

No(AC) Free Lunches: Promises and Pitfalls of Novel Oral Anticoagulants

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For decades the only chapters in major pharmacology textbooks to remain unchanged were those dealing with laxatives and anticoagulants. Now, laxatives stand alone. Twenty years ago the advent of low molecular weight heparins radically changed the way in which parenteral anticoagulation is administered. In the second decade of the 21st century, we are finally witnessing a similar phenomenon regarding oral anticoagulation.

Vitamin K antagonists such as warfarin sodium (Coumadin[®], Bristol-Myers Squibb), the mainstay of oral anticoagulation for atrial fibrillation and venous thromboembolism, are notorious for their user-unfriendliness. Problems such as a narrow therapeutic window that needs constant laboratory monitoring and numerous food and drug interactions make these drugs both inefficient and, if poorly controlled, potentially dangerous. In fact, physician reluctance to prescribe VKAs because of the difficulties encountered with their use has been blamed for the low number of patients with atrial fibrillation who are ever prescribed an anticoagulant, despite these patients' proven risk of stroke and systemic embolism [1]. In those receiving VKAs, namely patients participating in highly monitored clinical trials, the time in therapeutic range, under the best circumstances, is only approximately 60–66% [2], while the annual risk of major hemorrhage

in AF patients on VKAs is in the region of 3–4% after the first 3 months of treatment [3]. The efficacy and safety of VKAs has been linked to the time patients spend in the therapeutic international normalized ratio range [4].

Enter the novel oral anticoagulants. This term refers to drugs designed to directly inhibit thrombin (dabigatran, Pradaxa[®]) or activated factor X (rivaroxaban, Xarelto[®], apixaban Eliquis[®], edoxaban, Lixiana[®]). These drugs were initially studied in low dose in the setting of venous thromboembolism prophylaxis following total joint arthroplasty where they were found to be non-inferior or superior to low molecular weight heparins and at least as safe [5]. They were then rapidly put through a series of phase III randomized controlled trials in AF and VTE patients [6]. In both of these clinical settings the NOACs demonstrated equal or superior efficacy compared to VKAs and did not cause an increase in incidence of major hemorrhage. Most significantly, a decrease in intracranial hemorrhage in AF patients treated with an NOAC was observed in a number of trials. In a recent meta-analysis the NOACs demonstrated an overall survival benefit compared to VKAs in AF patients, driven in the most part by this decreased incidence of intracranial hemorrhage [7]. On the down side, the NOACs, particularly dabigatran, are associated with increased gastrointestinal bleeding compared to VKAs. This may be due in part to their low bioavailability (6.5%) and resultant high concentrations in the feces, leading to a local anticoagulant effect at the bowel wall [8].

AF = atrial fibrillation
VTE = venous thromboembolism
NOAC = novel oral anticoagulant

Not surprisingly, the favorable clinical trial data resulted in rapid approval of the NOACs by regulatory agencies worldwide for use in AF and VTE. Dabigatran, rivaroxaban and apixaban are currently approved for use in Israel. Notably, clinical practice guidelines in Europe now recommend NOACs over VKA treatment for anticoagulation in AF [9], while the recently published guidelines of the American Heart Association available online place both classes of drugs on an equal footing [10].

However, along with the widespread use of NOACs in routine clinical practice – uptake of these drugs has been rapid as demonstrated by a Canadian study [11] – have come numerous reports of patients in whom major hemorrhage has occurred, to an extent perceived to be greater than that reported in the controlled trials [12,13]. In the current issue of *IMAJ*, Feinberg and colleagues [14] report one such case. Their description of a 91 year old woman treated with dabigatran who had renal failure and a fatal bleed highlights a number of the caveats associated with NOAC treatment. They discuss the problems associated with dabigatran treatment in routine practice, namely the lack of widely available specific laboratory monitoring and the absence of a reliable antidote that could be used for dabigatran reversal in the event of bleeding or sudden rise in plasma drug concentration, for example in the event of acute renal failure. While both the prothrombin time and activated partial thromboplastin time are elevated in cases of dabigatran overdose, there is no linear correlation between these test results and plasma dabigatran concentration, making them inappropriate for use

in monitoring. However, both the PT and aPTT are elevated when dabigatran is present in the plasma, and so these readily available tests may provide a semi-quantitative estimate of drug levels. More specific assays measuring dabigatran levels are available, and one such assay (Hemoclot[®], Hyphen-Biomed) is now used in Israeli hospitals. These tests are based on a modification of the thrombin time assay and will make monitoring of complicated cases such as the one reported by Feinberg et al. more accurate. The lack of antidotes to the NOACs is also being addressed, and a number of molecules, both monoclonal antibodies and chemical compounds, are in the clinical phase of development and should be available for clinical use in the near future [15].

As the NOACs enter clinical practice, the next level of clinical data that physicians need is that obtained from large registry and population-based studies, which will assist in evaluating their efficacy and safety in real-life practice. Such reports are forthcoming. Studies of the routine clinical use of NOACs in AF patients have been performed in Denmark [16,17]. These report the same incidence of major hemorrhage in routine practice as that seen in the randomized clinical trials. Encouragingly, the Food and Drug Administration sentinel reporting system, which was employed to capture bleeding events reported during routine clinical use of dabigatran, concluded that the incidence of major hemorrhage is no greater in community-treated patients than in those treated in randomized clinical trials [18].

Physicians and patients are now blessed with abundance when deciding upon which oral anticoagulant to choose. Data from individual trials buttressed by convincing meta-analysis results favor the use of NOACs over VKA, specifically in AF. Moving forward, we now need to apply

these data thoughtfully when consulting on individual cases. A pattern is emerging, suggesting that older, more frail patients with renal dysfunction may be more safely treated with lower doses of dabigatran (110 mg bid) or edoxaban (30 mg bid) [7] than higher doses of these drugs (150 mg bid and 60 mg bid respectively). Apixaban may also be particularly useful in elderly patients with renal failure, being associated with 50% less bleeding than VKAs in these patients [19]. Furthermore VKA-treated patients with AF in whom time in therapeutic range is particularly low (< 58%) are at high risk for bleeding in addition to thrombosis, and such patients may benefit from transitioning to NOACs [20].

The only thing that is clear in these exciting times in the world of anticoagulation for AF is that, as physicians, we need to keep our collective finger on the pulse.

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PT = prothrombin time

aPTT = activated partial thromboplastin time

"Boredom is the feeling that everything is a waste of time; serenity, that nothing is"

Thomas Szasz (b. 1920), American psychiatrist and academic. He was a well-known social critic of the moral and scientific foundations of psychiatry, of the social control aims of medicine in modern society, and of scientism