The importance of excellence in the quality of anticoagulation control whilst taking vitamin K antagonists

Vanessa Roldán¹; Francisco Marín²

¹Department of Hematology and Clinical Oncology, Hospital Universitario Morales Meseguer, University of Murcia, Instituto Murciano de Investigación Biosanitaria Virgen de la Arrixaca (IMIB-Arrixaca), Murcia, Spain; ²Department of Cardiology, Hospital Universitario Virgen de la Arrixaca, University of Murcia, Instituto Murciano de Investigación Biosanitaria Virgen de la Arrixaca (IMIB-Arrixaca), Murcia, Spain

The efficacy and safety of vitamin K antagonist (VKA) therapy are closely associated to the quality of oral anticoagulation (OAC) management (1, 2), as reflected by the average percentage of the time in therapeutic range (TTR) of the international normalised ratio (INR) 2.0–3.0. Indeed, various studies have shown how a high TTR translates into a lower risk of stroke and bleeding, whilst on OAC (3–6). A recent European consensus document recommends that an average individual time in therapeutic range (TTR) should be >70% for optimal efficacy and safety outcomes whilst on a VKA and this is also recommended in the European Guidelines (7). In the National Institute for Health and Care Excellence (NICE) guidelines, a TTR of >65% is recommended for patients with AF who are on VKA therapy (8).

The VKAs have several limitations mainly due to its narrow therapeutic window and its variable dose requirement. The maintenance dose of VKAs is influenced by many different factors, including race, dietary vitamin K intake, comorbidities (eg. liver disease and acute illness) or whether the patient may be taking interacting drugs (2). Maintenance dose is also partly influenced by genetic polymorphisms, although the percentage of dose variability attributable to genetic variants plus clinical factors is only about 50% (9).

Thus, pharmacogenetics-guided dosing of warfarin has not yet demonstrated the ability to decrease out-of-range INRs, to improve TTR, reduce labile INRs, and consequently, to decrease thromboembolic and bleeding events and to be cost-effective in patients taking VKAs (10). Also, patients in ‘real life’ clinical practice tend to be older, with associated comorbidities and polypharmacy, which often results in VKAs underuse and poor quality of anticoagulation evaluated as a low TTR (11).

The difficulties in achieving a high TTR as well as the inconvenience of regular anticoagulation monitoring and the various food/drug restrictions associated with the VKAs have led to the recent introduction of the non-vitamin K antagonists (NOACs, previously referred to as new or novel OACs), which offer improved efficacy, safety and convenience compared to the VKAs (12). Thus, poorly controlled VKA-therapy patients would benefit from switching to anticoagulant therapy with any NOAC, especially if they were experienced VKA patients.

What about decision making in anticoagulation-naive patients, choosing between VKA or NOAC? VKAs remain the main OAC used in many countries, especially where economic considerations are a factor. One criterion often used to sanction NOAC use is a ‘trial of VKA’ or ‘VKA stress test’ to see what the TTR value is at six months, with a NOAC only allowed if TTR <65% (13). Thus, many patients have to undergo this trial of VKA to show that high TTRs cannot be achieved, before a NOAC prescription is reimbursed. This is especially important in patients who initiate conventional OAC as more INR fluctuations occur during the first 3 months, resulting in a higher risk of thromboembolic and haemorrhagic events (14, 15).

Rather than a ‘trial of VKA’ for everyone, decision-making for the prescriber could be easier, with the availability of a simple easy clinical tool to identify which patients who would do well on VKAs (with high TTRs) or conversely, who would on probability be likely to have low TTRs. In this regard, Apostolakis et al. (16) proposed and validated the SAME-TT²R² score [Sex, Age (< 60 years), Medical history (at least 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 eg amiodarone for rhythm control) (all 1 point), as well as current Tobacco use (2 points) and Race (non-Caucasian; 2 points)]. This simple clinical score (SAME-TT²R²) could help decision making by identifying those AF patients that would probably do well on VKAs with a high average TTR (ie. those with SAME-TT²R² score 0–2), or those unlikely to achieve a good TTR (SAME-TT²R² score >2).

Although validation studies on the SAME-TT²R² score (1, 17, 18) have been performed on retrospective cohorts, this score needs validation in a contemporary prospective population of AF patients who were initiating OAC with a VKA. Also, this score has only been evaluated in patients with AF and not in patients with venous thromboembolism (VTE), where ‘rhythm control drugs’ did not play any role, and clinical risk factors may be different. This is pertinent given that anticoagulant therapy in VTE patients usually lasts for 3–6 months and underanticoagulation may leads to post-thrombotic syndrome or pulmonary hypertension (19).

Regardless of the choice of OAC drug, patient education to warranted treatment

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Thrombosis and Haemostasis 113.4/2015
adherence is mandatory, as well as appreciating patient’s values and preferences balancing thromboembolism and bleeding risks (20, 21). The NICE guidelines recommended addressing the following factors that may contribute to a poor INR control: impaired cognitive function, adherence to prescribed therapy, illness, interacting drug therapy lifestyle factors including diet and alcohol consumption (8). The 9th ACCP conference established as a best practice statement that health-care providers who manage OAC therapy should incorporate patient education, systematic INR testing, tracking, follow-up, and good patient communication of results and dosing decisions (22). Thus, patients are best managed in specialised anticoagulation clinics, which usually achieves higher values of TTR and generally provides the best outcomes (2, 14, 23-25). In clinical trials, patients in centres with high average centre-based TTRs have less profound differences in efficacy and safety outcomes between NOACs and warfarin (26). A recent ‘real world’ study from Hong Kong shows that stroke prevention improved with better TTRs, but dabigatran incrementally improved stroke prevention (27).

The average individual TTRs generally increases over time, but even in very well and experienced patients, their TTR value can decrease during follow-up (1). In this issue of Thrombosis and Haemostasis, Kooistra et al.(28) demonstrated how a single extremely high INR (>8) translates to poor anticoagulation quality and a significantly higher risk for bleeding and thrombosis, in a cohort of initially stable patients on OAC (including both AF and VTE patients). However, half of these patients reported an inadequate individual TTR before their over-anticoagulation episode. The strengths of the study are not only the large size of the cohort and the prospective design of patients who were managed in a specialised thrombosis service.

VKAs have been the unique OAC option for the last 60 years. Although its management has much improved in order to optimise its efficacy and safety (and thus, patients outcomes), these drugs do still have important shortcomings. If VKAs are chosen as a therapeutic option, all efforts should be directed to achieve and maintain a high TTR. On the other hand, NOACs offer a very good alternative option for patients in whom VKAs are not effective, safe nor suitable. All efforts should be made in identifying these patients and avoiding ‘VKA stress test’ before a NOAC is prescribed. In this regard the SAME-TT₂R may help decision making between VKA and NOACs, and the ‘trial of VKA practice should be abolished given the likely initial increased risks of thromboembolism during the initial period whether TTRs are suboptimal.

Conflicts of interest
None declared.

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