Should patients on vitamin K antagonists be treated differently?

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This editorial refers to ‘Edoxaban vs. warfarin in vitamin K antagonist-experienced and naive patients with atrial fibrillation’1, by M.L. O’Donoghue et al., on page 1470.

Relative to warfarin, non-vitamin K oral anticoagulants (NOACs) are at least as good at preventing stroke or systemic embolism, cause less haemorrhagic stroke, and result in modestly lower mortality.1 Thus, the European Society of Cardiology has recommended NOACs in place of vitamin K antagonists (VKAs) in most patients with atrial fibrillation (class IIa, level of evidence A).2 According to one report, the use of NOACs in the USA has increased to > 60% of prescriptions for patients being initiated on oral anticoagulation.3 However, patients already treated with VKAs are usually not switched to NOACs.4 The low rates of switching from VKAs to NOACs relate to multiple factors including patient preference, medication cost, and clinical factors such as severe renal impairment. There is a common perception that a patient who is stable on a VKA will derive less benefit from a NOAC than a “VKA-naive”, patient who has not been previously treated with a VKA. The question remains whether or not this perception is supported by evidence.

Not only does prior use of a VKA influence decisions to use a NOAC, but so does the degree of International Normalized Ratio (INR) control on a VKA, as measured by the time in therapeutic range (TTR). The prevailing opinion is that switching to a NOAC is less beneficial for patients on a VKA with a high TTR. In the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W) trial, patients who were at centres with higher average TTR did better on warfarin than on clopidogrel and aspirin, which was not the case for patients at centres with low TTR.5 While this finding seemed logical from a clinical perspective, this “subgroup” was defined by post-randomization features and was confounded by other factors, and thus should be interpreted with caution. In aggregate, when analyses according to TTR were done in the four large trials comparing NOACs with warfarin, stroke rates were lower at centres with high TTR in the warfarin group—but also in the NOAC group, showing that TTR is reflecting more than quality of VKA treatment. Overall, there was modestly less treatment benefit with NOACs vs. warfarin in the centres with high TTR, although the lower rate of haemorrhagic stroke with NOAC vs. warfarin was consistent regardless of TTR. Therefore, despite some uncertainty related to the limitations of the analyses, it appears that the benefits of NOACs, while somewhat less, are generally consistent regardless of INR control at the level of the centre.

The issue of INR control is also relevant to the discussion of prior VKA treatment, since patients with a history of VKA treatment have modestly higher TTR values than patients that are VKA naive in the clinical trials (Table 1).6–8

In this issue of the journal, O’Donoghue et al. describe the results of the Edoxaban versus Warfarin in VKA experienced and naive patients from the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction 48 trial (ENGAGE AF) according to prior VKA use.9 The ENGAGE AF trial randomized 21 105 patients to warfarin, high-dose edoxaban, or low-dose edoxaban.10 Patients treated with a VKA for > 60 days prior to enrolment in the trial were considered VKA experienced, and 94% of these patients were on a VKA at the time of randomization.

Patients with a history of VKA use had higher stroke risk profiles than patients without prior VKA use, with more patients with age ≥75 years (42% vs. 38%), prior stroke or transient ischaemic attack (29% vs. 27%), diabetes mellitus (38% vs. 33%), and CHADS2 score ≥3 (23% vs. 22%). There were other differences as well. Patients in certain geographic regions, such as North America and Western Europe, were much more likely to be VKA experienced, whereas VKA-naive patients had a higher rate of aspirin use (42% vs. 21%) at baseline and at 1-year follow-up (27% vs. 19%). The median TTR was higher for VKA-experienced patients (71% vs. 65%, P < 0.001), a difference that persisted over the 3-year course of the trial.

Within ENGAGE AF, the effect of edoxaban vs. warfarin differed according to prior VKA use. The reduction of stroke or systemic embolism with each dose of edoxaban vs. warfarin was greater in

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the VKA-naive than in the VKA-experienced population, with interaction P-values of 0.019 for the low dose and 0.028 for the high dose. Focusing on the high dose, which was the dose approved by the Food and Drug Administration (FDA), the hazard ratios for the effect of edoxaban for stroke and systemic embolism were 0.71 [95% confidence interval (CI) 0.56–0.90] for VKA-naive and 1.01 (95% CI 0.82–1.24) for VKA-experienced patients. For other important outcomes of major bleeding and intracranial haemorrhage, the benefits of edoxaban were consistent in patients with and without prior VKA use.

How should the clinician interpret these results? Given the known challenges in initiation of a VKA (even more so than in clinical trials, where protocols guide rigorous early warfarin dose adjustment) and the greater benefit observed in the VKA-naive population, should we factor prior VKA use in the decision as to whether to use edoxaban? While it would be reasonable to take this into account, it should not be a major factor in the decision for the following reasons.

First, prior VKA use defines differences that go beyond the pharmacological effects of VKAs themselves. For example, patients

Table 1. Features regarding prior vitamin K antagonist treatment of trials of non-vitamin K oral anticoagulants vs. warfarin

<table>
<thead>
<tr>
<th>VKA-naive</th>
<th>Dabigatran 110 mg dose (RE-LY)</th>
<th>Dabigatran 150 mg dose (RE-LY)</th>
<th>Rivaroxaban (ROCKET)</th>
<th>Apixaban (ARISTOTLE)</th>
<th>Edoxaban low dose (ENGAGE)</th>
<th>Edoxaban high dose (ENGAGE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA-experienced definition</td>
<td>&gt; 62 days prior to screening</td>
<td>≥ 6 weeks at screening</td>
<td>&gt; 60 days prior to screening</td>
<td>&gt; 60 days prior to screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>No, yes</td>
<td>3011 (50%), 3004 (50%)</td>
<td>7897 (55%), 6367 (45%)</td>
<td>10 401 (57%), 7800 (43%)</td>
<td>12 441 (59%), 8663 (41%)</td>
<td></td>
</tr>
<tr>
<td>Mean (or median*) TTR</td>
<td>No, yes</td>
<td>67%, 62%</td>
<td>N/A</td>
<td>71%, 65%*</td>
<td>69%, 61%</td>
<td></td>
</tr>
</tbody>
</table>

TTR, time in therapeutic range; N/A, not available.

Figure 1. Forest plot of hazard ratios for stroke or systemic embolism and intracranial hemorrhage by VKA status (for illustrative purposes only; no head-to-head comparison).
with prior VKA use were more likely to be from Western Europe. We should be cautious to ascribe the difference in treatment effect solely to prior VKA use, when the effects may be, in part, a marker for other characteristics that are responsible. Secondly, if the difference in treatment effect is related to avoiding the early liabilities of starting a VKA, one would have expected a greater benefit of edoxaban confined to the early study period, but this was not the case, with a greater treatment effect distributed over the 2.8 years of the trial. Thirdly, subgroup findings—even statistically significant ones—are often due to the play of chance. One way to assess if this may be the case is to look for consistency, or lack thereof, in the other related trials of NOACs vs. warfarin.

Features of prior VKA use in these trials are shown in Table 1. Figure 1 shows that rates of stroke were higher among VKA-naive patients, regardless of treatment with NOAC or warfarin, in ROCKET-AF and ARISTOTLE, but not RE-LY or ENGAGE AF. There is no consistent pattern of differing treatment effect for NOACs vs. warfarin across the trials with respect to stroke or systemic embolism and intracranial haemorrhage, as shown in Figure 1. A meta-analysis (using a random effects model; Figure 1) of the data shows no association between VKA status and treatment effect on stroke or systemic embolism (VKA-naive vs. VKA-experienced interaction P-value = 0.65). Thus, the ENGAGE AF finding of a significantly different treatment effect on stroke and systemic embolism according to prior VKA use lacks external consistency, which should make us sceptical that it is a finding with major clinical implications. To the extent that stroke and systemic embolism rates are higher among VKA-treated patients who are VKA naive, the absolute benefit, even with a similar relative risk reduction, would be greater in this population.

A common question is whether patients stable on a VKA would derive important benefits from switching to a NOAC. With the current report from ENGAGE AF, we now have analyses according to prior VKA use and according to centre-based INR control for each of four large trials. In aggregate, we do not have strong or consistent evidence that the treatment effects of the NOACs differ considerably in patients who have (vs. those who have not) been on a VKA in the past or at centres according to INR control. Similarly, the trial data do not support a substantially larger benefit of NOACs for patients who have “failed” VKA due to occurrence of clinical events or poor INR control. On the other hand, there may be modestly greater absolute benefits from NOACs within patients who are naive to oral anticoagulation. In the end, we are left with the need to make decisions regarding anticoagulation on an individualized basis, given the proven clinical benefits of NOACs over warfarin, in the context of cost and patient preferences.

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References