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Vitamin K antagonists are hard to beat by the price – are they? Some answers, new questions and the GPs' dilemma

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With dabigatran and rivaroxaban, two new promising anticoagulants (NOACs) are now approved and available in most countries including Switzerland and cover the indication of atrial fibrillation, and in the case of rivaroxaban also the prophylaxis after venous thrombosis and the prophylaxis after orthopaedic surgery. At least 2 other substances (apixaban, edoxaban) are expected to enter the market in 2013 and 2014. Apixaban has been approved in the EU (December 2012). They will compete with vitamin K antagonists (VKA) and each other. Since a daily dose of the VKA marcoumar costs approximately 0.34 CHF, and the new oral anticoagulants are >10x higher, currently both at approximately 4.03 CHF daily (October 2012; remarkably similar!), it is appropriate to check for cost-effectiveness in general and in the Swiss health care setting in particular. An almost identical development can be observed with aspirin and the new anti-platelet agents (NAPAs: Prasugrel and Ticagrelor are approved, and more NAPAs will stream into the market); combinations of NOACs and NAPAs will be a major challenge for doctors, their patients (effectiveness vs. bleeding concerns!) and politicians alike (economical impact).

Dabigatran has been analysed in atrial fibrillation with two dosing regimen compared to warfarin in the large phase 3 RELY trial (18,113 pts) and has been shown to be superior in the higher dose (2x150 mg) for the primary endpoint of stroke or systemic embolisation (efficacy, ARR = 0.58%) and non-inferior for major bleeds (safety; ARR 0.25%), whereas the lower dose was non-inferior to warfarin in efficacy (ARR 0.16%) and superior in safety (0.65%). Of importance, the intra-cerebral bleeds were, as with the other NOACs, significantly lower (ARR = 0.28 resp. 0.26%).

It is intuitively clear that a reduction of only a few of the devastating events of ischemic or hemorrhagic stroke, which easily cost up to 50–100,000 CHF and more in Switzerland [1] will reduce costs and increase the number of quality adjusted life years (QUALY)s. Since INR-controls will not be required anymore and the frequency of private practice visits will likely drop, these savings will compensate or even overcompensate for the price of the drug.

Mark Pletscher et al. [2] have addressed this question systematically and carefully and have tried to answer it for Switzerland, based on the RELY data set. They provide us with the ICERs (incremental cost effectiveness ratio) and QUALYs (quality adjusted life years) and confirm that the higher drug costs are compensated by savings in INR monitoring, lower costs due to fewer severe clinical events (ischemic and hemorrhagic strokes) and gains of QUALYs. They also give even more precise messages: With 110 mg twice daily, they find costs of 25,000 CHF per QUALY and with 150 mg 9,700 CHF. They interestingly suggest a sequential regimen with 150 mg before and 110 mg after age 80 which results in an ICER of 10,000/QALY; this appears attractive in cross comparison with other newer drugs and with the 75,000–100,000 CHF Switzerland is prepared to pay annually per dialysis patient or per year of myozyme [2].

This message is timely and the authors are to be congratulated for their careful work. The question will be increasingly debated; the costs for dabigatran spent in the US has just recently surpassed the costs for warfarin [3] and more than 1 million person years of exposure with dabigatran worldwide have been reported (still, the majority of patients are on VKA). It is certainly reassuring that the author have found similar data as reported internationally [4, 5].

What are the uncertainties and question marks for this type of calculation? As the authors point out, there are a number of issues that deserve attention. First, the conclusion is based on the RELY study data of the included patients (selection bias). Registries will have to tell us about the "real world" and are under way.

Second, doctors in private practice often provide "collateral benefits" by the INR monitoring visits. Particularly unstable and polymorbid patients profited from these "preventive" visits that keep many patients compensated. The doctor's assistant has a still under-recognised but paramount role of detecting early complications during the weekly (or bi-/tri-weekly) INR checks: General condition, deteriorating heart failure, shortness of breath, tachyarrhythmic problems, infectious diseases for example are recognised early and may significantly reduce the hospitalisation rates.

Third, the necessity to control the creatinine clearance in patients with borderline renal functions and in patients with changing medication, intermittent heart failure, contrast material exposure, and with episodes of diarrhoea for example will partly compensate for the "saved" INR visits [6]; in some patients, a multiplication of visits will even overcompensate if borderline creatinine values are reached, particularly in the frail elderly with diuretics therapy for heart failure. If these patients are not followed closely, additional acute emergency hospitalisations will be the consequence.

Fourth, the role of the TTR (time in therapeutic range of the INR) may importantly affect the clinical (and financial) outcome. TTRs of 80% and higher can be achieved nowadays [7]. As others [4, 8] found earlier, the authors conclude that the better the INR, the less the patients may profit from the new drug. While this appears plausible and may well be true [4, 8], it has been challenged by the studies with rivaroxaban and apixaban. The conclusion that the use of dabigatran is more preferable, the worse VKA patients are managed, needs careful reconsideration. The patients with low TTR due to poor compliance [9] may be at risk with the new drugs given the short half-lives without monitoring and will possibly suffer from an elevated event rate.

Finally, incentives will shift: GPs complain that they lose some of their preventive roles for their patients, and that they will gain less, drug companies will increase their revenues (the potential of new blockbusters is given) and insurance companies will profit from fewer hospitalisations. All these constellations may call for an altered structure of compensation and incentives for GPs. Of note, Boehringer sponsored the study but the study team comes from an independent organisation.

For the time being, the recommendations as published recently in the European Heart Journal [10] suggest a IIA indication for the NOACs over VKA in non valvular atrial fibrillation and this is supported by the present cost effectiveness analysis. Nevertheless, it appears wise to keep well controlled (TTR >75%) patients on VKA, while patients with newly detected atrial fibrillation, poorly controlled patients (but not those with an obviously poor compliance [9]), frequent travellers as well as patients with individual personal preferences will be candidates for NOACs instead. Long-term observational studies will confirm for us whether Pletscher et al. were correct with their findings. Analogous data for rivaroxaban, and apixaban and edoxaban are eagerly awaited, also in the presence and absence of the (N)APAs; they will help us with the decision making in the future. A recent abstract has been presented (December 2012) for all NOACs and comes to similar, favorable conclusions for the NOACs, particularly for dabigatran 110 mg [11]. Direct comparisons *between* NOACs will remain the gold standard, although unfortunately an unlikely scenario.

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Figures (large format)