregulation of Nox and 'uncoupled' NOS in the atria of patients prone to AF could also reflect a process of systemic inflammation related to the atherosclerotic process.²⁹ Thus, atherosclerosis is suggested to gradually reduce blood supply to myocardial tissue and cause atrium damage, which eventually leads to premature myocytes apoptosis, fibrotic replacement, and electrical changes associated with re-entry processes.⁶ Up-regulation of Nox-derived oxidative stress has been documented in patients with risk factors associated with AF. In particular, up-regulation of NOX2 or increased urinary excretion of isoprostanes or cellular over-production of ROS have been detected in patients with hypertension, diabetes, metabolic syndrome and dyslipidaemia, which may all predispose to AF.35 In this context, it is worthwhile mentioning that two prospective studies demonstrated that patients with sub-clinical atherosclerosis and no overt manifestation of cardiovascular disease are more prone to developing AF and that atherosclerosis may favour the occurrence of AF.³⁶ Based on this it is possible to postulate that systemic inflammation including a process involving leucocyte activation with ensuing release of MPO and/or atrial up-regulation of enzymes regulating ROS production such as NADPH oxidase may occur in the atria of patients prone to AF. Classic atherosclerotic risk factors such as hypertension, diabetes, dyslipidaemia, and obesity may favour structural and functional remodelling that ultimately lead to atrial fibrosis and changes in electrical atrium excitability via an inflammatory process including ROS over-production. These changes, in combination with clotting and platelet activation, which are potentially triggered by local/ systemic inflammation, may contribute not only to local thrombosis in the left atrium but also to athero-thrombosis occurring in the systemic circulation (Figure 1). This pathophysiologic scheme, which seeks to unify the mechanism accounting for thrombo-embolism and athero-thrombosis in AF needs, however, to be substantiated by interventional trials aimed at investigating if lowering inflammation and/or oxidative stress is of benefit for preventing or ameliorating the clinical course of AF.

Clinical Outcome Management In Atrial Fibrillation Stroke

Management of AF have been addressed essentially in lowering

thrombo-embolic stroke by anticoagulants and/or by antiplatelet drugs. Thus, a risk score has been validated to identify patients' categories, which could better benefit from antiplatelet or anticoagulant treatment. The CHADS, score,37 which includes Congestive heart failure, Hypertension, Age, Diabetes and previous Stroke, was firstly introduced to identify patients to be treated or not with an antithrombotic treatment (aspirin or oral anticoagulant). In the attempt of better discriminating patients at low or high risk of stroke the new CHA, DS, -VASc score³⁸ was recently introduced. This new score, which is characterized for the inclusion of two age cut-off,38 female gender and vascular disease as independent risk factors for stroke, divides AF patients in two categories: patients at low risk (score 0-1), and patients at high risk (score ≥ 2) of future cerebrovascular events. This classification has important implications for clinical management and treatment of patients.³⁹ In fact, while AF patients with CHA₂DS₂-VASc score of 0 are not candidates to receive any anti-thrombotic prophylaxis (truly low-risk patients), those with CHA, DS, -VASc score of 1 could be treated with an oral anticoagulant or, alternatively, with aspirin but a clear definition of this approach is still lacking .³⁹ Finally, all AF patients with CHA₂DS₂-VASc score ≥2 should receive an anticoagulant therapy with oral vitamin K antagonists (VKAs) or with the new oral anticoagulants (NOACs), in the absence of contraindications to these treatments.

Globally considered, trials with anticoagulants clearly demonstrated a net clinical benefit, which in fact was documented by a 68% risk reduction compared to untreated patients.⁴⁰ Concerns related to bleeding complication, particularly in the brain, blood monitoring and underuse of VKAs⁴¹ lead to develop NOACs which include dabigatran etexilate, a direct thrombin inhibitor, and inhibitors of factor Xa, such as rivaroxaban, apixaban, and edoxaban.⁴²

The use of NOACs presents some considerable benefits, consisting in fewer drug interactions than warfarin, and having a predictable anticoagulant effect, thereby apparently not requiring a continuous monitoring of laboratory values. A recent meta-analysis by Ruff⁴³ examined the four phase III trials that compared, for non-inferiority, warfarin versus dabigatran, rivaroxaban, apixaban and edoxaban respectively. The meta-analysis included 42411 participants receiving a NOAC and 29272 subjects on warfarin treatment. NOACs significantly reduced stroke or systemic embolic events, haemorrhagic stroke and intracranial haemorrhage and all-cause mortality but increased gastrointestinal bleeding. The benefit of NOACs compared with warfarin in reducing stroke or systemic embolic events was consistent across all subgroups examined.

Although these new drugs significantly enlarge the medical toolbox, NOACs are not currently suitable for all AF patients and some caveat must be taken into account before prescribing them.

An important relevant point concerns the differences between patients with a good time in therapeutic range (TTR) defined as a TTR>66% and those below. The pooled analysis of the trials performed by a recent meta-analysis⁴¹ demonstrated that the favourable effect

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Table 2:	Open issues	
-Treatment of elderly AF patients with novel oral anticoagulants still needs to be properly addressed		
- Therapeutic strategies to reduce the risk of myocardial infarction in atrial fibrillation patients must be planned		

-Knowledge of blood concentration of novel oral anticoagulants is mandatory

-Large randomized prospective clinical trials are needed to investigate the effect of combining oral anticoagulants with statins for cardiovascular event prevention

-The association of anti-platelet drugs with oral anticoagulants increases the risk of bleeding without a clear benefit on ischemic events

of NOACs in the reduction of bleeding events is evident only in patients with a low quality anticoagulation (TTR<66%).⁴¹ As a result, NOACs should not be the first choice of treatment for patients with good anticoagulation control with VKAs.

Even if globally considered NOACs reduce cardiovascular events, a sub analysis showed that low-dose NOAC regimens are able to reduce the incidence of haemorrhagic stroke, but are not as effective as warfarin to prevent ischemic stroke and myocardial infarction. Another point that needs to be taken into consideration concerns the use of NOACs in patients with renal failure. Patients with severe renal failure (eGFR <30 ml/min) and/or on dialysis treatment were not included in clinical trials, so VKAs are still the recommended treatment for these patients.

Apart from these specific issues, there is also another relevant point, which must be taken into account. The real advantage of NOACs compared to warfarin would consist on unnecessary monitoring of drug concentration in the blood. From patients with eGFR between 30-50 ml/min recent analysis from the RE-LY trial,44 outlined the wide variation in term of dabigatran concentration in blood with an increase of 47% compared to those with eGFR >80 ml/min. Of particular relevance was the fact that in patients with 30-50 ml/min dabigatran concentration could vary from as low as 28 ng/ml from as high as 215 ng/ml depending on the dosage used; age >75 years and female gender could be associated with 68% and 30% increase of dabigatran concentration respectively. Such variations were of particularly relevance for safety and clinical outcomes as low or high dabigatran concentration were associated with an enhanced risk of stroke or bleeding respectively. Analysis of dabigatran concentration, which was putatively associated with lower risk of stroke and bleeding, suggested that values around 100 ng/ml would be theoretically optimal, with an increased risk of stroke and bleeding for values <40ng/ml and >200ng/ml respectively. Based on this, predicting the risk of stroke and bleeding in old patients and females is almost difficult without precise information on drug blood levels. According to recent literature data, such wide variation of dabigatran levels is likely to account for the increased risk of bleeding and death which has been observed particularly in elderly patients.^{45, 46} Thus, in a recent survey from nationwide study the shift from VKSs to dabigatran was associated with a surprisingly enhanced risk for both thrombo-embolism and bleeding disorders clearly indicating the need for an accurate follow-up of AF patients on NOACs.⁴⁷ This finding questions the assumption that dabigatran can be used at fixed doses and raises concern on the claim that this drug category does not need blood monitoring. Unfortunately, data regarding the other NOACs are not yet available; thereby it remains to be clarified if the wide blood variability of NOACs is limited to dabigatran or can be observed with the other new anticoagulants.

Myocardial Infarction

A recent work by Soliman and colleagues⁴⁸ analysed the incidence

of MI in a population-cohort study including 1631 participants with AF. During a median follow-up of 4.5 years, the incidence rate of MI was 1.2 per 100 person-years, which was significantly higher compared to patients without AF also after adjustment for traditional atherosclerotic risk factors; this finding suggested, therefore, that AF per se is an independent predictor of MI. The incidence rate of MI reported by Soliman et al. is apparently higher compared to that recently shown by the interventional trial with the NOACs. Thus, globally considered, the rate of MI was in average 0.8% per year, with a range from 0.5 to 4%/year.⁵ Even if such difference may perhaps be explained by the fact that <50% of AF patients on the Soliman' study were on treatment with warfarin, other reports indicated, however, that in the real word of AF patients on treatment with warfarin the annual incidence rate of MI is actually elevated (> 1% year), and even more frequent than stroke.49 This difference with the interventional trials may depend on the fact that patients in the real world are older and at higher risk of athero-thrombosis despite adequate anticoagulation. At this regard, a previous study demonstrated that a good anticoagulation is associated with a lower risk of MI in AF⁵⁰ but the interplay between TTR and MI rate in AF population has not been clarified. The relationship between MI and AF is even more complicated when the NOACs are taken into account. Thus, no differences in MI rate were observed between NOACs and warfarin when all NOACs dosages were considered; conversely, compared to warfarin, a significant increase of MI rate was detected in AF patients with low NOACs doses. Even if such apparent paradox has not been explained, treatment of AF patients with or at risk of MI with low doses of NOACs should be carefully considered .

Management of AF patients at risk or with previous MI is, therefore, becoming a novel hot topic which needs to be addressed soon, as preventing MI in AF would reduce the risk related of combining oral anticoagulants with aspirin. Such association is quite frequent in AF as shown by interventional trails with NOACs in which 29-41% of patients included were treated with such combination despite no evidence of a clear benefit and serious risks of bleeding.^{51,52} So far, however, no strategy has been planned to reduce the risk of myocardial infarction in AF and its sequelae, nor it has been clarified if there are AF patients without previous coronary events who are at higher risk of myocardial infarction. In this context statins may be an attractive option as they have been able to reduce the risk of myocardial infarction in primary and secondary prevention trials.53 Furthermore, stating possess antithrombotic properties which may return useful in this setting, which is associated with a systemic and local on-going pro-thrombotic state.⁵⁴ Statins have been described to be useful to reduce new onset AF,^{55, 56} the recurrences of AF after electrical cardio-version/ablation,^{57, 58} after cardiac surgery⁵⁹ or in patients presenting with acute coronary syndrome.⁶⁰ Nevertheless, the effect of statin use in reducing vascular events in AF patients has never been investigated in prospective randomized trials.

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Conclusion:

NOACs are likely to be a step forward for the treatment of AF as they can strongly reduce the number of patients who cannot otherwise be anti-coagulated or are inadequately anti-coagulated. The claim of not monitoring this class of the drug in a population on multiple therapy seems to be unrealistic and potentially dangerous for both ischemic and bleeding outcomes; hence, developing laboratory device to monitor NOACs could be considered in patients potentially at risk of high blood levels variation. Management of AF patients at risk or with MI is another serious issue which deserves careful attention as in old AF population the rate of MI is elevated despite the use of oral anticoagulants.

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