New Oral Anticoagulants in Atrial Fibrillation Forever?

Running title: Verheugt; New Oral Anticoagulants Forever?

Freek W. A. Verheugt, MD

Dept of Cardiology, Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, Netherlands

Address for Correspondence:
Freek W.A. Verheugt, MD
Department of Cardiology
Heartcenter, Onze Lieve Vrouwe Gasthuis (OLVG)
Oosterpark 9
1091-AC Amsterdam, Netherlands
Tel: +31-20-5993421
Fax: +31-20-5993997
E-mail: f.w.a.verheugt@olvg.nl


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Atrial fibrillation is the most common chronic cardiac arrhythmia in clinical cardiology. It affects about 1% of the population, and of individuals over the age of 80 about 10% have this rhythm disturbance. Due to the loss of the atrial contribution to ventricular filling, left ventricular function is diminished resulting in a propensity to heart failure, fatigue and disability. Furthermore, the sensation of palpitations can be very disturbing for younger patients and may hamper them in their physical and professional activities. Finally, the diminished blood flow through the heart, especially the left atrium, may lead to thrombosis in the left atrium and the left atrial appendage resulting in systemic embolisation. Although many of the characteristic risks and consequences of atrial fibrillation are known for several decades, little progress has been made in the management of the disease until the last 10 years. Correction of the heart rhythm either pharmacologically or by electrocardioversion has not improved clinical outcome\(^1\)\(^-\)\(^3\). Pharmacological management of atrial fibrillation can be helpful in slowing the heart rate but restoring sinus rhythm is rarely successful over time and may even be deleterious\(^1\)\(^,\)\(^2\). Prevention of thromboembolism and stroke can be achieved by the use of oral anticoagulation with vitamin K antagonists. Although this is very successful\(^4\), the therapy is laborious and is associated with severe bleeding in up to 3% of patients per year\(^5\). Recently, new oral anticoagulants have been developed, tested and introduced in clinical practice. They are at least as effective as warfarin, and are safer, especially with respect to the occurrence of intracranial bleeding\(^6\). However, long-term data on efficacy and safety of this new treatment strategy are lacking.

In today’s issue of *Circulation* long-term outcome data are presented from the first successful trial with the new oral anticoagulant dabigatran in stroke prevention (RE-LY) in atrial fibrillation\(^7\). About half of the patients randomized to dabigatran in RE-LY and maintained on study drug consented to continue study medication for over 2 years. In the RELY-ABLE study,
the safety profile of dabigatran with regard to major bleeding and/or intracranial hemorrhage seen in RE-LY, seems maintained over the years, although there was no control group to confirm these findings. Also the rate of stroke or systemic embolism remained within acceptable limits.

**Why the FDA decision was wrong.**

Remarkably, the differences in the rate of stroke between the 2 doses tested in RELY-ABLE are very small, where they were not in the main RE-LY trial (Table 1). This may be due to the patient selection in RELY-ABLE as mentioned by the authors, or to a true long-term phenomenon. Unfortunately, the total 4-year follow-up of the RELY-ABLE patients including their RELY-phase is not given. Only the outcome before and after they entered RELY-ABLE is described, and a Kaplan-Meyer curve is not provided. The long-term stroke outcome of both doses of dabigatran is so close, that the 2010 Food and Drug Administration (FDA) decision to withhold the 110 mg bid dose of dabigatran to American patients becomes cumbersome, because the rate of major bleeding in RELY-ABLE strongly favors the lower dose as it did in the RE-LY main trial. The FDA decision was mainly based on the less favorable, but still significant non-inferiority to warfarin of the 110 mg bid dose (p < 0.001) when compared to the higher dose (p < 0.001). For each extra stroke prevented with the high dose in RELY-ABLE there are 4 excess major bleeds (Table 1). In the RE-LY main trial, the high dose prevented 1 stroke at the cost of 1 major bleed when compared to the lower dose. Doctors like to choose between options including doses of medication, but in the USA both physicians and patients are left without a choice in the prescription of an effective and safe dose of dabigatran.

**The new oral anticoagulants forever?**

In principle oral anticoagulation in atrial fibrillation is a life-long treatment. Are the RELY-ABLE data sufficient to advise long-term treatment with dabigatran for stroke prevention?
RELY-ABLE patients were selected since they were randomized into a clinical trial with its inherent exclusion and inclusion criteria. Secondly, the patients did not discontinue study drug over time in RE-LY. Third, they were willing to continue randomized treatments in the RELY-ABLE study. They had a lower risk profile than the patients who did not enter the RELY-ABLE study: they were younger, had a lower heart rate, more paroxysmal atrial fibrillation, had been more often users of vitamin K antagonists, had less heart failure and used more often beta blockers and statins. Consequently, they had less bleeding, stroke and myocardial infarction than those who were not enrolled in RELY-ABLE. Therefore, it cannot be concluded that dabigatran on the long-term is as safe and effective as found in RE-LY. Although the authors did not come to that conclusion, they suggest that this is the case, because they do not have a control group on vitamin K antagonists in a similar selected population. Only with a control group can a definitive conclusion be drawn.

Can we do away forever with vitamin K antagonists? As clearly shown, this is likely, especially in countries where there is no network of anticoagulation clinics. But for many patients who are stable on oral anticoagulants without apparent bleeding or strong fluctuations of the INR a farewell to anticoagulation clinics will be difficult. Most patients feel comfortable seeing nurses and doctors regularly in these clinics and they even make friends among their fellow patients. Furthermore, the switch from warfarin to the new oral anticoagulants has only been studied in the 3 large trials on efficacy and safety\textsuperscript{8,10,11}. RELY-ABLE is the first to give a glimpse on longer treatment, but still in a selected population. RELY-ABLE says more about differences in dosing, because that was randomized, than that dabigatran is an agent for long-term use. Furthermore, patients with severe kidney failure and those with artificial heart valves cannot switch so far to the new agents. Finally, there is no antidote available that is proven
effective, and therefore the long-term safety of the new oral anticoagulants still has to be established.

**Further evidence of safety?**

Yes, there is some hope. The lack of an antidote does not result in excess fatal bleeding in the comparative trials\(^\text{12}\). On the contrary, the new agents - all lacking an antidote - reduce fatal bleeding by 40% compared to warfarin, where we do have antidote strategy. This was also observed for dabigatran alone: in 5 large trials major bleeding seen with dabigatran resulted in less mortality compared to standard anticoagulation\(^\text{13}\). Finally, in an FDA mini-sentinel registry in over 54,000 patients with atrial fibrillation, dabigatran proved safer than warfarin\(^\text{14}\).

In conclusion, most of the aspects of atrial fibrillation treatment have not changed significantly in the last decades. The only positive development which has been clearly tested and established is the introduction of the new oral anticoagulants. Yet, the question whether these drugs are a real leap forward, can only be answered in the near future when these agents are applied extensively in large populations with atrial fibrillation. Long-term registries like GLORIA (NCT01468701) and GARFIELD (NCT01090362)\(^\text{15}\) may help us in the evaluation of these potential improvements in management of atrial fibrillation and are currently ongoing.

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**References:**


2. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, Said SA,


**Table 1. Differences in major outcomes in RE-LY and RELY-ABLE**

<table>
<thead>
<tr>
<th>Study</th>
<th>Dabigatran 150 mg bid</th>
<th>Dabigatran 110 mg bid</th>
<th>HR</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-LY</strong> <em>patients</em> (n = 18,113)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke (/yr)</td>
<td>1.0%</td>
<td>1.4%</td>
<td>0.70 (0.56–0.89)</td>
<td>0.003</td>
</tr>
<tr>
<td>major bleeding (/yr)</td>
<td>3.1 %</td>
<td>2.7 %</td>
<td>1.16 (1.00-1.34)</td>
<td>0.05</td>
</tr>
<tr>
<td><strong>RELY-ABLE</strong> <em>patients</em> (n = 5,671)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>stroke (/yr)</td>
<td>1.2 %</td>
<td>1.4 %</td>
<td>0.89 (0.66-1.21)</td>
<td>n.a.</td>
</tr>
<tr>
<td>major bleeding (/yr)</td>
<td>3.8 %</td>
<td>3.0 %</td>
<td>1.26 (1.04-1.53)</td>
<td>n.a.</td>
</tr>
</tbody>
</table>
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