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Direct oral anticoagulation and severe obesity – One size fits all?

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ABSTRACT

Oral anticoagulation is obligatory in patients with atrial fibrillation (AF) to prevent thromboembolic stroke. Direct direct oral anticoagulants (DOAC) exhibit improved safety over Vitamin K antagonists, but any interference in haemostasis can impact on bleeding. Optimal anticoagulation remains challenging particularly in patients with co-morbidities. International Society of Thrombosis and Haemostasis (ISTH) guidelines recommend avoiding DOAC in patients with severe obesity, and systematic data on individual DOAC drug concentrations, clinical efficacy and safety in relation to body weight are lacking. A new study now provides reassurance that DOAC are safe and effective in a real-world cohort of morbidly obese patients, going some way to fill the knowledge gap pertaining to optimal management of concomitant obesity and AF.

1. Introduction

Thromboembolism leading to ischemic stroke is the most serious complication of atrial fibrillation (AF). Patients with AF generally display an activated coagulation system with abnormal fibrinolysis, and frequently show altered platelet reactivity and molecular phenotype. Even during phases of sinus rhythm, blood from patients with AF exhibits enhanced capacity for thrombin generation along with an increased clot density and resistance to thrombolysis [1]. Haemostatic deregulation progresses with AF severity in disease-matched patient cohorts, indicating that shifts in coagulation and fibrinolysis can be independently associated with the state of AF *per se*, and do not arise solely from the accompanying cardiometabolic co-morbidities [2]. Yet the causal relationship between AF and thromboembolism is complex and not fully understood. There is a temporal disconnect between episodes of AF and stroke [3], and culprit atrial thrombi are often not macroscopically evident at autopsy after a fatal cerebral embolism. Masawa et al. over 20 years ago proposed „rough endocardium“ as the smoking gun that indicates atrial thrombosis in the absence of macroscopically visible clots. Atrial autopsy biopsies from patients with AF after fatal cerebral infarct were noted to feature a wrinkled, granular appearance caused by fibrous and oedematous remodeling, consistently with distinguishable fibrin deposits, visible mural thrombi and neutrophil infiltration [4].

Nowadays, oral anticoagulation (OAC) is obligatory for guideline-conform management of patients with AF. The direct oral anticoagulants (DOAC) are largely replacing traditional coumarin-based drugs due to improved safety profiles, but any interference in haemostasis could cause excess bleeding, ranging from relatively harmless forms of haemorrhage to devastating gastrointestinal or intracranial bleeds. Optimal anticoagulation therefore remains challenging, particularly in patients with co-morbidities that additionally alter haemostasis and promote thrombosis. One example is morbid obesity. Current International Society of Thrombosis and Haemostasis (ISTH) guidelines recommend avoiding DOAC in patients with a body mass index (BMI) exceeding 40 kg/m^2 or a body weight above 120 kg. The pharmacokinetics of many drugs including the DOAC are skewed in patients with BMI deviating extremely from the norm, due to altered volumes of distribution and clearance rates. Such patients were generally underrepresented in the major clinical DOAC trials, so there are few robust data available regarding DOAC pharmacodynamics and pharmacokinetics in severe obesity. Accordingly, uncertainty exists regarding DOAC use, agent selection and dose adjustment in such patients.

A number of recent literature reviews, meta-analyses and retrospective cohort studies have sought to fill this knowledge gap by examining DOAC efficacy and safety in relation to BMI, particularly with very high body weight [5–9]. Data, however, remain sparse and conflicting regarding the impact of extreme BMI on the clinical pharmacology of individual DOAC. The present study published in this journal [10] shows that standard-dose DOAC are safe and effective in a real-world cohort of morbidly obese patients as compared to a general patient population. Minor bleeds were even half as frequent in the obese cohort as in the normal weight group. The fact that the morbidly obese subjects were younger, had a lower incidence of renal impairment and lower CHA_2DS_2-VASc and HAS-BLED scores must be considered when interpreting the findings, together with the retrospective study design and relatively small sample size (n = 135). Nevertheless, the finding that DOAC safety and efficacy is retained with severe obesity is consistent with a just-published study in patients with venous thromboembolism receiving rivaroxaban or apixaban [11].

A statement by the American Heart Association this year highlights obesity as a critical culprit driver of cardiovascular diseases including AF [12]. Obesity induces an atrial cardiomyopathy that provides the vulnerable substrate for AF evolution, along with aggravation of the

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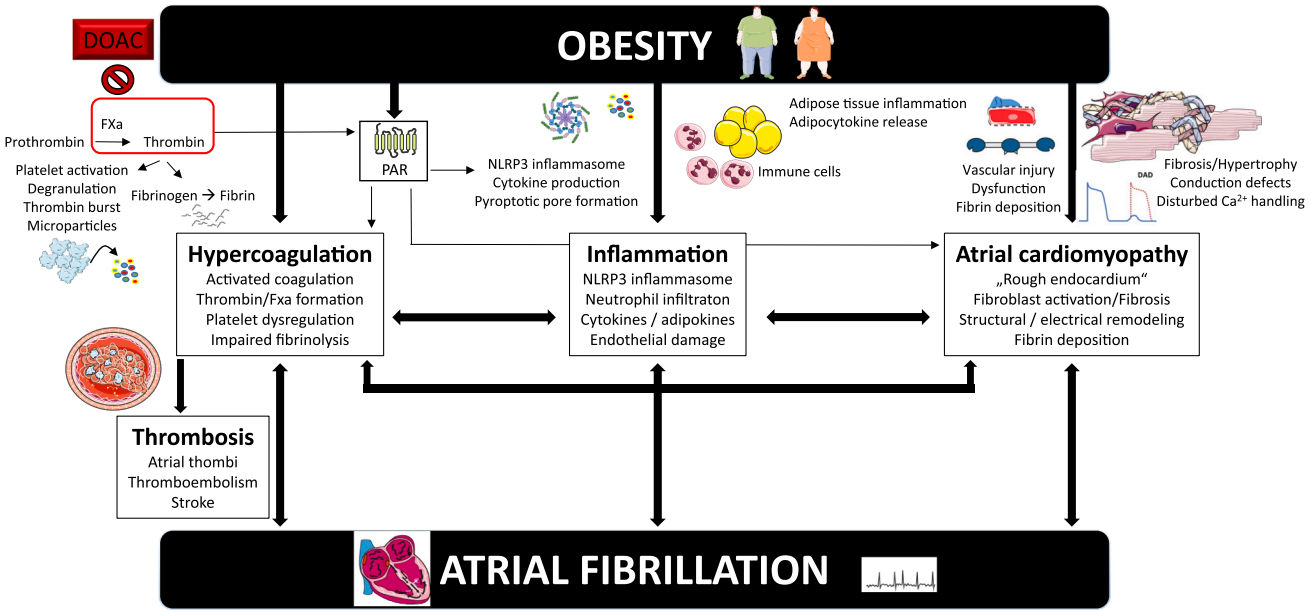

Fig. 1. DOAC are candidate master inhibitors of the inflammation/thrombosis/atrial cardiomyopathy axis in obesity**.** The causes and consequences of atrial fibrillation (AF) are closely linked to a prothrombotic state, sterile inflammation and an atrial cardiomyopathy that encompasses structural, mechanical and functional remodeling of the atrial myocardium. The same constellation of deleterious changes is associated with obesity, a major driver of AF. The direct oral anticoagulants (DOAC) may represent master inhibitors of this pathological interaction. The inhibitory targets of DOAC, the coagulation factors thrombin and activated factor X (FXa), promote clot formation and the activation, aggregation and degranulation of platelets, culminating in thromboembolism and stroke. Via protease-activated receptors (PAR), thrombin and FXa also trigger coagulation-independent inflammatory, structural and functional alterations in adipose tissue, blood cells and the heart and vasculature, thereby supporting the inflammatory atrial cardiomyopathy that provides a vulnerable substrate for AF. By disabling this thromboinflammatory interplay, DOAC may suppress both the evolution and the thrombotic consequences of AF in patients with obesity.

procoagulant state. One master switch linking adiposity, thrombosis and pro-arrhythmic atrial remodeling is inflammation. Particularly inflammatory and metabolic remodeling of the epicardial fat depot and its inter-organ communication with the atrial myocardium and blood compartment is increasingly considered to govern obesity-driven AF and thrombosis [13,14]. DOAC interfere in this self-perpetuating cross-talk to suppressing obesity-driven inflammatory sequelae and reducing atrial fibrosis and electrical remodeling in various experimental models (reviewed in [15]). Mechanistically, this can be attributed to reduced signalling through protease-activated receptors (PAR), a family of four G-protein coupled receptors activated by proteolytic cleavage of the extracellular domain in response to thrombin, FXa and other serine proteases. We recently identified PAR4 as an upstream regulator of the NACHT, LRR, and PYD domains containing protein 3 (NLRP3) inflammasome in human atrial fibroblasts, with increased PAR4 expression in atrial appendages of diabetic obese patients correlating positively with indices of NLRP3 inflammasome activation [16]. Sterile inflammation triggered and propagated by the NLRP3 inflammasome critically facilitates AF evolution [17,18], also in the setting of obesity [19].

Both AF pathophysiology and its thromboembolic sequelae in obesity thus encompass a complex constellation of derailed haemostasis and inflammation (Fig. 1). The major DOAC trials did not entail electrocardiogram monitoring, so if DOAC affect the incidence of AF and its recurrence rate remains to be verified. Systematic study of individual DOAC drug concentrations, clinical efficacy and safety in relation to BMI is lacking, and it is not clear why anticoagulants reduce but do not completely prevent thrombosis, or why atrial thrombi dislodge to cause stroke in some patients but remain *in situ* in others. The present study by Navarro-Almenazarr [10] does not answer these open questions, but at least provides reassurance that DOAC as a group are safe to use in patients with severe obesity.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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