Therapeutic uncertainties: first finding of atrial fibrillation in acute coronary syndrome

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KEYWORDS
Atrial fibrillation; Coronary artery disease; Acute coronary syndrome; Antithrombotic therapy

Atrial fibrillation (AF) and coronary artery disease share several risk factors and their simultaneous presentation in the same patient, sometimes in the course of acute coronary syndrome (ACS), is not a rare occurrence. Patients with AF and ACS represent an important clinical challenge in terms of diagnosis, prognosis and therapy. From a diagnostic point of view, AF may be new onset as a complication of ACS, or a pre-existing asymptomatic AF that is occasionally diagnosed during ACS. Regarding the prognosis, AF, whether new onset or already known, has been shown to exert a negative prognostic impact during ACS. Finally, the main therapeutic dilemma concerns the selection of the optimal antithrombotic therapy, which, at least in the first period following ACS, would require the combination of anticoagulant and antiplatelet drugs, with a consequent increase in the risk of bleeding complications. Several randomized studies have evaluated the therapeutic options in patients with AF and coronary artery disease, overall showing the advantage of a dual therapy with an antiplatelet and an anticoagulant compared with a long-term triple therapy with dual antiplatelet and anticoagulant therapy; the analyses of the ACS subgroups of these randomized studies confirmed such results also in the acute setting.

Introduction

Atrial fibrillation (AF) is the most common adult arrhythmia in the world population, with a prevalence of 8.8 million cases in Europe in 2010 and an estimated 17.9 million in 2060.1 Prevalence of AF is steadily increasing due to the increased life expectancy of the general population and a wider application of screening strategies and techniques for the early detection of subclinical AF.2 The main risk factors for the onset of AF include older age, hypertension, diabetes, obesity, chronic kidney disease, heart failure and obstructive sleep apnoea.2

The large overlap of risk factors for AF and coronary artery disease (CAD) means that their coexistence in the same patient is not a rare occurrence: in fact, AF is present in about 10% of patients with CAD, while 20-40% of patients with AF present with CAD or develop it over time, sometimes starting with an acute coronary syndrome (ACS). The analysis of mechanisms underpinning ACS is essential to understand the implications and reciprocal influences of AF and CAD on clinical management and, in particular, on therapy selection.

AF-ACS patients represent an important clinical challenge in terms of diagnosis, prognosis and therapy. The main diagnostic question concerns the temporal relationship between AF and ACS: in fact, AF could be of new onset as a complication of ACS or pre-existing but asymptomatic and therefore occasionally diagnosed during ACS. It is also important to understand whether AF affects the prognosis of ACS patients in terms of both morbidity and mortality. Finally, from a therapeutic point of view, a careful evaluation of the patient’s risk profile is necessary, since, at least in the early post-ACS period, a triple antithrombotic therapy (TAT) is theoretically indicated, contributing to an increased risk of bleeding events.3

Pathophysiological interactions

The mechanisms underlying the pathogenesis of AF are complex and multifactorial: in fact, they include

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mechanical (e.g. atrial stretch), functional (e.g. ischaemia, inflammation and autonomic dysfunction) and metabolic (e.g. catecholamines and atrial natriuretic peptides) factors. The pathophysiological interaction between AF and ACS is bidirectional, mainly taking place in one of the following two categories: (i) patients in whom AF acts as a risk factor for the onset of ACS and (ii) patients in whom ACS is a potential trigger of AF.

AF can adversely affect the development or progression of CAD acting as an irritative substrate, exacerbating endothelial dysfunction and systemic inflammation, which play a key role in the pathogenesis of CAD; in addition, the chaotic atrial activity typical of AF increases oxygen consumption at the atrial level and can reduce cardiac output, thus increasing the risk of Type 2 myocardial infarction (i.e. discrepancy between oxygen supply and demand); finally, in rare cases, ACS could be caused by AF with a cardioembolic mechanism.4

The presence of CAD can predispose to the development of AF with different mechanisms: it can favour re-entry phenomena by altering the electrical characteristics of the cardiomyocytes or by causing an atrial infarction with the formation of fibrotic areas; ischaemia can also promote focal ectopic activity (due to increased automatism), which can trigger AF; finally, after ACS, there is an autonomic imbalance in favour of the sympathetic system that, together with the oxidative stress and the inflammatory response during ACS, determine a neuro-autonomic remodelling, responsible for the initiation or stabilization of AF in the course of ACS. An important predictor of new-onset AF during ACS is the presence of CAD at the level of the proximal segments of the right coronary artery and the circumflex artery (i.e. before the emergence of the atrial branches).4

**Diagnostic challenges**

Diagnosing AF in a patient presenting with ACS does not come without difficulties. In particular, it is not easy to understand whether AF arose during ACS (perhaps even with a causal link suggesting its possible resolution following ACS treatment) or it was an accidental finding of a pre-existing AF that was asymptomatic and therefore unrecognized.

In this regard, it has been shown that about 15% of patients with no history of AF and with cardiac implantable electronic devices (i.e. pacemakers or defibrillators) have atrial high rate episodes or subclinical AF, which are associated with an increased risk of cardioembolic stroke and hospitalization for heart failure.

Furthermore, the presence of AF can make the electrocardiographic diagnosis of ischaemia or myocardial infarction less accurate: in fact, in the course of AF with high ventricular rate, a St-segment depression may be noted even in the absence of underlying CAD.

**Prognostic impact**

A fundamental question concerns the impact of AF on the prognosis of patients with ACS. This is an unresolved and debated issue, with some studies showing a negative impact on mortality and others denying it.5 Several factors contribute to the increase in mortality attributed to AF: the ACS population with concomitant AF is more likely to be older, to have more comorbidities and therefore to have an increased risk of mortality perse; in addition, the high heart rate during AF can shorten the duration of diastole and reduce cardiac output, therefore predisposing to adverse cardiovascular events (e.g. cardiogenic shock); finally, patients with AF are at high risk of cardioembolic stroke and therefore require the administration of long-term oral anticoagulation (OAC), with a consequent increased risk of bleeding.

An analysis of 161 266 patients with ACS from the Danish national registry showed a higher incidence of stroke at 1 year in patients with AF compared with those without AF, regardless of whether this was new onset [hazard ratio (HR) 1.67, 95% confidence interval (95% CI) 1.38-2.01] or pre-existing (HR 1.38, 95% CI 1.22-1.56); similarly, 1-year mortality was also higher in patients with new-onset (HR 1.52, 95% CI 1.43-1.62) and pre-existing AF (HR 1.25, 95% CI 1.21-1.31) compared with controls with no history of AF; finally, an increased risk of bleeding events was observed among subjects with new onset (HR 1.28, 95% CI 1.15-1.43) or pre-existing AF (HR 1.22, 95% CI 1.14-1.30) compared with those who have never been diagnosed with AF, possibly as a consequence of an increased intensity of antithrombotic therapy.6

**Selection of therapy**

In patients with AF and ACS, the main therapeutic dilemma concerns the selection of antithrombotic therapy. Indeed, ischaemic events occurring during AF or ACS are surrounded by different pathophysiological bases, theoretically requiring different classes of drugs for their prevention.7 In particular, thrombi formed in the left atrium as a consequence of blood stasis during AF are mainly flavoured by thrombin and therefore OAC is indicated for their prevention; on the contrary, cardiovascular adverse events after percutaneous coronary intervention (PCI) with stent implantation are mostly due to the exposure of a metal surface and the consequent aggregation of platelets, therefore requiring antiplatelet therapy, which consists of a dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor in the early period after ACS or PCI.8

Theoretically, a long-term TAT (OAC plus DAPT) would therefore be indicated, but it is not a valid option due to its detrimental impact in terms of bleeding complications; to minimize this risk, antithrombotic therapy should be modulated over the individual patient’s risk profile.9

The first randomized trials investigating TAT regimens [i.e. WOEST (What is the Optimal antiplatelet and anticoagulant therapy in patients with OAC and coronary StenTIng) and ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation)] were conducted before the advent of
direct oral anticoagulants (DOACs) and mainly showed a reduction in bleeding with dual antithrombotic therapy (DAT) with an antiplatelet agent and a vitamin K antagonist (VKA) compared with TAT with DAPT plus VKA.

Subsequently, four randomized studies were conducted to compare DAT with a DOAC plus an antiplatelet and TAT.

The PIONEER AF-PCI (A Study Exploring Two Strategies of and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention) trial compared three antithrombotic strategies in 2124 patients with AF undergoing PCI: (i) DAT with rivaroxaban 15 mg once daily (OD) and a P2Y12 inhibitor; (ii) TAT with DAPT plus rivaroxaban 2.5 mg bis in die (BID), followed by DAT with aspirin and rivaroxaban 15 mg OD and (iii) TAT with DAPT plus VKA. Both rivaroxaban strategies reduced the incidence of clinically relevant bleeding at 1 year compared with TAT with VKA (HR 0.59, 95% CI 0.47–0.76, \( P < 0.001 \) for rivaroxaban-based DAT; HR 0.63, 95% CI 0.50–0.80, \( P < 0.001 \) for rivaroxaban-based TAT); a subgroup analysis of this study showed no difference in the primary endpoint according to clinical presentation (i.e. ACS vs. non-ACS), in the absence of statistical interaction (\( P = 0.181 \) for rivaroxaban-based DAT and 0.726 for rivaroxaban-based TAT). 10

The RE-DUAL PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) trial randomized 2725 AF-PCI patients to one of three strategies: (i) DAT with dabigatran 110 mg twice daily (BID) and a P2Y12 inhibitor; (ii) DAT with dabigatran 150 mg BID and a P2Y12 inhibitor and (iii) TAT with DAPT plus VKA. After a mean follow-up of 14 months, DAT with dabigatran 150 mg was non-inferior to TAT (HR 0.72, 95% CI 0.58–0.88, \( P = 0.001 \) for non-inferiority), while DAT with dabigatran 110 mg improved to be superior to TAT (HR 0.52, 95% CI 0.42–0.63, \( P < 0.001 \)). A further analysis demonstrated the non-inferiority of the combination of the two DAT groups compared with TAT with regard to the composite of death, myocardial infarction, stroke, systemic embolism or unplanned revascularization (HR 1.04, 95% CI 0.84–1.29, \( P = 0.005 \) for non-inferiority).11 In a subgroup analysis of the RE-DUAL PCI, the benefit of dabigatran-based strategies in reducing the primary endpoint compared with TAT (HR 0.47, 95% CI 0.35–0.63 for dabigatran 110 mg and HR 0.67, 95% CI 0.50–0.90 for dabigatran 150 mg) was maintained regardless of clinical presentation (\( P > 0.10 \) for interaction).12

The AUGUSTUS (An Open-label, 2×2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention) trial involved a 2×2 factorial randomization to separately examine the effects of DAT vs. TAT and of apixaban vs. VKA: 4614 patients with AF and ACS or undergoing PCI were randomized to apixaban 5 mg BID or VKA and also to aspirin (TAT arm) or placebo (DAT arm). At 6 months, apixaban reduced the incidence of clinically relevant major or non-major bleeding events (HR 0.69, 95% CI 0.58–0.81, \( P < 0.001 \)), the composite of death or hospitalization (HR 0.83, 95% CI 0.74–0.93, \( P = 0.002 \)) and stroke (HR 0.50, 95% CI 0.26–0.97) compared with VKA, with no difference in the primary ischemic endpoint (HR 0.93, 95% CI 0.75–1.16). Additionally, there were more clinically relevant major or non-major bleeding events with TAT than with DAT (HR 1.89, 95% CI 1.59–2.24, \( P < 0.001 \)), with no difference in the composite of death or hospitalization (HR 1.08, 95% CI 0.96–1.21) and in the composite ischemic endpoint (HR 0.89, 95% CI 0.71–1.11).13 Apixaban was also superior to VKA in the reduction of clinically relevant major or non-major bleeding events in all treatment subgroups (\( P = 0.052 \) for interaction), including ACS patients treated with medical therapy (HR 0.44, 95% CI 0.28–0.68) and those undergoing PCI (HR 0.68, 95% CI 0.52–0.89); furthermore, no statistical interaction with the subgroups of clinical presentation was detected for the risk of death or hospitalization (\( P = 0.345 \) for interaction) or the composite ischemic endpoint (\( P = 0.356 \) for interaction).14 In the comparison of aspirin and placebo, aspirin confirmed the association with a higher incidence of clinically relevant major or non-major bleeding events compared with placebo in both ACS patients undergoing PCI (HR 2.02, 95% CI 1.53–2.67) and those treated with medical therapy (HR 1.49, 95% CI 0.98–2.26), in the absence of statistical interaction (\( P = 0.479 \) for interaction); furthermore, no statistical interactions were found with clinical presentation for the composite of death or hospitalization (\( P = 0.787 \) for interaction) or the composite ischemic endpoint (\( P = 0.710 \) for interaction).14

Finally, the ENTRUST-AF PCI (Edoxaban Treatment vs. Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention) trial randomized 1506 AF-PCI patients to DAT with edoxaban 60 mg OD and a P2Y12 inhibitor or TAT with DAPT plus VKA. At 1 year, DAT was non-inferior (but not superior) to TAT in terms of clinically relevant major or non-major bleeding events (HR 0.83, 95% CI 0.65–1.05, \( P = 0.001 \) for non-inferiority, \( P = 0.115 \) for superiority), with no difference in the composite ischemic endpoint (HR 1.06, 95% CI 0.71–1.69).15 A pre-specified sub-analysis of the ENTRUST-AF PCI showed the absence of statistical interactions of trial results with clinical presentation (ACS vs. chronic coronary syndrome): in the ACS subgroup, edoxaban did not reduce the primary bleeding endpoint (HR 0.73, 95% CI 0.59–1.02, \( P = 0.063 \), P.0.274 for interaction) nor the composite ischemic endpoint (HR 1.16, 95% CI 0.47–1.78, \( P = 0.557 \) for interaction).16

Based on this evidence, current guidelines of the European Society of Cardiology recommend the use of a DOAC over VKA [class of recommendation (COR) I, level of evidence (LOE) A]. To minimize the risk of bleeding, it is also recommended to prefer dabigatran 110 mg and rivaroxaban 15 mg over higher doses for the period of concomitant antiplatelet therapy (COR Ila and LOE B). In patients with AF-ACS, the administration of a short periprocedural TAT with aspirin, clopidogrel and OAC is recommended (COR I and LOE A), followed by DAT with an antiplatelet agent (preferably, clopidogrel) and a DOAC for up to 12 months (COR I and LOE A).
Alternative regimens can be implemented based on the individual patient risk profile. For example, it is recommended that patients at high risk of bleeding with no particular risk factors for stent thrombosis discontinue TAT within 1 week from PCI and continue with DAT for up to 1 month (COR I and LOE A).2,17 Conversely, if the risk of stent thrombosis prevails over the risk of bleeding, an initial one-month TAT should be considered (COR IIa and LOE C).2,17 Finally, although prasugrel and ticagrelor are not recommended in the context of a TAT (COR III and LOE C), they can be used as part of a DAT in patients at high or moderate risk of stent thrombosis (COR IIb and LOE C).17

**Conclusion**

Patients presenting with AF and ACS constitute a subgroup of particular interest in cardiology and present various areas of diagnostic, prognostic and therapeutic uncertainty. It is not always easy to distinguish new-onset AF from pre-existing unrecognized AF, but both forms appear to be associated with an increased risk of morbidity and mortality. From a therapeutic point of view, the main dilemma consists in the choice of the optimal antithrombotic therapy that, in AF-ACS patients, theoretically combines two classes of drugs, namely antiplatelet agents and anticoagulants. To minimize the impact of such regimen on the risk of bleeding, a proper ischaemic and bleeding risk stratification is of fundamental importance in order to make the best decision at the individual level based on patient characteristics, procedural aspects and clinical scenario.

**Conflict of interest:** None declared.

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