The impact of oral anticoagulants on haemostasis

VALORISATION

Venous thrombosis, coronary artery disease and stroke are among the most prevalent cardiovascular diseases in the western population, and thus pose a significant healthcare problem to our society.[1] According to the Dutch Federation of Anticoagulation clinics, about 1.5 million people in the Netherlands are using anticoagulant drugs for prevention or treatment of thrombosis. Although treatment will decrease the individual's risk of (recurrent) thrombosis, it will inevitably increase the risk of bleeding. The balance between the risk of bleeding and thrombosis is crucial in adequate anticoagulant treatment. Vitamin K antagonists (VKAs) have dominated prevention and treatment of thrombosis for over half a century. These drugs are administered and controlled by specialized anticoagulation clinics. The effect of VKAs is influenced by food and co-medication; therefore, treatment with VKAs requires regular monitoring of the effect using a prothrombin time test. Based on the plasma clotting time, a personalized dosage is determined for each patient. This need for monitoring significantly adds to the burden of healthcare cost.

In the last decade new drugs, commonly referred to as direct oral anticoagulants (DOACs), have taken over the prominent place of VKAs in treatment and prevention of thrombosis. After the failed launch of two predecessors, four DOACs have been approved by the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA). DOACs are claimed to be more stable than VKAs due to less interactions with food or drugs. Clinical trials have shown that the treatment of venous thromboembolism (VTE) with DOACs without monitoring, and prophylaxis in patients with atrial fibrillation (AF) is not inferior to treatment with VKAs.[2-9] Consequently, it was determined that routine monitoring can be omitted and dose adjustments are only made in selected cases (e.g. patients with reduced renal/hepatic clearance or extreme body weights).[10] This became the major selling point of DOACs, because monitoring and personalized dosages can be a burden for patients as well as for physicians. Moreover, omitting visits to specialised anticoagulation clinics could potentially reduce the costs. At the same time, DOACs are currently more expensive as compared to the generic VKA's, such that the total cost for VKA management is still lower than the cost for DOACs without monitoring. Although the real prices of the DOACs are confidential as part of a government negotiated price agreement, most sources estimate the costs of a DOAC around €839per patient per year versus €244for monitored VKA treatment per patient per year in the Netherlands.[11-13] On the other hand, a cost-effectiveness study

which investigated apixaban versus low molecular weight heparin (LMWH)/VKA treatment, showed that treatment with apixaban increases the anticoagulation costs, but decreases the total event-related costs compared to LMWH/VKA treatment (€8178 versus €8414 per treatment per year).[14]

All in all, the question remains if the 'one-size-fits-all' approach is the best way to go when it comes to patient care? Standard dosing goes against the modern trend in many areas of medicine, for example in cancer and cardiovascular medicine, where a development is seen *towards* personalized medicine. When a modern drug (DOAC) in standard dosage is as good as an old drug (VKAs) in personalized dosage, wouldn't a modern drug in personalized dosages be even better?

During the preparation of this thesis the DOACs have evolved from relatively new and "unknown" drugs to *the* drugs of choice for patients with VTE as well as AF. Real-life data on the efficiency and safety were not yet available. At first, physicians hesitated to prescribe new drugs without monitoring and some are still tempted by off-label use (i.e. reducing the dose without approved indication). That the effect of DOACs on coagulation cannot be tested at the moment contributes to this problem. Currently, underdosing is a substantial problem that will require further attention in the future, starting by improving the education and awareness of physicians.[15] Another pitfall of DOAC management is non-adherence. The short half-life of the DOACs comes with the consequence that missing a dose could lead to almost immediate loss of protection against thrombosis. Also in this case, education of the patient, family or other caretakers is important to counter this problem, but assessing DOAC levels could also give more insight in therapy adherence, or drug failure. Furthermore, the rate of clinically relevant bleeding due to oral anticoagulants is still substantial, i.e. 10-17% per treatment year, which leaves room for improvement in DOAC management.[2,3] Recently, the question whether or not laboratory monitoring of DOACs is necessary has been debated extensively. This thesis connects to this debate and proposes new ways to measure the effect of DOACs. The topic of this thesis not only concerns an increasingly large population, but is particularly relevant in the light of optimizing DOAC treatment. The research in this thesis was driven by curiosity arising during my clinical residency, in the time that the DOACs were first introduced in the Netherlands. The experiments have been performed in a laboratory with special focus on translational research. In short, it went from bed, to bench and back again.

With the findings in chapter 2 we show that whole blood thrombin generation (WB TG) and TG might be able to identify patients with a higher risk of bleeding while using VKAs, better than the prothrombin time (PT) from which the international normalized ratio (INR) is calculated. The INR is valuable to determine the current state of (anti)coagulation of a patient, but does not indicate a future bleeding risk. TG by itself, is not able to predict bleeding in individual patients either, but can help to identify patients at risk. The TG parameters could potentially be incorporated in a prediction score. This could ultimately reduce the risk of bleeding complications during treatment.

Chapter 3 investigates the potential benefit of TG in more detail. The limited number of studies that have been performed investigating the potential of TG to detect a bleeding tendency, stresses the need for more research. Interestingly, we found many studies that used TG to investigate the reversibility of DOACs, but no study investigated the relation between TG and the risk of bleeding in patients on DOACs directly. Additionally, TG was used to assess the global coagulation of patients included in some of the large clinical trials, which led to the implementation of DOACs in clinical practice.

There is evidence from the randomized clinical trials with dabigatran and edoxaban, that inter-individual variation in plasma concentrations of DOACs (pharmacokinetics (PK)) relates to outcomes (thrombosis or bleeding)[5,16]; furthermore, Testa et al provided evidence for an association of DOAC levels and thrombotic outcomes[17], whereas similar associations with peak height and bleeding have been observed in the same observational study (Testa, personal communication 2018). It therefore makes sense that introducing any form of laboratory fine-tuning of DOACs (selecting the right drug and proper dose) will improve DOAC management and reduce complications. The latter would ideally be proven through randomized intervention trials.[18] DOAC levels can be measured with several newly developed DOAC-specific assays. These are quantitative assays that can reliably measure the amount of DOAC present, but not necessarily the effect of DOACs on coagulation.

In the present thesis the effects of different DOACs on coagulation are investigated in more detail by using more functional assays, in most cases TG. A recently published article has examined the value in determining edoxaban levels versus the effect on coagulation (measured with a newly developed technique), related to clinical outcomes (thrombosis and bleeding).[19] This paper showed a favourable effect of a functional assay, such as TG. In chapter 5 of this thesis the development of a new assay is described, that can measure rivaroxaban levels as

well as the effect on coagulation using the same TG set-up. If future research would demonstrate that quantitative and functional measuring of DOACs has a beneficial effect on patient care, the use of such an assay should be considered.

In chapter 6 we have confirmed that in vitro, the response to a fixed dose of rivaroxaban and apixaban on TG varies widely between individuals. Within individuals this variation is less, indicating that the effect of DOACs is quite stable over time. This could lead to the assumption that patients might benefit from initial personalization of the dose, but will not need frequent regular monitoring afterwards. In that case, DOACs (certainly future generic compounds) will remain a more practical and potentially cheaper choice than VKAs.

The question whether high responders will have a higher bleeding risk and low responders will have a higher risk of thrombosis has been addressed in aforementioned trials and observational studies. Critics claim that this evidence cannot be translated to dose adjusted therapy, because fixed doses were studied in clinical trials and consequently doses based on clinical characteristics were registered. Eikelboom and colleagues propose a randomized clinical trial comparing current DOAC policy with laboratory adjusted DOAC dosing. However, in their calculation such study would have immense proportions and would essentially not be feasible.[18] I would propose that no specific clinical trial is required in order to optimize selection of the proper DOAC for the individual patient, potentially even for guidance of the proper dose. Important is to remain within correct dose ranges, registered for the appropriate indication. At the same time, more evidence would help to support such a strategy and hopefully more studies like the one from Testa et al. will be performed.

An additional aspect to be taken into account is the genetic variation that plays a role in pharmacokinetics and -dynamics. DOACs, studies are limited to dabigatran, showing that genetic variation could lead to higher or lower peak and trough levels, which are associated with an increased risk of bleeding or thrombosis. The (genetic) impact could not only influence drug levels but also functional markers such as TG. From existing literature it is known that the heritability estimate for TG parameters is ± 50%, i.e. around 50% can be contributed to genetic factors.[20,21] In newly initiated research we have started to investigate to what extent the response to rivaroxaban is genetically determined. Theoretically, in the future, pharmacogenetics could play a role in the decision making process for the determination of the initial dose when prescribing DOACs, redirecting the treatment of thrombosis back towards the paradigm of personalized medicine.

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