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Editorial

Recent Clinical Assessment Tools to Predict the Quality of Oral Anticoagulants in Patients with Atrial Fibrillation

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The prevalence of atrial fibrillation in Europe is more than double that reported just one decade earlier, it is now ranging from 1.9% in Italy, Iceland, and England to 2.3% in Germany and 2.9% in Sweden in the adult population [1].

A meta-analysis of different trials on patients with non-valvular atrial fibrillation (NVAF) had demonstrated an average annual stroke rate of 4.5% for patients without a previous stroke and 12% for patients with a previous history of stroke in those patients not receiving antithrombotic therapy [2]. It is clear that the most important treatment goal in atrial fibrillation is to reduce thromboembolic complications.

In a large meta-analysis, the relative risk (RR) reduction of stroke with vitamin K antagonists (VKAs) was highly significant and amounted to 64%. All-cause mortality was significantly reduced (26%) by adjusted-dose VKAs versus control [2].

To achieve the optimal balance between embolic stroke risk with low international normalized ratios (INRs) and an increasing bleeding risk with high INRs, the INRs need to be in the optimal range of 2-3 for the prevention of stroke and systemic embolism in patients with non-valvular atrial NVAF on VKAs [3,4].

Despite 60 years of clinical experience, the maintenance of stable INR in patients using VKAs remains a challenging task.

It is well known that the efficacy and safety of VKAs therapy are closely associated to the quality of oral anticoagulation management [5,6]. The quality of anticoagulation can be measured by a number of methods. A meta-analysis of 47 studies of patients with atrial fibrillation on oral anticoagulation treatment with VKAs demonstrated that the time in therapeutic range method (TTR) measured by the Rosendaal method and the proportion of INR in range (PINRR) were the most frequently reported measures to determine the therapeutic effectiveness of oral anticoagulation proved that both method have a significant correlation ($r = 0.99$, $p = 0.001$) [7].

Several studies have shown how a high TTR translates into a lower risk of stroke and bleeding, whilst on VKAs [7,8]. A recent European consensus document recommends that an average individual TTR should be > 70% for optimal efficacy and safety outcomes whilst on VKAs and this is also recommended in the European Guidelines [9].

The Non-vitamin K antagonist oral anticoagulants (NOACs) have revolutionized the landscape of anticoagulation management and greatly increased the interest toward finding an easy clinical tool to identify those patients who would do well on VKAs or conversely, to be a good candidate for one of the NOACs.

A meta-analysis of four landmark NOAC trials in non-valvular atrial fibrillation revealed a significant 19% stroke risk reduction versus VKAs, which was driven by the reduction in haemorrhagic stroke [10]. The quality control of oral anticoagulation is the most important risk factor for bleeding and intracranial haemorrhage [10].

In this regard, Apostolakis., *et al*. proposed the SAME-TT2R2 score [Sex, Age (< 60 years), Medical history (more than two of the following: hypertension, diabetes, coronary artery disease/myocardial infarction, peripheral arterial disease, congestive heart failure, previous stroke, pulmonary disease, hepatic or renal disease), Treatment (interacting drugs, e.g. amiodarone for rhythm control) (all 1 point), as well as Tobacco use (2 points) and Race (non-Caucasian; 2 points)] to predict the quality control of VKAs [11].

The SAMe-TT2R2 might be criticized at two levels:

- First, at predicting good anticoagulation control (i.e. high PINRR or TTR), the performance of categorical SAMe-TT2R2 (0 - 1 point vs. ≥ 2 points) was rather modest [12,13]. Moreover, SAMe-TT2R2 was found to have suboptimal performance in external validation populations (i.e. area under receiver operating characteristic curve [AUC] for relevant clinical end points < 0.6) [5,14].
- Second, several clinical important predictors which have shown significant association with poor anticoagulation control with VKAs were not included in the SAMe-TT2R2 score [13,15,16].

Taken into consideration the possible limitations of SAMe-TT2R2, a new clinical tool to predict anticoagulation control of VKAs in elderly patients has been proposed by Lin., *et al*. the PROSPER score [pneumonia; 1 point, Renal dysfunction; 2 points, Oozing blood (i.e. bleeding history); 1 point, Staying in hospital ≥ 7 days; 1 point, Pain medication; 1 point, No Enhanced anticoagulation care; 4 points, Rx for antibiotics; 1point]. The proposed PROSPER outperformed the SAMe-TT2R2 at predicting TTR ≥ 70% for those patients aged ≥ 65 years, the findings suggest that a PROSPER score > 2 is predictive of having poor TTR; therefore, may be a good indicator to prescribe NOACs [17]. More validations of the PROSPER score in large cohorts of patients with NVAF from different races will determine its usefulness in the real world practice.

In the real world daily practice the clinicians highly appreciate the introduction of reasonable clinical tools which could refine their judgement and help the decision making process.

The estimation and further refinement of the current risk assessment tools is a continuous process which deserves more efforts. Really, future research are needed to improve our daily clinical practice regarding this dilemma.

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