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Anticoagulation in difficult settings RELOADed: Evidence for applicability of direct oral anticoagulants in patients with atrial fibrillation, renal impairment and cancer

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Atrial fibrillation (AF) is the most common form of cardiac arrythmia and a predominant risk factor for thromboembolism, ischemic stroke and myocardial infarction. There are many translational challenges for new therapeutic approaches and novel antiarrhythmic drug options providing long-term safety and efficacy are emerging only slowly [1,2]. Prior stroke may itself promote AF development [3], strongly indicating that the relationship between these pathological entities is bidirectional. Oral anticoagulation (OAC) is therefore an indispensable component of the clinical management of patients with AF, but its application is often suboptimal [4,5]. Current OAC options comprise the classical coumarin-derivatives such as warfarin or phenprocoumon, or the direct OACs (DOACs) dabigatran, rivaroxaban, apixaban or edoxaban. The coumarin-derivatives inhibit the hepatic synthesis of the clotting factor precursers FII (prothrombin), FVII, FIX and FX. Accordingly, full anticoagulation is achieved only after already secreted clotting factors are eliminated. This delay a delay of up to 2 weeks makes bridging anticoagulation with heparins obligatory, especially since production of the short-lived endogenous antithrombotic proteins C and S are also suppressed. The DOAC by contrast do not prevent clotting factor synthesis, but act as direct small-molecule inhibitors of activated coagulation factor II (FIIa or thrombin, in the case of dabigatran) or of activated coagulation factor X (FXa, in the case of the xabans rivaroxaban, doxaban and apixaban). The anticoagulant effect shows a rapid onset but the relatively short half-life (for rivaroxaban approximately 5-9 h) means that a missed dose will immediately restore thrombotic risk [6].

Interference with the haemostatic system always carries the risk of excessive bleeding, with intracranial haemorrhage being the most devastating form of OAC-associated bleeding. And as if weighing up the essential thromboprophylaxis benefit against the devastating risk of bleeding were not difficult enough for the treating physician, matters are further complicated by common co-morbidities such as coronary artery disease, liver or kidney diseases [4,7]. Real-world evidence how different approaches fare in routine care is therefore critical to guide the clinician's decision-making, all the more so for management of specific patient subgroups, who often display both high thromboembolic risk and high predisposition to adverse bleeding.

Renal dysfunction is quite frequent in patients with AF, and both its clinical prognosis and its inflammatory pathophysiology are intimately linked to those of AF [8]. Kidney dysfunction per se increases the dual risk of thromboembolism and bleeding, and impacts detrimentally on DOAC pharmacokinetics, which are renally cleared to different extents [9]. Although the clearance of coumarins is not directly dependent on renal function, warfarin is subject to a multitude of drug interactions, which occur in part through its high degree of serum albumin binding [10,11] and which are more likely to occur with the polypharmacy that is common practice in patients with kidney disease. Accordingly, kidney disease remains a difficult scenario for anticoagulant management of patients with AF [7].

In this issue of the journal, Bonnemeier et al. [12] report on the RELOAD retrospective German database study, which assessed outcomes of phenprocoumon and rivaroxaban in patients with AF, renal impairment, and cancer. The sub-study analysis highlighted the superior safety profile of rivaroxaban in patients with concomitant renal impairment and no evidence of cancer at baseline. The DOAC was associated with a significantly lower incidence of ischaemic stroke than phenprocoumon (2.40 vs 3.51 events per 100 patient-years, respectively, hazard ratio [HR] = 0.72, 95% confidence interval [CI] 0.55–0.94, $p = 0.015$), and a numerically lower incidence of intracranial haemorrhage (0.57 vs 0.89 events per 100 patient-years, respectively, HR = 0.66, 95% CI 0.38–1.14, $p = 0.14$). In patients with evidence of cancer at baseline, the favourable profile of rivaroxaban vs. phenprocoumon was blurred, although numerically the benefit was retained. Malignancy with concomitant AF is a difficult scenario for anticoagulant management, since cancer heightens both thrombotic risk and at the same time predisposes to more bleeding events [13,14]. Afflicted patients therefore require aggressive yet careful OAC treatment, although the precise regimen with which this can be accomplished remains unclear. The recent Hokusai VTE Trial highlighted the non-inferiority of edoxaban compared to a low molecular weight heparin, the gold-standard for OAC care in cancer patients, with better thromboembolic protection and modestly heightened gastrointestinal and urogenital bleeding [15]. In another recently reported retrospective database analysis of patients with AF and malignancy treated with rivaroxaban, dabigatran or apixaban versus warfarin [16], ischemic stroke rates were similar between all treatments, but the DOACs achieved lower rates of venous thromboembolism. In terms of bleeding, stratified analyses showed that rivaroxaban led to more severe bleeding

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than warfarin in women but not men, while dabigatran increased the risk of severe bleeding within the first 90 days of anticoagulation, but not thereafter. The new findings from the RELOAD study [12] now provide further evidence that, overall, the DOACs appear to be a suitable alternative to coumarin-derivatives in patients with cancer, although to date only apixaban has been approved for this patient population.

Between the concept of "one pill fits all" and personalized medicine lies a wide spectrum, and the physician is obliged to carefully weigh risks and benefits in the light of new developments and evidence. Further prospective evidence on how different approaches actually fare in the real-world setting are therefore invaluable to guide not only the individual clinician's decision-making but also to guide evolution. The new data provided by Bonnemeier et al. [10] may help to manage AF patients with renal impairment and concomitant cancer.

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Disclosures

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