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Informed decisions about treatment with anticoagulants

J.H.A. van Miert

Colofon

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Contents

Chapter 1	Introduction	9
Chapter 2	Choosing between continuing VKA or switching to a DOAC in currently well-controlled patients on VKA for atrial fibrillation a randomised controlled trial (GAIInN)	25
Chapter 3	Quality of life after switching from well-controlled vitamin K antagonist to direct oral anticoagulant little to GAIInN	41
Chapter 4	Clinical usefulness of the SAMe-TT2R2 score a systematic review and simulation meta-analysis	59
Chapter 5	Is the time in therapeutic range on coumarins predicted by previous time in therapeutic range?	77
Chapter 6	An easy-to-use tool to flag patients at risk of poor INR control a streak of subtherapeutic INRs	91
Chapter 7	More precise dosing of acenocoumarol for better control in patients aged above 80 years a randomised controlled pilot study	103
Chapter 8	Effect of switching from acenocoumarol to phenprocoumon on time in therapeutic range and INR variability a cohort study	117
Chapter 9	Summary, Discussion and Future Perspectives	139
Chapter 10	Nederlandse samenvatting	163
Appendices	Online supplements	174
	Dankwoord	176
	About the author	180
	List of publications	182

Introduction

1

Introduction

The 2010s can well be regarded as the decade of the DOACs (direct oral anticoagulants). The first successful member of this new class of anticoagulants, dabigatran, was introduced to the scientific audience in 2009[1, 2]. In the following years, other DOACs were introduced: rivaroxaban[3–5], apixaban[6, 7] and edoxaban[8, 9]. They would take the world by storm, replacing vitamin K antagonists (VKA) as the first-choice treatment for atrial fibrillation[10, 11] and most venous thromboses[12]. Between 2014 and 2018, the number of Dutch patients prescribed DOACs increased sixfold, to over 250,000[13]. After this revolutionary decade, I hope the 2020s will see a DOAC evolution instead, answering the important questions that remain.

For instance, there are still hundreds of thousands of patients using VKA in the Netherlands alone. Some of them could switch to a DOAC; others, such as those with mechanical heart valve replacements, are confined to VKA. Who should remain on VKA? Who should switch to a DOAC? What can we do to improve the quality of treatment for patients who remain on VKA? I am going to address these questions in my thesis.

But before we can discuss the ins and outs of this topic, allow me to introduce coagulation and anticoagulation.

Coagulation

Haemostasis: stopping the bleeding

Blood is vital for life. Its red blood cells squeeze through capillaries to deliver oxygen to our organs. It transports hormones and building blocks to tissues, and rids them of waste products. It is important to maintain an optimal environment for chemical reactions, by creating a constant temperature, pH and maintain electrolyte concentrations within narrow boundaries. One can imagine the body does not want to lose such a precious resource. The process to stop bleeding is called haemostasis.

The body's first mechanism to prevent blood loss is the blood vessel: as long as the vessel wall is intact, the blood is safely contained within. When the blood vessel is severed, muscle cells in its wall contract to minimise the area through which blood can escape.

The vessel endothelium separates the blood from the proteins underneath it. When the vessel wall is damaged, the blood gets exposed to collagen. This starts

the primary haemostasis. Von Willebrand Factor, which circulates through the blood vessels, binds to collagen on one end and to platelets on the other end. Platelets (a.k.a. thrombocytes) then adhere to the damaged vessel walls and become activated. In the process, platelets let out numerous substances to attract and activate other platelets. A platelet's normal lens-shape changes to form "tentacles," that intertwine with other platelets to form a so-called primary platelet plug. This puts a first, but fragile, stop to the bleeding.

The secondary haemostasis strengthens the primary plug with a mesh of fibres. It is a complex process, where one protein cleaves another, that cleaves yet another, until fibrin fibres are formed. These fibrin fibres are then formed into a mesh for extra stabilisation. Because this process is driven by plasma proteins, and not by cells, the secondary haemostasis is also referred to as the "plasmatic coagulation."

This might seem quite straight-forward, but all the steps have their own (counter-intuitive) name and there are several feedback loops to complicate things. That is why, as a medical student, I despaired about learning the "horrible" coagulation cascade. Nevertheless, it is a fascinating process to look at based on a clinical problem, or thinking about anticoagulation. That is why I would like to review the secondary haemostasis in more depth.

Classically, the secondary haemostasis is further divided into two separate pathways (the intrinsic and extrinsic pathway), sharing the end of the cascade (where thrombin and fibrin are formed). This distinction is based on the behaviour of blood in a test tube. This already implies that this does not cover the mechanisms inside the body. I have never found this distinction particularly clear or helpful, except in the interpretation of the anticoagulation tests, which I will cover shortly below.

In vivo, haemostasis is initiated in response to damage of the vessel wall (see above). I mentioned before that proteins that are normally separated from the blood can then suddenly make contact with blood, and work there. Another one of such proteins is tissue factor. When the blood is no longer kept from tissue factor, a protein from the blood binds to it and forms a complex, that activates the rest of the secondary haemostasis as summarised in Figure 1. This protein is called Factor VII. Like most coagulation factors, it is numbered in Roman numerals. Unfortunately, these numbers were awarded in order of discovery; this means that the order does not really make sense today. Furthermore, other factors turned out not to be proteins, and have thus been removed from the equation.

The complex of factor VII and tissue factor (TF) is “activated”: it can cleave its target protein. The activated form of a coagulation factor is indicated by adding a lowercase “a” to their name. The TF/VIIa-complex activates factor X (which is then called Xa), which leads to the formation of thrombin (factor IIa) out of prothrombin. Thrombin causes the formation of small amounts of fibrin. At the same time, a positive feedback loop has started by the TF/VIIa-complex and predominantly by thrombin. This positive feedback loop, comprised of factors XIa, IXa, VIIa and Va, accelerate the formation of more thrombin and thus more fibrin fibres. This, in turn, produces a stable clot, or thrombus. As a side-note: the absence of factor VIII or IX causes haemophilia A and B, respectively, a disease where patients have severely impaired blood clotting and suffer from haemorrhages in muscles and joints.

Figure 1. The coagulation cascade. By an anonymous Wikipedia user.

Natural inhibitors of coagulation

The positive feedback loop allows for the quick formation of vast amounts of thrombin and fibrin. This is useful to combat a major haemorrhage, but is overkill for a paper cut. Luckily, our body has mechanisms in place to prevent massive coagulation after a minor bleed.

The cells that line the vascular lumen (endothelial cells) prevent platelet activation via the production of prostacyclin, nitric oxide, amongst others. The main inhibitors of the secondary haemostasis are antithrombin (which restrains the function of factors X and II), the protein C/protein S/thrombomodulin system (mainly affecting the feedback loop of factors V and VIII) and the tissue factor pathway inhibitor (its name speaks for itself, denoted as TFPI in Figure 1). The endothelium produces thrombomodulin and tissue factor pathway inhibitor; the liver produces antithrombin and proteins C and S.

A deficiency in one of these inhibitor systems increases the risk of inappropriate clot formation (thrombosis, see below). At the same time, these inhibitor systems are under research to treat bleeding disorders, as downregulation of the inhibitor systems may restore haemostatic balance.

Inappropriate clotting: thrombosis

We saw that the blood has the potential to coagulate quickly to limit blood loss, but at the same time flow freely through the vasculature. Unfortunately, this balance is sometimes lost, which can lead to inappropriate thrombus formation. Coagulation of blood while it's still in the blood vessel is called thrombosis.

The main causes of thrombosis are now described as a combination of inadequate blood flow (stasis), injury to the vascular lining or endothelium, and problems of the blood itself (hypercoagulability). The description of these three factors is (mis)attributed to Rudolf Virchow[14].

Atrial fibrillation and the risk of stroke

An interesting example is atrial fibrillation (AF), a heart rhythm disorder that often presents with palpitations or shortness of breath. Regardless of these symptoms, it increases the risk of stroke. Part of the pathophysiological mechanisms can be traced back to Virchow's triad. The most intuitive mechanism is stasis; because the atria do not produce a proper atrial systole the blood can swirl. Furthermore, atrial fibrillation is often accompanied by atrial dilation, which allows for more stasis. The atrial appendage is a notorious location for thrombus formation[15].

At the same time, atrial fibrillation is associated with inflammation and fibrosis of the inner lining of the atria (endocardium, continuous with endothelium in vessels). Inflammation is expressed as changed levels of collagen degradation products, matrix metalloproteinases and their inhibitors, and growth factors[15].

Whether this is caused by atrial fibrillation itself, or that both are a manifestation of underlying conditions should be further elucidated.

The coagulability of the blood itself might be altered in patients with AF: they express higher levels of von Willebrand Factor (see above) and substances involved in fibrinolysis[15]. Again, this can be caused by AF itself, or by an underlying condition. At the same time, we interfere with the blood's coagulability to prevent stroke, by giving anticoagulants (see below).

Venous thromboembolism

The factors in Virchow's triad can also be used to explain risk factors for venous thromboembolism. Venous thromboembolism is an umbrella term for deep-venous thrombosis in the leg, pulmonary embolism, and other venous thromboses. Here, immobilisation, long-haul flights, and venous compression are examples of stasis. The blood's coagulability can be affected by hereditary thrombophilias (such as antithrombin or protein C or S deficiency), active cancer and inflammation. Vascular injury can occur through chemotherapy and vasculitis, among others.

Arterial thrombosis

Both these types of thrombosis have in common that the thrombus forms in the "venous side" of the body: either in the veins or in the atria. Another type of thrombosis, that is probably better known by the general public, is arterial thrombosis. It differs from venous thrombosis in clot composition, cause, and treatment, even though there is considerable overlap. Arterial thrombosis can manifest as a heart attack (myocardial infarction) or stroke (ischaemic cerebrovascular accident). The most common cause is the rupture of a plaque of atherosclerosis, which results in massive platelet activation and the formation of a clot. This can block off blood supply to downstream tissues. Atherosclerosis occurs with age in everybody to some extent, but is aggravated by smoking, diabetes mellitus, hypertension, too high levels of LDL cholesterol, alcohol, a sedentary lifestyle, etc.

Treatment and prevention of thrombosis

General measures

To prevent thrombosis, we can once again look at the factors mentioned in Virchow's triad. Measures to protect the vessel wall mainly focus on the prevention of atherosclerosis: smoking cessation, improving glucose control in patients with diabetes mellitus, maintaining a healthy body weight, etc. The stasis component can be addressed by walking during long-haul flights, pneumatic compression

stockings after surgery, etc. These measures might suffice for primary prevention, but for secondary prevention in patients at increased risk, or treatment of actual thrombosis, we have to resort to pharmacological measures.

Pharmacological therapy

The current pharmacological measures to prevent thrombosis interfere with the haemostatic system. This is unfortunate, because indiscriminately inhibiting the blood's ability to clot also tampers with the body's ability to stop a bleeding, and thus causes a bleeding risk. Physicians and their patients should balance the bleeding and thrombotic risks before prescribing an anticoagulant.

Medication affecting the primary haemostasis

We can interfere in the primary haemostasis by administering drugs that inhibit the aggregation of platelets. There are several mechanisms to achieve this goal: e.g. inhibiting the formation of thromboxane A₂ by inhibiting the enzyme cyclo-oxygenase (aspirin), or antagonise the P2Y₁₂-receptor (clopidogrel, prasugrel, ticagrelor). Platelet aggregation inhibitors are often prescribed for arterial problems, such as heart attacks and strokes caused by atherosclerosis. I will not further elaborate on platelet aggregation inhibitors, because they fall outside the scope of my thesis. It should, however, be noted that the balance between bleeding and thrombotic risks is also applicable here: the combination of multiple platelet aggregation inhibitors or the combination with inhibitors of the secondary haemostasis increase the bleeding risk.

Medication affecting the secondary haemostasis

There are multiple classes of drugs that work on the secondary haemostasis: vitamin K antagonists, direct oral anticoagulants, and heparin-like substances. They have in common that they inhibit the production or function of the coagulation factors mentioned above. However, they differ in mode of administration, indications, and tests required. I will refer to this class of medicines as anticoagulants; when I want to include platelet aggregation inhibitors as well I will call this antithrombotics.

Heparin-like substances

Heparin is the oldest anticoagulant still in use. It potentiates the function of antithrombin in its inhibition of factors IIa and Xa. Heparin occurs naturally in the body, but for medicinal use, heparin is isolated from bovine or porcine livers (hence the name) and intestinal mucosa.

Heparin can be administered intravenously or subcutaneously. Because “regular” heparin consists of polymers of different lengths, its function is hard to predict and needs to be monitored. More homogenous, fractionated heparins were

developed to overcome these limitations. These “low molecular weight” heparins behave more predictably and do not require monitoring except in special circumstances. This allows them to be used at home by patients themselves[16]. They are used as thromboprophylaxis in medically ill patients or patients who undergo orthopaedic surgery, and in the treatment of cancer-associated venous thromboembolism or thrombosis when oral therapy is impossible.

Continuing on the route of minimalisation, fondaparinux was developed. Fondaparinux is a synthetic pentasaccharide that selectively blocks factor Xa. Its shorter form allows its use in heparin-induced thrombocytopenia (HIT).

All heparin-like substance share an unfriendly mode of administration. Therefore, we try to switch to oral medication whenever safe and possible.

Vitamin K antagonists

Vitamin K antagonists (VKAs) have been the mainstay of oral anticoagulation for decades. They are prescribed for the prevention of thrombosis in atrial fibrillation and after heart valve replacement, and the treatment of venous thromboembolism. Acenocoumarol and phenprocoumon are two VKAs available in the Netherlands. Internationally, warfarin is often used. These three drugs differ in the duration of their effect (half-life), but their pharmacological action is the same. VKA tamper with the production of coagulation factors II, VII, IX and X (and the inhibitors protein C and S) by inhibiting the vitamin K recycling with vitamin K epoxide reductase. The effect of the medication differs from patient to patient and within patients based on genetic markup, dietary vitamin K intake, production of vitamin K by the microbiome in the gut, interaction with other medication, etc. Therefore, the effect of VKA on the coagulability of the blood (expressed as the international normalised ratio, INR) needs to be monitored. The INR is calculated based on the prothrombin time (PT), which measures the time from the addition of tissue factor to plasma to the formation of a clot (extrinsic pathway). The patient’s PT is then divided by the “normal” PT of non-VKA-users, and adjusted for laboratory specifics: $INR = \left(\frac{PT_{patient}}{PT_{normal}} \right)^{ISI}$. An INR between 2 and 3, or between 2.5 and 3.5, is targeted, depending on the indication. The development of the INR over time can be used to calculate indicators of the quality of the treatment, as described in the next chapter.

Direct oral anticoagulants

Instead of inhibiting the production of coagulation factors, the newer medication directly inhibits the function of one specific coagulation factor; hence their name of direct oral anticoagulants (DOACs). (At first they were referred to as *novel* oral anticoagulants (NOACs); this was a mistake because all novelty fades. Some try to keep the acronym alive by re-branding the drugs as non-VKA oral anticoagulants,

but I will try to use DOAC throughout this thesis). Currently, four DOACs are available in the Netherlands: apixaban, rivaroxaban and edoxaban inhibit factor Xa; dabigatran targets thrombin. The exact registrations differ from drug to drug, but they are all approved for stroke prevention in atrial fibrillation, and the treatment of deep venous thrombosis and pulmonary embolisms. Because of their predictable pharmacokinetics and -dynamics, they do not require laboratory monitoring. The DOAC dose is reduced when kidney function is (severely) impaired or the patient is frail.

Problems

The introduction of the direct oral anticoagulants was exciting, yet introduced uncertainty at the same time. The thrombosis services in the Netherlands prided themselves upon the quality of treatment they achieved with vitamin K antagonists. Would a Dutch adoption of the DOAC be a step forward, or throwing the baby out with the bathwater?

Who should switch from VKA to DOAC, and who should not? Can we predict the benefit switchers will experience? Are DOACs the right choice for the “older elderly,” who have an altered body composition and are often frail? How can we maintain high-quality treatment for patients whose comorbidities or comedication forbid switching to a DOAC? What would be the position of the thrombosis services when the number of patients drops dramatically?

Choosing an anticoagulant

I have introduced three classes of anticoagulants above. Some indications can be treated with any of the three, while others require a specific anticoagulant. In practice, heparins are mainly used in short-term thromboprophylaxis (e.g. during hospital admissions); long-term use is reserved for special patient groups (e.g. when oral medication is unreliable, during pregnancy, in certain cancers or during certain chemotherapies). For “conventional” long-term therapy, we often prefer oral therapy.

In some patients, the choice for a particular anticoagulant is limited. Cancer-associated thrombosis should not be treated with VKAs[17, 18]. DOACs are just as effective as LMWH, but might lead to an increased bleeding risk, especially with intracerebral metastases or intraluminal tumour growth[19]. On the other hand, DOACs are contraindicated in patients with mechanical heart valve replacement (MVR), because dabigatran was far inferior to VKAs[20]. The same might be

true in the antiphospholipid syndrome, where VKAs are the drug of choice[21]. Due to a lack of evidence, DOACs are not given in patients with more “special” venous thromboses (e.g. thrombosis in the cerebral sinus or portal vein), nor in patients with kidney failure. The use of DOACs in patients with obesity is under research[22–24]. Interacting medication could also rule out one anticoagulant or another (e.g. some treatments for epilepsy, HIV or fungal infections forbid the use of DOAC). Therefore, the choice for a DOAC or a VKA is most prominent in atrial fibrillation (AF), deep venous thrombosis of the extremities (DVT) and pulmonary embolism (PE).

The DOACs have been tested in large studies where they demonstrated non-inferiority compared with warfarin for AF[1, 4, 6, 8] and for DVT/PE[2, 3, 5, 7, 9]. DOACs are now preferred over VKA for patients with a new DVT or PE[25] and patients with new-onset AF[10, 11, 26]. No recommendations for a specific DOAC are made. Only indirect comparisons between DOACs are available[27, 28] and they have not yet influenced treatment guidelines. The decision is now made based on the frequency of administration (once daily for long-term treatment with rivaroxaban and edoxaban, twice daily for apixaban and dabigatran), side-effects, and the availability of an antidote[29, 30] (the high price of the antidote for the factor Xa inhibitors could limit its availability), doctor’s experience, etc.

Guidelines are less decisive for patients already on VKA. Switch from VKA to DOAC can be considered based on patient preference (see also chapters 2 and 3), or when the quality of VKA treatment is low[10, 26, 31]. This touches on the heterogeneity of the effect of VKA, based on the quality achieved (operationalised as time within therapeutic range and INR variability, see below).

Quality of treatment with vitamin K antagonists

From the information above follows that the group of patients using a vitamin K antagonist will shrink (with a decline of over 50 000 patients in 2018 in the Netherlands alone[32]) and will consist of more and more frail patients with a contraindication for DOAC. These patients are more at risk of adverse clinical events. Therefore, it is crucial to ensure treatment with VKAs is as effective and safe as possible.

Time in therapeutic range

Treatment with vitamin K antagonists can be heterogeneous. As mentioned before, the VKA dose is titrated to maintain an INR in the therapeutic range (2.0–3.0 for AF and most VTEs, 2.5–3.5 for MVR). The proportion of time an individual spends with an INR in this therapeutic range is called TTR (time within therapeutic range). TTR is calculated by linearly interpolating INRs over time[33].

In a group of patients with a low TTR, more events occur than in a group with a higher TTR[34–37].

The TTR is used in many different settings. It is used as a quality measure for anticoagulation clinics, to appraise the therapy a patient has received, and to make predictions about future therapy. The Dutch anticoagulation clinics report an average TTR of approximately 73% in target range 2.0-3.0 and 65% in range 2.5-3.5 over the year 2018[32]. This is higher than in many other countries[38]. Treatment with a TTR $\geq 70\%$ is considered “high quality”[39].

INR variability

The INR variability can be used in addition to the TTR: a more volatile INR is associated with an increase in events[36, 37, 40–42]. However, the practical use of INR variability is less well-defined. This can be in part due to different methods used to calculate INR variability[40, 41, 43] and the lack of a target value.

VKA quality and clinical decisions

The DOAC trials[1–9] demonstrated non-inferiority of the respective DOAC compared with warfarin. However, we have seen that the effect of vitamin K antagonists on clinical events varied with TTR. This led to the hypothesis that the non-inferiority of DOAC could also depend on the TTR.

Post-hoc analyses of the original trials[44–46] and registry studies[47, 48] followed, but failed to resolve the controversy. One could argue that a comparison between the on-treatment periods in the DOAC trials is not completely clinically useful, because one cannot be certain in advance what TTR an individual would achieve. This evidence gap will be addressed in this thesis.

When a patient has poor VKA control (e.g. low TTR and high variability) and no alternatives for VKA, the increased bleeding risk could outweigh benefits. When no improvement can be expected, discontinuing treatment should be discussed with a patient. Unfortunately, data on when risks outweigh benefits are scarce, nor do we know what improvements to expect.

Outline of this thesis

This thesis focusses on the role of the proportion of time in the therapeutic range in making decisions about anticoagulants.

In chapters two and three, we explore our hypothesis that patients with a high TTR are better off continuing VKA therapy, instead of switching to a DOAC. We have performed a randomised controlled trial with 241 patients whom we randomised to either continue their VKA treatment, or switch to a DOAC. Whether patients had more clinical events is described in chapter two; how patients valued their treatment on quality of life is described in chapter three.

Chapter four evaluates whether the quality of VKA therapy (TTR) can be predicted based on clinical factors available before starting treatment, using a proposed decision-making tool (the SAME-TT2R2 score). Chapters five and six are aimed at foreseeing TTR during treatment. Chapter six helps clinicians to translate the current TTR into an expected TTR, while chapter five introduces an easy-to-use tool to flag patients at risk of poor VKA control.

Chapters seven and eight describe mechanisms that could potentially increase the TTR and reduce INR variability. Chapter seven determines whether more precise dosing, using tablets of half a milligram of acenocoumarol instead of the regular one-milligram tablets, can increase VKA control in elderly patients who require only a low dose of VKA. Chapter eight examines the effect of switching from the short-acting acenocoumarol to the long-acting phenprocoumon on TTR and variability.

This thesis concludes with the discussion of the impact on clinical management, and future applications.

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Choosing between continuing VKA or switching to a DOAC in currently well-controlled patients on VKA for atrial fibrillation: a randomised controlled trial (GAINN)

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Abstract

Background Adverse clinical events during vitamin K antagonist therapy (VKA) occur predominantly in patients with a poor time within the therapeutic INR range (TTR). An overall non-inferiority of direct oral anticoagulants (DOAC) compared to VKA was found in previous trials in atrial fibrillation. However, this might be the result of superiority in those with poor TTR, and inferiority in those with high TTR. We aimed to determine whether it is likely that those patients with previously well-controlled VKA would be harmed by switching to a DOAC.

Methods Randomised controlled pilot study in a dedicated first-line thrombosis service in the Netherlands. Adults treated with VKA for atrial fibrillation with a $TTR \geq 70\%$ and no thrombosis or major bleed during VKA were randomised to continuing VKA or switching to a DOAC. Outcomes were net clinical benefit (composite of stroke, systemic embolism, myocardial infarction, vascular death and major bleed), efficacy, and safety, over one year of follow-up.

Findings 241 patients were randomised (120 to VKA and 121 to DOAC) and analysed. Four in each group experienced a net clinical benefit endpoint (hazard ratio [HR] 1.00, 95% CI 0.25–4.00). The efficacy endpoint occurred in 4 patients on VKA and 3 on DOAC (HR 0.75, 95% CI 0.17–3.35). The safety endpoint occurred in 12 and 14 patients (HR 1.17, 95% CI 0.54–2.53).

Interpretation We found no evidence that continuing VKA is superior to switching to DOAC in previously well-controlled patients on VKA.

Introduction

Atrial fibrillation (AF) increases stroke risk. Treatment with anticoagulants reduces the risk of stroke while increasing the risk of bleeding. Except for those at the lowest stroke risk, anticoagulation provides a net clinical benefit[1] and is recommended by guidelines[2]. Direct oral anticoagulants (DOAC) have been proven to be non-inferior to treatment with vitamin K antagonists (VKA)[3–6] and are now favoured for new AF patients[2].

Current international[2] and Dutch[7] guidelines do not advise switching patients with uncomplicated VKA therapy to DOAC. VKA therapy is safest and most effective when patients have a high time within the INR target range[2, 8] (TTR). Events cluster in patients with lowest TTR[9–11]. Although unknown, such a clustering is not likely for DOAC. Consequently, this could mean that the overall non-inferiority of DOAC is the result of superiority in those with the poorest TTR, and inferiority in the other groups (this is illustrated in Figure 1). This would be important information: if well-controlled VKA is superior, then switching to a DOAC would harm these patients.

Data on this issue are scarce: results from post-hoc analyses on data from the original DOAC trials are contradictory and based on centre or predicted (instead of an individual's actual) TTR[12–15]. Comparisons based on data from retrospective registries[16, 17] are prone to selection bias and are therefore considered “low-grade” evidence. We have conducted an industry-independent study to obtain more direct data on this issue: the Good Anticoagulation In the north of the Netherlands (GAINN) pilot study.

Hypothesis: effect of time within therapeutic range (TTR) on the effect of VKA relative to DOAC

Figure 1: The hypothesis for this study, as extrapolated from the ROCKET-AF[4] and White et al.[11].

Methods

Trial aims and design

We performed a small randomised controlled trial to explore bleeding and thrombotic risks of continuing VKA or switching to a DOAC in VKA-experienced patients with currently well-controlled VKA therapy for non-valvular atrial fibrillation in an anticoagulation clinic in the Netherlands. We hypothesised that VKA would be superior to DOAC in this group of patients. If indications for VKA superiority arose, we would determine the feasibility of a larger study.

This study was registered in the Netherlands Trial Registry (NTR4770) and the EU Clinical Trials Register (2013-004805-14), and was approved by the local research ethics committee at the University Medical Center Groningen (METc UMCG 2014/002). An independent Data Safety and Monitoring Board monitored the safety of study. In addition, an independent adjudication committee adjudicated all potential endpoint events.

Participants

Patients were recruited from Certe Trombosedienst, a large thrombosis service for the northern provinces in the Netherlands. First, records were extracted for all patients who satisfied the inclusion criteria: adults aged 18 and above, who were treated with a vitamin K antagonist for non-valvular atrial fibrillation and were managed by Certe Trombosedienst for at least six months at the time of selection, and had a time within the therapeutic range (INR 2.0 - 3.5) of at least 70% over the previous four months. From all consecutive patients, we randomly selected eligible subjects and consulted their referring physician. When (s)he did not object, we mailed the subjects information about the study. They could express interest by phone or returning a postcard. We sent one reminder to subjects who did not reply.

Patients who were interested were invited to the Thrombosis Service for a personal information visit with a study physician. After the patient had provided written informed consent, eligibility was re-checked. Exclusion criteria were: a thrombo-embolic event or major bleeding ever while on VKA; indication for anticoagulation other than atrial fibrillation; contra-indication to receive any kind of DOAC; a life expectancy less than 1 year.

We aimed at including 240 patients in this trial. No formal sample size calculation was performed due to the pilot nature of this project, but we judged this number to be sufficient to get robust point estimates to design the planned full scale randomised controlled trial, if there were indications of VKA superiority.

Randomisation, masking, and study drugs

We randomised all patients who were eligible and provided informed consent in a 1:1 ratio to either continuing treatment with vitamin K antagonists, or switching to a direct oral anticoagulant. Randomisation was performed using an interactive computer system provided by the hospital's trial coordination centre, without stratification. Blocks of 4 and 6 were used in random order. This was an open-label study.

Treatment with VKA was continued as usual, following the Thrombosis Service's standard protocol for dose adjustments and INR determination periods. In the Netherlands, either acenocoumarol or phenprocoumon is used. Before January 1st, 2016, an INR therapeutic range of 2.0 - 3.5 (target range 2.5 - 3.5) was used; afterwards all Dutch thrombosis services targeted a range of 2.0 - 3.0. The maximum period between INR checks was 6 weeks.

Treatment with DOAC was started in accordance with local guidelines. In practice, most patients received apixaban 5 mg bid, with a dose reduction according to the instructions in the registration texts.

We assessed the quality of anticoagulation treatment in the two groups. A strong indicator of the quality of treatment with VKA is the time within the therapeutic range (TTR). We calculated TTR using the Rosendaal method[18] if data on 90 days or more were available. For DOAC no measurable quality parameter exists. Instead, we used data from the patient pharmacy to calculate approximate adherence. We requested the number of tablets and the dates they were dispensed, and calculated the number of days a patient could not have the drugs at their disposal. This was converted to a percentage of days covered.

Study outcomes

The primary study outcome was net clinical benefit: a composite of stroke, systemic embolism, myocardial infarction, vascular death, and major bleed. Secondary study outcomes were efficacy (composite of ischaemic or unspecified stroke, systemic embolism, myocardial infarction and vascular death) and safety (composite of major bleed (including haemorrhagic stroke) and non-major clinically relevant bleed and all-cause mortality). All components were also assessed separately. We used the same outcome definitions as previous studies[4, 19], summarised in the Appendix Table 1.

In addition to the usual care provided by the Thrombosis Service, patients were seen twice a year for a research visit. Study outcomes were assessed at a six-month visit by a study nurse or physician and at one year after randomisation by a study physician. Patients received a booklet to log all potential events

between visits. It contained contact details of the study team for questions and the regular thrombosis service's phone number for emergency inquiries. All clinical outcomes were adjudicated by an independent endpoint adjudication committee of two experienced physicians, who were blinded for the treatment the patient received.

Statistical analysis

We counted the number of clinical endpoints per treatment group in the intention-to-treat population (primary evaluation) and in the per-protocol population (secondary evaluation, where a subject contributed until he or she stopped the allocated treatment). Absolute risk differences were calculated based on event rates after one year, and hazard ratios (HR) with 95% confidence intervals using a Cox proportional hazard model. We analysed sex differences in the composite outcomes with stratified Cox regressions if enough events occurred. Because this was a pilot study aimed at determining the feasibility of a full-scale trial, we did not perform formal hypothesis testing and hence do not report p-values.

All statistical analyses were performed using R 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria) in combination with the “survival” package. Data are reported as mean $\pm$ standard deviation or median (interquartile range), as appropriate. Analyses were performed in accordance with the pre-defined statistical analysis plan.

Results

Patient flow and follow-up

The flow of participants is outlined in Figure 2. 5502 patients were randomly selected and contacted by the Thrombosis Service. We enrolled 241 patients who provided informed consent between January 13th, 2015, and November 1st, 2016. 121 patients were randomly assigned to DOAC treatment; 120 were assigned to VKA. All randomised patients started their allocated treatment; all of them were included in the analysis. The study was closed when the last patient completed the one-year follow-up on October 17th, 2017. Median follow-up time was 364 (362-369) days, leading to 240 patient-years of follow-up.

Baseline characteristics

Baseline characteristics are summarised in Table 1. The mean age was 72.3 $\pm$ 6.89 (range 46-91). 75.9% was male. Subject-reported hypertension was prevalent (75%). CHADS2 and CHA2DS2-VASc scores were 1.8 $\pm$ 1.0 and 3.2 $\pm$ 1.2, respectively. Almost all patients were treated with acenocoumarol, reflecting

local preference. In both groups, there was 1 patient who used phenprocoumon at randomisation.

The included patients were comparable with the selected patients in age (mean 72.3 versus 72.8 years), but were more likely to be male (75.9% versus 67.3% male).

Figure 2: Subject flow in this study.

	DOAC (N = 121)		VKA (N = 120)	
Age - years	73.0	± 7.5	71.5	± 6.1
Sex female - no. (%)	29	(24.0)	29	(24.2)
Systolic blood pressure - mm Hg	135	± 15.2	136	± 18.3
Diastolic blood pressure - mm Hg	80	± 10.1	82	± 8.8
BMI - kg/m ²	28.3	± 4.7	28.4	± 4.7
CHA ₂ DS ₂ -VASc score				
1 - no. (%)	6	(5.0)	9	(7.5)
2 - no. (%)	29	(24.0)	26	(21.7)
3 - no. (%)	43	(35.5)	49	(40.8)
4 - no. (%)	26	(21.5)	23	(19.2)
5 - no. (%)	10	(8.3)	8	(6.7)
6 - no. (%)	6	(5.0)	5	(4.2)
7 - no. (%)	1	(0.8)	0	
Prior stroke or TIA - no. (%)	12	(9.9)	11	(9.2)
Heart failure - no. (%)	34	(28.1)	25	(20.8)
Hypertension - no. (%)	92	(76.0)	89	(74.2)
Diabetes mellitus - no. (%)	25	(20.7)	29	(24.2)
Vascular disease - no. (%)	28	(23.1)	25	(20.8)
Platelet aggregation inhibitor - no. (%)	3	(2.5)	9	(7.5)
Double anti-platelet therapy - no. (%)	0		1	(0.8)
Nonsteroidal anti-inflammatory agent - no. (%)	5	(4.1)	3	(2.5)
Creatinine clearance - mL/min	78.4	± 26.0	83.5	± 23.4
Creatinine clearance <50mL/min - no. (%)	16	(13.2)	6	(5.0)

Table 1: Demographic and clinical characteristics of subjects, according to assigned treatment strategy. Values are reported as mean±SD, or no. (%). Abbreviations: BMI, body mass index; DOAC, direct oral anticoagulant; TIA, transient ischaemic attack, VKA, vitamin K antagonist.

Study drugs

All 120 patients randomised to VKA continued their respective treatment at the beginning of the trial. No patients switched to a different type of VKA during the study, but two switched to a DOAC: 1 because of the patient's preference for DOAC; 1 was switched by the general physician in the context of a DOAC project in his practice. A valid TTR could be obtained for 98% of VKA patients. The time within an INR range of 2.0-3.5 was 87 (79-96)% for the entire study period, and 67 (56-78)% for range 2.0-3.0 in the applicable period.

All 121 patients randomised to DOAC initiated DOAC treatment. In total, 120 received apixaban (115 the regular dose of 5.0 mg twice daily, 5 the adjusted

dose of 2.5 mg twice daily). One patient received rivaroxaban 20 mg once daily to prevent a possible interaction with other medication (i.e. diltiazem). Twelve DOAC users switched back to VKA during the trial: 2 because of a clinical event; 1 because another indication for VKA emerged; 9 switched back due to side effects or their express wish. DOAC users resumed VKA treatment relatively early on in the study, after 134 (42-204) days, with 4 switching back in the first 45 days. Pharmacy data could be retrieved for all patients on DOAC. The median percentage of days covered, i.e. the percentage of days the patient could have taken the drug, was 100% (IQR 97-100). The percentage of days covered was at least 80% in 94% of patients.

Clinical outcomes

Primary outcome

The clinical outcomes are reported in Table 2 and composite outcomes are shown in Figure 3. The primary outcome of net clinical benefit occurred in 4 (3.3%) patients in the DOAC group and 4 (3.3%) patients in the VKA group (hazard ratio 1.00, 95% CI 0.25–4.00).

Endpoint	DOAC (N = 121)	VKA (N = 120)	ARD	HR
Net clinical benefit	4	4	0.0 (-4.5 to 4.6)	1.00 (0.25– 4.00)
Efficacy	3	4	0.9 (-3.4 to 5.1)	0.75 (0.17– 3.35)
Stroke	2	0	-1.7 (-3.9 to 0.6)	-
Systemic embolism	0	1	0.8 (-0.8 to 2.5)	-
Myocardial infarction	1	2	0.8 (-2.0 to 3.6)	0.50 (0.05– 5.55)
Vascular death	1	1	0.0 (-2.3 to 2.3)	1.01 (0.06–16.20)
Safety	14	12	-1.6 (-9.4 to 6.3)	1.17 (0.54– 2.53)
Major bleeding	2	0	-1.7 (-3.9 to 0.6)	-
Clinically relevant non-major bleeding	10	10	0.1 (-6.9 to 7.0)	1.00 (0.42– 2.41)
All-cause mortality	3	2	-0.8 (-4.4 to 2.8)	1.51 (0.25– 9.06)

Table 2: Number of patients with an endpoint after 1 year of follow-up in the intention-to-treat analysis.

Abbreviations: ARD, absolute risk difference between DOAC and VKA, in percentage points; DOAC, direct oral anticoagulant; HR, hazard ratio; VKA, vitamin K antagonist.

Figure 3: Kaplan-Meier cumulative incidence of net clinical benefit, efficacy, and safety.

Secondary outcomes

The efficacy endpoint occurred in 3 (2.5%) patients in the DOAC group, compared with 4 (3.3%) patients in the VKA group (HR 0.75, 95% CI 0.17–3.35). The safety endpoint occurred in 14 (11.6%) and 12 (10.0%) patients in the DOAC and VKA group, respectively (HR 1.17, 95% CI 0.54–2.53). The safety endpoint was mainly driven by clinically relevant non-major bleedings.

Clinical outcomes separately are summarised in Table 2.

Sex differences

Outcomes stratified by sex are summarised in Appendix Figure 1. Of the women on DOAC, 1 (3%) experienced a net clinical benefit endpoint; 1 (3%) had an efficacy endpoint. These events did not occur in women using VKA. The safety endpoint occurred in 1 (3%) and 2 (7%) women on DOAC and VKA, respectively, versus 13 (14%) and 10 (11%) in men. Sex-specific hazard ratios were 0.51 (95% CI 0.05 - 5.58) in women, and 1.30 (95% CI 0.57 - 2.97) in men.

Per-protocol analysis

Results of the per-protocol analysis are summarised in Appendix Table 2. Two events in the DOAC group were excluded from the per-protocol analysis because the DOAC was discontinued prior to one non-vascular death and one clinically relevant, non-major bleed. The number of events in the VKA group was the same in the intention-to-treat and per-protocol analyses. This shifted the absolute risk reduction for VKA instead of DOAC towards null or negative.

Serious adverse events

Excluding the events described as endpoints, 27 serious adverse events (SAEs) occurred. Twelve patients on DOAC had 13 SAEs. Fourteen serious adverse events occurred in 13 VKA patients. More information on the type of SAEs is provided in Appendix Table 3.

Discussion

This pilot study assessed the hypothesis that continuing vitamin K antagonist therapy is superior to switching to a direct oral anticoagulant in patients currently well controlled on VKA for atrial fibrillation. The data do not support our hypothesis. The net clinical benefit endpoint occurred equally in both groups (HR 1.00, 95% CI 0.25–4.00). The efficacy endpoint occurred slightly more often in the VKA group (HR 0.75, 95% CI 0.17–3.35), whereas the safety endpoint incidence was slightly higher in patients using DOAC (HR 1.17, 95% CI 0.54–2.53). In the

pre-specified per-protocol analysis, the difference in safety endpoints was fully mitigated.

This study differs from earlier randomised controlled trials that evaluated DOAC and VKA in the setting of atrial fibrillation[3–6]. We included only the “best” patients on VKA: those with a high TTR ($\geq 70\%$ in range 2.0–3.5) and no thrombosis or major bleeding ever during VKA. This is reflected in the low bleeding incidence, compared with previous studies[3–6, 20]. Efficacy endpoints occurred infrequent too, as can be expected in a population with a low CHA₂DS₂-VASc score.

We can speculate about why we could not confirm our hypothesis in this study. If the TTR that patients achieved in this study were low, this could conceal the superiority of well-controlled VKA. This was not the case: the TTR in our study was high (median 67% for INR target range 2.0–3.0). This is roughly comparable to the DOAC landscape trials[3, 5, 6], except for the ROCKET-AF, where twice as many patients had a poor TTR ($< 45\%$)[4]. We infer that other factors that predispose a patient to achieve a high TTR (e.g. good medication adherence, a good clinical condition) also improve prognosis under DOAC. The DOAC adherence was high in the current study: 94% of patients had a percentage of days covered of at least 80%. This is much higher than previously described in real-life settings in the United States[21, 22].

A strength of this study is the trial design, which approached the real-life situation as much as possible. We minimised the number of study visits. Patients on VKA had their regular INR testing performed outside the scope of this study, which was not indicated for patients on DOAC. This way we could address the theoretical concerns about lower DOAC compliance in real-life, which would lead to worse DOAC outcomes than reported in the trials. In our study, however, DOAC adherence was high.

At the same time, the different frequency of contact with a healthcare professional could lead to bias, when patients on DOAC would forget to report an event that happened some time ago. To counteract this, all patients were handed out a diary to note all potential side-effects or study outcomes.

We aimed to compare treatment strategies with VKA and DOAC, instead of a specific DOAC with VKA. Guidelines do not prescribe a specific DOAC, and no clinical algorithms exist to favour a particular DOAC for a particular patient. We, therefore, choose the DOAC we considered the best, to anticipate reviewer questions in the event of VKA superiority. We started apixaban in most patients, because we judged this drug to have the best trade-off between efficacy and safety.

Indeed, this decision was later supported by a network meta-analysis, where apixaban rated superior[23]. We will not speculate which results we would have obtained if we had used another DOAC. The debate about which DOAC is superior should preferably be supported by head-to-head comparisons. If apixaban were to be confirmed superior, then patients would switch to apixaban and our study would remain relevant. If apixaban were to be found inferior, then VKA superiority over the “best DOAC” would be even less likely.

Our study also has several potential limitations. First, acenocoumarol, the most commonly used VKA in our Thrombosis Service, is not widely used in other countries. However, due to the identical pharmacological effect, generalization for VKA as a class action is common and accepted. Second, only 4.4% of potentially eligible patients were enrolled. The most important reason for this was because patients did not respond to the invitation to our study. Costs will not have played a big role: in the Dutch system, use of DOAC instead of VKA would only lead to increased out of pocket costs for the small minority who had no other health care costs. This is more a feasibility outcome than a weakness, though, as the enrolled patients were similar in age, and the difference in the proportion of men was not too big to hinder generalization. Third, the confidence intervals we obtained were wide. This fits the non-definite aim of this study; to gather more information about our hypothesis (which extrapolates from literature) and obtain more reliable estimates to calculate a sample size for a definite study.

Before this study, physicians were uncertain whether previously well-controlled patients on VKA could be switched to a DOAC. We have found no evidence that continuing well-controlled VKA is superior to DOAC. With a hazard ratio of 1.0, it is incorrect to calculate a sample size for a larger study. From a clinical point of view, we lay aside the hypothesis and conclude that there are no indications that continuing VKA should be preferred over DOAC in patients who are currently well-controlled on VKA for atrial fibrillation. Other factors should guide the decision which anticoagulant to prescribe.

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**Quality of life after switching from well-controlled
vitamin K antagonist to direct oral anticoagulant:
little to GAIInN**

3

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Abstract

Background Direct oral anticoagulants (DOAC) and vitamin K antagonists (VKA) prevent thromboembolism in atrial fibrillation (AF). DOAC have a fixed dosing regimen and obviate INR monitoring. Therefore, DOAC presumably affect quality of life (QoL) less than VKA.

However, some VKA users appreciate the monitoring. A high time in the therapeutic range (TTR) leads to a lower impact on QoL. We assessed the influence of switching from well-controlled VKA to a DOAC on QoL.

Methods In the GAIInN study, 241 patients with AF, a $TTR \geq 70\%$, and neither bleeding nor thrombosis while on VKA were randomised to switching to DOAC (n=121) or continuing VKA (n=120). Health-related (SF-36) and anticoagulation-related QoL (PACT-Q) was assessed at baseline and after six and twelve months of follow-up.

Results and Conclusion SF-36 development did not differ between groups. After one year, average PACT-Q Convenience improvement was 2.5 (95% CI 0.3 - 4.7) higher on DOAC. DOAC users were 6 percentage points (95% CI -4 to 16) more likely to improve >5 points on Convenience; 22% (95% CI 1 to 43) in patients who scored <95/100 at baseline. The probability to meaningfully improve on PACT-Q Satisfaction was 12% (95% CI 0 to 25) higher on DOAC.

However, 5 (4.1%) and 4 (3.3%) DOAC users resumed VKA because of side-effects and patient preference.

Switching from well-controlled VKA to DOAC for AF leads to a higher probability of improved PACT-Q convenience and satisfaction, but also to a higher risk of side-effects. Arguably only patients who are not satisfied with VKA should switch, because they have more to gain by switching.

Introduction

Atrial fibrillation (AF) is a cardiac arrhythmia that will affect one in five persons during their lifetime[1]. A feared complication of atrial fibrillation is stroke, with a debilitating impact on quality of life[2]. Although anticoagulation reduces the risk of stroke, its impact on quality of life is not just positive: anticoagulation aggravates bleedings that, in turn, impair quality of life[3, 4].

Two types of anticoagulants are commonly prescribed in AF: vitamin K antagonists (VKAs) and direct oral anticoagulants (DOACs). VKAs have been prescribed for decades, and are used by hundreds of thousands of patients in the Netherlands alone. Because of its small therapeutic window, VKA therapy needs to be regularly monitored, and the dose titrated, to maintain an anticoagulation intensity (international normalised ratio, INR) within the therapeutic range. This can be cumbersome and could affect the quality of life of its users. DOACs have been introduced as a more convenient alternative for VKAs. They are non-inferior to VKAs for stroke prevention in AF[5], have a fixed dosing regimen, and do not require INR monitoring. Therefore, DOAC could have a favourable effect on quality of life.

However, vitamin K antagonists only have a limited effect on quality of life. After the first three months of therapy, quality of life is restored to that of the general population[4]. Furthermore, patients who use VKA with a high time within the therapeutic range have lower bleeding and thrombotic risks[6] and require less frequent INR monitoring than patients with poor VKA control. At the same time, VKA may also come with an advantage over DOAC with respect to quality of life, as many patients find the INR monitoring reassuring.

All other things being equal, impact on quality of life could be decisive in the choice for a particular anticoagulant. We aimed to establish whether switching to a DOAC would improve quality of life in the subgroup of patients who were previously well-controlled on VKA.

Methods

Trial aims and design

The Good Anticoagulation In the north of the Netherlands (GAINN) study explored bleeding and thrombotic risks of continuing VKA or switching to a DOAC in patients with atrial fibrillation who were currently well-controlled on VKA. As part of this study, we assessed quality of life.

This study was registered in the Netherlands Trial Registry (NTR4770) and the EU Clinical Trials Register (2013-004805-14), and was approved by the local research ethics committee at the University Medical Center Groningen (METc UMCG 2014/002).

Participants and study procedures

Records of patients who satisfied the inclusion criteria were extracted by Certe Trombosedienst, a large, first-line, thrombosis service for the northern provinces of the Netherlands. Inclusion criteria were: patients aged 18 and above who were treated with VKA for non-valvular atrial fibrillation and managed by Certe Trombosedienst; a minimum duration of treatment of six months at the time of selection; a time within the therapeutic range (INR 2.0 - 3.5) of at least 70% over the previous four months. From all consecutive patients, we randomly selected eligible subjects who were sent patient information and contact information to plan an information visit if they were interested.

After the patient had provided written informed consent, eligibility was re-checked. Exclusion criteria were: a thrombo-embolic event or major bleeding ever while on VKA; indication for anticoagulation other than atrial fibrillation; contra-indication to receive any kind of DOAC; a life expectancy less than 1 year. We aimed to include 240 patients to obtain a reliable estimate of the effect on clinical outcomes; sample size calculation was based on the primary objective of the trial and not on a difference in quality of life.

Participants had four study visits: the first one to provide informed consent and be checked for eligibility, a second one a few weeks later for randomisation, followed by visits six and twelve months later (end of study).

Randomisation, masking, and study drugs

We randomised all eligible and willing patients in a 1:1 ratio to either continuing treatment with vitamin K antagonists, or switching to a direct oral anticoagulant. Randomisation was performed using an interactive computer system provided by the hospital's trial coordination centre, without stratification. Blocks of 4 and 6 were used in random order. Patients were unblinded for their allocated treatment to allow proper assessment of quality of life.

Treatment with VKA was continued as usual. The time between INR monitoring visits was based on the INR and was 6 weeks at most. Treatment with DOAC was started following local guidelines. Most patients received twice-daily apixaban; one patient received rivaroxaban because of concurrent use of diltiazem.

Study outcomes

The primary outcomes of the GAIIn study were clinical events and have been described elsewhere[7]. The secondary outcome was quality of life. We assessed general health-related and anticoagulation-related quality of life, using the Medical Outcomes Study Short-Form 36 (SF-36)[8] and Perception of Anticoagulant Treatment Questionnaire (PACT-Q)[9]. Patients filled in the questionnaires before randomisation and during the research visits six and twelve months later.

The PACT-Q consists of two parts. The first part assesses treatment expectations for new patients. Because all our patients were, by definition, experienced users, we did not administer this part of the questionnaire. The second part consists of eleven questions about convenience, two about burden of disease and treatment, and seven about satisfaction. All questions were scored on a five-point Likert scale. The answers to the questions about satisfaction were summed and rescaled from 0-100 to produce the satisfaction scale. The responses to the questions about convenience and burden of disease and treatment were combined to produce the convenience scale[9]: first, the answers were inverted, then summed, and then rescaled from 0-100. A higher score indicates higher satisfaction or higher convenience.

The SF-36 is scored to obtain eight scales, and two summary component scores: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health, and the physical and mental component scores. The physical and mental components scores were determined by norming on a Dutch population[10], using weights from the United States of America[11] because data from the Netherlands are not available. A priori we considered it unlikely that anticoagulants would have an effect on the scales for bodily pain, physical functioning, role emotional and role physical. However, the SF-36 needs to be administered in full. We chose not to postulate hypotheses for these subscales, and will not analyse differences from baseline for these subscales.

We assessed overall treatment satisfaction highlighting one item in the PACT-Q questionnaire: "Overall, how satisfied are you with your anticoagulant treatment?" The answer to this question is on a five-point (Likert) scale. For the baseline value, the answer to this question at the time before randomisation was used. For development during the study, we also looked at whether a patient decided to switch from their allocated treatment to the other treatment (e.g. because of side-effects). If that was the case, the answer to the treatment satisfaction question could no longer be unambiguously interpreted. We then interpreted the switch as a sign that the patient was less satisfied with the allocated treatment. If the

patient was still on the allocated treatment when (s)he filled in the questionnaire, we used the answer to the question.

Statistical analysis

We calculated differences from baseline for every subject for all quality of life outcomes. We assessed between-group differences using an independent t-test or Mann-Whitney U test, as appropriate.

We assessed an individual's probability to obtain a relevant improvement or decline in quality of life. We considered a change of 5/100 or less irrelevant; an improvement of >5 was considered a relevant improvement, a decline of >5 a relevant decline. This a priori set threshold was chosen arbitrarily: there is no consensus about a cut-off for relevance. We calculated absolute risk differences (ARD) for a relevant improvement or relevant decline on all PACT-Q scores, the SF-36 component scores, and the SF-36 scales for which an effect was not a priori unlikely (see above). All changes in the 5-point scale of treatment satisfaction were considered relevant. In addition, a switch based on patient preference, side effects, or clinical events was considered a relevant decline.

If subjects scored $\geq 95/100$ on a particular scale at baseline, they could not experience a relevant improvement. As a sensitivity analysis, we re-assessed absolute risk differences in the group of patients who did not score $\geq 95/100$ at baseline.

All analyses were performed in the intention-to-treat group, using R version 3.6.1 (2019-07-05) (R Foundation for Statistical Computing, Vienna, Austria). Data are reported as mean $\pm$ standard deviation or median (interquartile range), as appropriate.

Results

Patient flow and follow-up

The flow of participants is outlined in Figure 1. 5,502 patients were randomly selected and contacted by the Thrombosis Service. Between January 13, 2015, and November 1, 2016, 241 patients provided informed consent and were enrolled in the study. 121 patients were randomly assigned to DOAC treatment; 120 were assigned to VKA. All randomised patients started their allocated treatment; all of them were included in the analysis. The study was closed when the last patient completed the one-year follow-up on October 17, 2017. Median follow-up time was 364 (362-369) days, leading to 240 patient-years of follow-up.

The included patients were comparable with the selected eligible patients in age (mean 72.3 versus 72.8 years), but were more likely to be male (75.9% versus 67.3%).

Figure 1. Patient flow in this study.

Baseline characteristics

Baseline characteristics are summarised in Table 1. The mean age was 72 ± 6.9 (range 46-91). 76% was male. The majority of participants had comorbidities, with hypertension (75%) being the most common. Fewer subjects reported a stroke before starting VKA (10%) or vascular disease (22%). Beta-blockers were prescribed in 65% of participants; 13% used digoxin. Almost all patients were treated with acenocoumarol, reflecting local preference. In both groups, there was 1 patient who used phenprocoumon at randomisation.

	DOAC (n=121)	VKA (n=120)
Age (years) - mean (SD)	73.1 ± 7.5	71.5 ± 6.1
Sex female - n (%)	29 (24%)	29 (24%)
Body mass index (kg/m ²) - mean (SD)	28.3 ± 4.6	28.4 ± 4.7
CHA ₂ DS ₂ -VASc - median [IQR]	3.0 [2.0 – 4.0]	3.0 [2.0 – 4.0]
Prior stroke - n (%)	12 (10%)	11 (9%)
Heart failure - n (%)	34 (28%)	25 (21%)
Hypertension - n (%)	92 (76%)	89 (74%)
Diabetes mellitus - n (%)	25 (21%)	29 (24%)
Vascular disease - n (%)	28 (23%)	25 (21%)
Betablocker use - n (%)	79 (65%)	77 (64%)
Digoxin use - n (%)	20 (17%)	11 (9%)
Platelet aggregation inhibitor - n (%)	3 (2%)	9 (8%)
Non-steroidal anti-inflammatory agent - n (%)	5 (4%)	3 (2%)

Table 1. Patient characteristics.

Quality of Life

Quality of Life scores are summarised in Table 2. Before randomisation, patients were very content with their treatment. Patients rated their overall treatment satisfaction on average 4.2 ± 0.8 out of 5. 79 (65.3%) patients gave the maximum rating of 5. The PACT-Q treatment satisfaction score was lower: median [IQR] 64 [57 – 71] out of 100. Patients found their treatment very convenient (PACT-Q convenience scale 98 [92 – 100], with 156 (64.7%) patients scoring $\geq 95/100$). The relevant SF-36 scales were well-balanced between the two groups. Scores on a priori irrelevant SF-36 scales are reported in Supplementary Table 1.

In general, the relevant health-related quality of life scores remained constant during follow-up (Table 2) and changes during follow-up were the same in both groups. Social functioning was an exception: its score decreased over time in both groups. When excluding the 115 patients with a score of $\geq 95/100$ at baseline, scores on social functioning remained constant. After one year of follow-up, more patients on DOAC than on VKA said their health was “somewhat” or “much better” than at the start of the study: 24 versus 12 (absolute risk difference 10% (95% CI 1 to 19)). A similar number of patients reported “somewhat” or “much” worse health compared with one year earlier: 17 versus 19 (ARD -2% (95% CI -11 to 7)).

Patients on DOAC reported an average increase in convenience, compared with VKA: a difference of 1.8 (95% CI 0.3 - 3.3) after six months. This effect persisted after one year: 2.5 (95% CI 0.3 - 4.7). In 156 patients who did not score $\geq 95/100$ at baseline the difference between DOAC and VKA was more pronounced: 5.1 (95%

CI 1.7 - 8.4) after six months and 5.3 (95% CI 1.8 - 8.9) after one year, versus 0.3 (95% CI -0.6 to 1.2) and 1.4 (95% CI -1.3 to 4.0) in patients with a baseline convenience score $\geq 95/100$.

The average PACT-Q Satisfaction score initially improved as well, but this effect was not significant (3.3 (95% CI -1.4 to 8.1)) and the difference shrank after one year (1.6 (95% CI -3.3 to 6.5)).

Patients on DOAC were more likely than patients on VKA to improve >5 points on PACT-Q convenience, during six months of follow-up: their probability was 11% (95% CI 2 to 21) higher than for patients on VKA (Figure 2). After one year of follow-up, this difference had diminished: patients on DOAC then only had a 6% (95% CI -4 to 16) higher probability to improve (Figure 3), which was no longer significant. The likelihood to experience a decline was the same in both groups, with a difference in probabilities of -2% (95% CI -8 to 4) after six months and 0% (95% CI -7 to 8) after one year. Likewise, patients on DOAC were more likely to improve on PACT-Q satisfaction at six months, but no longer after one year, as illustrated in Figures 2 and 3. The probability to decline was similar on VKA and DOAC.

We found no differences in probabilities to improve or decline on the SF-36 scales after either six months or one year.

Patients on DOAC were more likely to experience an improvement in general treatment satisfaction (the probability was 10% (95% CI -1 to 20) higher than on VKA after six months), yet also more likely to experience a decline or reason to switch (difference in probabilities 8% (95% CI -2 to 18)). After one year, the probability to improve was 5% (95% CI -6 to 16) higher on DOAC, and the probability to decline or switch was 8% (95% CI -2 to 18) higher than on VKA.

Scale	Baseline		Change after six months			Change after one year		
	DOAC	VKA	DOAC	VKA	p	DOAC	VKA	p
Full study population								
PACT-Q convenience	98 [92 – 100]	96 [92 – 99]	2.6 ± 6.9	0.8 ± 4.2	0.02	2.4 ± 7.4	-0.1 ± 9.7	0.03
PACT-Q satisfaction	64 [57 – 71]	64 [57 – 71]	4.7 ± 19.2	1.4 ± 16.9	0.17	3.9 ± 18.7	2.3 ± 18.9	0.51
General Health	67 [52 – 77]	62 [52 – 77]	-0.9 ± 13.3	1.3 ± 13.4	0.22	-1.0 ± 13.2	0.5 ± 14.0	0.41
Vitality	70 [55 – 80]	75 [65 – 85]	-0.4 ± 14.3	-2.3 ± 11.9	0.29	-0.6 ± 12.3	-1.8 ± 13.1	0.49
Social Functioning	88 [75 – 100]	88 [75 – 100]	-2.4 ± 18.0	-2.8 ± 15.8	0.85	-4.1 ± 15.9	-3.2 ± 17.5	0.68
Mental Health	82 [72 – 92]	84 [76 – 92]	-0.3 ± 13.3	-1.7 ± 12.4	0.42	0.1 ± 10.9	0.1 ± 10.1	0.96
SF-36 Physical component	47 [40 – 52]	51 [44 – 54]	-0.7 ± 7.0	-0.6 ± 6.9	0.87	-0.6 ± 6.7	-1.6 ± 7.1	0.28
SF-36 Mental component	55 [49 – 58]	55 [49 – 58]	0.0 ± 8.2	-0.8 ± 6.9	0.45	0.0 ± 6.7	0.1 ± 7.2	0.94
Subjects with baseline score <95								
PACT-Q convenience	88 [80 – 92]	90 [88 – 92]	7.9 ± 9.3	2.9 ± 5.2	0.004	8.4 ± 9.4	3.1 ± 6.1	0.004
Social Functioning	75 [62 – 88]	88 [62 – 88]	3.6 ± 18.3	0.9 ± 16.8	0.40	-0.6 ± 18.2	-0.8 ± 21.9	0.95

Table 2. General health-related, and anticoagulation related quality of life. Values are given as median [IQR] or mean ± SD as appropriate. Ps from unpaired t-tests. No Ps are given for baseline, because the subjects were randomised. No hypothesis testing was performed for scales that are unlikely to be affected by anticoagulants. Abbreviations: DOAC, direct oral anticoagulant; VKA, vitamin K antagonist.

Figure 2. Quality of life after six months.
Difference in proportions of patients experiencing a relevant decline resp. improvement on a direct oral anticoagulant, compared with a vitamin K antagonist, after six months of follow-up.
Items marked with * exclude subjects with a score of $\geq 95/100$ or 5/5 at baseline.

Figure 3. Quality of life after one year.
Difference in proportions of patients experiencing a relevant decline resp. improvement on a direct oral anticoagulant, compared with a vitamin K antagonist, after 1 year of follow-up.
Items marked with * exclude subjects with a score of $\geq 95/100$ or 5/5 at baseline.

In another analysis, we only included patients who could actually improve, because they scored $<95/100$ or $<5/5$ at baseline. They were even more likely to increase in PACT-Q convenience under DOAC (as indicated by the asterisk in Figures 2 and 3). Although the effect attenuated after one year in this group as well, it remained significant. The subgroup of patients who were not fully satisfied with their treatment at baseline was far more likely to increase in overall satisfaction after the switch to a DOAC: the probability was 18% (95% CI 4 to 33) higher than that on VKA after six months. In contrast to the overall group, the probability to decline was not higher on DOAC: the difference was -1% (95% CI -10 to 8) after six months. After one year of follow-up, patients remained more likely to improve (difference 13% (95% CI -2 to 28)) and less likely to decline (difference 4% (95% CI -5 to 13)) than the complete population, but the differences diminished and were no longer statistically significant.

At the end of the study, DOAC patients could choose whether to continue DOAC or switch back to VKA. Out of the 121 patients randomised to DOAC, 105 (86.8%) chose to continue their DOAC. 12 (9.9%) had switched back to VKA during the study (mainly over perceived side-effects: one developed another indication for VKA; two had an event under DOAC). 2 (1.7%) patients had died. 2 (1.7%) patients preferred to switch back to VKA at the end of the study (mainly because of the higher out-of-pocket expense of DOAC).

Discussion

In patients who were well-controlled on VKA, we found that switching to a DOAC only marginally improved average treatment convenience and did not affect other parameters of quality of life. On the individual level, a minority of patients experienced a “relevant improvement” of > 5 points on anticoagulation-related, but not general, quality of life. However, the effect of a switch to a DOAC was not just positive: the number of patients who were more satisfied overall was the same as the number of patients who were less satisfied or decided to switch back to a VKA. Only in the subgroup of patients who were not fully satisfied at baseline did the DOAC cause more patients to improve than to decline or switch.

Our study is the first to focus exclusively on patients who were well-controlled on VKA at baseline. Our findings are in line with results from the RE-LY trial[12], where no differences were found in quality of life between patients randomised to dabigatran or warfarin. Other studies assessed quality of life outside a randomised controlled setting. This makes results more difficult to interpret, as patients with lower thrombotic and bleedings risks are switched more often[13]. Differences in clinical characteristics can confound the relationship between

prescribed anticoagulant and quality of life scores. One study accounted for this with propensity score matching and found no difference in quality of life between DOAC and VKA[14]. Another study used regression analysis to correct for confounders and found that patients on DOAC experienced less burden and more benefit from treatment[15]. Other studies that report a higher quality of life on DOAC should be interpreted with caution, because they did not address baseline differences[16, 17].

Our study benefits from randomisation while maintaining a design that closely resembles “real-life.” Patients randomised to DOAC had no appointments at the anticoagulation clinic, except for a study visit at six months and one year. This allowed them to experience the absence of INR monitoring visits (which was impossible in the registration trials) and associated reassurance.

A potential limitation of the randomised setting is the generalisability: patients with a strong preference to continue VKA have not been included in the study. However, these patients would not be switched with current shared decision making either. Enrolled subjects were representative of the identified patients in age but slightly more often male.

Because this study was a pilot study aimed at clinical events, we did not perform a sample size calculation for quality of life outcomes. In our study, we adopted an arbitrary cutoff of more than five points. Most analyses have been performed according to the intention-to-treat principle: patients who discontinued their allocated treatment were analysed in their allocated group. Theoretically, the switch away from the allocated treatment could lead to an improvement in quality of life (e.g. when a patient no longer suffered side-effects); if this were attributed to the allocated treatment this could distort the results. This effect would be strongest on the single question about general treatment satisfaction. We therefore took switching into account for this question; for the other questions we maintained the intention-to-treat principle. However, results in the per-protocol analyses were not meaningfully different, making this distortion unlikely. Symptoms of AF, such as palpitations and dyspnoea, also affect quality of life[18]. We have not assessed symptom severity but an effect of anticoagulation on AF symptoms is pathophysiologically implausible. Furthermore, we have excluded SF-36 scales most sensitive to AF symptoms.

Overall, patients in our study already scored high on treatment convenience at baseline. These patients were selected because they had a high TTR, which allows for more time between INR monitoring. This lowers treatment burden[19] and increases convenience[4]. Furthermore, they are less likely to suffer from bleeding and thrombotic events than patients with a poor TTR[6]. Another explanation for the high convenience would be that these patients are managed by a well-

organised, dedicated, anticoagulation clinic with wide opening hours. Patients from this clinic expressed high convenience before[4].

With treatment convenience already so high, switching to a DOAC could not make much of a difference. Indeed, an increase in convenience was confined to patients who scored <95 on convenience at baseline (the difference was 5.3 (1.8 - 8.9) points relative to VKA, versus 1.4 (-1.3 to 4.0) in patients who scored ≥ 95 at baseline). Of these patients, 1 additional patient out of every 4.6 (95% CI 2.3 - 140.5) who switched experienced a relevant increase in convenience. A possible explanation is that patients prefer taking a fixed dose of 1 tablet of apixaban twice daily, compared with multiple and a variable number of tablets for acenocoumarol once daily.

Furthermore, switching to a DOAC did not result in a meaningful difference on other measures of quality of life. Nevertheless, the majority of patients on DOAC preferred to continue their DOAC at the end of the study, instead of switching back to VKA. This could indicate that patients favour DOAC over VKA, despite the only small difference in anticoagulation-related quality of life.

Another explanation, however, for their preference to continue DOAC could be that patients dread drug changes when they do not expect much benefit. This could also explain the low participation rate in our study. 5 (4.1%) patients on DOAC experienced side-effects; an additional 4 (3.3%) patients had another reason why they wanted to resume VKA therapy. This effect negated the positive effects on general treatment satisfaction that other patients experienced.

However, even if switching to a DOAC would have no positive effect on quality of life, switching could still be justified if it would lead to better clinical outcomes. In this study, we hypothesised that well-controlled patients on VKA would actually be harmed by switching to a DOAC. However, we found no evidence to support this hypothesis: clinical endpoints were distributed evenly between the two groups[7]. In a more general study population, DOACs lead to a reduced risk of intracranial haemorrhage and ischaemic stroke, although the absolute risk reductions are modest[5]. Although well-controlled patients who find VKA therapy inconvenient have more to gain by switching to a DOAC, we believe all patients should be counselled about the different options available for stroke prevention in AF. This study can be helpful in shared decision making and weighing a possible improvement in treatment convenience against the risk of side-effects.

Conclusion

In a population with good VKA control, a switch to a DOAC has no effect on general health-related quality of life, but leads to a small increase in anticoagulation-related quality of life. However, the switch introduced side-effects and other reasons patients decided to resume VKA therapy. These should be considered before switching from well-controlled VKA to a DOAC. Patients who are not satisfied with treatment with VKA have more to gain by switching to a DOAC. Physicians and their patients should together weigh the advantages and disadvantages.

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Clinical usefulness of the SAME-TT₂R₂ score: a systematic review and simulation meta-analysis

4

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Abstract

Background Vitamin K antagonist (VKA) therapy is safer and more effective when patients have a high time within the therapeutic range and low international normalised ratio variability. The SAME-TT₂R₂ score aims to identify those at risk for poor VKA control.

Objectives To evaluate the predictive value and clinical usefulness of the SAME-TTR score to identify those at risk for poor VKA control.

Methods We performed a systematic review in MEDLINE and Embase for original research papers assessing the SAME-TT₂R₂'s relation to poor TTR. We performed a meta-analysis where scores ≥ 2 and ≥ 3 predicting TTR < 70%. When studies evaluated other cutoffs for TTR or SAME-TT₂R₂, they were harmonised by multiple simulations with patient characteristics from the individual studies, if the data were available.

Results 16 studies were identified and used in the meta-analysis: 4 and 2 times directly, 8 and 8 times harmonised for scores ≥ 2 and ≥ 3 , respectively (not all studies provided information about both cutoffs). The sensitivities and specificities were too heterogeneous to pool. The positive likelihood ratios were 1.25 (95% CI 1.14-1.38) for a score ≥ 2 , and 1.24 (95% CI 1.09-1.40) for a score ≥ 3 ; the negative ones were 0.87 (95% CI 0.82-0.93) and 0.96 (95% CI 0.91-1.02), respectively. This shows that the post-test probabilities hardly differ from the prior probability (prevalence).

Conclusion The SAME-TT₂R₂ score does predict low TTR, but the effect is small. Its effect on individual patients is too limited to be clinically useful.

Introduction

Vitamin K antagonist (VKA) therapy is safer and more effective when patients have a high time within the therapeutic INR range (iTTR)[1] and low INR variability[3]. However, the quality of anticoagulation achieved differs greatly between individuals. The first period of anticoagulant treatment provides some information about future quality[4], but it is unclear how long this “trial of VKA” should be. Ideally, one could identify patients prone to poor VKA control before starting treatment. Separate predictors have been identified before, but their combination was prognostically weak[5–7].

Apostolakis et al. developed a new tool to identify those prone to poor VKA control before starting treatment: the SAMe-TT₂R₂ score[8]. The score awards one point each for female sex; age <60 years; 2 or more of certain comorbidities; and the presence of interacting medication, and two points each for tobacco use and non-Caucasian race. The score was initially developed to identify “outliers” (i.e. those below a certain percentile of TTRs)[10]. After further assessment in other studies, it evolved into proposed decision rules to give patients with a score of 2 or higher extra care[11], or suggest that those with a score >2 start a NOAC instead of trying VKA[12].

While it is not uncommon for a risk score’s area of use to expand, this could jeopardise the score’s validity. The aim of this study is to assess the predictive performance and added clinical benefit of the SAMe-TT₂R₂ score, using a systematic review and meta-analysis.

Methods

Selection criteria

Studies were required to meet all the following pre-defined inclusion criteria for the systematic review:

- Participants: patients on VKA, naive or experienced
- Test: SAMe-TT₂R₂ score
- Outcome: quality of anticoagulation (time in therapeutic range[13] or percentage of international normalised ratios in therapeutic range (PINRR); both henceforth called “TTR” for brevity)
- Type of study: published original research paper

The studies were required to provide data to derive or calculate test statistics (such as predictive values and likelihood ratios) from a 2x2 contingency table for inclusion in our meta-analysis.

Data sources and searches

We searched MEDLINE and Embase and included studies indexed up to 12 January 2017, the date of our last search. We used the search term *SAMe-TT₂R₂*, without limits on language or otherwise. We excluded MEDLINE citations in Embase. We checked references of the included studies.

Study selection

Two independent reviewers (JvM and SB) performed the study selection individually based on the predefined inclusion and exclusion criteria. They screened all titles and abstracts of the articles to identify potentially eligible studies. The full text of these potentially eligible studies was then evaluated to determine eligibility for the systematic review and meta-analysis. Disagreements were resolved through discussion. There were no unresolved disagreements among the reviewers, which needed the advice of a third reviewer. When multiple studies were conducted on the same population of patients, we would extract data from the most complete publication or combine the results. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement for reporting of systematic reviews and meta-analyses of randomised clinical trials was followed[14]. The PRISMA flowchart in Figure 1 shows the selection process; the PRISMA checklist is included in Supporting Information S1. The study was not prospectively registered.

Data collection process

Two reviewers extracted data from each article independently (JvM and SB). Discrepancies between the reviewers were resolved by consensus. The following data were extracted from the included trials: indication for anticoagulation therapy, quality of anticoagulation achieved and its measurement method, numbers of patients, TTR cutoffs, *SAMe-TT₂R₂* cutoffs, and test specifics. When the *SAMe-TT₂R₂* cutoffs used in the study differed from those we chose, we modelled the different cutoffs if possible (see below).

Quality assessment

We rated the overall quality of evidence using the revised Tool for the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2[15] see Supplementary Table 1). Agreement on the quality of the individual studies was obtained after discussion (JvM and SB). If information to score a particular part of the assessment tool was absent we defined this risk of bias as unclear. Risk of bias of the index test was defined as unclear whenever *SAMe-TT₂R₂* of 2 or 3 was not

used as a cutoff to predict poor anticoagulation. We visually inspected funnel plots and performed a mixed-effects meta-regression model to assess possible publication bias.

Figure 1. PRISMA flowchart[14] detailing the search strategy used.

Data synthesis

Test statistics from original studies

We analysed SAMe-TT₂R₂ cutoffs of ≥ 2 and ≥ 3 (following from the aforementioned decision rules) to predict a TTR <70% (a TTR below the benchmark for high quality anticoagulation[11]). From articles that used the same TTR cutoff, we derived test statistics from the 2x2 contingency table (we algebraically calculated one based

on information from the text when the contingency table was unavailable) with a spreadsheet tool[16].

Harmonising cutoffs using a simulation

When a different TTR cutoff was used, we gathered the mean and standard deviation for each SAME-TT₂R₂ category. This allowed us to simulate a TTR for every subject by sampling from a beta distribution set up to mimic a truncated normal distribution (because TTR is always between 0 and 100%). We created a 2x2 contingency table using cutoffs for TTR and SAME-TT₂R₂, and used this to calculate test statistics. Every study was simulated thousand times, to incorporate the sampling uncertainty. These simulations were performed in R (R Foundation for Statistical Computing, Vienna, Austria) on Windows, using a script that is available as a supplement.

Data analysis

To assess the performance of our simulation, we simulated all studies with their original cutoff values, and compared the simulated test statistics with those originally found in the article.

We presumed heterogeneity in studies as a result of variation in VKA control achieved in different settings by different clinics, and indication for treatment. We pooled data using a random effects model, unless the outcomes were too heterogeneous in effect sizes (based on the forest plots) or had a too large I². Likelihood ratios, negative and positive predictive values, sensitivity, specificity, and power of separation (difference between the post-test probabilities of the two groups[17]) are reported.

The meta-analysis was performed in R using the metafor package[18]. We report data as point estimate (95% confidence or reference interval) unless otherwise indicated.

Results

Study selection

We identified 57 distinct articles. We excluded 41 records, so 16 studies[33] could be included in the systematic review and meta-analysis (see S1 Supporting Information).

Study characteristics

14 studies were performed in patients with atrial fibrillation; 2 were done in patients with venous thromboembolism. 5 studies reported on VKA naive patients;

5 on experienced patients and for 6 this was not reported. Study characteristics are summarised in Table 1.

16 different studies were included in the meta-analysis: 12 for a SAME-TT₂R₂ cutoff of ≥ 2 , 10 for a cutoff ≥ 3 . 8 and 8 studies were simulated before inclusion, respectively.

Quality assessment

The risk of systematic bias within studies was low. However, the specific methodology of many studies was unclear. Some studies provided insufficient data on patient selection; many studies did not provide enough information about the timing of the calculation of the SAME-TT₂R₂ score and quality of anticoagulation. This could introduce survival bias: patients with poor VKA control may cease treatment. Multiple studies did not evaluate a cutoff for the SAME-TT₂R₂ score or the TTR, but chose to evaluate the variables continuously. The quality assessment is summarised in Supplementary Table 1.

Due to the limited number of studies for each combination of score and TTR cutoffs, we could not assess publication bias for every combination. For those combinations where it was possible, we found no evidence for publication bias.

Results of individual studies

The articles used myriad ways to evaluate the SAME-TT₂R₂ score: some authors used a high score to predict low TTR[8, 19, 22, 26, 27, 30, 31, 33]; others a low score to predict high TTR[21, 33]. This affects the sensitivity and specificity. The cutoffs used to define a “high” score or a “low” TTR varied as well. Some studies evaluated multiple cutoffs for quality of anticoagulation or SAME-TT₂R₂[19, 21, 26, 30, 33]. The SAME-TT₂R₂ cutoff ≥ 2 in combination with a TTR cutoff of 65 was studied most often: in 6 studies including 5393 patients. 6 studies[8, 20, 23–25, 29] were performed without cutoffs for SAME-TT₂R₂ score or TTR, including 3817 patients. The results of the individual studies (recalculated to have a SAME-TT₂R₂ $\geq$ cutoff predict a TTR < cutoff) are summarised in Supplementary Table 2.

The prevalence of TTR below the cutoff was 39-89%. The prevalence of a SAME-TT₂R₂ score above the cutoff was 21-46% and 5-82% in studies that evaluated cutoffs ≥ 2 and 3, respectively. Sensitivity and specificity ranged from 6-82% and 14-96%, respectively. 4 studies[21, 22, 28, 32] showed that a high score made poor anticoagulation less likely (LR+ < 1).

Study	Score	TTR	Indication	N	Cohort	Period excluded	TTR duration	TTR method
Abumuaileq	≥2	<70	AF	911	inception	first month	12 months or until event	PINRR
Abumuaileq	≥2	<65	AF	911	inception	first month	12 months or until event	PINRR
Apostolakis	-	-	AF	286	not reported	not reported	not reported	Rosendaal
Bernaitis	-	-	AF	1137	not reported	not reported	not reported	Rosendaal
Chan	>2	>70	AF	1428	not reported	first 6 weeks	not reported	Rosendaal
Chan	>3	>70	AF	1428	not reported	first 6 weeks	not reported	Rosendaal
Demelo	≥2	<65	VTE	135	inception	first month	not reported	Rosendaal
Gallego	-	-	AF	972	experienced	none	6 months	Rosendaal
Gorzelał	-	-	AF	104	experienced	none	6 months back	Rosendaal
Lip	-	-	AF	229	experienced	not reported	not reported	Rosendaal
Lobos	≥2	<65	AF	1524	not reported	not reported	12 months back	Rosendaal
Lobos	≥2	<70	AF	1524	not reported	not reported	12 months back	Rosendaal
Lobos	≥3	<65	AF	1524	not reported	not reported	12 months back	Rosendaal
Palareti	≥2	<65	VTE	1308	inception	not reported	not reported	Rosendaal
Park	-	-	AF	380	not reported	first month	not reported	Rosendaal
Poli	-	-	AF	1089	inception	none	not reported	Rosendaal
Proietti	>2	<70	AF	3624	mixed	mixed	not reported	Rosendaal
Proietti	>2	<65	AF	3624	mixed	mixed	not reported	Rosendaal
Roldan	≥2	<65	AF	459	inception	not reported	6 months	Rosendaal
Ruiz	<2	>65	AF	1056	experienced	not reported	6 months back	Rosendaal
Ruiz	<2	>70	AF	1056	experienced	not reported	6 months back	Rosendaal
Szymanski	-	-	AF	211	experienced	not reported	not reported	Rosendaal

Table 1. Study characteristics.

AF: Atrial fibrillation; N: number of patients included; period excluded: period excluded in calculation of the TTR; PINRR: proportion of INRs in range; TTR: time in therapeutic range (here also percentage of INRs in therapeutic range); VTE: venous thromboembolism.

There were no patients with a SAME-TT₂R₂ score < 2 in three Asian studies[20, 21, 28], because the SAME-TT₂R₂ score awards two points for non-Caucasian race. Another study's[30] results could not be used for the simulation, so only the original cutoff could be used. Therefore, these studies could only be used to assess the score's performance with a cutoff ≥ 3 . Other studies only reported dichotomised SAME-TT₂R₂ scores with a cutoff of 2[22, 24–26, 31, 32]. These studies were excluded for the evaluation of the cutoff ≥ 3 . From the study that introduced the SAME-TT₂R₂ score[8], we only used the external validation cohort.

Validation of the simulation

We simulated all studies with their original cutoff values and compared the simulated point estimates and boundaries of the reference interval with their counterparts found in the studies. We did this for sensitivity, specificity, positive and negative predictive values, and prevalence of low TTR. This is graphically shown in Figure 2. Pearson's correlation was 99%. The simulated point estimate fell in the original confidence interval in 82% of cases, and the differences between the original and simulated point estimates were small: mean < 0.01 , SD = 0.03 (see also Supplementary Figure 1).

Figure 2. Calibration plot comparing simulated values with the corresponding values from the original studies.

Meta-analysis

The results of the meta-analysis are summarised in Table 2, Figure 3 and Supplementary Figure 2. We decided not to pool the data for sensitivities and specificities, because they were too heterogeneous (see Figure 3; lower bound of 95% CI of $I^2 > 97\%$).

cutoff	LR-	LR+	PSEP
≥ 2	0.87 (0.82-0.93)	1.25 (1.14-1.38)	0.08 (0.05-0.11)
≥ 3	0.96 (0.91-1.02)	1.24 (1.09-1.40)	0.06 (0.02-0.10)

Table 2. Performance of the SAME-TT2R2 score to predict TTR <70%.

LR-, LR+: negative and positive likelihood ratio, respectively; PSEP: power of separation; TTR: time in therapeutic range

Figure 3. Forest plots showing positive and negative likelihood ratios (LR+, LR-) of the SAME-TT2R2 score, using cutoffs of ≥ 2 and ≥ 3 to predict a TTR < 70%.

Discussion

Vitamin K antagonist (VKA) therapy is safer and more effective when patients have a high time within the therapeutic INR range (iTTR)[1] and low INR variability[2, 3]. The SAME-TT₂R₂ score[8] was developed to identify VKA control outliers before they started treatment. While the score has been adopted in AF guidelines[1], the added benefit of this score remains unclear. We evaluated how well the score identified those with a poor TTR (< 70%, which is below the European Society of Cardiology's cutoff for high-quality anticoagulation[11]) with cutoffs from proposed decision rules[11, 12], using a systematic review and meta-analysis.

There is a striking difference in how studies applied and validated the SAME-TT₂R₂ score. This process, from identifying those with poorest VKA control[8, 10] to evaluating the relationship with continuous[19, 20, 23] or categorised TTR values[21, 27, 28, 31, 33], fits the exploration of the score's usefulness for individual patient care. This heterogeneity is however confusing, which is why we harmonised the different cutoffs. We evaluated SAME-TT₂R₂ cutoffs of ≥ 2 ("patients who might need extra care"[11]) and ≥ 3 ("should start a direct oral anticoagulation instead of VKA"[12]).

The score's sensitivity and specificity to identify a TTR <70% differed substantially between studies. A more consistent finding was that a test outcome does not decrease the uncertainty about VKA control substantially: the prior and posterior probabilities hardly differ (0.08 (0.05-0.11) and 0.06 (0.02-0.10) for cutoffs 2 and 3, respectively). This is also reflected in the likelihood ratios (LR+ 1.25 (1.14-1.38) and 1.24 (1.09-1.40); LR- 0.87 (0.82-0.93) and 0.96 (0.91-1.02)), which are very close to unity and graphically shown in Figure 4.

More important for clinical practice is whether a test manages to make the post-test probability surpass a clinical probability threshold: from a "grey area" of clinical uncertainty, to the certainty treatment is (un)necessary. It is unlikely that the SAME-TT₂R₂ score is able to do this: the change in probabilities is too small. The pre-test probability of a poor TTR varies from setting to setting (e.g. by country, or with manual versus computer-assisted dosing). An estimate of this probability can be based on the TTRs achieved by other patients managed in a particular setting. In the Netherlands patients are managed by dedicated thrombosis services that publish statistics on the TTRs of their patients in their annual reports.

The other way around, one could ask the question in which populations the score could change clinical decision making. This depends on the clinical probability thresholds used. Imagine one wants to be 70% certain of poor VKA control before

withholding VKA therapy, and will definitely start VKA therapy if the probability of poor TTR is less than 20%. A score ≥ 2 is only useful when the prior probability is between 65.1% (lowest prior probability which will result in a post probability $\geq 70\%$) and 69.9% (if the prior probability already equals the threshold, we do not need additional information). Likewise, a score < 2 is only useful for prior probabilities 20.1–22.2%. For a score cutoff of 3, these numbers are 65.3–69.9% and 20.1–20.6%, respectively. This underlines the limited clinical usefulness from the score.

Figure 4. Pre-test and post-test probabilities plot for the possible SAME-TT2R2 scores. Results from individual studies are indicated by dots, with the horizontal and vertical lines representing the 95% confidence interval.

Others have tried to predict an individual's TTR. Rose et al. developed a more extensive prediction model, but its explained variation was low (3.2–6.8%)[5]. The same is true for the work of MacEdo et al. (7% variation explained)[6]. Mueller et al.[7] did not report the variance in TTR explained by the HAS-BLED score, but we estimated it with a simulation to be around 12%. Even pharmacogenetics-based warfarin dosing only moderately improved TTR[34]. This shows that there is a large unexplained inter-individual difference in the response to VKA.

Strengths and limitations

Our study has strengths and limitations. The studies we identified were heterogeneous in many aspects: the cutoffs used for the SAME-TT₂R₂ score and TTR, the method to determine quality of anticoagulation, and the indication for anticoagulation therapy.

We used a simulation method to uniform the cutoffs and calculate their outcomes. This is a not yet established method, but we have shown this works very well. It allowed us to meta-analyse the results with established methods.

There was one study that did not report the TTR with the Rosendaal method, but instead counted the number of INR measurements within range. The two methods are not equivalent[35]. Sensitivity analysis showed the results did not change meaningfully when only studies using the Rosendaal method were included (see Supplementary Figure 3 and Supplementary Table 3).

There was no difference in the score's performance in patients with atrial fibrillation, compared with those with venous thromboembolism (Supplementary Figure 3 and Supplementary Table 3). The assumption that the SAME-TT₂R₂ score performs best in populations with a high probability of a low TTR and a large spread in TTRs could not be substantiated in post-hoc sensitivity analyses (Supplementary Figure 3 and Supplementary Table 3).

Many studies conclude that the SAME-TT₂R₂ score performs well based on a statistically significant C statistic or statistically significant differences in mean TTR between SAME-TT₂R₂ groups. To answer our question, we evaluated different outcomes. Post-test probabilities of certain cutoffs (in this case SAME-TT₂R₂ score ≥ 2 and ≥ 3) are relevant for clinical decision making. The C statistic summarises the performance of all possible cutoffs, and is more appropriate when no cutoffs have been defined. Furthermore, it assesses the probability of a certain test outcome given the presence or absence of disease, instead of the probability of poor TTR given a certain SAME-TT₂R₂. A different mean TTR in SAME-TT₂R₂ groups does not address the score's discriminatory performance; there may be considerable overlap.

Conclusion

The SAME-TT₂R₂ score does predict low TTR, but the effect is small. Its effect on individual patients is too limited to be clinically useful. Therefore, the evidence does not support the use of the aforementioned decision rules.

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**Is the time in therapeutic range on coumarins
predicted by previous time in therapeutic range?**

5

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Abstract

Background Benefit of vitamin K antagonists depends on the time within the therapeutic range (TTR). A patient's previous TTR could be a factor in the decision to change the anticoagulation regimen. However, the predictive value of a previous TTR for a future TTR is not well-established, nor is it clear which TTR should prompt action.

Objectives To investigate the predictive performance of a TTR, and identify a threshold below which no recovery of TTR should be expected.

Patients/Methods From 18,031 patients who used acenocoumarol in a first-line anticoagulation clinic, a TTR was calculated over multiple periods of 90/180/365 days each. We assessed the correlation between baseline and later TTR, and the separation between groups by quintile of baseline TTR. We describe the proportion of patients who obtain a $\text{TTR} \geq 70\%$ conditional on baseline TTR.

Results and Conclusions The correlation between baseline and later TTR was 0.25 (95% CI 0.24 - 0.26), 0.27 (95% CI 0.26 - 0.28) and 0.34 (95% CI 0.32 - 0.35) for analyses over 90, 180 and 365 days. Corresponding c statistics for discrimination by baseline group were 0.60, 0.61 and 0.63. The probability to obtain a $\text{TTR} \geq 70\%$ increased with baseline TTR: from 42% with a baseline TTR of 50% to 65% when TTR was 100% (TTR calculated over 180 days). We conclude that a current TTR hardly predicts a future TTR. Physicians and patients should deliberate together which probabilities to accept, take measures to improve TTR, and consider potential alternatives.

Introduction

Vitamin K antagonists are widely used to treat and prevent thrombosis. Their unpredictable effect and narrow therapeutic window necessitate monitoring and dose adjustments to maintain the anticoagulation intensity (expressed as the international normalised ratio, INR) within a specified range, where the combined risk of bleeding and thrombosis is lowest. The higher the proportion of time a patient's INR is within this therapeutic range (TTR), the fewer adverse events[1–3]. Therefore, the TTR is used as a quality indicator for anticoagulation clinics.

The role of TTR in individual patient care is less clear. The current guideline by the American College of Chest Physicians (ACCP) recommends to switch to a direct oral anticoagulant (DOAC) or consider intervening to improve TTR when TTR is consistently low[4], to prevent complications in the future. Intuitively, this is reasonable advice. However, it is partly founded on the assumption that a patient's past TTR predicts future TTR or clinical events. Data for this are scant. Furthermore, it is not clear which TTR can still be accepted, or when action is required. The mentioned ACCP guidelines give the example of a TTR <65%[4] to intervene, while the HAS-BLED score identified a TTR <60% as a risk factor for bleeding[5]. The European Society of Cardiology, in contrast, defines “high-quality treatment” as a TTR $\geq 70\%$ [6]. However, the TTR threshold below which the risk of adverse events increases starkly could very well be much lower: 45%[2] or even less.

We performed this study to investigate the predictive performance of a TTR, and identify a threshold below which no recovery of TTR should be expected.

Methods

Participants and period

Certe Trombosedienst is a large first-line anticoagulation clinic in the north of the Netherlands. We extracted all data from patients using acenocoumarol (the most commonly used VKA in our clinic) for any indication with INR target range 2.0-3.0 and 2.5-3.5. These target ranges are in effect since January 2016; before 2016, wider target ranges were used. Hence, data collection ranged from January 1st, 2016, to June 30th, 2018 (date of extraction). We excluded data from the first 90 days of treatment with vitamin K antagonist, as the initial treatment phase is known to be unstable.

Patients are included when they have enough INRs to provide a baseline period and an outcome period. We perform the analyses with periods of 90 days, 180 days or one year. This could lead to small differences in the number and characteristics of patients included in analyses with different durations. For brevity, characteristics will be given for the 180-day sample only.

Outcomes

The time within the therapeutic range (TTR) was derived using linear interpolation according to the Rosendaal method[7]. No interpolations were performed when the number of days between INR measurements exceeded 56 (the average time between measurements was around 3 weeks, with a maximum of 6 weeks for stable patients). We defined a “good TTR” as a TTR $\geq 70\%$, based on the cutoff by the European Society of Cardiology[6].

We performed separate analyses for the prognostic value of a TTR calculated over 90 days, 180 days, and one year. For the 90-day-analysis, the first INR after 90 days of follow-up was defined as time point zero. Hence, the baseline TTR is calculated over the period between -90 days and day zero. Therefore, the TTRs dated > 90 days do not share any INRs with the baseline TTR. The same is true, *mutatis mutandis*, for analyses over 180 days or one year. This is illustrated in Figure 1.

Figure 1. Periods for calculations.

At the top, an example of an individual TTR. Periods marked with solid circles and squares were used as predictors; hollow symbols indicate outcome data.

Analyses

To investigate the predictive performance of the TTR, we first assessed the stability of an individual's TTR over time. We calculated the correlation between a patient's TTR in the baseline period and their TTR in the consecutive period.

Furthermore, we assessed the stability of the TTR on the group level. Patients were divided into five groups based on their baseline TTR (by quintile). A follow-up TTR was calculated every fifteen days (see Figure 1). These TTRs were summarised as median and interquartile range, and plotted. We also assessed the separation between the baseline groups, expressed as the c statistic from a multiclass receiver operator characteristics curve[8]. We also calculated the proportion of the variance that was explained (R^2) by baseline group membership as a categorical variable in linear regression.

Lastly, we assessed the probability to obtain a good TTR (a TTR $\geq 70\%$) based on a previous TTR. For this analysis, we used two consecutive periods of the same length (see Figure 1). The TTR over the first period was binned (in bins with a width of 5%); for every bin, we obtained the percentage of subjects who achieved a TTR $\geq 70\%$ in the second period. We constructed 95% confidence intervals using a binomial test.

All analyses were performed in R version 3.6.1 (2019-07-05) using the pROC package[9]. We primarily report the analyses with target range 2.0-3.0; target range 2.5-3.5 is only reported in the Supplementary Material because there were fewer patients in this target range.

Results

Patient characteristics

Patient characteristics are summarised in Table 1. Patients in the different strata were similar in the distribution of age, sex, indications, dose and experience with vitamin K antagonists (Supplementary Table 1). Supplementary Table 1 also includes patient characteristics for the auxiliary analyses on target range 2.5-3.5.

Stability of TTR

The correlation between baseline TTR and later TTR was weak: for TTRs calculated over 90 days, the correlation coefficient r was 0.25 (95% CI 0.24 - 0.26). For that over 180 days, r was 0.25 (95% CI 0.24 - 0.26); for that over 365 days, it was 0.34 (95% CI 0.32 - 0.35).

N	18031	
Age, years - mean (SD)	78.1	(11.1)
Female sex - n (%)	8855	(49%)
VKA experience, years - mean (SD)	5.6	(5.2)
Atrial Fibrillation - n (%)	15267	(85%)
VTE - n (%)	3119	(17%)
Mechanical valve - n (%)	139	(1%)
Mean acenocoumarol dose, mg - mean (SD)	2.2	(1.0)
Follow-up duration in days, median (IQR)	690	(IQR 450 – 705)
TTR >70% - n (%)	7602	(42%)
Time within range (%), median (IQR)	66	(IQR 51 – 80)
Time below range (%), median (IQR)	7	(IQR 0 – 18)
Time above range (%), median (IQR)	21	(IQR 9 – 36)

Table 1. Baseline characteristics of the patients included in the 180-days analyses.

Baseline groups initially clearly differed in TTRs: the c statistics were 1.0 (by definition). There remained some variation in TTR within the groups, but most of the variance was explained: the proportion of variance explained was 94% for a calculation over 90 days, 92% over 180 days, and 91% over 365 days.

However, the groups became increasingly similar over time, as illustrated in Figure 2. A full period later, the c statistic for the analysis over 90 days had decreased to 0.60. The c statistic was 0.61 for the analysis over 180 days and 0.63 for that over 365 days, indicating poor discriminatory performance. Likewise, the proportion of variance explained was only 6%, 7% and 10%.

A prognosis by baseline TTR expires over time. When there is a one-year gap between the baseline period and the outcome period, the c statistic decreases to 0.54 for the 90-day analysis and 0.56 for the 180-day analysis. For the analysis over one year, we only had enough data to calculate the c statistic with a gap of 145 days; the c statistic then decreased to 0.62. The respective proportions of variance explained were 1%, 3% and 8%.

The correlations between baseline TTR and the later TTR were 0.08 (95% CI 0.07 - 0.10), 0.16 (95% CI 0.14 - 0.18) and 0.30 (95% CI 0.28 - 0.32).

There were no clear differences between males and females, or between different age groups.

The image in target range 2.5-3.5 was similar (Supplementary Material).

Figure 2. Median (interquartile range) of TTR by baseline TTR group, over time. The panels indicate the duration of TTR calculation; the vertical line indicates when no INRs overlap between current TTR and baseline TTR.

Probabilities to obtain a good TTR

Patients with a baseline TTR $\geq 70\%$ were not guaranteed to maintain a high TTR: only 60% achieved a TTR $\geq 70\%$ in the adjacent period. However, these patients had a higher probability than patients with a lower TTR, as the probability to obtain a good TTR ($\geq 70\%$) increased with baseline TTR (Figure 3). This relationship was also present in target range 2.5-3.5 (Supplementary Figure).

Irrespective of TTR duration, a baseline TTR of approximately 67% resulted in a 50% probability to obtain a good TTR over the same period in the future. Of patients with a perfect TTR of 100%, these probabilities were 60, 65 and 74% over 90, 180 and 365 days, respectively. A TTR of 50% resulted in a TTR $\geq 70\%$ in only 44, 42 and 36% cases.

Here, too, there were no clear differences between males and females, nor between different age groups. In target range 2.5-3.5, the probability to obtain a good TTR was lower across the baseline TTR groups (Supplementary Figure 2).

Figure 3. Probabilities to obtain a time in the therapeutic range (TTR) $\geq 70\%$, conditional on baseline TTR.

Discussion

We found that the TTR's capability to predict future TTR is very limited. Groups separated by baseline TTR obtain increasingly overlapping TTRs over time. However, for an individual patient, a lower baseline TTR predicts a lower probability to obtain a good TTR later on. Nevertheless, even patients with a TTR of 70% only maintain a good TTR in half of the cases. This probability was even lower in target range 2.5-3.5, reflecting a more volatile INR pattern in a smaller group of patients (Supplementary Material). We infer that a previous TTR might be less helpful for predicting future anticoagulation control than we initially thought.

Our findings are in line with a previous study, where only 56% of patients with a baseline TTR $\geq 70\%$ maintained a TTR $\geq 70\%$ over the following year[10]. In contrast to that study, which focussed on patients with a good TTR, we looked at patients with a poor TTR, because events cluster in this group and less in the “grey area” of mediocre TTR[2]. We aimed to identify a TTR below which therapy became unfeasible. How one defines “unfeasible therapy” depends on the availability of improvements or alternative anticoagulants. For example, if we strive for at least a 50% probability to obtain a TTR $\geq 70\%$ in the future, patients in target range 2.0-3.0 should have at least a baseline TTR of 70%. For target range 2.5-3.5, there was more uncertainty: only patients with a TTR of 90% or higher over one year had a 50% or higher probability (supplementary). Shorter periods had no realistic cutoff for this certainty.

It has proven difficult to predict TTR. Extremes in INRs, such as extreme over-anticoagulation[11] or successive subtherapeutic INRs[12] show an increased risk of worse TTR, but the effects are not very strong. The addition of clinical parameters might augment the prediction of TTR. Indeed, many clinical characteristics have been linked to VKA control[13–18].

Some clinical decision tools are used to distinguish groups that differ in mean TTR[16–18]. This can be problematic, because even significant differences between groups allow for considerable overlap (e.g. in our dataset, analysis of variance for TTR by strata resulted in a p-value < 0.01 for all time points in figure 2). Furthermore, these tools do not provide a probability for a certain TTR, making them less clinically useful[19].

Other tools that predict an individual's TTR[14] or the probability to obtain a TTR $< 70\%$ [15], report limited proportions of variance explained of approximately 7%.

Most of these tools use clinical parameters obtained at the start of anticoagulation therapy. This complicates their use during patient follow-up. Moreover, models that only use data available at treatment inception cannot incorporate events that occur during treatment.

The outcome of this study can be explained by a combination of several mechanisms: First, anticoagulation clinics strive to obtain a high TTR in all patients. If a patient obtains an inadequate TTR, dose adjustment and more frequent monitoring are employed to increase TTR. Second, a poor TTR could be caused by temporary factors, such as comorbidities and their treatment. When these are under control, TTR could improve again. A third factor would be “regression to the mean,” the phenomenon where patients with a high TTR tend to decrease and those with a low TTR increase as natural variation. The weight of these three factors depends on the time period used to calculate a TTR. If the TTR is poor over a whole year, it is less likely that this is just a temporal variation; instead, this may be due to a more profound cause.

Our study benefits from a large number of patients. The anticoagulant studied (acenocoumarol) could be a limitation, because warfarin is the most widely used vitamin K antagonist. It is controversial whether a longer-acting VKA causes a higher TTR. A French randomised controlled trial found no difference in TTR between patients on acenocoumarol or warfarin[20]. Even if warfarin leads to higher TTRs than acenocoumarol, this does not necessarily invalidate our findings about the stability of a TTR over time. While this study would, of course, benefit from external validation, we believe that the VKA effect is generalisable. This is supported by similarities in outcomes with a Danish study using warfarin[10].

Another limitation is that we lacked data on clinical events. Because of this, we can only make indirect inferences about the risk of a current TTR and the risk of thrombosis and bleeding. Clinical decisions based on TTR could have introduced bias in our analyses. If patients were more likely to continue or withhold VKA based on their TTR, this could affect follow-up time and could cause an overrepresentation of patients with a low TTR whom their physicians considered likely to improve. We lack the data to assess this bias. If the effect of this bias were large, this would “flatten” the association between baseline TTR and the probability of obtaining a good TTR. However, it is unlikely that this has markedly influenced our results: the large majority of physicians do not request TTR calculations from the Thrombosis Service, and those who do, lack information about the predictive value of a current TTR.

These data allow physicians to tailor their counselling to their individual patient. Patients with a lower TTR are unlikely to obtain a good TTR in the future, and

should thus be counselled on alternatives such as direct oral anticoagulants (DOAC). However, DOAC are contraindicated in mechanical valves and the antiphospholipid syndrome, and there is insufficient experience with venous thromboembolism outside the limbs and lungs. Furthermore, when therapy in adherence is the expected cause of a low TTR, DOAC might not be the right choice because adherence might decline and can no longer be assessed. In the most extreme cases, when the expected benefits do no longer outweigh the bleeding risk, a physician and their patient should consider stopping anticoagulation altogether. Based on these data, we cannot give strong advice regarding patients with a high TTR. They are more likely, but not guaranteed, to maintain a high TTR. A decrease in TTR would put them in a grey area, where the TTR is suboptimal but the incidence of adverse events is only mildly increased[2]. In a previous study, we found no evidence to advise against switching patients with a high previous TTR to a DOAC[21].

Conclusion

We conclude that a current TTR hardly predicts a future TTR. Even patients with a perfect TTR are at risk of obtaining a suboptimal TTR. Physicians and patients should deliberate together which probabilities to accept, take measures to improve TTR, and consider potential alternatives.

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An easy-to-use tool to flag patients at risk of poor INR control: a streak of subtherapeutic INRs

6

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Abstract

Introduction Vitamin K antagonist therapy is safest and most effective with a high time within the therapeutic range (TTR). The TTR is difficult to calculate in the consultation room, therefore physicians need an easier-to-use tool to predict poor VKA control.

We explored the prognostic value of subtherapeutic INRs on future TTR in two settings:

- (1) Clinical review setting, where a physician (bi)annually reviews a patient and uses the INRs since the last visit to predict the TTR up to the next visit;
- (2) Day-to-day INR management setting, where every new INR measurement prompts a new prediction over the next 90 days.

Materials and Methods Retrospective cohort of 17,711 patients from a dedicated thrombosis service, using acenocoumarol (target range 2.0-3.0), with a “streak” defined as four consecutive INRs <2.0.

- (1) Odds ratios of any streak in the last 180 days or 1 year on a TTR <45% over the same period in the future;
- (2) Odds ratio of a current streak on a TTR <45% over the next 90 days.

Results and Conclusions Clinical review setting: The occurrence of any streak in the last 180 days or 1 year increased the odds of a TTR <45%: ORs 2.84 (95% CI 2.41-3.34) and 3.25 (95% CI 2.72-3.87), respectively.

Day-to-day INR management setting: A current streak increases the odds of poor TTR over the next 90 days 3.58 (95% CI 2.64-4.87) fold.

We conclude that a streak of four consecutive subtherapeutic INRs can aid physicians in flagging at-risk patients.

Introduction

Vitamin K antagonists (VKA) effectively treat and prevent thrombosis in different clinical scenarios, such as atrial fibrillation and venous thromboembolism. Specific ranges of anticoagulant activity (international normalised ratio; INR) are targeted to strike a balance between efficacy and bleeding risk. The VKA dose is adjusted to maximise the proportion of time a patient's INR is within the therapeutic range (TTR). Patients with a lower TTR experience more thrombosis and bleeding[1, 2]. Furthermore, a recent TTR predicts future events[3, 4]. Sadly, the TTR is under-used in clinical practice, because it is difficult to calculate in the consultation room.

Physicians need easier to obtain information to identify patients at risk of subsequent poor VKA control. An example is the -always adverse- event of an INR ≥ 8 , which negatively affects future VKA control[5]. Subtherapeutic INRs might likewise predict poor VKA control. However, sometimes a low INR is intended, e.g. for surgery. Multiple, consecutive subtherapeutic INRs, on the other hand, are never intended. We, therefore, aimed to explore the prognostic value of consecutive subtherapeutic INRs to predict future VKA control, in two settings. First, the setting of physicians (bi)annually reviewing their patients. They need information on future VKA control to balance bleeding and thrombotic risk. Second, the setting of VKA dosing after a new INR measurement. Here, a streak could stratify patients for aggressive interventions to improve VKA control.

Methods

Patients

In the Netherlands, anticoagulation with VKA is managed by dedicated thrombosis services. We selected all patients from Certe Trombosedienst, the largest thrombosis service in the north of the Netherlands, who satisfied the following criteria: adults of at least 18 years of age, who were treated with acenocoumarol (the most common anticoagulant in this thrombosis service) with an INR target range of 2.0 - 3.0. We included all patients who were treated for at least 9 months between January 1st, 2016, and June 30th, 2018, excluding the first 3 months after initiation of VKA.

Study design

We retrieved all thrombosis service records for the patients who matched the criteria above. We determined whether they had a “streak” of four consecutive INRs below the target range (i.e. INR < 2.0). We chose this cutoff arbitrarily, based on our clinical intuition that four consecutive INRs below the target range “are

no coincidence.” Furthermore, this suggests a persisting problem for which intervention may be required.

We explored the predictive value of a “streak of lows” in two settings: the “clinical review setting” simulates a patient’s (bi)annual visit to the outpatient clinic, where the bleeding and thrombotic risks are weighed and risks are minimised. Secondly, we analysed the “day-to-day INR management setting.” In this more practical, executive, setting, the last INRs are used only to determine the next acenocoumarol dosing scheme.

Statistical analysis
Clinical review setting

In our clinic, we see a patient every six months or every year. We check the INR measurements since the last visit, and use this information to predict INR control up to the next appointment.

We simulated a doctor’s appointment on the date in the middle of the treatment period. We checked whether a streak of subtherapeutic INRs occurred anywhere in the preceding six months (and if so, how many days had since passed), and, alternatively, whether the TTR over the preceding six months was poor (less than 45%, because in this group more events occurred than in those with TTR 45-60% or >60%[3]). These predictors were used in a univariate logistic regression to predict a future poor TTR, and in a univariate linear regression to predict future TTR as a continuous variable. The same was done, *mutatis mutandis*, for a review every year. This method is summarised in Figure 1.

Figure 1. Time periods for the calculations in the clinical review setting.

Day-to-day INR management setting

In the day-to-day INR management setting, every new INR offers an opportunity for reassessment. For every INR, we checked whether it formed a streak of lows with the three preceding INRs. This was used to predict a poor TTR (TTR < 45%, see above) over the next 90 days, using a univariate logistic regression as described below. Alternatively, we used the TTR over the last 90 days, including the current INR, as a predictor. TTR was categorised as poor (TTR < 45%, see above) or not.

Each patient contributed a different number of INR measurements to the overall dataset, because treatment duration varied and the period between INR measurements is based on the previous INRs. Furthermore, measurements of the same patient are correlated; not just because they concern the same subject, but also because the predictors overlap: one INR is included 4 times for the streak (because a streak is length 4); and a variable number of times for previous TTR. The latter depends on the number of times the INR was determined in the 90-day period. Due to these dependencies, normal linear or logistic regressions were not suitable. Instead, we performed a regression on a data subset that contained 1 randomly selected INR assessment date per patient. This procedure was repeated a 1000 times (bootstrapping) to construct an empirical confidence interval (the 2.5th and 97.5th percentile of the 1000 observations) and point estimate (median). The method for the day-to-day INR management setting is summarised in Figure 2.

Day-to-day INR management setting

The procedure was repeated for every INR.
One INR per patient was randomly selected for the bootstrapping sample.

Figure 2. Time periods for the calculations in the day-to-day INR management setting. All analyses were performed in R. The TTR was calculated using the established Rosendaal method[6]. We report data as linear estimates (for continuous variables) or odds ratios (for binary variables), with their 95% confidence intervals.

Results

Patient selection and characteristics

We selected 17,711 patients who contributed 708,540 INR measurements. Patient characteristics of the included patients are outlined in Table 1. A streak occurred in 2750 (16%) patients at least once; 1119 (6%) had a poor TTR over the full study period. The mean time within the therapeutic range was 67% (SD 14), with 7832 (44%) patients having a TTR > 70%.

age (years, mean (SD))	77.8	(11.2)
age below 50 years	349	(2%)
male sex	9017	(51%)
time within range (% , mean (SD))	66.9	(13.5)
time below range (% , mean (SD))	11.6	(9.2)
time above range (% , mean (SD))	21.5	(11.0)
poor TTR (%)	1119	(6%)
mean INR (median (IQR))	2.6	(IQR 2.5 – 2.7)
any streak	2750	(16%)
measurement period length (days, mean (SD))	775	(180)
atrial fibrillation	14537	(82%)
venous thrombo-embolism	2972	(17%)
heart valve	301	(2%)
other indication	1953	(11%)

Table 1. Characteristics of the included patients (n = 17700).

Clinical review setting

Review every six months

When we looked back six months, 772 (5%) patients had a streak, and 2302 (14%) had a poor TTR. 406 (2%) had both.

Patients who had a streak in the previous six months, had a lower TTR in the next six months: 70% versus 58% (difference 12.5 (10.9 - 14.1)). For a previous poor TTR, the difference was 13.8 (12.8 - 14.7): 72% versus 58%.

The presence of a streak increased the risk of a poor TTR over the next six months: OR 2.84 (2.41 - 3.34). A poor TTR increased the odds 3.53 (3.18 - 3.91) fold.

As the streak happened longer ago, its predictive value diminished, as shown in Table 2.

Days since streak	TTR	OR of poor TTR
0 to 1 days	-21.7 (95% CI -26.5 to -16.8)	5.1 (95% CI 3.2 to 8.3)
1 to 30 days	-12.4 (95% CI -15.5 to -9.2)	3.4 (95% CI 2.4 to 4.7)
30 to 90 days	-12.7 (95% CI -15.7 to -9.8)	3.2 (95% CI 2.3 to 4.3)
90 to 180 days	-10.5 (95% CI -12.8 to -8.3)	2.1 (95% CI 1.6 to 2.7)

Table 2. Influence of time since streak on continuous TTR and OR of poor TTR in the next six months.

Absolute TTR difference in percentage points, or odds ratios. CI, confidence interval; OR, odds ratio; TTR, time within therapeutic range.

Review every year

Over a period a year, more patients had a streak (now 949 (7%)) and fewer a poor TTR (986 (8%)), compared with the six month period. 287 (2%) had both a poor TTR and a streak.

A streak sometime in the last year predicted a lower TTR over the next year: 70% versus 61% (difference 9.6 (8.5 - 10.7)). A poor TTR did as well: 71% versus 56% (difference 14.2 (13.1 - 15.4)).

The odds ratios for a poor TTR over the next year were 3.25 (2.72 - 3.87) for a streak and 5.80 (4.95 - 6.80) for a poor TTR.

Here, too, the predictive value of a more recent streak was higher (see Table 3).

Days since streak	TTR	OR of poor TTR
0 to 1 days	-12.8 (95% CI -17.3 to -8.2)	5.6 (95% CI 2.9 to 10.2)
1 to 30 days	-9.9 (95% CI -12.8 to -7.1)	3.3 (95% CI 2.1 to 5.2)
30 to 90 days	-12.1 (95% CI -14.9 to -9.3)	4.1 (95% CI 2.7 to 6.2)
90 to 180 days	-8.5 (95% CI -10.6 to -6.3)	3.7 (95% CI 2.6 to 5.1)
180 to 366 days	-8.9 (95% CI -10.4 to -7.4)	2.6 (95% CI 1.9 to 3.3)

Table 3. Influence of time since streak on continuous TTR and OR of poor TTR in the next year.

Absolute TTR difference in percentage points, or odds ratios. CI, confidence interval; OR, odds ratio; TTR, time within therapeutic range.

Day-to-day INR management setting

The percentage of INR measurements that was part of a streak varied from bootstrap sample to bootstrap sample, and was on average 0.8 (0.7 - 1.0)%. When the last four INRs were all subtherapeutic, the odds of a poor future TTR increased 3.58 (2.64 - 4.87) fold. A poor TTR over the previous 90 days resulted in an odds ratio of 2.29 (2.13 - 2.45).

Discussion

Vitamin K antagonist therapy is safer and more effective when patients achieve a high time within the therapeutic INR range (TTR). The TTR is however under-used in practice because it is difficult to calculate (as it requires software that is unavailable in the consultation room). We explored the predictive value of a “streak” of four consecutive subtherapeutic INRs as an easier alternative to flag patients with a poor future TTR. We found that the presence of a streak predicts an approximately 10 percentage point reduction in future TTR over six months and a year, and a threefold increase in the odds of a TTR <45%. The effect of a streak was largest when the streak persisted at the time of clinical review, and diminished with increasing time since streak. Patients remained at increased risk, even when the streak occurred more than six months ago.

We compared a streak with the TTR over the preceding period, to properly value our new method of identifying patients at risk of poor VKA control. In the day-to-day INR management setting (where the presence of a streak or a poor TTR was assessed with every new INR measurement available) a streak outperformed a poor previous TTR in predictive power for a poor future TTR. An added benefit of a streak is that it is generally quicker in flagging a patient, because it only requires four measurements instead of 90 days. During a six month observation, the predictive power of a streak is equal to that of the poor previous TTR. Looking back over a longer period, the TTR outperforms a streak. This is not surprising: extending the screening period from six months to a year will cause more patients to be flagged by the streak (simply because more measurements lead to a higher chance of forming a streak). Those streaks have occurred 7-12 months ago; patients have since recovered and hence obtained a better prognosis. These patients will dilute the prognostic effect. For a TTR the opposite is true: having a poor TTR over a period that is twice as long occurs less frequently. It indicates a longer lasting problem and therefore a worse prognosis. We stress that we were not looking for a replacement or a stronger alternative for the TTR, but just a measure that is easier to obtain and more likely to be actually used in practice.

Fewer patients are flagged by a streak than by a poor TTR. A streak and a poor previous TTR overlap to a limited extent. One reason for this is that a TTR can also be poor because the INR is too high. We focused on subtherapeutic INRs because the prognostic value of a high INR had already been established[5]. One should decide for oneself whether the lower flag rate is a strength or a weakness; this could differ from setting to setting. The flag rate depends on the cutoff used to define a streak. In this study we primarily used a streak of four consecutive subtherapeutic INRs. We also analysed different cutoffs: longer streaks predict a larger difference in TTR and odds for poor TTR, but occur less frequently (Figure 3).

Figure 3. Relationship between the length of a streak and its predictive value and prevalence.

Panel A shows the difference in future TTR between patients with and without a streak of a given length, in percentage points. Panel B shows the odds ratio (OR) of a poor TTR after a streak in the preceding period, compared with no streak (clinical review setting). Panel C shows the OR of a poor TTR when the current INR is part of a streak (thrombosis service setting). Panel D shows the prevalence of any streak in the preceding period. Panel E shows the prevalence of the current INR being part of a streak.

How can the physician or thrombosis service act, after a patient has been flagged using a streak? An important cause of a subtherapeutic INR is poor medication adherence. This might be improved by patient education[7], devices that remind patients to take their medication, multi-dose drug dispensing[8], or lottery systems[9]. Another option would be to switch to longer-acting VKAs (e.g. phenprocoumon), which are less sensitive to occasionally forgetting a dose. If poor medication adherence is ruled out, non-VKA, or direct, oral anticoagulants (NOACs/DOACs) may be an option.

Strengths of this study are the pragmatic approach, as well as the large number of patients. INR measurements were prospectively collected by the thrombosis service, while we analysed the value of a streak retrospectively. This way, the thrombosis service could not have acted based on our hypothesis to abate the effect on poor TTR. The other way around, the increased risk that we found could also be the result of inadequate reactions to a streak. The high average TTR over the entire study period makes this unlikely. As always, this study would benefit from external validation. Because acenocoumarol is shorter-acting than warfarin or phenprocoumon, it is not clear whether our findings can be generalised to patients using these drugs. The same is true for alternative therapeutic ranges. The number of patients using VKA has dropped significantly after the introduction of the DOACs. This makes quality assessment for patients using VKA even more vital: those with a poor TTR might have more to gain by switching to a DOAC than those with a high TTR[10] (but data are indirect).

Conclusion

A streak of four consecutive subtherapeutic INRs can aid physicians to flag at-risk patients.

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More precise dosing of acenocoumarol for better control in patients aged above 80 years, a randomised controlled pilot study

7

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Abstract

Introduction Many elderly patients are confined to treatment with vitamin K antagonists (VKA) instead of direct oral anticoagulants (DOACs). However, quality of VKA treatment declines with age. This might be caused by the lower dose requirements with increasing age, which result in relatively large day-by-day VKA dose differences. Therefore, more precise dosing with smaller dose increments might improve quality of VKA treatment in the elderly.

Methods We randomised 80 elderly patients (≥ 80 years, using 0.5-2 mg acenocoumarol daily) to either conventional dosing with 1.0 mg acenocoumarol increments, or more precise dosing with 0.5 mg increments, to assess effect sizes and feasibility of a larger trial.

We compared changes in the time in therapeutic range (TTR), INR variability and anticoagulation-related quality of life (measured with the PACT-Q) between treatment groups.

Results Overall, baseline TTR was 61.3 ± 19.2 . After six study months, TTR had improved to 69.5 ± 19.7 in the precise dosing group versus 67.7 ± 21.2 in the conventional dosing group (absolute difference 3.4 (95% CI -6.7 to 13.6)). The between-groups difference in INR variability was not assessed because of baseline differences.

PACT-Q convenience declined slightly with more precise dosing, compared with conventional dosing: 2.1/100 (95% CI 0.5-3.7). Satisfaction decreased equally in both groups with $-6.4 \pm 8.6/100$.

Four dosing errors occurred: three with precise and one with conventional dosing.

Conclusion Although more precise dosing of acenocoumarol leads to a slightly higher TTR, this effect is too small to convey a relevant clinical benefit and could be abolished by the increased risk of medication errors.

Introduction

Vitamin K antagonists (VKA) effectively prevent venous and arterial thrombosis. Despite the increased bleeding risk, this results in better survival in patients with an increased thrombotic risk[1]. Although the elderly suffer from a higher bleeding risk, there is increasing evidence that anticoagulation provides a net clinical benefit in elderly patients with atrial fibrillation (AF)[2, 3]. Older age is associated with more contraindications for the direct oral anticoagulants (DOACs), including renal function impairment, comorbidity and concomitant medication use. Indeed, elderly patients are overrepresented in the actual population using VKA and we can expect that this patient group still needs anticoagulation with VKA in the future.

However, the quality of VKA treatment declines significantly with rising age: the proportion of time spent in the therapeutic range (TTR) decreases, and the variability of the international normalised ratio increases[2]. A lower TTR[4–8] and a higher INR variability[8–13] are associated with higher risks of bleeding or thrombotic complications.

A possible cause for loss of quality of anticoagulation with rising age can be the concomitant lower required dosage of VKA with age[2]. Research in our study group showed a decline in the average daily dose from 2.3 mg acenocoumarol in patients aged 70–79, to 1.9 mg for those aged 80–89 and 1.6 mg for those aged 90 or above[2]. Because acenocoumarol is only available in tablets of 1 mg, low doses cannot be spread evenly over the week resulting in large relative differences in the daily doses and under- and over-anticoagulation. We hypothesise that more precise dosing by using smaller dosing increments (0.5 mg) will result in more stable anticoagulation control and consequently better clinical outcome.

Methods

Trial aims and design

The research question of our study was whether more precise dosing with smaller increments of acenocoumarol (0.5 vs 1.0 milligram) could lead to better TTR and INR variability. In this open-label, randomised controlled pilot-study we aimed to determine the effect size for, and feasibility of, a full-scale trial.

Furthermore, we assessed how more precise dosing alters treatment satisfaction and convenience, and the occurrence of errors in medication intake.

This study was registered in the Netherlands Trial Registry (NTR6093/NL5905) and the EU Clinical Trials Register (2016-004805-14), and was approved by the local research ethic committee at the University Medical Centre Groningen (METc UMCG 2017/018).

Participants

We recruited patients from Certe Thrombosis Service, a large anticoagulation clinic in the north of the Netherlands that manages over 20,000 patients who use a vitamin K antagonist. Employees of Certe Thrombosis Service handed out study information to each potentially eligible patient during a regular anticoagulation check at home or at the outpatient clinic. Patients could express their (dis)interest by returning the included reply card. Patients who did not reply were reminded once by telephone. When a patient was interested, a research assistant checked the in- and exclusion criteria. The inclusion criteria were: age ≥ 80 years, use of acenocoumarol for any indication with an average daily dose of less than 2 milligram in the previous three months, and dosing by Certe Thrombosis Service. Exclusion criteria were: initiation of acenocoumarol in the last nine months, expected termination of this medication within six months, and acenocoumarol use of less than 0.5 milligram per day. Eligible patients willing to participate were visited at home for a personal information visit by the research assistant and were randomised after providing written informed consent.

Randomisation and study drugs

Patients were randomised in a 1:1 ratio to continue their treatment with acenocoumarol dosed with either regular 1.0 mg increments (conventional dosing), or with 0.5 mg increments (precise dosing). Randomisation was performed on the spot, by using opaque, sealed and ordered envelopes, stratified by INR target range (2.0-3.0 or 2.5-3.5) and with random block sizes.

The University Medical Center Groningen Pharmacy manufactured and labelled tablets of acenocoumarol in 0.5 milligram in accordance with the guidelines of ICH-GCP and ICH-GMP. Patients in the control group used regular tablets of 1.0 mg of acenocoumarol. Both treatment-groups followed the standard protocol of Certe Thrombosis Service for dose adjustments and INR determination periods. The maximum period between INR checks was six weeks.

Study outcomes

The primary outcome of this study was the quality of anticoagulation operationalized as the time in therapeutic range (TTR) and the INR variability. TTR was calculated according to the Rosendaal method[14] over the six months before randomisation and over the six month study period. The INR variability was calculated using Fihn's method[15] (equation) over the same periods.

$$\text{INR variability} = \sqrt{\frac{1}{n-1} \sum_{i=2}^n \frac{(\text{INR}_i - \text{INR}_{i-1})^2}{\Delta t \text{ (days)}}}$$

The secondary outcome was the anticoagulation-related quality of life, assessed using the Perception of Anticoagulant Treatment Questionnaire (PACT Q)[16]. The full PACT Q includes three components: treatment expectation, convenience and satisfaction. Because all patients were experienced users of VKA at inclusion, we only used the latter two. Higher scores indicate higher degrees of convenience and satisfaction. The maximum score for both components is 100.

We also collected data on medication errors by patients or practitioners. These were reported by the participants, could be traced in the anticoagulation files or were documented in discharge information from a hospital. These were not counted as protocol violations, but as outcome data only.

Statistical analysis

We calculated the change in TTR, INR variability, PACT-Q convenience and PACT-Q satisfaction during the six months of study treatment, by subtracting the baseline value from the value obtained during the study. We assessed between-group differences using an independent t-test or Mann Whitney U, as appropriate.

Medication errors and serious adverse events were described per allocated treatment group.

Because of the exploratory nature of this study, no formal hypothesis testing was performed; statistical tests were only used to construct a 95% confidence interval. All analyses were performed in the intention-to-treat set, using R R version 3.6.3 (2020-02-29) (R Foundation for Statistical Computing, Vienna, Austria). Data are reported as mean $\pm$ standard deviation, or median [interquartile range], as appropriate.

Results

Patient flow and follow-up

The flow of participants is outlined in Figure 1. Between November 2017 and November 2018, 321 patients were informed and 80 were included in the study. Forty patients were randomly assigned to precise dosing and 40 patients to continue conventional dosing. All patients started their allocated treatment and

all of them were included in the analysis. The study was closed when the last patient completed the six months' follow up on May 22, 2019. One patient allocated to the conventional dosing group died 88 days after randomisation from a COPD exacerbation. Median follow-up was 189 [186 – 192] days, leading to 41.4 patient-years of follow-up.

Three questionnaires were not completed because of death (1), brain tumour (1), and logistic reasons (1).

Figure 1. Subject flow in this study

Baseline characteristics

Subject demographics are summarised in Table 1. The mean age of the patients was 84.4 ± 3.5 years (range 80-96); 45 subjects (56%) were male. Atrial fibrillation was the most common indication for VKA therapy (in 67 subjects (84%)). The target INR range was 2.0-3.0 in 72 (90%) subjects. Patients used on average 1.4 ± 0.4 mg of acenocoumarol per day. Sixty-three (79%) patients had polypharmacy, i.e. continuous use of five or more drugs including acenocoumarol.

In the six months preceding the study, TTR was 61.3 ± 19.2 and was similar in the two groups. The median INR variability was 0.252 [0.152 – 0.426]. Despite the randomised design, patients allocated to more precise dosing had a higher INR variability than patients allocated to conventional dosing (Table 1).

Characteristic	More precise dosing (n = 40)	Conventional dosing (n = 40)
Demographics		
Age	84 ± 3	85 ± 4
Female gender	19 (48%)	16 (40%)
Polypharmacy	31 (78%)	32 (80%)
Anticoagulant treatment		
Indication		
AF	34 (85%)	33 (82%)
VTE	3 (8%)	2 (5%)
Valve	1 (2%)	2 (5%)
Other	2 (5%)	3 (8%)
Target Range		
2.0 - 3.0	36 (90%)	36 (90%)
2.5 - 3.5	4 (10%)	4 (10%)
TTR	60.5 ± 18.8	62.1 ± 19.7
INR variability	0.31 [0.18 – 0.55]	0.23 [0.14 – 0.36]
Mean daily acenocoumarol dose	1.3 ± 0.4	1.4 ± 0.4
Anticoagulation-related quality of life		
PACT-Q convenience	98.1 [95.7 – 100.0]	98.1 [94.2 – 100.0]
PACT-Q satisfaction	57.1 [53.6 – 64.3]	57.1 [52.7 – 65.2]

Table 1. Baseline characteristics**Study drugs**

During the study, two patients who were allocated to the precise dosing regimen switched back to the conventional dosing regimen: one patient on the day after randomisation for social circumstances and the other patient 34 days after randomisation because of assumed side effects (itching). No patients switched from conventional to more precise dosing.

The mean daily acenocoumarol dose during the study was similar to that in the 6 months prior to the study: 1.3 ± 0.4 mg.

Primary Outcomes**Quality of anticoagulation**

Changes in the quality of anticoagulation are summarised in Table 2. Overall, the mean TTR improved significantly during the study, to 68.6 ± 20.4 . The improvement in the more precise dosing group was 3.4 (95% CI -6.7 to 13.6) percentage points larger than in the conventional dosing group.

During the study, the median INR variability remained constant: the median difference from baseline was 0.005 [-0.153 – 0.138]. The INRs of patients with a higher baseline variability were more likely to stabilise, whereas those patients with stable INRs at baseline became relatively more volatile (Spearman ρ -0.51). Following this pattern, patients in the more precise dosing group became more stable during the study (difference -0.067 [-0.228 – 0.057]), while patients in the conventional dosing group slightly increased in variability (difference 0.025 [-0.090 – 0.240]). Considering the presence of baseline differences, no between-group difference was calculated.

Outcome	More precise dosing (n = 40)	Conventional dosing (n = 40)	Between-group difference (95% CI)
TTR	9.0 ± 22.1	5.6 ± 23.4	3.4 (-6.7 to 13.6)
INR variability	-0.067 [-0.228 – 0.057]	0.025 [-0.090 – 0.240]	-

Table 2. Changes in the quality of anticoagulation during the study period

Quality of life

The main changes in the quality of life are summarised in Table 3.

At baseline, patients considered their treatment very convenient: median [IQR] score was 98.1 [94.2 – 100.0], with 33 (21%) awarding the maximum score of 100 (see Table 1). Compared with the pre-study period, the PACT-Q score for convenience declined somewhat in the precise dosing group (difference -0.9 ± 3.7), in contrast with a small improvement in the conventional dosing group (1.2 ± 3.2). The difference was mainly driven by the feeling of dependence on others: patients in the precise dosing group felt more dependent on others: 8 out of 40 participants in the precise dosing group reported an increase in dependence of ≥ 2 points (dependence is scored on a five-point scale), versus only 1 out of 37 in the conventional dosing group.

The average PACT-Q score for satisfaction worsened equally in the precise dosing and the conventional dosing group: -6.4 ± 8.6 . Especially the sense of reassurance as a result of the anticoagulation treatment decreased during the study period.

Outcome	More precise dosing (n = 40)	Conventional dosing (n = 37)	Between group difference (95% CI)
Convenience	-0.9 ± 3.7	1.2 ± 3.2	-2.1 (-3.7 to -0.5)
Satisfaction	-6.4 ± 8.2	-6.5 ± 9.2	0.1 (-3.9 to 4.0)

Table 3. Changes in quality of life

Medication errors

Four medication errors were registered in four subjects: three in the precise dosing group and one in the conventional dosing group.

Two errors occurred during hospitalisation when two patients were given 1 mg tablets instead of 0.5 mg tablets for two days each, using their Thrombosis Service dosing schedule, and thereby got a double dose. After discharge, their maximum INRs in the three weeks following the error were 4.7 and 2.5. One patient took 1mg tablets instead of 0.5 mg tablets at home during the last three days of the study, also leading to a double dose during three days. This led to a supratherapeutic INR of 5.9.

One patient in the 1 mg allocated group received an anticoagulation advice from the Thrombosis Service applicable for 0.5 mg tablets instead of 1 mg during his first fourteen days after inclusion in the study. His INR was elevated to ≥ 12 .

No bleeding complications were reported in relation to any of these errors.

Serious adverse events

Thirteen serious adverse events (SAEs) were reported in eleven participants. Three SAEs consisted of gastrointestinal bleedings. Two of these bleedings occurred in the same patient in the conventional dosing allocated group, one bleeding occurred in the precise dosing allocated group. The other ten SAEs, five in the conventional dosing allocated group and five in the precise dosing allocated group, were hospital admissions for non-anticoagulation related reasons. One of these patients died during admission for a COPD exacerbation.

Discussion

In our small randomised controlled trial, we found that more precise dosing of acenocoumarol with 0.5 mg increments instead of conventional dosing with 1.0 mg increments led to a limited improvement in TTR. However, more medication errors occurred in the precise dosing group, exposing the affected patients to an increased bleeding risk. Patients in the more precise dosing group found their treatment slightly less convenient than patients in the conventional dosing group. Both groups were strikingly less satisfied with their anticoagulant treatment.

To our knowledge, we are the first to assess whether reducing the VKA dose increments could improve TTR and INR variability. Others have tried to stabilise the VKA dose requirement by adding vitamin K, resulting in a higher VKA dose with relatively less day-to-day variation. This led to a limited improvement of

TTR, but did not result in fewer complications[17]. Instead of stabilising the dose, one could also switch to a drug whose plasma levels are inherently more stable because it has a longer half-life. Indeed, patients using the longer-acting phenprocoumon instead of acenocoumarol had a higher TTR and a lower INR variability[15, 18]. At the same time, the longer half-life of phenprocoumon slows interventions to lower the INR in the event of over-anticoagulation or emergency surgery.

Another important factor in the quality of treatment with vitamin K antagonists is medication adherence and appropriate intake. This is especially important in the elderly, who might have a declined and deteriorating cognitive function and use more other medications. Both decrease medication adherence[19, 20]. The improvement in TTR in both arms of the study could be explained by increased attention for adherence and intake during the study, despite our efforts to make the study resemble routine management as much as possible. However, the increased staff attentiveness could be regarded an intervention in itself, with positive effects on TTR but a possible negative effect on the reassurance the patients felt.

Strengths of this study were the randomised design and the unintrusive setting; apart from two study visits, patients were monitored as usual. We accommodated to also include the frailest patients to obtain a representative sample: patients were visited at home for randomisation and end of study visits. Study medication was delivered at home. Regular anticoagulation checks took place at home or at the outpatient clinic. A limitation of this study was the small sample size, resulting in wide confidence intervals. However, this was inherent to the pilot nature of this study.

TTR improved marginally more in the precise dosing group than in the conventional dosing group, namely 3.4 (95% CI -6.7 to 13.6). Patients with a higher TTR experience fewer bleeding of thrombotic complications[4–7]. However, on an individual level, the TTR improvement of more precise dosing is too limited to provide a relevant risk benefit.

The effect of more precise dosing on INR variability was impossible to quantify. Despite randomisation, baseline INR variability was higher in the precise dosing group. Patients with a higher INR variability were more likely to become more stable. We could not distinguish the effect of this regression towards the mean from a stabilising effect of a more precise dosing regimen.

We tried to correct for the baseline differences with regression analyses, but the transformations needed to obtain normally-distributed data complicated

interpretation of the results. Furthermore, the relation between INR variability and the risk of events is not linear[10, 11]; a certain change in INR variability could have a different clinical impact based on the baseline INR variability.

Patients in the more precise dosing group found their treatment slightly less convenient than patients in the conventional dosing group, with a difference of 2.1 (95% CI 0.5 - 3.7) on a 0-100 scale. We expected that patients would find their treatment more convenient if the number of tablets fluctuated less over the days. However, the higher number of tablets a patient had to take could also have made the treatment more burdensome.

Both groups experienced a sharp decline in treatment satisfaction: 6.4 ± 8.6 out of 100. Possibly, study participation or the insight that there are alternative treatment options lowers patients' feeling of reassurance.

Tablets of 0.5mg of acenocoumarol are not regularly used in the Netherlands. During the study, two patients were hospitalised and were administered an incorrect acenocoumarol dose in the hospital. This resulted in a supratherapeutic INR after discharge in one patient. In this case, the increased bleeding risk associated with supratherapeutic anticoagulation did not materialise. However, this temporary elevated bleeding risk could abolish the small risk-benefit of an improved TTR. The other medication errors, i.e. inadequate dosing at the anticoagulation clinic or a patient taking her old tablets of 1.0mg, are less likely to occur if acenocoumarol dosing with 0.5mg increments becomes common practice.

Conclusion

Although more precise dosing of acenocoumarol leads to a slightly better TTR, this effect is probably too small to convey a relevant clinical benefit and does not outweigh the increased risk of medication errors. We will not proceed with a full-scale RCT.

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Effect of switching from acenocoumarol to phenprocoumon on time in therapeutic range and INR variability: a cohort study

8

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Abstract

Background Treatment with vitamin K antagonists (VKA) requires a high proportion of time in the therapeutic range (TTR) and a low international normalised ratio (INR) variability to be maximally safe and effective. Switching from short-acting acenocoumarol to long-acting phenprocoumon could improve VKA control.

Aims We assessed whether switching from acenocoumarol to phenprocoumon improves the time in the therapeutic range (TTR) and INR variability.

Methods and Results In a retrospective cohort with data on 236,957 patients-years of VKA management from two first-line anticoagulation clinics in the Netherlands, we identified 124 patients in target range 2-3, 269 patients in target range 2-3.5 and 98 patients in target range 2.5-3.5 who switched from acenocoumarol to phenprocoumon. They were matched in a 1:2 ratio to non-switching controls using propensity score matching.

Over the first 180 days after a switch, switchers' TTR declined 5 (95% CI 1 to 10), 10 (95% CI 7 to 13) and 5 (95% CI 0 to 11) percentage points relative to non-switchers, in target ranges 2-3, 2-3.5 and 2.5-3.5. Anticoagulation was more often supra-therapeutic in switchers, and switchers had a higher INR variability.

In the following 180 days, TTR in switchers became 1 (95% CI -4 to 6), 4 (95% CI 0 to 7) and 6 (95% CI 1 to 12) percentage points better than in non-switchers. Switchers' INRs were much more stable than non-switchers'.

Conclusion Eventually, a switch from acenocoumarol to phenprocoumon leads to a higher TTR and a lower INR variability. However, this is preceded by a transition period with opposite effects. An improved conversion algorithm could possibly shorten the transition period. Until then, physicians and patients should decide whether switching is worth the increased risk during the transition phase.

Introduction

Vitamin K antagonists (VKAs) are prescribed to treat and prevent thrombosis in venous thromboembolism, atrial fibrillation, heart valve replacement, and some other indications. Their effect is unpredictable and requires frequent monitoring to obtain an anticoagulation intensity (international normalised ratio (INR)) within the therapeutic range. Treatment is safest and most effective when the time within the therapeutic range (TTR) is high[1, 2] and the INR variability is low[3]. Unfortunately, despite frequent monitoring, not all patients achieve this.

With the introduction of the direct oral anticoagulants (DOACs), the treatment arsenal expanded. Many patients have switched from a VKA to a DOAC. However, DOACs are contraindicated in mechanical heart valves, renal insufficiency, and in combination with certain interacting drugs. Furthermore, because a poor TTR can be the result of poor medication adherence, physicians may be reluctant to switch such patients to a DOAC. Therefore, interventions to optimise VKA treatment remain relevant.

A possible intervention is to switch to a vitamin K antagonist with a longer half-life. Theoretically, a longer-acting drug would be less sensitive to suboptimal medication adherence and produce more stable INRs. In the Netherlands, only short-acting acenocoumarol (half-life 8-11 hours) and long-acting phenprocoumon (half-life 160 hours) are available. Data on the effect of switching from acenocoumarol to phenprocoumon on TTR are lacking completely; studies with other VKAs ignore natural variation in TTR. We aimed to determine whether switching from acenocoumarol to phenprocoumon increased TTR and decreased INR variability in practice.

Methods

This is a retrospective cohort study with patients from two first-line thrombosis services in the Netherlands. Of patients who switched to phenprocoumon, we compared TTR and INR variability before and after the switch. We also assessed whether this change differed from that in matched non-switchers, to account for the natural evolution of TTR and INR variability over time. We hypothesised that the switch to phenprocoumon would increase TTR and decrease INR variability.

Data sources and patient selection

In the Netherlands, VKA management is delegated to dedicated first-line regional “Thrombosis Services” that organise INR checks and adjust the VKA dose. Each thrombosis service uses one preferred VKA. Certe Trombosedienst and Trombosedienst Maastricht UMC+ are two thrombosis services, in the north and south of the Netherlands, respectively, that routinely use acenocoumarol. Thrombosis Service physicians can suggest switching a patient to phenprocoumon; the treating physicians usually follow this suggestion.

We extracted INR and VKA dosing records of adult patients who used acenocoumarol or switched from acenocoumarol to phenprocoumon, in target ranges 2–3, 2.5–3.5 or 2–3.5 (used for low-intensity anticoagulation before switching to the internationally recommended target range of 2–3 on January 1st, 2016), indicated for atrial fibrillation (AF), venous thromboembolism (VTE) or mechanical heart valve replacement (MVR). Data were extracted on July 17th, 2018 (Certe Trombosedienst) and June 20th, 2019 (Trombosedienst Maastricht UMC+). We excluded the first 90 days of treatment with vitamin K antagonists because INRs are unstable in the initiation period.

All data were anonymised before they were provided to the researchers. The Medical Ethics Review Board of the University of Groningen confirmed that this study required no ethical approval.

Switchers

We selected patients who used acenocoumarol for at least 180 days (excluding the initial 90 days) before switching to phenprocoumon, and had follow-up INR measurements for at least a further 180 days. The study size was based on the number of patients who switched.

Non-switchers

Non-switchers were defined as patients who used acenocoumarol during their entire treatment course or up to date of data extraction. For every calendar date on which a switcher switched, we selected patients who used acenocoumarol for the previous 180 days (excluding the initial 90 days) and next 180 days, with the same target range. At this stage, one non-switcher could be selected to be a control for multiple switch dates, if their follow-up was long enough. We then later randomly selected one instance per patient, to prevent over-representation of long-term non-switchers in the matching strategies.

Subgroups

We defined subgroups of special interest, based on the prompt for switching and special clinical considerations. A switch could be prompted by a low

acenocoumarol dose requirement, a suboptimal TTR or high variability. We separately analysed patients who used less than 1.5mg acenocoumarol per day, patients who had a TTR <60% and patients with a baseline INR variability above the 75th percentile in their target range. In addition, we provide specific information about patients with a mechanical heart valve (who are confined to VKA), and the elderly (aged ≥ 70 years; who are more likely to have contraindications to restrict other forms of anticoagulation).

Outcomes

We calculated the proportion of time in the therapeutic range (TTR) as well as the time below and above the range for each patient using linear interpolation according to the Rosendaal method[4]. Additionally, TTR was dichotomised with a cut-off of 65% because patients with a TTR $\geq 65\%$ have a favourable risk profile for bleeding and thrombosis[1]. INR variability was calculated using Fihn's method[5] (equation). Furthermore, we determined the mean INR (without interpolation), the mean time between INR measurements, and the mean VKA dose in milligrams.

$$\text{INR variability} = \sqrt{\frac{1}{n-1} \sum_{i=2}^n \frac{(\text{INR}_i - \text{INR}_{i-1})^2}{\Delta t \text{ (days)}}}$$

We distinguished three periods: the 180 days before a patient's switch to phenprocoumon, the 180 days after switch, and a period from 180 to 360 days (see Figure 1). For non-switchers, we used the switch date from the corresponding switcher. All differences were calculated with the 180 days before the switch (baseline) as reference. Because the distribution of the INR variability is skewed, the difference of the log-transformed INR variability was used (which is equivalent to the log-transformed ratio of INR variabilities). The VKA dose is reported as the mean dose during a certain period, and as a percentage of a patient's mean dose during the 180 days before the switch.

Figure 1. Periods distinguished in the analyses.

Solid lines indicate the time period used in the analyses. A period in which acenocoumarol was used, is shown in grey; phenprocoumon is shown in black.

Statistical analyses

Switchers over time

For the initial analysis, we summarised the TTR and INR variability as median and interquartile range. Differences were tested using a one-sample Wilcoxon rank-sum test. Intra-individual correlations were summarised using the Spearman correlation.

Switchers compared with non-switchers

We compared the differences in VKA quality parameters between switchers and non-switchers, to isolate the effect of the switch to phenprocoumon. Non-switchers were matched to switchers in a 2:1 ratio using propensity scores based on age, sex, indication for VKA therapy, duration of VKA therapy until (virtual) switch, the mean acenocoumarol dose in the six months before (virtual) switch, the times below and above range and the log-transformed INR variability. The propensity score was determined by logistic regression, and matching was performed using the MatchIt package[6] in R version 3.6.1 (2019-07-05) (R core team, Vienna, Austria). This matching procedure was repeated for every group of special interest.

Differences from baseline were analysed using a mixed linear effects model[7] to account for non-independence within matched sets. The time between INR measurements was compared in the later periods independent from the time between INR measurements during baseline, to prevent distortion by any extra monitoring before the anticipated switch. The time between INR measurements was log-transformed to approach normality. We calculated the difference in probability to obtain a good TTR ($\geq 65\%$) between switchers and matched non-switchers based on the observed frequencies.

Reporting

Values are reported as mean $\pm$ SD or median [interquartile range], as appropriate. A p-value below 5% was considered significant for all analyses; estimates are given as point estimate (95% confidence interval).

Results

Patient selection

Patient selection is outlined in Figure 2.

The thrombosis service Groningen contributed 28,756 eligible patients from September 25, 1991, onwards, with a total follow-up of 207,963 patient-years. The thrombosis service Maastricht contributed 3,645 patients from January 02, 1997, onwards, with 28,994 patient-years of follow-up.

There were relatively more switchers in Maastricht than in Groningen. Although Maastricht contributed only 11% of patients, they contributed 47% of switchers (234, versus 264 in Groningen). Four hundred and ninety-one switchers could be matched to 982 controls.

Figure 2. Flowchart of patient selection in this study.

Patient characteristics

Characteristics of switchers are summarised in Table 1; characteristics of all potential controls, and subgroups of switchers, are shown in the Supplementary Material.

Switchers achieved a lower TTR and their INRs were more volatile in the period before they switched than unmatched non-switchers.

The daily acenocoumarol dose differed between cases and controls as well: switchers from Maastricht, where a low dose requirement is a trigger to consider switching, indeed required a lower dose than unmatched non-switchers. In Groningen, where no such trigger is formally defined, switchers generally use a higher dose than the other patients in the anticoagulation clinic.

Men are less likely to be switched across all target ranges, yet they still outnumber women in target range 2.5 - 3.5, as they are more prone to cardiac indications for anticoagulation.

	2 - 3 (n = 124)		2 - 3.5 (n = 273)		2.5 - 3.5 (n = 101)	
Demographics						
Age	80	[68 , 85]	73	[62 , 80]	65.0	[56 , 74]
Male gender	56	(45.2)	123	(45.1)	55	(54.5)
Center						
Groningen	30		166		68	
Maastricht	94		107		33	
Indication for treatment with anticoagulation						
Atrial fibrillation (%)	96	(77.4)	223	(81.7)	43	(42.6)
Venous thromboembolism (%)	27	(21.8)	52	(19.0)	12	(11.9)
Mechanical heart valve (%)	6	(4.8)	5	(1.8)	64	(63.4)
Anticoagulant treatment						
VKA experience	5.0	[3.0, 11.0]	2.0	[1.0, 5.0]	6.0	[2.0, 12.0]
Average dose	1.1	[0.9, 2.8]	2.7	[1.5, 4.3]	3.1	[1.8, 4.3]
Acenocoumarol dose <1.5mg	75	(60.5)	68	(25.3)	21	(21.4)
TTR	45.3	[33.6, 53.7]	64.1	[47.0, 79.0]	36.5	[21.5, 47.5]
TTR <60%	106	(85.5)	119	(43.6)	89	(88.1)
Time below range	23.8	[15.5, 37.7]	13.8	[4.4, 27.6]	28.7	[10.5, 49.2]
Time above range	27.9	[15.7, 40.5]	14.4	[2.2, 29.8]	32.0	[13.3, 46.4]
Mean INR	2.7	[2.3, 2.9]	2.8	[2.4, 3.2]	3.2	[2.6, 3.6]
INR variability	0.5	[0.3, 0.8]	0.4	[0.2, 0.7]	0.5	[0.3, 0.9]
Mean number of days between INRs	11.7	[9.6, 14.6]	14.0	[10.7, 17.6]	11.9	[9.2, 14.6]

Table 1. Characteristics of patients included in the study.

Values are displayed as n (%), median [interquartile range].

Abbreviations: INR, international normalised ratio; TTR, time in therapeutic range; VKA, vitamin K antagonist

Switching: dosing and monitoring

Patients who switched from acenocoumarol to phenprocoumon were given a lower VKA dose in milligrams. For target range 2-3, the phenprocoumon dose was lowered to 91 [78 – 101]% of the acenocoumarol dose (in mg) in the first 180 days. In the other target ranges, the conversion factors were lower: 86 [75 – 97]% for target range 2-3.5 and 88 [73 – 96]% for target range 2.5-3.5.

Patients in target ranges 2.0-3.5 and 2.5-3.5 were monitored more often than before their switch; this was not observed in patients in target range 2.0-3.0 (Table 2). Patients who required more INR measurements before their switch, were checked more often after their switch (Spearman ρ 0.35 (95% CI 0.19 to 0.50), 0.46 (95% CI 0.36 to 0.55) and 0.54 (95% CI 0.38 to 0.66) for target ranges 2 - 3, 2 - 3.5 and 2.5 - 3.5).

After the first 180 days, the phenprocoumon dose was lowered further, to 85 [71 – 99]% of the baseline acenocoumarol dose in target range 2-3, 78 [67 – 92]% in target range 2-3.5 and 79 [66 – 94]% in target range 2.5-3.5.

Monitoring intervals were prolonged across all target ranges (Table 2). For target range 2-3, the monitoring interval was no longer related to the monitoring interval at baseline (ρ 0.08 (95% CI -0.11 to 0.25)).

Effect of switching

The evolution of VKA quality parameters after switching from acenocoumarol to phenprocoumon is summarised in Tables 2A-2C. Patients in target range 2-3 showed a marked immediate improvement in TTR. This was not true for patients in the other target ranges, where the improvements were only seen in the long-term period (180 to 360 days after the switch). In these target ranges, the time above the target range increased at the expense of not only the time below the range, but also the time in the therapeutic range. INR variability decreased across all target ranges.

The TTR achieved after the switch was only weakly related to the TTR before the switch: Spearman ρ was 0.26 (95% CI 0.09 to 0.42) for target range 2 - 3, 0.22 (95% CI 0.10 to 0.33) for target range 2 - 3.5 and 0.05 (95% CI -0.15 to 0.24) for target range 2.5 - 3.5. In target range 2.5-3.5 there was a moderate positive association between the time above the range at baseline and after the switch (ρ 0.43 (95% CI 0.26 to 0.58)), that persisted in the later period (ρ 0.45 (95% CI 0.27 to 0.59)). The same was found for the time below the range (ρ 0.41 (95% CI 0.24 to 0.56) and 0.37 (95% CI 0.19 to 0.53)). In other target ranges, this effect was not observed.

Parameter	Before switch		Short-term			Long-term		
	PE	IQR	PE	IQR	p	PE	IQR	p
TTR	45%	[34 – 54]	51%	[37 – 64]	0.001	62%	[43 – 75]	<0.001
above range	28%	[16 – 40]	24%	[12 – 39]	0.589	17%	[0 – 36]	0.045
below range	24%	[15 – 38]	18%	[9 – 33]	0.011	11%	[0 – 27]	<0.001
INR variability	0.52	[0.32 – 0.80]	0.28	[0.19 – 0.44]	<0.001	0.17	[0.12 – 0.26]	<0.001
mean INR	2.7	[2.3 – 2.9]	2.6	[2.3 – 3.0]	0.773	2.5	[2.3 – 2.9]	0.385
dose	1.1	[0.9 – 2.8]	1.1	[0.8 – 2.3]	<0.001	1.1	[0.8 – 2.2]	<0.001
dose ratio	ref		91%	[78 – 101]	<0.001	85%	[70 – 99]	<0.001
mean number of days between INRs	12	[10 – 15]	11	[10 – 14]	0.401	17	[13 – 20]	<0.001

Table 2A. VKA quality parameters in patients in target range 2.0-3.0 who switched from acenocoumarol to phenprocoumon.

P-values from Wilcoxon rank-sum test.

Abbreviations: PE, point estimate; IQR, interquartile range.

Parameter	Before switch		Short-term			Long-term		
	PE	IQR	PE	IQR	p	PE	IQR	p
TTR	64%	[47 – 79]	62%	[48 – 73]	0.173	77%	[60 – 92]	<0.001
above range	14%	[2 – 30]	25%	[16 – 38]	<0.001	15%	[0 – 26]	0.850
below range	14%	[5 – 28]	7%	[2 – 17]	<0.001	0%	[0 – 12]	<0.001
INR variability	0.40	[0.23 – 0.67]	0.32	[0.22 – 0.50]	<0.001	0.18	[0.12 – 0.32]	<0.001
mean INR	2.8	[2.4 – 3.2]	3.0	[2.7 – 3.4]	<0.001	3.0	[2.7 – 3.2]	<0.001
dose	2.7	[1.5 – 4.3]	2.3	[1.5 – 3.3]	<0.001	2.0	[1.2 – 3.1]	<0.001
dose ratio	ref		86%	[75 – 97]	<0.001	78%	[67 – 92]	<0.001
mean number of days between INRs	14	[11 – 18]	12	[10 – 15]	<0.001	19	[14 – 27]	<0.001

Table 2B. VKA quality parameters in patients in target range 2.0-3.5 who switched from acenocoumarol to phenprocoumon.

P-values from Wilcoxon rank-sum test.

Abbreviations: PE, point estimate; IQR, interquartile range.

Parameter	Before switch		Short-term			Long-term		
	PE	IQR	PE	IQR	p	PE	IQR	p
TTR	36%	[22 – 47]	36%	[24 – 51]	0.684	49%	[34 – 66]	<0.001
above range	32%	[13 – 47]	38%	[22 – 56]	0.003	30%	[7 – 43]	0.774
below range	28%	[10 – 49]	12%	[5 – 34]	<0.001	10%	[0 – 27]	<0.001
INR variability	0.50	[0.31 – 0.93]	0.45	[0.31 – 0.61]	0.037	0.22	[0.14 – 0.43]	<0.001
mean INR	3.2	[2.7 – 3.6]	3.3	[2.9 – 3.8]	0.012	3.2	[2.9 – 3.5]	0.804
dose	3.1	[1.8 – 4.3]	2.4	[1.6 – 3.5]	<0.001	2.2	[1.6 – 3.2]	<0.001
dose ratio	ref		88%	[73 – 96]	<0.001	79%	[66 – 93]	<0.001
mean number of days between INRs	12	[9 – 15]	11	[9 – 13]	0.013	16	[12 – 20]	<0.001

Table 2C. VKA quality parameters in patients in target range 2.5-3.5 who switched from acenocoumarol to phenprocoumon.

P-values from Wilcoxon rank-sum test.

Abbreviations: PE, point estimate; IQR, interquartile range.

Comparison with non-switchers

Four hundred and ninety-one switchers could be matched with 982 non-switching controls, with a high similarity between the two groups (standardised mean difference in propensity scores was 0.08 for target range 2-3; 0.02 for target range 2-3.5 and 0.07 for target range 2.5-3.5). The coefficients from the propensity score matching and the patient characteristics from matched patients are shown in Tables S3 and S4, respectively. The difference in outcomes between switchers and matched non-switchers is shown in Tables 3A-3C and Figures 3-5.

When comparing switchers with non-switchers, the initial effect of switching is negative: TTR decreases mainly owing to an increase in the time above the range. At the same time, the INR variability increases, though only statistically significantly in target range 2-3.5. In the first six months, switchers are less likely to obtain or maintain a TTR $\geq 65\%$: the absolute risk difference was -13 (95% CI -22 to -3) percentage points for target range 2.0-3.0; for target range 2.0-3.5 it was -20 (95% CI -27 to -12); for target range 2.5-3.5 the risk difference was -5 (95% CI -12 to 3). Switchers' INRs were monitored more often, with 24% (95% CI 18 to 29) less time between INR measurements for target range 2-3; 22% (95% CI 18 to 25) for target range 2-3.5 and 29% (95% CI 23 to 35) for target range 2.5-3.5.

Positive effects occur in the second six-month period after switching. TTR mildly increases, with 0.8 (95% CI -4.4 to 6.1), 3.9 (95% CI 0.4 to 7.4) and 6.4 (95% CI 0.8 to 12.1) percentage points in target ranges 2 - 3, 2 - 3.5 and 2.5 - 3.5, respectively. The INR variability strongly decreases across all target ranges. During this period, switchers in target ranges 2-3 and 2-3.5 were slightly more likely to obtain a

TTR $\geq 65\%$: absolute risk differences were 2% (95% CI -9 to 13) and 6% (95% CI -1 to 13). The effect was more pronounced in target range 2.5-3.5, where patients were 15 (95% CI 6 to 25) percentage points more likely to obtain a TTR $\geq 65\%$. Switchers in target ranges 2-3 and 2.5-3.5 were no longer monitored more often than their matched non-switching controls (they had 2% (95% CI -6 to 12) and 2% (95% CI -6 to 12) more time between measurements). Patients in target range 2-3.5 had 14% (95% CI 8 to 22) more time between INR measurements.

Variable	Short-term difference	Long-term difference
TTR	-5.5 (-9.6 to -1.3)	0.8 (-4.4 to 6.1)
above range	5.8 (0.8 to 10.8)	0.8 (-4.9 to 6.4)
below range	-0.3 (-4.9 to 4.3)	-1.8 (-6.8 to 3.2)
INR variability*	0.03 (-0.18 to 0.24)	-0.34 (-0.57 to -0.12)

Table 3A. Difference in changes since baseline of switchers versus matched non-switching controls in target range 2.0-3.0, with 95% confidence interval. Differences in time in/above/below therapeutic range are displayed as percentage points.

An asterisk indicates that values were log-transformed in the analyses.

Variable	Short-term difference	Long-term difference
TTR	-9.8 (-12.9 to -6.7)	3.9 (0.4 to 7.4)
above range	12.3 (9.2 to 15.4)	1.7 (-1.3 to 4.7)
below range	-2.5 (-4.9 to 0.0)	-5.6 (-8.4 to -2.8)
INR variability*	0.08 (-0.06 to 0.23)	-0.35 (-0.50 to -0.21)

Table 3B. Difference in changes since baseline of switchers versus matched non-switching controls in target range 2.0-3.5, with 95% confidence interval. Differences in time in/above/below therapeutic range are displayed as percentage points.

An asterisk indicates that values were log-transformed in the analyses.

Variable	Short-term difference	Long-term difference
TTR	-5.4 (-10.8 to 0.0)	6.4 (0.8 to 12.1)
above range	6.2 (0.2 to 12.3)	-1.3 (-7.6 to 4.9)
below range	-0.8 (-6.3 to 4.6)	-5.1 (-10.6 to 0.4)
INR variability*	0.14 (-0.06 to 0.34)	-0.55 (-0.76 to -0.34)

Table 3C. Difference in changes since baseline of switchers versus matched non-switching controls in target range 2.5-3.5, with 95% confidence interval. Differences in time in/above/below therapeutic range are displayed as percentage points.

An asterisk indicates that values were log-transformed in the analyses.

Figure 3. Proportion of time spent in, above or below the target range of 2.0 - 3.0, and INR variability, in switchers and matched non-switchers. Median and interquartile range.

Figure 4. Proportion of time spent in, above or below the target range of 2.0 - 3.5, and INR variability, in switchers and matched non-switchers. Median and interquartile range.

Figure 5. Proportion of time spent in, above or below the target range of 2.5 - 3.5, and INR variability, in switchers and matched non-switchers. Median and interquartile range.

Effect in subgroups

We compared the effect of a switch in several groups of special interest. Patient characteristics of switchers in these groups, and their matched non-switchers, are summarised in Table S4. Again, matching was successful: standardised mean differences in propensity scores were <0.1 in all subgroups, except in some subgroups in target range 2.5-3.5: patients with high INR variability (standardised mean difference (SMD) in propensity scores 0.13), elderly patients (SMD 0.20), and patients with mechanical heart valves (SMD 0.12).

The effect of a switch relative to non-switchers is summarised in Table S5 and shown in Figures 6-8.

Figure 6. Changes in time in the therapeutic range (TTR) of 2.0 - 3.0 and international normalised ratio (INR) variability in patients who switched from acenocoumarol to phenprocoumon, relative to matched non-switchers. The grey area indicates the 95% confidence interval of the difference in the overall analysis.

Figure 7. Changes in time in the therapeutic range (TTR) of 2.0 - 3.5 and international normalised ratio (INR) variability in patients who switched from acenocoumarol to phenprocoumon, relative to matched non-switchers. The grey area indicates the 95% confidence interval of the difference in the overall analysis.

Figure 8. Changes in time in the therapeutic range (TTR) of 2.5 - 3.5 and international normalised ratio (INR) variability in patients who switched from acenocoumarol to phenprocoumon, relative to matched non-switchers.

The grey area indicates the 95% confidence interval of the difference in the overall analysis.

The effect of a switch on TTR was consistent in groups with different prompts for switching (a low dose, a poor TTR or a high INR variability). In target ranges 2-3 and 2-3.5, patients with a poor TTR and patients with high INR variability who switched were initially relatively over-anticoagulated compared with patients with a low VKA dose before their switch. This difference disappeared after the first 180 days. In target range 2-3.5, the INRs of patients whose switch was prompted by a low VKA dose stabilised quicker than the INRs of patients with a poor TTR.

We also evaluated the effect of a switch in patients who require specific clinical consideration: i.e. the elderly and patients with a mechanical heart valve. Initially, the effect of a switch on TTR in these groups is comparable to the effect in the whole population. In the long term, however, the TTR of elderly patients in target ranges 2-3.5 and 2.5-3.5 seems not to improve by switching, nor does the TTR of patients with a mechanical heart valve and target range 2.5-3.5.

Discussion

In this study, we analysed the effect of switching from acenocoumarol to phenprocoumon on the achieved quality of anticoagulation in patients from two Dutch anticoagulation clinics. We found that patients' time in the therapeutic range and INR variability do not improve in the first six months, compared with non-switching matched controls. In the second six-month period after a switch, however, INR variability decreases and TTR improves.

Although the question which vitamin K antagonist to prefer is far from new, we are the first to observe the real-life effect of switching from acenocoumarol to phenprocoumon using matched non-switchers. Previous research only compared groups of patients using different VKA. Already in the 1960s and early 1970s phenprocoumon showed favourable properties compared with warfarin[8] and acenocoumarol[9, 10] on then-used monitoring parameters. After the development of the international normalised ratio (INR) to monitor VKA, several additional studies have been performed, with mixed results. The proportion of INR measurements in range was higher on warfarin than on acenocoumarol in an Italian retrospective cohort study[11], but not in one from Bosnia and Herzegovina[12]. Two retrospective studies from the Netherlands found a higher TTR in patients on phenprocoumon, compared with acenocoumarol[5, 13]. In clinical practice, anticoagulation clinics in the Netherlands report higher TTRs in patients on phenprocoumon than patients on acenocoumarol[14]. A retrospective study focussing on self-managed patients found a higher TTR on phenprocoumon than on warfarin[15]. A French randomised controlled trial showed no difference in TTR between patients initiated with warfarin versus those with acenocoumarol, but INR variability was lower in the warfarin group[16]. This implies that phenprocoumon (with the longest half-life) might lead to a higher TTR than warfarin (with the intermediate half-life); warfarin, in turn, could cause a higher or similar TTR to acenocoumarol (with the shortest half-life). However, these studies did not assess the effect of switching from one VKA to another on the quality of anticoagulation.

Two studies describe the switch from acenocoumarol to warfarin. An Italian group found no increase in the number of prothrombin times in range[17]. The results of this study are difficult to generalise because the group of patients had heterogeneous indications for anticoagulation and it is unclear how these patients were selected. A Polish study, confined to younger patients with arbitrarily defined "unstable anticoagulation," found a marked increase in TTR after the switch[18]. Because both studies lacked a control group, and TTR is not stable over time[19], their results could be distorted by "regression" to the mean.

In our study, we separated the switching effect from the natural course of anticoagulation therapy and bias by indication with the use of matched non-switching controls. However, matching is sensitive to unmeasured confounders. We have included almost all the limited data available to anticoagulation clinics in the matching, and we believe they included the most relevant confounders. However, we could not control for a switch due to the start of interacting medication (e.g. rifampicin).

We could not assess the effect of a switch on the incidence of bleeding and thrombotic events, because we lacked the data. Instead, we measured TTR and INR variability. TTR and INR variability link the joint pharmacological effect of all vitamin K antagonists to bleeding and thrombotic complications[1–3]. Additional mechanisms leading to bleeding or thrombosis, specific to one vitamin K antagonist, are unknown and implausible. Therefore, TTR and INR variability are accepted proxy measures.

The observational nature of our study only allowed us to analyse patients who actually switched. Strictly speaking, our study cannot be generalised to patients whose physicians do not see an indication to switch. However, our results are similar to those from earlier studies comparing patients on the two drugs without switching[5, 13]. Nevertheless, the TTR improvement in our study seems smaller than the TTR difference observed between anticoagulation clinics using primarily phenprocoumon instead of acenocoumarol[14]. We have insufficient data to assess whether this effect persists after adjustment for differences in casemix. Another explanation would be a difference in experience with managing phenprocoumon.

Other strong points of our study are the real-life setting and the analysis in contemporary target ranges; previously, higher intensity anticoagulation therapy was prescribed. Our findings are more robust because they stem from two independent thrombosis services.

The eventual increase in TTR and decrease in INR variability after switching to phenprocoumon are intuitive; factor VII levels fluctuate more during the day under acenocoumarol than under phenprocoumon[20, 21]. This effect could be more prominent in higher target ranges, where small variances in coagulation factors result in higher changes in the INR than in lower target ranges[22]. However, it is unknown whether the increased stability of factor VII levels on phenprocoumon also extends over periods of weeks instead of a single day. Furthermore, this cannot explain why the beneficial effect is only seen after a “transition period.”

The transition period following a switch is characterised by unfavourable effects on VKA control: a decreased TTR and a higher INR variability. Patients are more prone to bleeding, owing to a higher proportion of time above the target range[2]. A possible cause is the trial-and-error during the determination of the optimal individual phenprocoumon dose. In general, the anticoagulation clinics follow the Dutch guideline, which prescribes a conversion factor of 84%[23]. However, the resulting over-anticoagulation and the later dose reductions suggest that this factor, identified in stable patients in higher target ranges[24], might not be applicable anymore.

In the long run, switching from acenocoumarol to phenprocoumon leads to improved VKA control. In all target ranges, the switch to phenprocoumon significantly decreases INR variability. A lower INR variability reduces the risk of bleeding and thrombosis[25–29], but to which extent is difficult to quantify since different authors use different methods to calculate INR variability. There is no consensus about risk categories based on absolute values of INR variability, and it remains unclear whether INR variability should be interpreted similarly in different target ranges.

A switch to phenprocoumon also significantly improves TTR in target ranges 2-3.5 and 2.5-3.5, relative to non-switching controls. The TTR improvement is most pronounced in target range 2.5-3.5, with a difference of 6.4 (95% CI 0.8 to 12.1) percentage points. The associated clinical benefit cannot be quantified exactly because the relationship between TTR and incidence of events is not linear[2]. Patients with a TTR $\geq 65\%$ have substantially reduced risks of bleeding, thrombosis and death, compared with patients with a TTR $< 65\%$ [1]. One additional patient out of every 6.5 (95% CI 4.0-18.1) patients in target range 2.5-3.5 who switch, attains a TTR in this favourable risk category. TTR differences were smaller in target ranges 2-3 and 2-3.5, and more patients need to switch to cause an additional TTR $\geq 65\%$: 48.0 (95% CI NNT 7.7 to ∞ to NNH 11.3) and 16.9 (95% CI NNT 7.7 to ∞ to NNH 84.5), respectively. One could argue that the effect of moving from a TTR $< 65\%$ to a TTR $\geq 65\%$ with a small TTR difference is trivial, because the differences in these categories will be driven by a larger TTR variation.

The benefit of an improved TTR does not extend to patients with a mechanical heart valve prosthesis, nor to elderly patients in target range 2-3.5 or 2.5-3.5 (the latter even seem to decline). Although the findings in this group are less robust, owing to the smaller sample size and less perfect matching, they are cause for concern. The efficacy and safety of VKA are paramount in these groups because alternative forms of anticoagulation might be contraindicated.

Fortunately, elderly patients in target range 2-3 do increase in TTR after the switch. Elderly patients across the target ranges, and patients with mechanical heart valves, obtain a lower INR variability. However, it is questionable whether the decreased INR variability cancels out the neutral or unfavourable effect on TTR, the risks associated with the transition period, and the risk of medication errors with drugs that are less commonly used.

Conclusion

Eventually, the switch from acenocoumarol to phenprocoumon improves the time in the therapeutic range and decreases the INR variability. However, this is preceded by a transition period, where TTR is lower and mostly the time above the range is increased. Physicians and their patients should weigh the benefit of a small improvement in VKA control and the risk of the transition period.

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Summary, discussion and future perspectives

9

The quality of treatment on vitamin K antagonists might modify the benefit of a direct oral anticoagulant

This thesis aims to improve our understanding of two central questions: Who should switch from a vitamin K antagonist (VKA) to a direct oral anticoagulant (DOAC), and who should continue VKA? What can we do to improve the quality of treatment with VKA for the ones who cannot, or do not want to switch?

For both questions, it is important to note that VKA therapy is heterogeneous. Treatment is safest and most effective when the anticoagulation intensity is kept within the narrow therapeutic range. Patients in whom this is achieved most of the time, i.e. who spend a high proportion of time in the therapeutic range (TTR), suffer from fewer bleeding and thrombotic complications[1–4]. This makes the TTR a possible mechanism to differentiate patients who have a lot to gain by switching to a DOAC from those who should continue VKA. In addition, TTR and INR variability are good targets to improve to decrease the incidence of complications.

DOACs have been developed to provide a more stable form of anticoagulation, obviating the requirement for INR monitoring. Hence, one would presume there is no concept complementary to the TTR on VKA. DOACs are overall non-inferior to VKA for AF[5–8]. However, this overall non-inferiority could very well be a façade, a compound of three discerned groups:

- A group where DOACs have a clear benefit over VKA, i.e. VKA with poor TTR;
- A group where DOACs might be inferior to VKA with a good TTR;
- A “middle group”

Although it seems easy to perform post-hoc analyses on the DOAC trials, it is complicated to properly assess the effect of TTR on the benefit of DOACs. For one, the relationship between TTR and events is bi-directional: TTR might predispose to events, but the management of events might decrease TTR. Especially in the context of a major bleeding, anticoagulation is withheld and time below the target range follows. Naïvely separating patients based on TTR could thus create a self-fulfilling prophecy. Therefore, stratified analyses based on centre TTR were performed, with mixed results[9, 10]. The impact of these findings on individual patient care is open to dispute, because a person is reduced to the average of their centre in these analyses.

Nevertheless, the use of centre TTR might not be the largest problem limiting the use for individual patient care. A TTR can only be obtained retrospectively, and

new information is only available with a new INR measurement (e.g. at the time of an event). In retrospective research, it is tempting to say that the event could have been predicted[11], but this information is unavailable to the physician. Therefore, for individual risk prediction, the question should be rephrased as “does a patient’s currently obtained TTR influence the estimation of a DOAC’s benefit?”

The benefit of a DOAC in patients with a good TTR

We performed a randomised controlled pilot trial, called *Goede Antistolling In noord-Nederland (GAIInN)*, to explore this question, reported in chapters two and three. We included 241 patients who had been, so far, exquisitely anticoagulated, with a high TTR ($\geq 70\%$, the cutoff for high-quality anticoagulation[12], in the former therapeutic range of 2.0-3.5) and no bleeding or thrombotic events ever on VKA. Half of this group was randomised to switch to a DOAC ($n=121$), while the other half continued their VKA therapy ($n=120$). Patients in our study showed a low rate of major or clinically relevant non-major bleeding, and a low rate of thrombotic complications. These endpoints were evenly distributed over the two groups. Therefore, we concluded that there was no evidence for our hypothesis that a group of patients who had been well-controlled on VKA should not switch to a DOAC based on clinical endpoints.

DOACs differ from VKAs in that they do not require INR monitoring. The INR is a blood test; based on the results the VKA dose is adjusted. At first, blood was drawn from a vein and sent to a laboratory. In the last years, the INR is more and more often determined by finger prick instead. Either way, monitoring could be cumbersome for some patients, while other patients appreciate the reassurance. Furthermore, patients could value social contact with the thrombosis service, and the availability when questions arise. This is unavailable for patients on a DOAC. Again, the TTR might be a distinguishable factor on the quality of life. Not just owing to the lower risk of quality of life decline due to bleeding[13, 14], but also because of less frequent monitoring visits, and more stable doses. In the GAIInN study, we also administered questionnaires for general health-related quality of life and anticoagulation-related quality of life. We discovered that patients found treatment with a DOAC more convenient, especially patients who were not fully satisfied with VKA. Nevertheless, a considerable number of patients decided to return to VKA therapy due to side-effects. We conclude that switching patients with a high TTR to a DOAC might better be reserved for patients who are not fully satisfied with VKA.

Can TTR be predicted?

We selected patients for the GAIIn study based on their good performance on VKA, with a TTR $\geq 70\%$ and without ever having had a haemorrhage or thrombosis on VKA. Implicitly, we assumed these patients would maintain a high TTR during the study. Guidelines follow the same line of reasoning and advise to consider a DOAC when TTR is low [15, 16]. We should, however, note that the role of TTR as a quality indicator is based on the number of events during the period used to calculate the TTR. In a way, this makes a previous TTR irrelevant: all risks associated with said TTR will have already materialised (i.e. the events will have already occurred). Instead, we should be interested in a future TTR and its associated risks.

A predicted TTR can be useful in clinical decision making. When it is likely that TTR will be poor, e.g. when a patient requires interacting medication such as cotrimoxazole, starting a DOAC can be considered. The European Society of Cardiology guideline alludes that a clinical decision score (the SAME-TT₂R₂ score [17]) can predict whether a patient will obtain a good TTR, before starting treatment [16]. Others propose that patients with a high score should avoid VKA altogether, and instead start a DOAC [18]. Even when treatment has already begun, patients should be periodically monitored to weigh the pros and cons of anticoagulation, consider alternatives, and minimise risk factors. Here, a predicted TTR can be helpful to assess the net clinical benefit of continuing VKA, and identify patients who require more frequent re-assessment or interventions to improve TTR. Whether we can predict a TTR has been covered in chapters four to six.

The SAME-TT₂R₂ score

To determine the clinical usefulness of the SAME-TT₂R₂ score, we performed a systematic review and meta-analysis. We identified 16 studies that assessed the SAME-TT₂R₂ score in relation to the TTR the patients attained. We performed a simulation to tidy-up the farrago of different cut-offs and different definitions for a positive test. Many studies reported the mean and standard deviation of TTR by SAME-TT₂R₂ score. If we assumed that the data were, indeed, from a normal distribution, we could use the mean and standard deviation to define a distribution from which we could sample to construct a dataset (technical details are outlined in chapter four). Our novel simulation technique worked well: deviations from observed data were small. We performed a meta-analysis to appraise the SAME-TT₂R₂ score's performance to predict a TTR $< 70\%$, using cut-offs of ≥ 2 and ≥ 3 . Sensitivity and specificity varied considerably from study to study. However, likelihood ratios were homogeneous enough to allow pooling. The differences in TTR between patients with a high versus a low SAME-TT₂R₂

score were less than 10%. These small differences, combined with likelihood ratios close to unity, show that this score is not clinically useful. I doubt the continuous addition of new papers regarding the score will ever lead to a different conclusion, but the procedure for our meta-analysis is freely available online if one wants to update it.

Previous TTR

In chapter five, we assessed to what extent a previous TTR predicts future TTR, and we tried to define when therapy with VKA is no longer feasible. Based on data from approximately 18 000 patients from Certe Trombosedienst, we conclude that the predictive performance of a previous TTR is disappointing. The correlation between a patients' previous and future TTR ranged from 0.25 to 0.35, depending on the duration of TTR measurements. Groups created by quintiles of TTR become more and more alike over time as well: c statistics were approximately 0.60 (a c statistic of 0.50 is non-informative). We calculated the probability that a patient would achieve "good anticoagulation" in the future, dependent on the most recent TTR. We confirmed earlier findings[19] that only half of the patients with a TTR $\geq 70\%$ will maintain a TTR $\geq 70\%$. This shows that the TTR might be less stable than we previously thought. The value for patient counselling remains to be seen.

We currently lack guidelines about TTR interpretation, especially for patients who cannot or do not want to switch to a DOAC. There is an inverse dose-response relationship between TTR and events. However, bleeding and thrombotic events even occur in patients with a TTR $>75\%$ [2], so a high TTR is no guarantee (if guarantees even exist). Likewise, a lower bound for TTR (a "cut-off for catastrophe") cannot be easily established. A decline in TTR down to 60% only leads to a limited increase in events[2, 20]. Some data suggest that the stroke reduction benefit in AF is lost with a TTR below 60%[20], but a TTR $\geq 45\%$ (in an even wider target range) was relatively well-tolerated in VTE[1]. Cut-offs for TTR might, therefore, also depend on other risk factors for thrombosis or bleeding.

Issues with TTR reporting

The interpretation and reproducibility of findings in the research on TTR are complicated, owing to bad reporting. It is rarely made clear how long the period was over which a TTR was calculated, suggesting this differed from patient to patient. This does not lead to bias in itself (unreported experiment), but complicates application in clinical practice. Consider a patient with a TTR of 100% over the last year. If, somehow, the TTR over the following 3 months is 0%, calculations over different time periods yield widely different results: 80% if the whole period is used, 75% over the last year, 50% over the last six months and

0% over the last three months. Therefore, authors should report the duration of TTR calculation used.

Another issue is that it is often not specified whether any period was excluded from the analyses. Due to the large interindividual variation, the VKA dose has to be empirically determined. After this dose-finding period, the TTR is generally higher than before (unreported experiment). Including this period could distort results, especially when the TTR duration is short or variable. Authors should report whether they include this period in their analyses, and provide proper justification.

Extreme INRs are easier to use

The adoption of the TTR in clinical practice has also been hindered by the difficulty to calculate it. The linear interpolation[21] is not easily performed without software. As an alternative, some physicians calculate the proportion of INR measurements in range (PINRR). The PINRR leaves out the time component of the TTR. There are clinically relevant differences in the two measures[22], and less research into the clinical use of PINRR has been performed. Therefore, the PINRR is probably not a good replacement for the TTR.

An easy alternative way to predict a poor outcome is to look for INR extremes. Earlier research from our group demonstrated that extreme overanticoagulation ($\text{INR} \geq 8.0$ or unscheduled vitamin K supplementation) was associated with a long-lasting inferior TTR and a higher risk of bleeding, thrombosis and death related to treatment with VKA[23]. Following up on this idea, we determined whether low INRs also predict an unfavourable prognosis (see chapter five). Instead of a single subtherapeutic INR, which can be desired e.g. for surgery, we used a sequence of four subtherapeutic INRs to predict a low future TTR (<45%) in over 17 000 patients from Certe Trombosedienst, who were anticoagulated with target range 2.0–3.0. We demonstrated that patients with a “streak” of subtherapeutic INRs had a lower average TTR (the difference was 12.5 (10.9–14.1) percentage points over a six-month period, and 9.6 (8.5–10.7) over one year, looking for a streak in the same period in the past). Furthermore, a streak resulted in a threefold increased odds of poor future TTR. This effect is smaller than that of an extreme overanticoagulation. This is not surprising, considering that the INR of ≥ 8 is further from the target range than an INR <2, and a supratherapeutic INR is never intended even though a subtherapeutic INR can be. Nevertheless, a streak can be an easy-to-use tool to flag patients at higher risk of poor TTR.

Improving the quality of anticoagulation

Fortunately, a patient with a poor predicted TTR is not doomed. Many interventions aim to improve medication adherence (more about those below). In chapters seven and eight, we report on two changes in the drug regimen that could potentially improve the quality of treatment. The first one, in chapter seven, was born out of the observation that, with increasing age, INR variability increased. At the same time, the average dose of acenocoumarol decreased. We suspected a connection: because acenocoumarol is dosed as a whole number of tablets spread out over fourteen days, a lower dose would result in relatively more day-to-day dose variation (compare a dosing scheme of 7-6-7-6 with 2-1-2-1). Maybe, a higher day-to-day dose variability caused the higher INR variability.

More precise dosing

We performed a small randomised controlled trial to test whether more precise dosing of acenocoumarol improved INR variability and TTR in the elderly. We included 80 patients aged 80 and above, who used between 0.5 and 2.0 mg of acenocoumarol daily. Forty of them were randomised to more precise dosing using 0.5mg increments; the other forty were dosed with the regular 1.0mg increments. Unfortunately, our randomisation was unsuccessful in balancing the two groups: patients allocated to more precise dosing had a higher baseline INR variability. A person's change in INR variability depended heavily on their baseline variability, and this imbalance could not be corrected with linear regression.

The groups were balanced for TTR at baseline, however, and we found that more precise dosing marginally increased TTR.

However, this does not mean that we should all adopt more precise dosing immediately. Using non-standard dosing could (and does) cause dosing errors: we saw that some patients received double doses during the study, which led to over-anticoagulation. In our study, this did not lead to bleeding or thrombotic events, but antithrombotics are one of the main causes of hospital admissions related to medication[24]. If different “strengths” of acenocoumarol become more commonplace, the number of errors could decrease. This could favourably shift the balance between risk and benefit.

The clinical benefit of more precise dosing, however, is difficult to quantify. The clinical impact of INR variability is less established than that of TTR. This can in part be explained by different methods to calculate INR variability[25–27]. Furthermore, many studies only compare the most variable half of patients with the least variable half. Because we cannot assess the relationship between the

absolute INR variability and the incidence of events, we do not know which value is sufficiently low.

Apart from effects on quality of VKA control, this study also affected quality of life. Patient allocated to the intervention group experienced a small, but statistically significant, decline in treatment convenience, compared with the control group. The intervention group had to take twice as many pills of acenocoumarol and complained about the packaging of the custom-made tablets.

Another interesting finding was that treatment satisfaction decreased by an average of six points in both study groups. This phenomenon has not been described in the literature before, and we did not observe it in the GAIInN study, in which the participants were younger and had a higher TTR. We speculate that it is caused by old age, where one's health can deteriorate rather quickly. This is supported by higher scores on dependency on others, although the questionnaire used should be specific to treatment with anticoagulants. Another explanation could be that participating in a study is stressful for the elderly. Maybe, ignorance truly is bliss, as patients reported they felt less reassured by their anticoagulant treatment during the study. These findings should be taken in mind when performing studies in the elderly.

A longer-acting medicine

Apart from creating a more stable dosing pattern, we could also switch patients to a drug that is considered inherently more stable. Phenprocoumon is another vitamin K antagonist whose mechanism of action is similar to that of acenocoumarol, but with a much longer half-life (160 hours instead of 8-11 hours). The idea is that a VKA with a longer half-life stabilises mainly factor VII levels and thus the INR. However, studies that addressed the effect on TTR were prone to indication bias, and disregarded the natural development of TTR (see above and chapter five).

In collaboration with the anticoagulation clinic from Maastricht, we evaluated the effect of patients who switched from acenocoumarol to phenprocoumon during the course of their anticoagulant treatment. We analysed 491 patients who switched, for reasons varying from a low acenocoumarol dose requirement to a poor TTR. In general, these patients' TTR increased after the switch, and their INR variability decreased. However, these favourable developments could also be caused by "regression to the mean," where a TTR that has reached its nadir is most likely to improve.

We tried to isolate the effect of the switch by using the other almost 30,000 patients as potential controls. Using propensity score matching, we identified the patients

who were most similar to the switchers in clinical characteristics and quality of treatment, but who did not switch. Comparing to these controls, the switchers initially do worse, i.e. the switchers improve less than similar patients who did not switch. However, after this transition period, switchers outperform the non-switchers.

This supports that switching patients with a reason to switch indeed improves the quality of treatment. Nevertheless, the transition period is a period characterised by over-anticoagulation (and therefore increased bleeding risk). Future research should focus on how we can shorten this transition period, so patients can benefit from the switch as soon as possible. Again, physicians and patients should deliberate whether deviating from the local protocol (which prescribes primarily acenocoumarol) is worth the risk of medication errors.

Summary

To recapitulate: patients with a high TTR and low INR variability experience fewer clinical adverse events, such as bleeding and thrombosis. A patient and their physician can make a joint decision, also based on a patient's predicted future TTR. TTR can, to a limited extent, be predicted by a patient's previous TTR or by INR extremes. Physicians should not recommend against switching to a DOAC based on clinical outcomes in patients who currently achieve a high TTR; one should weigh the risk of side-effects against the dissatisfaction on VKA. Although TTR can be slightly improved by more precise dosing or switching from acenocoumarol to phenprocoumon, using non-default treatment options could lead to an increased risk of medication errors.

Methodological considerations

In this thesis, we used different study designs to answer our research questions. We performed two randomised controlled trials (RCTs; see chapters two, three and seven), analysed observational data (chapters five, six and eight), and performed a simulation meta-analysis (chapter four).

RCTs are considered the gold-standard for etiological research. The between-groups difference is an unbiased estimate of an individual's -not directly observable[28]- treatment effect. However, a large enough sample size is required to balance other factors that influence the outcome between groups. (In the acenocoumarol dosing study, randomisation did not prevent a relevant difference in INR variability at baseline.)

A disadvantage of RCTs is that it can be difficult to recruit enough patients. In the GAIInN study, we had to invite over five thousand potential participants to reach the recruitment target of 240 patients. In the acenocoumarol dosing study, three-quarters of the informed patients declined participation. Demographic changes will make performing RCTs in VKA patients more challenging: VKA users will become frailer and more difficult to recruit. Moreover, we are picking ever higher-hanging fruit, which necessitates larger sample sizes to detect smaller differences. This will make it increasingly difficult to perform drug trials with vitamin K antagonists.

Fortunately, we can also learn from evaluating what we are already doing. The Dutch system of centralised thrombosis services effectively forms large cohorts (in the case of Groningen of over 17000 patients). The thrombosis services conscientiously record INR measurements and VKA dosing advice, and consequently form a treasure of data about VKA management. This makes data acquisition for researchers much easier. The analyses of observational data, however, are less straightforward than for a large-scale RCT.

In observational research, one cannot simply compare two groups, because they likely differ in aspects relevant to the outcome: physicians and patients do what they think is best given the circumstances, introducing confounding by indication. This was also the case in our study evaluating the switch from acenocoumarol to phenprocoumon, e.g. patients who switched had a much lower TTR than the general group. Put differently: baseline TTR affected the probability to switch. In addition, baseline TTR affects future TTR. We addressed this confounding by selecting a subgroup of controls, that was, based on their characteristics, just as likely to switch as a patient who actually switched. This “propensity score matching” should allow inferencing about the matched groups, but is sensitive to unmeasured confounders. In our study, though, we have included almost all information available to the thrombosis service, likely including all relevant confounders.

Another challenge in my research was non-independence in data: there are a lot of dependencies in TTRs; not just because they are from the same person but sometimes the periods used in the TTR calculation overlap, which causes the exact same data to be used. A further complicating factor is that the decision to monitor an INR at a specific time point is not random: patients with stable INRs will be monitored less often than patients with many INRs outside the therapeutic range. In the absence of models that properly account for this and are clinically understandable and applicable, we have managed this by randomly selecting an INR (chapters six and eight), or selecting the first possible INR (chapter five) from which to calculate TTR. This prevents bias at the expense of discarding a lot of the available data.

Future perspectives

Future perspectives for clinicians

Developments in DOAC

Although I suggested that the 2020s might become calmer regarding the DOACs, I still predict interesting developments. More patients might become eligible to start a DOAC, as preliminary evidence in patients with high body weight[29–35] and renal failure[36–39] is mounting. After a period of silence following the disappointment of dabigatran in thromboprophylaxis in patients with mechanical heart valve replacement[40], an RCT looking into rivaroxaban is recruiting[41].

Many studies use pharmacokinetic endpoints as a first step. This is not surprising, but contradicts one of the principal benefits of DOAC: the end of regular monitoring. Pharmacokinetic studies might pave the way for individual DOAC level monitoring and dose adjustments for all patients in the upcoming era of “precision medicine.” However, will the clinical benefit outweigh abolishing the advantage of a fixed dose for many?

DOAC level measuring has also been suggested to assess adherence to DOACs[42]. I doubt this will give a reliable estimate of adherence, given the short half-life of most DOACs (and don't people start flossing just hours before they go to the dentist?). The relative lack of adherence monitoring with DOACs was one of the reservations about their introduction in the Netherlands[43]. Medication adherence for chronic conditions is shockingly low[44] for a myriad of reasons[45]. DOACs are no exceptions[46]. Lower real-life adherence to DOACs could jeopardise the non-inferiority of DOACs in clinical trials. However, this effect is not observed in real-life registries[47]. Nevertheless, some authors suggest that even low-key monitoring in these registries improves adherence over real-life[46]. I am curious to see what will happen in the future: will patient education[48] and multi-dose drug dispensing (“*Baxter-rol*”)[49] guarantee adequate adherence, or was obviating INR monitoring indeed like throwing the baby out with the bathwater?

Developments in VKA

Meanwhile, the thrombosis services will see a further decline in the number of patients. This in itself will create logistical challenges: can outpatient clinics be maintained, or is centralisation inevitable? How can thrombosis services cater to the needs of a population that becomes frailer and frailer, as relatively more patients with contra-indications for DOACs and a higher age continue VKA? (The safety of DOACs in frail elderly is disputed, but a Dutch study[50] is trying to fill the knowledge gap.) This group might benefit less from e-health than other patients[51].

This demographic development will also take a toll on the average quality achieved by thrombosis services. I believe the monitoring of VKA patients should be more intensive. Not necessarily by shortening the dosing interval (the optimal duration has been studied before[52, 53]), but by using TTR, INR variability, or INR extremes to prompt a critical re-evaluation of a patient, possibly even triggering a conversation about whether the current anticoagulant regimen is adequate for this patient.

Choosing the right anticoagulant

New patients

With so many different anticoagulants available, it is difficult to choose. For most new patients, guidelines advise “a DOAC”[16, 54], without recommending a specific one. At first glance, this makes sense. The three factor Xa inhibitors (apixaban, edoxaban and rivaroxaban) only have minuscule differences in pharmacokinetic properties. Many consider studies into a specific factor Xa inhibitor applicable to the whole class, e.g. edoxaban for cancer-associated VTE[55] or rivaroxaban in anti-phospholipid syndrome[56]. One could argue that the longer list of indications for rivaroxaban is probably more a result of more research being done (e.g. for acute coronary syndrome[57] and peripheral[58] or coronary[59] artery disease), than of a truly broader area of application. Therefore, one could wonder whether the availability of more than one factor Xa inhibitor fulfils unmet health need.

Dabigatran forms a separate class of thrombin inhibitors, and has the (emotional) advantage of an available antidote with a proven effect on proxy measures[60] (although the factor Xa inhibitor antidote andexanet alfa[61] is being introduced in the Netherlands). Does dabigatran have other advantages over factor Xa inhibitors? It is difficult to say, as head-to-head comparisons between different DOACs are scant. Network meta-analyses suggest that apixaban has the most favourable safety profile of all DOACs in atrial fibrillation[62] and venous thromboembolism[63, 64]. I am curious to see whether guidelines will prescribe apixaban anytime soon, since their authors will have to weigh other aspects in their decision as well.

Patients currently on VKA

What should patients currently on VKA do? In general, over 300 patients need to use apixaban instead of VKA during one year to prevent one additional ischaemic stroke, and over 100 to prevent one additional ISTH major bleeding[7]. For an individual, these reasons might not be the most compelling. Furthermore, many patients dislike changing medication (experience from the GAIInN study, chapter three). On the other hand, we could not substantiate our hypothesis that patients who perform well on VKA will be harmed by switching them to a DOAC (chapter two). This gives rise to a new theory: that TTR in itself is partly a manifestation

of underlying “frailty.” Indeed, changes in TTR[65] and INR variability[66] are predictors of mortality. But “frailty” is more than physical sickness in the narrow sense; I would also include a predisposition to thrombosis[67] and health literacy. It could be that this underlying frailty causes heterogeneity in the effect of any anticoagulants, but that we happen to observe it in vitamin K antagonists. If that were true, a person’s TTR could predict how well a patient fares on a DOAC.

Increasing experience with DOACs might lead to the identification of subgroups who can better be treated with one anticoagulant than another. Dose reductions of apixaban[68] and rivaroxaban[69] after the initial treatment of VTE are recommended in *Farmacotherapeutisch Kompas*, but it is controversial whether this extends to patients with a recurrent VTE or severe thrombophilia. After the introduction and broad adoption of the DOACs, results of the TRAPS-trial[56] led to a warning not to use DOACs in triple-positive antiphospholipid syndrome. Further data could lead to guidelines increasingly tailored to the individual patient.

New anticoagulants

Current counselling of anticoagulants always weighs the risks of bleeding and thrombosis. This is intuitive; one cannot have the good without the bad. This dilemma might (hopefully) become outdated in the future: inhibition of factors XI or XII seems to be leading to no or only little increased bleeding risk[70]. Augmentation of tissue factor pathway inhibitor could be another target for a future anticoagulant[71] (and inhibition of TFPI might become a prophylactic treatment for haemophilia[72]). This shows that the introduction of the DOACs far from concluded the race towards safe and effective treatment and prevention of blood clots.

Future perspectives for researchers

Research questions

Interventional research comparing DOACs with VKAs will become increasingly unfeasible: with DOACs the uncontroversial first-choice instead of low-intensity VKA, the number of patients on the latter will concentrate in niches. To answer questions in these groups requires multi-centre efforts. Smaller-scale investigators, on the other hand, can excel at refining treatment in daily practice.

Practical adjustments can improve the quality of care. However, it is important to challenge ideas that are apparently true or effective. For instance, in this thesis, I described that multiple subtherapeutic INRs in a row predict poor anticoagulation later on. For many people, that goes without saying. Nevertheless, this research allowed us to quantify just how bad a “streak” is.

However, other “obvious” ideas turned out worse than we initially thought. Some patients are prescribed custom-made tablets to more precisely dose acenocoumarol. When we performed a trial to test the benefit of this strategy, we found that it only had a limited effect on VKA control, that is not worth the risk of medication errors.

Likewise, switching a patient from acenocoumarol to phenprocoumon has been promoted for patients with unstable INRs[73]. We discovered that switching has an important drawback: a transition period where switchers generally do worse than non-switchers.

Healthcare providers can critically evaluate their own practice. How often does a clinic visit lead to changes in clinical regimen or patient behaviour? How much care and counselling do patients value and need? This is difficult to assess, because one ought to avoid the risk of under-treating patients to find a minimal viable threshold. However, as I write this during the lockdown to prevent the spread of SARS-CoV-2, outpatient clinic appointments have largely been rescheduled or replaced by video or telephone consultation. This provides a unique opportunity to investigate the consequences.

Likewise, in this pandemic, the thrombosis services are allowed a peek into their future. What will be the impact of the restriction of the number of INR monitoring locations? What do patients do when they have to travel farther for their monitoring visits? Do they choose to extend their dosing interval themselves? What will be the impact on the quality of anticoagulation control? Will it drive the switch to DOACs? This information will help to prepare for imminent changes in the thrombosis services, that probably cannot sustain the current level of service for a shrinking clientele.

Antithrombotics are among the top causes of medicine-related hospital admission[24]. Prescribing anticoagulants is not easy. Dutch guidelines on VKA dosing comprise over 150 pages[73]. For low molecular weight heparins the branding of nadroparin as either Fraxiparine or Fraxodi/Fraxiparine Forte, depending on the concentration, is unnecessary at best and error-inducing at worst. Even prescribing direct oral anticoagulants is less intuitive than the “fixed dose” suggests: the starting dose depends on the indication (and sometimes requires a few days’ pre-treatment with another drug), and dose reduction rules differ from DOAC to DOAC and depend on time, the indication and concomitant drugs. Inappropriate dosing of DOACs is common[74–76]; up to half of the dose reductions is inappropriate[77]. How should we avert errors? By educating physicians (by writing yet another protocol to be buried on the intranet)? Or can we use technology to make it easier to write the right prescription?

In theory, electronic prescribing systems are well suited to assist physicians in the specifics of prescribing anticoagulants. In practice, however, the systems are incapable to do so: anticoagulation prescriptions are not linked to their indication[78]; physicians have to prescribe a specific tablet instead of an active compound and dose (which complicates dosing advice)[79, 80]; rigid systems force prescribers to use free-text (causing inconsistencies[81] and errors[82]) or cause a delay in treatment[83], and information exchange between systems and healthcare providers is limited[78, 84]. This is not, however, an argument to abolish all electronic prescribing altogether; it is merely an invitation to rise to the high expectations we have of technology in 2020.

I am happy to see that electronic medical record improvements for anticoagulation are being investigated[85–87]. In the UMC Groningen, we collaborated with pharmacists to alert prescribers of the contraindicated combined prescription of heparins and DOACs. Further possibilities include advice on anticoagulation interruption and bridging (based on predicted stroke risk) and automated dose information retrieval from anticoagulation clinics. Researchers can investigate which interventions are helpful, and which induce automation bias[88].

Analysis tools

In this thesis, we applied a simulation technique to appraise a risk score’s clinical usefulness in the absence of the underlying patient data. Many researchers do not want to share “their” data (which has been linked to the quality of statistical analyses and strength of evidence[89]). However, even for those who do, sharing patient-level data could be complicated by an ongoing ethical debate, lengthy and complex legal procedures, and ambiguity in informed consent procedures. Until data sharing becomes commonplace, the simulation technique can support additional inquiries into clinical usefulness.

Other technological advances can enhance the analyses of observational data. Above, I described the vulnerability of propensity score matching to model misspecification (see “Methodological considerations”). In the final phases of my thesis, I came across another technique, called targeted maximum likelihood estimation. It is similar to analyses using propensity scores in that it estimates the treatment effect conditional on variables that predispose a subject to a certain treatment, but promises to be more robust against model misspecifications[90]. Improved statistical methods could improve the inferences we draw from observational data.

Another problem we could address better is the non-independence of an individual’s INR data. The TTR is a “rolling average” in a sense, because it “summarises” INRs over a given period. Any overlap in windows complicates

analyses (see above, “Methodological considerations”). Other subfields of medicine hardly use time-averaged data and thus have not come up with solutions. In the field of time series analyses, the issue is handled by applying various models such as autoregressive integrated moving average (ARIMA) models. However, these models require a fixed period for measurements, which INRs purposefully lack. Although interpolating INRs could create a uniform period, it is unfeasible, because one ought not to interpolate into the future. This issue seems difficult to solve by clinicians, but the advent of “big data,” with the accompanying influx of model-builders, could propel the development of a suitable model.

Conclusion

In this thesis, I elaborated on two questions: Who should switch from a vitamin K antagonist (VKA) to a direct oral anticoagulant (DOAC), and who should continue VKA? What can we do to improve the quality of treatment with VKA for the ones who cannot, or do not want to switch?

Although I have not definitively answered these questions, I have provided you, the reader, with information to better counsel your patients: methods to better predict a patient’s prognosis on VKA, and why we do not recommend against switching a patient with a high TTR to a DOAC. Furthermore, we have evaluated two possible interventions to increase the treatment quality of patients on VKA, that you could (chapter eight) or should not (chapter seven) bring into practice. I am excited to see how future researchers refine anticoagulant care.

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Nederlandse samenvatting

10

Nederlandse samenvatting

Introductie

Bloedstolling is wonderbaarlijk. Het lichaam zorgt ervoor dat het grootste deel van de bloedingen wordt gestelpt, zonder dat we dat merken. Natuurlijk gaat er ook weleens iets mis: soms blijkt dit systeem niet opgewassen tegen het geweld dat de bloedvaten wordt aangedaan (denk hierbij aan operaties en ongelukken, maar ook aan jarenlange hoge bloeddruk) en ontstaat er wel een ernstige bloeding. Ook het tegenovergestelde gebeurt: dat het bloed gaat stollen terwijl het nog gewoon in het bloedvat zit. Dit kan gevaarlijk zijn. Voorbeelden hiervan zijn een hartinfarct, een herseninfarct en een trombosebeen. Om dat te voorkomen, gebruiken veel Nederlanders bloedverdunners (in medische termen: antistollingsmiddelen). In de afgelopen tien jaar zijn er nieuwe bloedverdunners beschikbaar gekomen. Artsen kunnen nu uit meer medicijnen kiezen voor hun patiënten. In dit proefschrift heb ik onderzocht wat de beste bloedverdunner is voor welke patiënt.

Om antistollingsmiddelen te begrijpen, moeten we eerst weten hoe het bloed normaal stolt. Het lichaam heeft drie “systemen” om ons te beschermen tegen bloedingen. Als eerste is er de wand van de bloedvaten, die zorgt dat het bloed in het bloedvat blijft. Als de vaatwand beschadigd raakt, knijpt het bloedvat samen om het bloed toch zo veel mogelijk binnen te houden. Als het bloed in contact komt met diepere lagen van de bloedvatwand, treden de andere twee systemen in werking. Het eerste systeem bestaat uit de bloedplaatjes, die met bepaalde eiwitten gaan vastzitten aan de wond. De bloedplaatjes vormen een voorlopig bloedstolsel door aan elkaar te plakken. Het tweede systeem vormt een verstevigend net rondom het voorlopig bloedstolsel. Dat net wordt opgebouwd uit een eiwit dat fibrine heet. De aanmaak van fibrine is het resultaat van een opeenvolging van chemische reacties tussen stollingsfactoren.

Met medicijnen kunnen we het bloed minder goed laten stollen, om ongewenste bloedstolling (trombose) te voorkomen. Dat kunnen we doen op het systeem van de bloedplaatjes, maar in dit proefschrift gaat het vooral over het tweede systeem; van het verstevigende net. We hebben daarvoor twee groepen medicijnen: vitamine-K-antagonisten (VKA's) en directe orale anticoagulantia (DOAC's; de nieuwe medicijnen van de inleiding). VKA's zorgen ervoor dat er minder stollingsfactoren worden aangemaakt; DOAC's zorgen dat een specifieke stollingsfactor niet goed werkt. Beide manieren zorgen dat het bloed minder goed kan stollen; dit beschermt tegen trombose maar vergroot de kans op bloedingen.

Vitamine-K-antagonisten worden al decennialang in Nederland gebruikt. Het zijn ingewikkelde medicijnen om te gebruiken: de dosis die iemand nodig heeft verschilt van persoon tot persoon. Ook voor dezelfde persoon kan de dosering in de tijd sterk wisselen. Trombosediensten begeleiden de behandeling met VKA's: ze meten het antistollingseffect in het bloed en passen hierop de dosis aan. Het antistollingseffect van VKA's wordt uitgedrukt in de *international normalised ratio*, beter bekend als de INR, waarbij een hoge waarde betekent dat het bloed minder goed kan stollen. Om het voordeel (voorkómen van trombose) en het nadeel (risico op bloedingen) in balans te houden, mikken de trombosediensten op een bepaalde INR-bandbreedte of -streefgebied.

Het lukt niet altijd om de INR binnen het streefgebied te krijgen of houden. Als de gezondheidstoestand van patiënten verandert, ze andere medicijnen krijgen, of heel anders gaan eten, heeft dat invloed op de INR. Het is belangrijk dat de INR zo vaak mogelijk binnen het streefgebied ligt: het netto-voordeel van de behandeling is dan het grootst. We kunnen berekenen hoe groot het aandeel van de tijd is dat de INR binnen het streefgebied ligt; we noemen dat de *time in therapeutic range* (TTR). We kunnen ook kijken naar de mate waarin de INR schommelt. Het is het beste als de INR niet te variabel is.

De DOAC's zijn makkelijker in het gebruik: een patiënt gebruikt een vaste dosis, één of twee keer per dag. DOAC's zijn daarbij gemiddeld genomen net zo goed als VKA's in het voorkomen van trombose. Ze zorgen ook voor minder bloedingen, en worden daarom aangeraden voor vrijwel alle patiënten die nu boezemfibrilleren (een bepaalde hartritmestoornis), een trombosebeen of een longembolie krijgen.

Maar wat moeten de patiënten die nu een VKA gebruiken doen? Kunnen ze beter overstappen op een DOAC, of niet? En hoe -overwegende dat de uitkomsten van behandelingen afhankelijk van de TTR sterk verschillen- beïnvloedt de TTR deze keuzes? Hoe kunnen we ook patiënten die niet over kunnen stappen op een DOAC een betere behandeling geven? In dit proefschrift beschrijf ik de onderzoeken die ik heb gedaan om deze vragen beter te kunnen beantwoorden.

Een behandeling kiezen voor patiënten met een goede TTR

Bloedingen en tromboses vergeleken

Gemiddeld genomen zijn DOAC's minstens zo goed als VKA's bij boezemfibrilleren. De uitkomsten van behandeling met VKA variëren sterk afhankelijk van de bereikte TTR: er treden beduidend minder bloedingen en tromboses op bij patiënten met een hoge TTR, dan bij patiënten met een lage TTR. De idee van de directe remming van stollingsfactoren met DOAC's is dat die veel stabielier verloopt en er dus geen concept bestaat dat analoog is aan de TTR. Hierdoor rijst de vraag of de gelijkwaardigheid (beter gezegd: non-inferioriteit) van DOAC's misschien bestaat door een sterk voordeel ten opzichte van een VKA-behandeling met slechte TTR, dat een nadeel ten opzichte van een VKA-behandeling met goede TTR verbloemt.

Om deze hypothese te onderzoeken hebben we het *Goede Antistolling In noord-Nederland* (GAINN) onderzoek uitgevoerd. 241 patiënten die heel goed waren ingesteld op een VKA (hoge TTR én geen bloeding of trombose tijdens de behandeling) hebben meegedaan. Zij werden door het toeval in twee groepen verdeeld: de ene helft ging door met hun huidige behandeling; de andere helft stapte over op een DOAC. We hebben de deelnemers voor een jaar gevolgd, en gekeken hoeveel mensen overleden of een trombose of (ernstige) bloeding kregen.

In beide groepen bleken deze uitkomsten samen even vaak voor te komen. Hiermee vonden we dus geen ondersteuning voor onze hypothese. Dit betekent dat we een patiënt met een hoge TTR dus niet hoeven af te raden over te stappen op een DOAC.

Kwaliteit van leven vergeleken

Patiënten die een VKA gebruiken, moeten geregeld bloed laten prikken om hun INR te bepalen zodat de dosis aangepast kan worden. Bij de DOAC's zijn INR-bepalingen en dosisaanpassingen passé. Dit kan voor- en nadelen hebben: sommige patiënten geeft het meer vrijheid, maar andere patiënten worden onzeker van het gebrek aan controle, of missen de trombosedienst als aanspreekpunt bij vragen. Patiënten met een hoge TTR hoeven minder vaak hun INR te laten monitoren. De INR-controles zullen voor hen dus een kleinere belasting zijn. Misschien valt het voordeel van een DOAC hierdoor weg, of valt het anders uit. In hoofdstuk 3 hebben we de effecten van de antistollingsbehandeling op de kwaliteit van leven beschreven.

Bij de 241 deelnemers aan de GAIInN-studie (zie hierboven) hebben we vragenlijsten afgenomen: aan het begin van de studie, voor ze wisten welk medicijn ze toegewezen zouden krijgen; na een halfjaar; en na een jaar. In de vragenlijsten vroegen we naar hun gezondheidsgerelateerde kwaliteit van leven, en naar aspecten van kwaliteit van leven specifiek voor behandeling met antistollingsmiddelen. Alle onderdelen van de vragenlijsten worden gescoord van 0 (heel slecht) tot 100 (heel goed).

Patiënten bleken in het begin al erg tevreden met hun antistollingsbehandeling. Bij de mensen die overstapten naar een DOAC verbeterde dit nog iets verder: ze vonden de nieuwe behandeling gemiddeld genomen iets handiger, en waren gemiddeld tevredener. Maar gemiddeldes zeggen niet alles: voor de meeste mensen waren de verschillen slechts klein. Er waren in beide groepen ook mensen die wel wezenlijk tevredener werden. Als een deelnemer overstapt naar een DOAC, heeft hij of zij een 5% grotere kans om in het algemeen wezenlijk tevredener te worden. Dit percentage is groter bij mensen die aan het begin van de studie niet helemaal tevreden waren met VKA: 13%.

Helaas brengt de overstap naar een ander medicijn ook risico's met zich mee. Een aantal patiënten kreeg klachten die zij toeschreven aan de overstap naar een DOAC. Vijf van de 121 patiënten stapten om die reden terug over naar een VKA; vier patiënten hadden daarvoor een andere, niet-medische reden. Als we hieruit opmaken dat deze mensen ook minder tevreden waren met een DOAC, blijkt de extra kans om ontevredener te worden 8%. In de groep die vooraf niet volledig tevreden was met VKA was deze kans kleiner: 4%.

Aan het eind van de studie wilden de meeste mensen die toen nog een DOAC gebruikten daarmee door blijven gaan. Het zou zo kunnen zijn dat een DOAC een fijnere optie voor hen was (ondanks dat dit er qua scores op de vragenlijsten niet echt uitkwam), maar het zou ook kunnen dat mensen het overstappen van het ene naar het andere medicijn vervelend vinden. Uit dit onderdeel van de GAIInN-studie concluderen we dat een veronderstelde winst in kwaliteit van leven geen goede reden is om alle patiënten met een hoge TTR te adviseren om over te stappen op een DOAC. Patiënten die niet tevreden zijn op VKA hebben meer te winnen bij de overstap naar een DOAC.

Voorspellen van kwaliteit van de behandeling met VKA

In het verleden behaalde resultaten bieden geen garantie voor de toekomst. Toch gingen we daar impliciet van uit, toen we de GAIN-studie deden: we dachten dat patiënten die voorheen goed ingesteld waren, dat ook zouden blijven. Ook de richtlijnen maken zich hier schuldig aan: ze adviseren om patiënten met een slechte TTR om te zetten op een DOAC. Maar de keuzes die we met een patiënt maken, moeten gericht zijn op de toekomst; we kunnen het verleden tenslotte niet meer veranderen. Ik heb daarom onderzocht in hoeverre we de TTR kunnen voorspellen, zodat we daarop de behandeling kunnen aanpassen.

Voorspellen voor start van de behandeling: de SAME-TT₂R₂-score

In de Europese richtlijnen werd een makkelijk hulpmiddel genoemd om de TTR van een patiënt te kunnen voorspellen: de SAME-TT₂R₂-score. Bij dit hulpmiddel worden punten gegeven voor bepaalde patiëntkarakteristieken (geslacht, leeftijd, gebruik van bepaalde medicijnen, aandoeningen waaraan een patiënt lijdt, roken, en etniciteit). De auteurs beweerden dat hiermee de TTR van een patiënt al vóór de start van de behandeling goed ingeschat kan worden: laag of hoog.

In hoofdstuk 4 hebben we het klinisch nut van de SAME-TT₂R₂-score onderzocht. We hebben alle toen beschikbare onderzoeken over de score opgezocht. We wilden deze samenvoegen om daarmee een beter beeld te krijgen (een meta-analyse uitvoeren). Dat kon niet direct, omdat de studies verschilden in hun opzet. Met een nieuwe simulatietechniek konden we dit harmoniseren, en zo toch de studies samenvoegen.

De SAME-TT₂R₂-score deelt patiënten in in twee groepen: patiënten met een hoge kans op een slechte TTR, en die met een kleine kans op een slechte TTR. Patiënten met een hoge SAME-TT₂R₂-score hadden gemiddeld genomen een lagere TTR. Er zat echter veel overlap tussen de TTR's die de twee groepen behaalden. Hierdoor verschilde de kans om een TTR $\geq 70\%$ te krijgen nauwelijks tussen de twee groepen. De score voegt dus weinig toe, en ik zou hem niet adviseren in de medische praktijk.

Voorspellen tijdens de behandeling

In hoofdstuk 5 hebben we gekeken in hoeverre een vorige TTR een toekomstige TTR voorspelt. Hiervoor konden we putten uit de schat aan gegevens van Certe Trombosedienst. Voor ongeveer 18.000 patiënten vergeleken we de TTR over de drie maanden voor en de drie maanden na een bepaald moment. Datzelfde hebben we gedaan met periodes van zes maanden en een jaar. We vonden dat

patiënten met een hoge TTR gemiddeld genomen een hogere TTR hielden. Dit verband was echter vrij zwak.

We hebben ook gekeken wat de kans is dat een patiënt een TTR $\geq 70\%$ houdt, afhankelijk van de TTR daarvoor. Om daarop 50% kans te hebben, moet een patiënt voorheen een TTR van 70% hebben. Patiënten met een hogere TTR hebben meer kans, en patiënten met een lagere TTR minder kans op een adequate TTR. Patiënten en hun artsen krijgen zo een beter idee wat ze kunnen verwachten, en kunnen hierop keuzes voor bepaalde behandelingen baseren.

Een nadeel van de TTR is dat deze niet makkelijk uit het hoofd te berekenen is. Dat beperkt het gebruik hiervan in de spreekkamer. In hoofdstuk 6 hebben we onderzocht of er een makkelijkere manier is om een slechte TTR ($<45\%$) te kunnen voorspellen. Onze onderzoeksgroep had al eerder aangetoond dat als iemand één keer een extreem hoge INR had ($\text{INR} \geq 8$), dit negatieve effecten had op de toekomstige TTR. In navolging daarvan hebben wij gekeken of dit ook geldt voor een te lage INR. Omdat een lage INR soms gewenst is (bijvoorbeeld vanwege een operatie), hebben we gekeken naar meerdere opeenvolgende INR's < 2 . Als een patiënt meer dan 3x achter elkaar een te lage INR had, bleek dit de kans op een slechte TTR te vergroten (odds ratio van ongeveer 3). De voorspellende waarde nam toe naarmate een patiënt vaker achter elkaar een te lage INR had. Dit is dus een makkelijke manier om patiënten die risico lopen op een slechte kwaliteit van antistolling te identificeren, in de hoop dit te kunnen behandelen.

Verbeteren van de kwaliteit van de behandeling met vitamine-K-antagonisten

Het kunnen voorspellen van de kwaliteit van behandeling met VKA is belangrijk, omdat hierop het beleid kan worden aangepast. Voor veel patiënten is de overstap naar een DOAC bijvoorbeeld het overwegen waard. Sommige patiënten komen hiervoor niet in aanmerking, bijvoorbeeld omdat ze medicijnen gebruiken die niet samengaan met een DOAC, hun nieren slecht werken, of ze een bepaald soort nieuwe hartklep hebben gekregen. Om te zorgen dat ook deze patiënten een zo goed mogelijke behandeling krijgen, hebben we onderzocht wat we kunnen verbeteren aan een behandeling met vitamine-K-antagonisten. We hebben hiervoor gekeken naar het preciezer doseren van acenocoumarol, en naar het overstappen op een langer werkende vitamine-K-antagonist.

Preciezer doseren

Acenocoumarol is in de regio Groningen de meest gebruikte VKA. Acenocoumarol bestaat alleen in tabletten van 1 milligram, die niet betrouwbaar in gelijke stukjes

gedeeld kunnen worden. Dat leidt ertoe dat patiënten die gemiddeld minder dan 1 mg aan acenocoumarol nodig hebben op sommige dagen geen acenocoumarol hoeven in te nemen. Dat kan problematisch zijn, omdat acenocoumarol een relatief korte werkingsduur heeft. Uit eerder onderzoek bleek dat patiënten naarmate hun leeftijd toeneemt gemiddeld genomen een lagere dosis nodig hebben. Tegelijkertijd gaat de bereikte TTR omlaag, en neemt de INR-variabiliteit toe. We vermoedden dat dit samenhangt met de relatief grote dagelijkse variatie in dosering van de acenocoumarol (vergelijk bijvoorbeeld een schema van 2-1-2-1 met 7-6-7-6).

Mogelijk kunnen we de kwaliteit verbeteren door acenocoumarol preciezer te doseren: bijvoorbeeld per halve milligram. Dit hebben we onderzocht in 80 patiënten van 80 jaar of ouder, met een lage dosis acenocoumarol (zie hoofdstuk 7). Zij werden door het toeval in twee groepen verdeeld: de ene groep kreeg de standaardbehandeling, de andere een behandeling waarbij we de acenocoumarol per 0,5 mg doseerden. Hiervoor hebben we speciale tabletten laten maken. Patiënten konden hierdoor een minder sterk wisselend schema krijgen van bijvoorbeeld 3-3-3-3 tabletten (dus 1,5-1,5-1,5-1,5 mg acenocoumarol) in plaats van 2-1-2-1.

We zagen dat hierdoor de TTR iets verbeterde. Het was de bedoeling ook naar de INR-variabiliteit te kijken, maar dit bleek door een ongelukkig toeval niet mogelijk: de beide behandelingsgroepen waren te verschillend in INR-variabiliteit voor het begin van de studie. Een nadeel van de studiebehandeling was dat dit de kans op fouten vergrootte: in het ziekenhuis kregen sommige patiënten de verkeerde dosis, of patiënten gebruikten de verkeerde tabletten. Patiënten waren ook minder tevreden over de behandeling; mogelijk omdat ze meer tabletten moesten innemen, of omdat de studiemedicatie onhandig verpakt was.

Een langer werkend medicijn

Naast de eerdergenoemde poging om het doseerschema stabiel te maken, kunnen we ook een andere VKA gebruiken, die inherent meer stabiel is. Fenprocoumon is een andere VKA die in Nederland beschikbaar is. De halfwaardetijd van fenprocoumon is veel langer dan die van acenocoumarol: gemiddeld 160 uur in plaats van 8-11 uur bij acenocoumarol. Anders gezegd: fenprocoumon heeft een langere werkingsduur dan acenocoumarol. Hoewel acenocoumarol en fenprocoumon eerder vergeleken zijn op TTR en INR-variabiliteit, was nog niet duidelijk hoe goed de overstap van acenocoumarol naar fenprocoumon uitwerkte.

In samenwerking met de trombosedienst uit Maastricht hebben we de gegevens geanalyseerd van patiënten die overgestapt waren van acenocoumarol naar

fenprocoumon. We konden gegevens van 491 patiënten gebruiken. Zij waren om verschillende redenen overgestapt: bijvoorbeeld omdat ze een lage dosis acenocoumarol nodig hadden, of een slechte TTR. Over het algemeen verbeterden de TTR en de INR-variabiliteit van de patiënten na de overstap.

Daarmee is echter nog niet bewezen dat de stijging van de TTR het gevolg is van de overstap. Het zou ook kunnen zijn dat we eigenlijk kijken naar “regressie naar het gemiddelde,” waarbij de TTR vanzelf opkrabbelt uit het dal.

We hebben het effect van de overstap proberen te isoleren, door de andere bijna 30.000 patiënten als potentiële controlepatiënten te gebruiken. Hieruit selecteerden we de patiënten die erg leken op de patiënten die overgestapt waren, maar zelf dus niet overgestapt waren. Uit de vergelijking met deze controlegroep bleek dat de overgestapte patiënten het initieel juist slechter deden. Na de overgangsperiode ging het echter wel beter.

Dit ondersteunt onze hypothese dat de overstap naar fenprocoumon de kwaliteit van de behandeling kan verbeteren. Vervolgonderzoek kan zich richten op hoe we de overgangsperiode kunnen verkorten, omdat deze nu nog gepaard gaat met een hoger risico op bloedingen. In de tussentijd kunnen de patiënt en de arts samen de afweging maken of de uiteindelijke verbetering in kwaliteit het waard is om af te wijken van de lokale standaard, met een risico op medicatiefouten van dien.

Conclusie

Toen ik begon met mijn promotie-traject was men in Nederland nog terughoudend met het voorschrijven van DOAC's. Snel daarna begonnen de DOAC's echter aan een razendsnelle opmars. Inmiddels gebruiken meer patiënten een DOAC dan een VKA. Uit het GAIInN-onderzoek weten we dat we hiertegen geen bezwaar hoeven te hebben, in ieder geval niet omdat de TTR van een patiënt voorheen hoog was.

Aan de hand van de resultaten van onderzoek uit dit proefschrift kunnen zorgverleners een betere inschatting maken van de te verwachten TTR van een patiënt. Hiermee kunnen ze samen met de patiënten een geïnformeerd besluit nemen over hun behandeling. Gaat de patiënt overstappen op een DOAC? Als hij of zij dat niet wil of kan, wat voor mogelijkheden zijn er dan? Nu weten we ook of preciezer doseren of overstappen op een langwerkend medicijn zin heeft.

Appendices

A

Online supplements

To protect the environment, appendices to chapters 2–8 are not included in the printed thesis but are available online. A list with all appendices by chapter is available below.

Choosing between continuing VKA or switching to a DOAC in currently well-controlled patients on VKA for atrial fibrillation: a randomised controlled trial (GAINN)

All appendices are available from <https://www.jhavanmiert.nl/dissertation>; the study protocol can be accessed via the British Journal of Haematology via doi:10.1111/bjh.15856 (free access).

- Study protocol
- Outcome definitions
- Clinical endpoints in the per-protocol analysis
- Serious adverse events
- Sex differences in outcomes in the study

Quality of life after switching from well-controlled vitamin K antagonist to direct oral anticoagulant: little to GAINN

All appendices are available from <https://www.jhavanmiert.nl/dissertation> and via Thrombosis Research via doi:10.1016/j.thromres.2020.04.007 (open access)

- Study protocol
- Baseline values for excluded SF-36 scales

Clinical usefulness of the SAME-TT₂R₂ score: a systematic review and simulation meta-analysis

All appendices are available from <https://www.jhavanmiert.nl/dissertation> and via PLOS ONE via doi:10.1371/journal.pone.0194208 (open access). The software to reproduce the analyses is available on GitHub via doi:10.5281/zenodo.1187035.

- PRISMA checklist
- Table S1. Quality assessment of studies
- Table S2. Results from individual studies
- Table S3. Sensitivity analyses
- Figure S1. Bland Altman plot
- Figure S2. Forest plots showing sensitivity, specificity and power of separation (PSEP) of the SAME-TT₂R₂ score
- Figure S3. Sensitivity analyses

Is the time in therapeutic range on coumarins predicted by previous time in therapeutic range?

All appendices are available from <https://www.jhavanmiert.nl/dissertation> and via Research and Practice in Thrombosis and Haemostasis via doi:10.1002/rth2.12328 (open access).

- Table S1. Patient characteristics by baseline TTR stratum
- Figure S1. Median (interquartile range) of TTR by baseline TTR group, over time, in target range 2.5-3.5
- Figure S2. Probabilities to obtain a time in the therapeutic range (TTR) > 70%, conditional on baseline TTR, in target range 2.5-3.5

An easy-to-use tool to flag patients at risk of poor INR control: a streak of subtherapeutic INRs

This article has no supplements.

More precise dosing of acenocoumarol for better control in patients aged above 80 years, a randomised controlled pilot study

The study protocol is available from <https://www.jhavanmiert.nl/dissertation> and via Thrombosis Research via doi:10.1016/j.thromres.2020.10.018 (currently not open access).

Effect of switching from acenocoumarol to phenprocoumon on time in therapeutic range and INR variability: a cohort study

All appendices are available from <https://www.jhavanmiert.nl/dissertation> and via PLOS ONE via doi:10.1371/journal.pone.0235639 (open access). The software to reproduce the analyses is available on GitHub via doi:10.5281/zenodo.3831170.

- S1 Table. Patient characteristics from all potential controls.
- S2 Table. Direct effect of switching in subgroups.
- S3 Table. Coefficients from logistic regression used in the propensity score matching.
- S4 Table. Patient characteristics from switchers and selected non-switchers.
- S5 Table. Patient characteristics from switchers and selected non-switchers in subgroups.
- S6 Table. Effect of switching from acenocoumarol to phenprocoumon, compared with non-switchers.

Dankwoord

“The combined results of several people working together is often much more effective than could be that of an individual scientist working alone.”

(John Bardeen, natuurkundige en tweevoudig Nobelprijswinnaar)

To respect the privacy of the persons mentioned in this acknowledgment section, these pages are left blank in the online version of my thesis.

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Last but not least, wil ik graag alle patiënten bedanken die hebben deelgenomen aan de onderzoeken beschreven in dit proefschrift.

About the author

I, Jasper van Miert, was born on November 23rd in Eindhoven, the Netherlands. I graduated from Christiaan Huygens College in Eindhoven in 2009, and decided to study Medicine at Maastricht University.

During my bachelor's, I was a CPR instructor (*reanimatie-instructeur*) with Taskforce QRS. Taskforce QRS trained thousands of high school students, aiming to improve survival and outcomes after an out-of-hospital cardiac arrest. I was also part of a committee that organised a scientific conference for medical students: the Maastricht Medical Students Research Conference and Clinical Investigator Science Symposium (MMSRC-CISS, which was later rebranded as Mosa Conference). Maybe this would be the start of my academic career? After I obtained my bachelor degree, I did a holiday internship in Cameroon.

During my master's, I did internships in several hospitals in the Netherlands: Maastricht UMC+, Máxima Medisch Centrum, Catharina Ziekenhuis Eindhoven, Orbis Medisch Centrum and Atrium Medisch Centrum Parkstad (now jointly known as Zuyderland Medisch Centrum)). In addition, I did rotations with smaller healthcare providers (Huisartsenpraktijk Buysrogge in Maastricht, Mondriaan in Maastricht and ARBO Unie in Eindhoven). I did two internships abroad: one in Belgium (Oogkliniek Sint-Truiden, Sint-Truiden) and one in South Africa (Steve Biko Academic Hospital, University of Pretoria, Pretoria).

My experiences in South Africa seeded my later involvement in Universities Allied for Essential Medicines, a student organisation that promotes access to medicines and innovations by changing norms and practices around academic licensing and patenting. I was an active member from 2014 to 2019. As UAEM members, we organised, among other things, the Access to Medicines Week (an awareness campaign) and the Transparency Campaign (aiming to have the university endorse transparency principles for its research). Maastricht University and UAEM Maastricht have signed a Socially Responsible Research and Licensing policy; the University of Groningen has yet to do so.

In the last year of my master's, I did two big internships. First, a research internship about heart rate variability as a possible predictor for sudden cardiac death in three families with a hereditary abnormality in a sodium ion channel, under supervision of dr. R.M.A. ter Bekke and dr. P.G. Volders, cardiologists in the Maastricht University Medical Centre. This intriguing topic sparked my interest in scientific research.

My second big internship was in the Internal Medicine department of Orbis Medisch Centrum. I did rotations in the emergency department and the oncology and gastroenterology wards. I loved these internships, and graduated with distinction.

With my newly obtained MD in my pocket, I wanted to pursue a PhD. However, I felt it would be a shame to abandon the clinical side of the hospital altogether. Therefore, I was thrilled when I stumbled upon a job offer for a PhD student who would also work in the outpatient clinic. However, there was one problem... this opportunity was in Groningen, the farthest Dutch place from Maastricht. I am glad I have taken this leap of faith, that resulted in this thesis.

In June 2020, I started my Internal Medicine training. I am currently working in the Martini Hospital in Groningen.

List of publications

- **van Miert JHA**, Hop H, Borjas-Howard JF, Meijer K. A milder clinical course for severe hemophilia B: a true or biased effect? *Haematologica*. 2016 Jun;101(6):e266.
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- **van Miert J**, Piersma-Wichers M, Meijer K. Directe orale antistollingsmiddelen ook in Nederland een goede keus. *Huisarts en wetenschap*. 2019 Aug 24;62(8):54–54.
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- **van Miert JHA**, Kooistra HAM, Veeger NJGM, Westerterp A, Piersma-Wichers M, Meijer K. Choosing between continuing vitamin K antagonists (VKA) or switching to a direct oral anticoagulant in currently well-controlled patients on VKA for atrial fibrillation: a randomised controlled trial (GAIInN). *British Journal of Haematology*. 2019 Aug 6;186(3):e21–3.
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- **van Miert JHA**, Veeger NJGM, ten Cate-Hoek AJ, Piersma-Wichers M, Meijer K. Effect of switching from acenocoumarol to phenprocoumon on time in therapeutic range and INR variability: A cohort study. *PLOS ONE*. 2020 Jul 10;15(7):e0235639.

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