Warfarin treatment quality in stroke prevention

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–Det var bättre förr!

Ju förr desto bättre…

Ville Sjögren

List of original papers

This doctoral thesis is based on the following papers, which will be referred to by their Roman numerals.

I. **Bjorck F**, Sanden P, Renlund H, Svensson PJ, Sjalander A. Warfarin treatment quality is consistently high in both anticoagulation clinics and primary care setting in Sweden. Thrombosis research. 2015;136:216-20.

II. **Bjorck F**, Renlund H, Svensson PJ, Sjalander A. Warfarin persistence among stroke patients with atrial fibrillation. Thrombosis research. 2015;136:744-8.

III. **Bjorck F**, Ek A, Johansson L, Sjalander A. Warfarin persistence among atrial fibrillation patients – why is treatment ended? Cardiovascular Therapeutics. 2016 Aug 27. doi: 10.1111/1755-5922.12224. [Epub ahead of print].

IV. **Bjorck F**, Renlund H, Lip GYH, Wester P, Svensson PJ, Sjalander A. Outcomes in a warfarin treated population with atrial fibrillation. JAMA Cardiology. 2016;1(2):172-180.

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Abstract

Background

Ischemic stroke is a serious condition often associated to presence of atrial fibrillation (AF). Use of anticoagulants for AF patients greatly reduces the risk of stroke. Warfarin is the most commonly used anticoagulant in Sweden. The aim of this thesis was to study the impact of warfarin treatment quality in Swedish stroke prevention.

Methods

Study I, II and IV were relatively large multicentre, retrospective, cohort studies based on Swedish registries, especially AuriculA, a quality register for AF and anticoagulation. Background data as well as bleeding and thromboembolic complications were retrieved from the National Patient Register. The Cause of Death Register was used in study II and IV. The Swedish Prescribed Drug Register was used in study IV, for data on concomitant acetylsalicylic acid (ASA) use. Study period was January 1, 2006, to December 31, 2011.

Study III enrolled all warfarin treated AF patients in Sundsvall, registered in AuriculA on January 1, 2010. This smaller cohort was followed until discontinuation or study-stop December 31, 2013. All used data were collected from each patient's medical record.

Results

The annual risk of major bleedings and thromboembolic events for warfarin treated patients, including all different indications for warfarin, was relatively low (2.24% and 2.66%), with incidence of intracranial bleeding of 0.37% per treatment year. The overall mean time in therapeutic range (TTR) was 76.5%. Patients started on warfarin due to AF had a mean TTR of 68.6%, with an annual risk of major bleeding and thromboembolic events of 2.23% and 2.95%, and with 0.44% annual risk of intracranial bleeding. No significant differences in overall complications were found when comparing treatment monitored in anticoagulation clinics (ACC) with treatment

monitored in primary health care centers (PHCC). There were significantly increased risk of both overall major bleedings and thromboembolic events for those warfarin treated AF patients receiving additional ASA treatment, having individual TTR (iTTR) below 70%, or having high international normalized ratio (INR) variability. AF patients with low INR variability had generally lower complication rates, compared with patients with high INR variability. There were however no alteration on cumulative incidence of complications due to INR variability, for AF patients with iTTR ≥70%.

The overall proportion of persistence to warfarin treatment for stroke patients with AF was found to be 0.69 after 2 years treatment and 0.47 after 5 years. Stroke patients with diagnosed dementia at baseline were more than two-times likely of discontinuing warfarin than others. Excessive alcohol use, chronic obstructive pulmonary disease, cancer and chronic heart failure were baseline diagnoses each associated with over 20% increased risk of treatment discontinuation. Lower persistence to treatment was linked to increasing start-age and CHA_2DS_2-VASc scores.

As documented reasons for warfarin treatment discontinuation in AF patients, we found regained sinus rhythm as the most common addressed cause (31.2%), followed by problematic monitoring and bleedings. We estimated that only half (49.5%) of the treatment discontinuations were clinically well motivated.

Conclusions

Quality of Swedish warfarin treatment in initiated stroke prevention is high, with generally low rates of complications and high TTRs, no matter treatment in ACC or PHCC, including high long time persistence to warfarin in secondary stroke prevention.

For better outcome in future warfarin stroke prophylactic treatment clinicians should aim for iTTRs above 70%, avoid additional ASA therapy, support fragile patients like those with excessive alcohol use and dementia, and base decisions on treatment discontinuations on solid medical arguments.

Abbreviations

ACC	Anticoagulation clinics
AF	Atrial fibrillation
ASA	Acetylsalicylic acid
CDR	The cause of death register
CHA_2DS_2-VASc	Risk score for patients with atrial fibrillation: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA/thromboembolism, vascular disease, age 65–74 years, sex category
$CHADS_2$	Risk score for patients with atrial fibrillation: Congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke/TIA
CHF	Chronic heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
HR	Hazard ratio
ICD-10	International Classification of Disease, 10th edition
INR	International normalized ratio
NOACs	Novel oral anticoagulants, Non-VKA oral anticoagulants
NPR	The Swedish national patient register

PDR	The Swedish prescribed drug register
PHCC	Primary health care centers
TIA	Transient ischemic attack
TTR	Time in therapeutic range
VKA	Vitamin K antagonist

Svensk sammanfattning

Bakgrund

Hjärninfarkt är ett allvarligt tillstånd som många gånger är kopplad till förekomst av förmaksflimmer. Behandling med antikogulantia vid förmaksflimmer kan kraftigt reducera risken för stroke. Warfarin är den mest använda antikoagulantian i Sverige. Syftet med avhandlingen var att studera och klarlägga betydelsen av behandlingskvalitet vid svensk strokeförebyggande warfarinbehandling.

Metoder

Studie I, II och IV utgjordes av tämligen stora retrospektiva multicentre kohortstudier baserade på svenska register, med tonvikt på AuriculA, ett kvalitetsregister för förmaksflimmer och antikoagulation. Bakgrundsdata samt blödnings- och tromboemboliska komplikationer extraherades från patientregistret. Dödsorsaksregistret användes i studie II och IV. Läkemedelsregistret användes i studie IV, för data om samtidig behandling med acetylsalicylsyra. Studieperioden var från och med första januari 2006 till och med sista december 2011.

Studie III omfattade alla warfarinbehandlade förmaksflimmerpatienter i Sundsvall registrerade i AuriculA den första januari 2010. Den här mindre kohorten följdes till behandlingsavslut eller till studiens slut den sista december 2013. All använd data insamlades från varje patients medicinska journaler.

Resultat

Den årliga risken för blödning och tromboembolisk händelse, inkluderande alla möjliga indikationer för warfarinbehandling, var relativt låg (2.24 % respektive 2.66 %), med 0.37 % incidens för intracerebral blödning per behandlingsår. Medelvärdet för den totala tiden i terapeutisk nivå (TTR) var 76.5 %. Patienter som påbörjade warfarinbehandling på grund av förmaksflimmer hade medel-TTR 68.6 %, med en årlig risk för blödning och tromboembolisk händelse av 2.23 % respektive 2.95 %, samt 0.44 % årlig

risk för intracerebral blödning. Ingen statistisk signifikant skillnad i övergripande komplikationsfrekvenser påvisades mellan behandlingar styrda via antikoagulationsmottagningar eller via primärvårdsenheter. Det fanns en signifikant ökad risk för både allvarliga blödningar och tromboemboliska händelser hos de warfarinbehandlade förmaksflimmerpatienter som; erhöll samtidig förskrivning av acetylsalicylsyra, hade individuella TTR (iTTR) lägre än 70 %, eller hade hög variabilitet av den internationella normaliserade kvoten (INR). Patienter med låg INR variabilitet hade generellt lägre komplikationsfrekvens, jämfört med patienter med hög INR variabilitet. Hos förmaksflimmerpatienter med iTTR lika med eller högre än 70 % påverkades dock inte de kumulativa komplikationsincidenserna signifikant av variabeln INR variabilitet.

För strokepatienter med förmaksflimmer var andelen som kvarstod på initierad warfarinbehandling 0.69 efter 2 års behandling och 0.47 efter 5 år. Strokepatienter med diagnostiserad demens vid behandlingsstart hade jämfört med andra patienter över dubbelt så stor sannolikhet att avbryta warfarinbehandlingen i förtid. Alkoholöverkonsumtion, kronisk obstruktiv lungsjukdom, cancer eller hjärtsvikt vid behandlingsstart associerades vardera med över 20 % ökad risk för förtida behandlingsavslut. Lägre uthållighet till behandling sågs i takt med stigande ålder och CHA_2DS_2-VASc poäng vid behandlingsstart.

Den vanligaste dokumenterade orsaken till avslut av warfarinbehandling hos förmaksflimmerpatienter var återställd sinusrytm (31.2 %), följt av problematisk monitorering och blödningar. Vi uppskattade att bara hälften (49.5 %) av dessa behandlingsavslut var kliniskt väl motiverade.

Konklusion

Kvaliteten av svensk warfarinbehandling vid initierad strokeprevention är hög, med generellt låga komplikationsfrekvenser och höga TTR-nivåer, oavsett behandling via koagulationsmottagningar eller primärvårdsenheter,

inkluderande en stor andel av patienter som kvarstår på behandling vid långtidsuppföljning.

För bättre utfall vid framtida warfarinbehandling i strokepreventivt syfte bör behandlande läkare sträva mot iTTR över 70 %, undvika samtidig utskrivning av acetylsalicylsyra, stödja sköra patientgrupper som de med alkoholöverkonsumtion och demens, och basera eventuella beslut om behandlingsavslut på solida medicinska argument.

Introduction

Stroke

Epidemiology

Stroke is a common and serious disease. Annually approximately 26 000 persons in Sweden suffers a stroke, a disease that is the leading cause of adult disability [1-4]. Even though stroke can affect all ages, it's most common among the elderly with a mean-age of 76 years. The overall incidence of stroke in Sweden has decreased in the last decade, in the older and the middle-aged groups, but has increased in persons younger than 45 years [1, 5]. After ischemic heart disease and cancer, stroke is the third leading cause of death in Sweden [6].

Types of stroke

Stroke is a heterogeneous disease with a broad variety of genesis, but is the result of either an interruption in the blood flow to a part of the brain (ischemic stroke) or bleeding into and around the brain due to a ruptured artery (intracerebral or subarachnoid haemorrhage). In Sweden approximately 85% of strokes are ischemic [4]. In this thesis focus lays on ischemic stroke.

Genesis of ischemic stroke

Every stroke is unique. It is crucial to understand underlying mechanism of stroke, to be able to design best medical treatment. The distinction between haemorrhage and ischemic stroke is often uncomplicated, when computerised tomography is performed in clinical routine, and single out apparent haemorrhage. Understanding genesis and pinpointing the specific cause of a unique ischemic stroke is harder. When subtyping ischemic stroke it might be helpful following classification systems like the causative classification system for ischemic stroke [7], to form a hypothesis of underlying cause for the treated stroke. In clinical reality there is however

not possible to *exactly* establish genesis of every ischemic stroke. For example every ischemic stroke in an atrial fibrillation (AF) population can't be directly related to the known arrhythmia, as these patients often have advanced atherosclerosis, which also is a common cause of stroke. On the other hand, in secondary treatment it's seldom necessary with this distinction, since every treatable genesis needs to be dealt with simultaneously and separately.

Medical stroke prophylaxis

Cornerstones in primary medical stroke prophylactic treatment are optimal treatment of hypertension, diabetes mellitus and AF. Secondary stroke prophylactic treatment is based on attacking the genesis of occurred stroke. Except for more uncommon reasons for stroke like arterial dissection, antiphospholipid syndrome and vasculitis, the focus in every day practice often lies in preventing thrombosis due to atherosclerosis and preventing embolization due to AF. When appearance of atherosclerosis, treatment with platelet inhibitors, statins and antihypertensives are indicated [8, 9]. When appearance of AF, anticoagulants should be considered [10].

Atrial fibrillation

AF is the most common clinical relevant arrhythmia with a prevalence of about 3% in Sweden [11], and is a strong independent risk factor for ischemic stroke [12, 13].

Mechanisms of thromboembolism due to AF are not fully understood, but evidence suggests that the thrombogenic tendency in AF is related to several underlying pathophysiological mechanisms with abnormal changes in:

- blood flow, with stasis in the left atrium. The most common site of atrial thrombus formation is the left atrial appendage, with its narrow inlet predisposed to blood stasis [14, 15].

- vessel walls, including progressive atrial dilatation and oedematous or fibroelastic infiltration of the extracellular matrix, rendering anatomical and structural defects.
- blood constituents, including haemostatic and platelet activation, as well as inflammation and growth factor changes [16, 17].

These changes all result in a prothrombotic or hypercoagulable state in AF [18].

Age and other comorbidities can, using scoring systems like $CHADS_2$ and CHA_2DS_2-VASc, predict a yearly stroke risk up to 18% due to AF [19, 20] (Figure 1).

		SCORE
C	Congestive heart failure (Left ventricular dysfunction)	**1**
H	Hypertension	**1**
A_2	Age ≥75 Years	**2**
D	Diabetes mellitus	**1**
S_2	Stroke / TIA (Transient ischemic attack) / Thromboembolism	**2**
V	Vascular disease (Myocardial infarction, peripheral artery disease, aortic plaque)	**1**
A	Age 65–74 Years	**1**
Sc	Sex Category (Female)	**1**

C	Congestive heart failure	**1**
H	Hypertension	**1**
A	Age ≥75 Years	**1**
D	Diabetes mellitus	**1**
S_2	Stroke / TIA (Transient ischemic attack)	**2**

Figure 1. CHA_2DS_2-VASc and $CHADS_2$ score.

High-risk AF patients, equalling CHA_2DS_2-VASc ≥ 2, should be offered anticoagulation therapy [10]. This means that all patients with AF already suffering a stroke (equals minimum 2 points in CHA_2DS_2-VASc) should be considered for anticoagulation treatment, regardless of which actual genesis of the stroke.

Anticoagulants

Coagulation

Coagulation is the process by which blood transforms from liquid to a forming of a clot, indeed a necessary process for human bodies for cessation of blood loss from a damaged vessel. This mechanism of coagulation involves both cellular (platelets) and protein (coagulation factors) components, resulting in formation of blood clots consisting of aggregated platelets and maturated fibrin strands. The formation of fibrin is via a complex coagulation cascade involving activation of mainly circulating protein enzymes, which acts by cleaving downstream proteins started by activation of tissue factor when tissue damage has occurred. Every step of this coagulation cascade, results in activation of multiple pro-enzymes leading to an amplified reaction. At the end of this cascade the enzyme thrombin, which plays a central part in coagulation and haemostasis, is generated. Thrombin converts the soluble fibrinogen to insoluble fibrin strands that serves as reinforcement in the aggregated platelet clot. Produced thrombin also generates, through an amplified phase of the coagulation cascade, additional greater amount of thrombin and activation of more platelets [21]. Anticoagulants act through different interactions in different levels of this coagulation cascade (Figure 2), mutually resulting in reduction of the fibrin production.

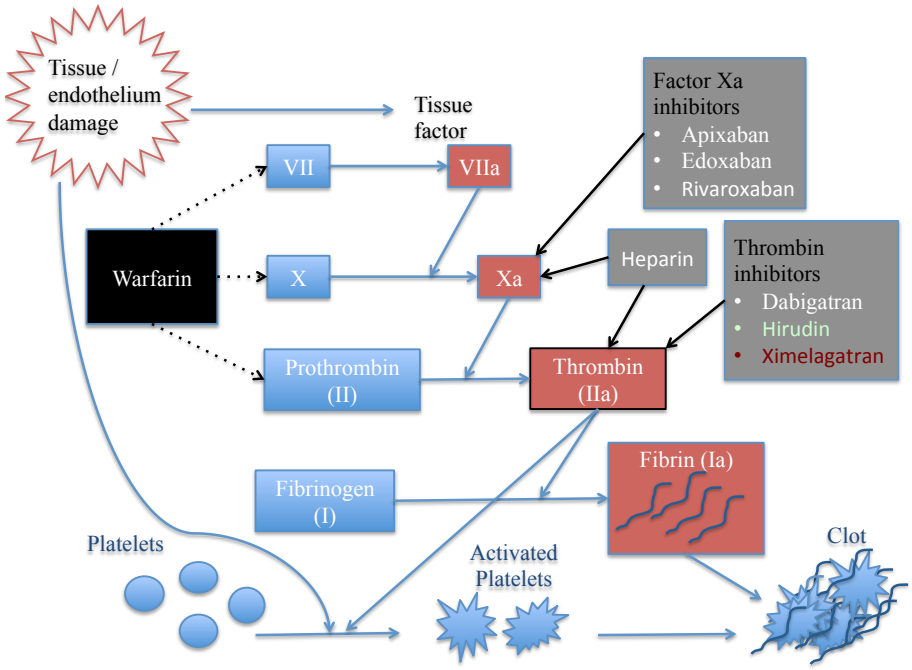


Figure 2. Simplified version of parts of the coagulation cascade with coagulation factors in Roman numerals, and action of some anticoagulants. Black arrows indicate inhibition, dotted arrows indicate indirect inhibition (via reduced liver synthesis of coagulation factors) and blue lines indicate activation.

History

The history of the traditional anticoagulants is fascinating and filled with serendipity and hard laboratory work, treatment successes and some setbacks. Hirudin extracts from the medicinal leech (hirudo medicinalis) were first used for parenteral anticoagulation in the clinic in 1909, but their use was limited due to adverse effects and difficulties in achieving highly purified extracts. Interestingly the use of medical leeches can be dated back to ancient Egypt [22]. Hirudin was the first direct thrombin inhibitor used.

McLean, a medical student, discovered the anticoagulant effect of heparin in 1915 while he was searching for a procoagulant in dog liver. This was during The Great War, why procoagulants rather than anticoagulants, were of better

use for the on-going medical efforts in the war. It was, however, not until in the early 1930s produced heparins were first launched for clinical use in intravenous treatment of thromboembolism [23, 24].

The story of the first oral anticoagulant begins on the prairies of Canada and the northern plains of America in the 1920s. Previously healthy cattle in these areas began dying of internal bleeding with no obvious precipitating cause. Frank Schofield, a veterinary pathologist in Alberta, discovered that the mysterious disease was connected to the consumption of spoiled sweet clover hay and he noted a prolonged clotting time. This haemorrhagic disease, which became known as 'sweet clover disease', became manifest within 15 days of ingestion and killed the animal within 30–50 days. Another local veterinary, L M Roderick, showed in 1929 that this acquired coagulation disorder was caused by what he called a 'plasma prothrombin defect'. A few years later a farmer brought a dead cow and a milk can of the unclothed blood to the University of Wisconsin. The legend says that only the door to the biochemical department of Karl Link was open. This event started an intense laboratory research lead by Link, where he and his co-workers successfully identified the anticoagulant agent *dicoumarol*, which was formed by microbial induced oxidation of coumarin in the mouldy sweet clover hay. They managed to synthesize over hundred dicoumarol-like anticoagulants. Dicoumarol itself, patented in 1941, was the first widely commercialized anticoagulant and was later used as pharmaceutical. However, it was a more potent coumarin-based agent, named WARFarin (an acronym from Wisconsin Alumni Research Foundation + the ending of coum*arin*) that lead to a commercial break through after its registration in 1948. It was launched and used as a highly potent rat poison. In 1954 it was approved for medical use in humans, and got an upswing in popularity when US president Dwight Eisenhower was treated with warfarin after suffering a heart attack in 1955 [23, 24].

Parallel and independent of the North American research there were similar research on per oral anticoagulants performed in Sweden. In Sweden dicumarol was synthetized and used for treating patients with thrombosis as

early as 1941 [25]. Dicumarol, named “Apekumarol”, was used parallel to warfarin in Swedish medical practice until 1999, when production of the substrate was stopped.

In the last decade several new oral anticoagulants have been created, giving patients and doctors treatment alternatives to warfarin (Figure 3), although this era of “new” oral anticoagulants started with a commercial setback in 2006 with the withdrawal of Ximelagatran, a direct thrombin inhibitor launched in 2004, due to reports of hepatotoxicity.

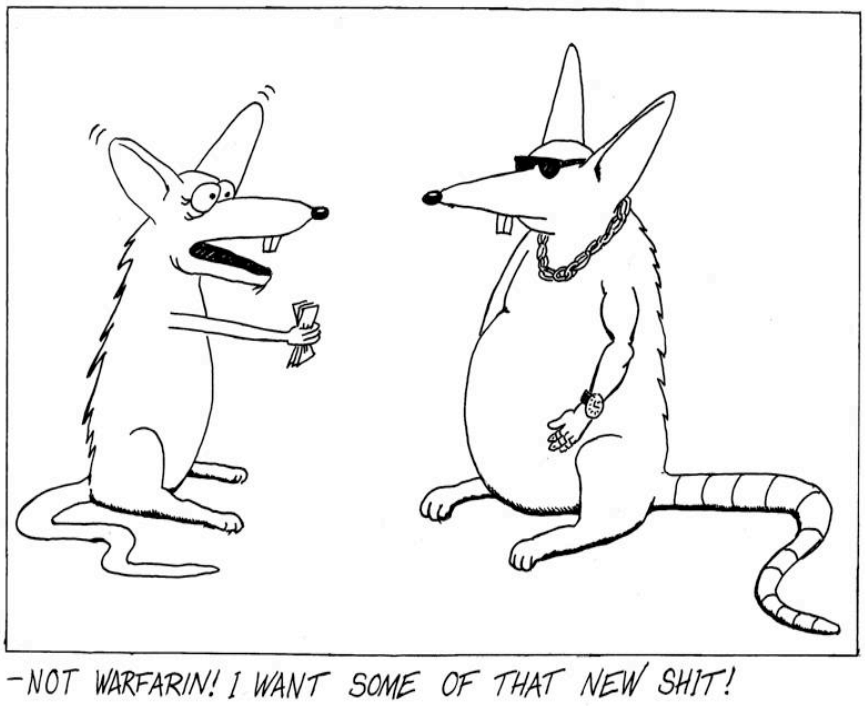


Figure 3. Oral anticoagulants. What is the drug of choice? Drawn by Erik Wallmark.

Warfarin

Warfarin is a vitamin K antagonist (VKA) reducing liver synthesis of coagulation factors II, VII, IX and X. This indirectly reduces formation of fibrin leading to poorer clot formation (Figure 2). Anticoagulation effect of

warfarin is slow (days), due to action through inhibited liver synthesis, and dependent on dietary vitamin K. Monitoring through INR (international normalized ratio) -evaluation is necessary due to a relatively narrow therapeutic index demanding individual dosing. Warfarin is accompanied with many drug interactions.

Warfarin treatment is effective, with reduction of the risk of all cause mortality by 26% and stroke by 64%, compared to control in patients with AF [26]. At the same time treatment with warfarin is associated to an increased risk of hemorrhage, where intracranial bleeding is the most feared [27-30]. The risk of major bleeding increases when warfarin treatment is combined with platelet inhibitors, such as acetylsalicylic acid (ASA) [31-33].

When treating patients with warfarin, monitoring and tight INR control reduces risk of both thrombosis and bleeding [34-40].

NOACs

NOACs is an acronym for Novel Oral AntiCoagulants, or Non-VKA Oral AntiCoagulants. The latter refers to their, from warfarin different, action on the coagulation system which is a more direct inhibition of different coagulation factors, rendering in sometimes used acronym DOACs (direct oral anticoagulants). Apixaban, dabigatran, edoxaban and rivaroxaban are NOACs approved by authorities for prevention of stroke in patients with AF. NOACs is a somewhat heterogeneous group of anticoagulants with differences in action (Figure 2), pharmacodynamics and -kinetics. In general, anticoagulation effect of NOACs is fast (hours), and is independent on dietary vitamin K. No monitoring is necessary due to use of fixed doses. NOACs have fewer drug interactions than warfarin.

Meta-analyses have shown that apixaban, dabigatran, edoxaban and rivaroxaban are more efficient than warfarin in prevention of stroke and systemic embolism [41, 42]. It seems to be a lower risk of intracranial bleeding for NOACs compared with warfarin, but frequency of gastrointestinal bleedings is higher for NOACs compared with warfarin [42].

Quality of anticoagulation treatment

Measurement of quality

The quality of *initiated* anticoagulation treatment, which is the focus in this thesis, is essential for maximizing effect of chosen anticoagulant for each treated patient. There are two principle ways of measuring quality of this treatment. The first is to count treatment complications in time, both bleedings and thromboembolic events, and calculate cumulative incidences or complication rates. This is a retrospective approach and is relevant for population basis, but does not help clinicians or patients in understanding relevant quality for their on-going treatment. The second is an indirect measurement of levels of anticoagulation by analysing INR from blood draws from treated patients. The latter approach is applicable for warfarin, but since the NOACs do not need dose titration or level measurement, such monitoring of NOAC treated patients are not performed, why measurement of individual quality of NOACs are limited.

For NOACs an alternative to INR monitoring could be pharmacist-led monitoring [43]. Other available support systems for better adherence to NOACs are electronic reminders for medication renewals and clinician-directed automated voice messaging. There are however no way of measuring individual treatment quality in these systems.

The level of anticoagulation for warfarin treatment, measured from INR control, can be expressed as time in therapeutic range (TTR) and/or INR variability.

TTR

TTR reflects the proportion of treatment time the patients were in the planned therapeutic range [44], often set to INR 2–3. TTR describes the intensity of anticoagulation based on individual INR values and is limited to a minimum of two INR values (Figure 4). A high TTR has been shown to correlate with a low risk of bleeding or thromboembolic events [36, 45, 46].

For warfarin treatment TTR is a simple quality measure, which in computer-based dosing systems can be directly reported back to each participating centre and enhance the quality of future warfarin dosing [47].

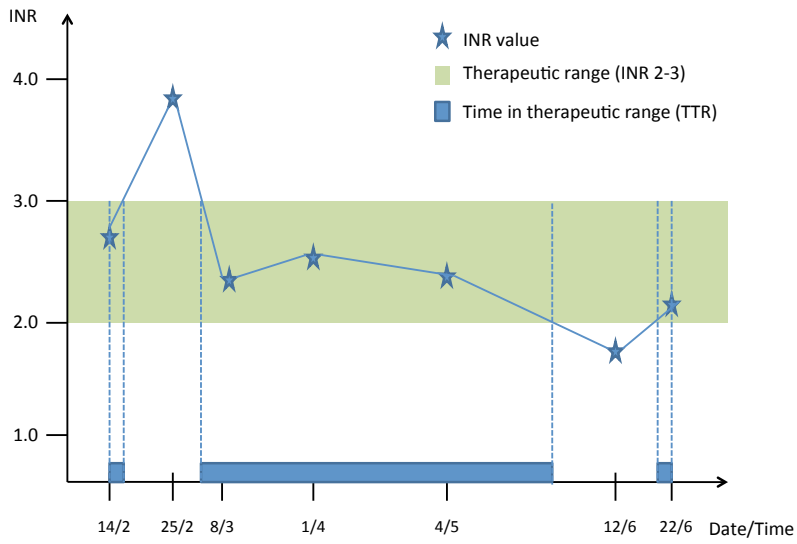


Figure 4. Illustration of time in therapeutic range (TTR), calculated from one patient's in time plotted INR values.

INR variability

INR variability measures the stability of the anticoagulation regimen and reflects the variation of a patient's INR values around the regression line, after transformation to the normal distribution [40]. Low INR variability equals stable anticoagulation therapy, while high variability equals unstable anticoagulation (Figure 5). It has been shown that patients with high INR variability have greater risk for treatment complications than patients with low INR variability [38, 40].

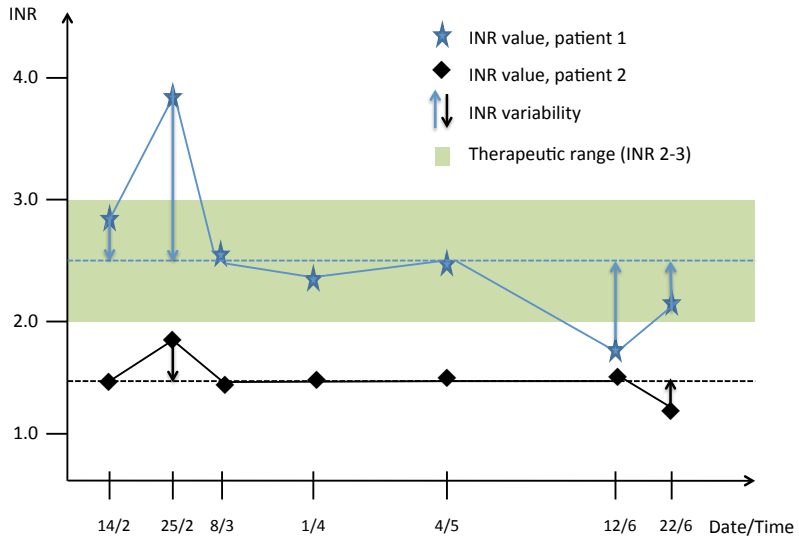


Figure 5. Illustration of INR variability for two different warfarin treated patients. Patient 1 (blue line and stars) has a decent TTR, but also show higher INR variability. Patient 2 (black line and squares) has a poor TTR (all INR values below therapeutic range), but lower INR variability.

Persistence and adherence

The effect of anticoagulants is like all other medical treatment directly dependent on the extent of the patient's participation in following treatment recommendations; "drugs doesn't work if the patient don't take them". Over the years many different terms, such as *compliance*, *adherence*, *persistence* and *discontinuation*, have been used to describe this ability to follow planned treatment, sometimes leading to confusions in the world literature and making it harder to compare results of scientific research in this field [48].

Adherence is defined as "the extent to which a person's behaviour – taking medicines, following a diet and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [49]. Adherence

differs from former more commonly used compliance, where there is not necessarily an agreement between the patient and the health care provider in the treatment.

The terms persistence and discontinuation are often used when focus lies on treatment duration and does not always account for the degree of adherence. Persistence is the length of time between first and last dose of prescribed medication, taken by the patient. Discontinuation occurs when the patient stops taking the prescribed medication, regardless of reason [48, 50].

In this sentence, in a study on persistence on long-term treatment such as anticoagulants in stroke prevention, a patient with poor persistence (e.g. stopping "life long" treatment ahead) can still have good adherence; if the involved clinician initiated the discontinuation, when for example bleeding complications had occurred. Another patient in the same study can be classified as having good persistence (on anticoagulants till time of death), despite poor adherence (for example taking anticoagulants in incorrect doses, at the wrong times and/or forgetting doses).

Adherence to medical treatment is known to overall vary considerably between patients, between types of preventive drugs, and over time, resulting in increased morbidity and mortality [49, 51-53]. Patients with chronic conditions generally adhere only to 50–60% of prescribed medications, despite evidence that medical therapy prevents death and improves quality of life [53].

Previous studies on warfarin treatment persistence among AF patients, describes relatively high discontinuation rates, with about 20–50% of the initially treated patients having stopped their treatment after only twelve months [54-57].

Studies in long-term adherence and persistence to NOACs are few or absent.

There are some previous studies performed on persistence and adherence to secondary preventive medications for patients who had suffered stroke, but data are limited and their results vary widely [56-60]. Studies based on

registers reports reasonable persistence for secondary preventives after stroke, with a one-year persistence of 86–88% for antihypertensive drugs, 79–87% for antiplatelet drugs and 73–76% for statins [58, 59]. Other studies in fact report even higher persistence rates, but had few enrolled stroke patients and were single-centre based [60, 61]. For the stroke population, the overall impression is that persistence to secondary preventive medications, in developed countries, is fairly high when compared to the general population where adherence to statins and antihypertensives are shown to be below 60% [52].

Quality of anticoagulation treatment in Sweden

In Sweden, a very high center-based TTR (cTTR) of above 75% has repeatedly been shown [36, 45, 46], and individual patients can achieve extremely high individual TTR (iTTR). Sweden is a world leading country in warfarin treatment quality, when looking at general level of TTR [45]. This is probably explained by well-developed monitoring structures and longstanding treatment traditions with computerised dosing systems and specialised nurses caring for these patients. In comparison, worldwide clinical randomized controlled trials with selected centers and patients as well as monitors who follow up their treatment report TTRs between 55 and 65% [42, 45]. In clinical practice American warfarin treatment has shown a TTR of 63% in specialist clinics and for public health centers only 51% [35]. This difference in outcome has raised the question of whether centralisation of warfarin monitoring is advisable.

Also when measuring rates of complications, Swedish warfarin treatment has overall been shown to hold high quality standard [37, 40]. Interestingly, no significant differences in bleeding frequency has been shown between Swedish anticoagulation clinics (ACC) and primary health care centers (PHCC) [27].

Ever since the introduction of NOACs there are alternatives to warfarin for stroke prevention treatment in AF patients. Since NOACs have been

compared to warfarin in global randomised trials where the mean TTR ranged from 55.2% to 64.9%, it is however not simple to apply these results to Swedish treatment conditions with far higher level of TTR [62-65].

When it comes to secondary stroke-prophylaxis for AF patients in Sweden, a study on persistence to medical treatment after stroke shows that only 45% are still on warfarin two years after start of treatment [59].

Aim

To study the impact of warfarin treatment quality in Swedish stroke prevention, through:

I. Comparison of warfarin treatment quality in ACC and PHCC in Sweden, expressed as both TTR and frequency of complications, and thereby evaluate whether the centralization of these patients is for the better.

II. Evaluation of warfarin persistence and variables associated with discontinuation in a large Swedish cohort with unselected patients with previous stroke or TIA (transient ischemic attack) and diagnosed AF under well-defined warfarin treatment.

III. Elucidations of predictors for warfarin treatment discontinuation in an unselected smaller cohort of AF patients, and to determine to what extent treatment discontinuations were clinically motivated.

IV. Reporting the safety and efficacy of well-managed warfarin for patients with non-valvular AF, and determination of the risk of major complications, especially intracranial bleeding, in the important subgroup of patient with concomitant ASA use, as well as the impact of INR control (including both iTTR and INR variability).

Material and methods

Data sources

The data sources for this thesis includes four national registers and databases and for paper III medical journals. Cross-linkage of data between registers was possible through the Swedish personal identity number.

Registers and databases

AuriculA is a Swedish national quality register for AF and oral anticoagulation. This register was started in 2006 and is since 2008 funded by the Swedish Association of Local Authorities and Regions. AuriculA is now nationwide and includes over 122 000 patients from 224 participating centers, represented by both primary health care centers and specialized anticoagulation clinics. In Sweden approximately 50% of all warfarin treated patients are included in AuriculA. Participation in AuriculA is mostly within whole county councils with no apparent selection bias. About two thirds of the registered patients are anticoagulated due to AF. Over 6 000 000 INR samples are registered [66]. Unless the patient has declined to participate, everything related to warfarin treatment documented in the anticoagulation centers in everyday clinical practice, is automatically transferred to AuriculA once every 24 hours.

AuriculA also provides a clinical decision tool, based on a dosing algorithm, aiding in the dosage of warfarin [47]. This algorithm can, if certain criteria are met, give a dose suggestion that can be either accepted or manually changed by the clinician.

The Swedish National Patient Register (NPR) was launched in 1964 and has since 1987 complete coverage of all in-patient care in Sweden, for patients with a Swedish personal identity number. Besides information about hospital admissions, since 2001 the NPR also contains information of outpatient visits in hospital-based clinics in Sweden [2]. Currently above

99% of all inpatient data are registered in the NPR. Information available in the register includes *patient data* (personal identity number, age, sex and place of recidence), *geographical data* (county council, hospital/clinic and department), *administrative data* (dates for admission and discharge and length of stay), and *medical data* (main diagnosis, secondary diagnosis, external cause of injury and poisoning, and procedures) coded according to the diagnose coding system International Classification of Disease, 10th edition (ICD-10).

The Cause of Death Register (CDR) includes deceased persons with a Swedish personal identity number, regardless of whether the death occurred in Sweden or outside the country. Emigrated Swedes who no longer are registered in Sweden are not included in the CDR. Data in the register includes patient data, date of death and the underlying cause of death, coded according to ICD-10, as well as information on whether or not autopsy was performed [6].

The Swedish Prescribed Drug Register (PDR) includes data on all prescriptions dispensed in Swedish pharmacies. Since 2005 the PDR also includes information on prescriptions per individual personal identity numbers [67].

Data acquisition and study cohorts

I. Study cohort included all patients registered in AuriculA in the study period January 1, 2006, to December 31, 2011. Data were collected from AuriculA and the NPR. Overall 77 423 patients were enrolled.

II. Study cohort included all patients registered with ischemic stroke or TIA in the NPR whom also were registered in AuriculA due to AF in the study period January 1, 2006, to December 31, 2011. All patients started their warfarin treatment during the study period. Data were collected from AuriculA, the NPR and the CDR. Overall 4 583 patients were enrolled.

III. All AF patients in Sundsvall, registered in AuriculA on January 1, 2010, were included. This cohort of 478 patients was followed until discontinuation of treatment or study-stop December 31, 2013. All used data were collected from each patient's medical record.

IV. All patients in AuriculA started on warfarin treatment due to AF during January 1, 2006, to December 31, 2011, were initially included. Children (persons under the age of 18 years) were excluded to avoid bias (one person). In the remaining cohort, 460 patients had in addition to AF valve malfunction (mechanical prosthetic valves (n=378) or mitral stenosis (n=82)) and were therefore excluded. Data for the final cohort of 40 449 patients were collected from AuriculA, the NPR, the CDR and the PDR.

Statistical methods

In all statistical analysis performed in this thesis the level of significance was set to 0.05, corresponding to the use of 95% confidence intervals (CI). Data were analysed using SPSS Statistics (Version 21; SPSS Inc., IBM Corporation, NY, USA), and R version 3.0.0, R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

I. Baseline characteristics were presented descriptively. Mean TTR and annual frequency of complications were calculated for patients treated in ACC and PHCC. A propensity score matching was also performed for the compared treatment groups with 2:1 nearest neighbour matching (ACC: PHCC).

II. Baseline characteristics were presented descriptively. For analysis of predictors of warfarin treatment discontinuation Cox regression analysis was used, while Kaplan-Meier-method with log-rank test was used when analysing treatment persistence for different

CHA_2DS_2VASc scores. Univariate logistic regression was used for calculating persistence depending on level of iTTR.

III. Baseline characteristics were presented descriptively. For analysis of predictors of warfarin treatment discontinuation Cox regression analysis was used.

IV. Baseline characteristics were presented descriptively. Annualized incidence of complications was calculated as event per treatment year. Cox regression analysis was used for calculating predictors for intracranial bleeding and for calculating differences in bleeding risks between patients with additional ASA and those without additional antiplatelet.

Ethics

Studies I, II and IV are based purely on data from national registers which, according to Swedish law, are under secrecy. This secrecy can be disregarded for research purpose, after approval from an ethical review board. Approved data extractions from the registers are delivered after removal of the Swedish personal identity number. The studies in this thesis were all approved by the regional ethical review board in Umeå, Sweden, and conform to the declaration of Helsinki.

I. EPN nr 2011-349-31M and 2014-191-32M

II. EPN nr 2011-349-31M and 2014-191-32M

III. EPN nr 2014-175-31M

As this study depends on retrospectively read medical records, the fundamental question of violence of personal integrity was raised. Currently, the requirement for informed consent is a cornerstone of research ethics. Our arguments for not needing informed consent in this study was accepted by the ethical review board and included:

- The design of this study equals quality follow-up in clinical

treatment. Results from this study can directly be in use for the warfarin treated patients if revealed weaknesses in treatment quality are corrected.

- This retrospective reading of medical records will not in any way affect the direct treatment of concerned patients. We have no reason to believe that anyone of the concerned patients can be harmed by this study.
- The study involves patients with AF and is performed during several years. Since it concerns a patient group of high age with several comorbidities, a relatively high proportion of the patients are expected to have diseased since the study start.
- It is problematic to inform a patient, or its surviving spouse or children, that a study with a retrospective design is set up to see if performed treatment was adequate or not. Such information can lead to unnecessary worry among the addressees.

IV. EPN nr 2011-349-31M and 2012-277-32M

Results

Synthetized baseline characteristics of the studied patients are presented in Table 1 and shows that these warfarin treated patients were typically about 70 years old with comorbidities corresponding to CHA_2DS_2-VASc scores above 3. There were differences in degree of comorbidities and mean age between the different studied cohorts, with the highest numbers seen in study II.

	I	II	III	IV
	n=72 267[a]	n=4 583	n=478	n=29 146
Indication for warfarin	**Any**	**AF + Stroke**	**AF**	**AF**
Age, mean year (SD)	70.5 (±11.9)	75.6 (±9.0)	69.5 (±8.9)	73.8 (±9.5)
Male	42 546 (58.9)	2486 (54.2)	317 (66.3)	16 903 (58.0)
Female	29 721 (41.1)	2097 (45.8)	161 (33.7)	12 243 (42.0)
Stroke	10 832 (15.0)	3548 (77.4)	76 (15.9)	5 647 (19.4)
TIA (transient ischemic attack)	4 696 (6.5)	1442 (31.5)	28 (5.9)	2 327 (8.0)
Hypertension	35 949 (49.7)	3022 (65.9)	405 (84.7)	17 435 (59.8)
Chronic heart failure	18 996 (26.3)	1001 (21.8)	171 (35.8)	8 341 (28.6)
Diabetes mellitus	11 397 (15.8)	872 (19.0)	99 (20.7)	5 215 (17.9)
Myocardial infarction	10 499 (14.5)	755 (16.5)	112 (23.4)[b]	6 292 (21.6)
Cancer	-	481 (10.5)	-	3 428 (11.8)
Chronic obstructive pulmonary disease	6 018 (8.3)	411 (9.0)	-	2 591 (8.9)
Renal failure	2 723 (3.8)	195 (4.3)	29 (6.1)	1 142 (3.9)
Excessive alcohol use	1 529 (2.1)	80 (1.7)	36 (7.5)	568 (2.0)
Liver disease	-	30 (0.7)	0 (0.0)	249 (0.9)
Dementia	548 (0.8)	45 (1.0)	12 (2.5)[c]	144 (0.5)
CHA_2DS_2-VASc score, mean (SD)	3.6 (±1.7)[d]	5.3 (±1.4)	3.4 (±1.8)	3.3 (±1.5)

Table 1. Baseline characteristics for the studied cohorts included in this thesis. Presented as n (%), if other not indicated. SD=standard deviation. AF=atrial fibrillation. [a] Treatment periods, [b] Vascular disease, [c] Cognitive impairment, [d] Score for patients with atrial fibrillation.

Complication rates

The annual risk of major bleedings and thromboembolic events was 2.24% and 2.66%, respectively, for patients with all different indications for warfarin (study I). The incidence of intracranial bleeding was found to be 0.37% per treatment year. For patients started on warfarin due to AF the annual risk of major bleeding and thromboembolic events was 2.23% and 2.95%, respectively (study IV), while the annual risk of intracranial bleeding was 0.44%, and all-cause mortality was 2.19% per treatment year.

No significant differences regarding overall bleeding or thromboembolic complications were found when comparing treatment monitored in ACC vs. in PHCC (Table 2). Patients treated and managed in PHCC were older than patients managed in ACC, 73.4 vs. 69.8 years ($p < 0.001$). The treatment indications "heart valve malfunction" and "planned direct current (DC) conversion in AF patients" were more common in the specialized centres compared to PHCC, 14.0% vs. 5.3% and 9.5% vs. 5.4%, respectively.

Study IV shows that warfarin treated AF patients, receiving additional ASA treatment had statistical significant increased risk of both overall major bleedings and thromboembolic events, compared to patients without concomitant antiplatelet therapy (Table 2). Patients with additional ASA treatment had in general more cardiovascular comorbidities, especially previous myocardial infarction, and consequently had higher mean CHA_2DS_2-VASc score than patients without additional antiplatelet treatment (3.9 vs. 3.2). In the subgroup of patients who received additional ASA, 113 (2.6%) patients were treated with coronary stenting during or within 12 months prior to warfarin treatment start, compared with 149 (0.6%) in the group of patients with no additional antiplatelet.

	I		IV	
	ACC	**PHCC**	**No antiplatelet**	**ASA**
All-cause mortality	**-**	**-**	**2.13 (2.01–2.26)**	**2.57 (2.23–2.91)**
Any major bleeding	**2.26 (2.18–2.33)**	**2.22 (2.09–2.35)**	**2.04 (1.92–2.16)**	**3.07 (2.70–3.44)**
Intracranial	0.36 (0.33–0.39)	0.41 (0.35–0.46)	0.41 (0.35–0.46)	0.62 (0.45–0.79)
Gastrointestinal	0.74 (0.70–0.79)	0.70 (0.63–0.78)	0.67 (0.60–0.74)	1.18 (0.95–1.41)
Other	1.18 (1.12–1.23)	1.13 (1.04–1.23)	1.13 (1.04–1.22)	1.67 (1.39–1.95)
Any thromboembolism	**2.66 (2.58–2.74)**	**2.66 (2.51–2.80)**	**2.12 (1.99–2.24)**	**4.90 (4.43–5.37)**
Arterial	1.34 (1.29–1.40)	1.52 (1.41–1.63)	1.54 (1.44–1.65)	2.72 (2.36–3.07)
Myocardial infarction	0.30 (0.27–0.32)	0.22 (0.18–0.26)	0.52 (0.46–0.59)	2.38 (2.05–2.71)
Venous	1.07 (1.02–1.12)	0.98 (0.89–1.07)	0.12 (0.09–0.15)	0.19 (0.10–0.28)

Table 2. Complication rates for warfarin treated patients in different aspects. Presented in complication per treatment year, with 95% confidence interval (CI). Study I included patients with any indication for warfarin, with focus on outcome when monitoring in anticoagulation clinics (ACC) vs. primary health care centers (PHCC). Study IV included patients with atrial fibrillation, denoting differences in outcome when simultaneous treatment with acetylsalicylic acid (ASA).

Level of INR control

TTR

For the largest studied cohort of patients (study I), those on warfarin treatment due to all sorts of indications and including both warfarin-experienced and treatment naïve patients, the overall mean TTR was 76.5%. For patients on warfarin due to AF with newly started treatment the mean TTR was 68.6%. When comparing treatment monitored in ACC vs. PHCC a significant higher TTR was found for PHCC as compared to ACC (79.6% and 75.7%, respectively, $p < 0.001$).

TTR vs. INR variability

Results from the AF cohort in study IV shows that patients with an iTTR of 70% or higher, had overall significantly lower incidence of treatment complications, compared with patients with an iTTR below 70%. Furthermore, patients with low INR variability had generally lower complication rates (only non significant for intracranial bleeding and venous thrombosis), compared with patients who had high INR variability (Table 3).

	iTTR <70%	iTTR ≥70%	High INR variability	Low INR variability
All-cause mortality	**4.35 (4.03–4.66)**	**1.29 (1.18–1.39)**	**2.94 (2.75–3.14)**	**1.50 (1.37–1.63)**
Any major bleeding	**3.81 (3.51–4.11)**	**1.61 (1.49–1.73)**	**3.04 (2.85–3.24)**	**1.47 (1.34–1.61)**
Intracranial	0.72 (0.59–0.85)	0.34 (0.28–0.39)	0.51 (0.43–0.59)	0.38 (0.31–0.44)
Gastrointestinal	1.26 (1.09–1.43)	0.56 (0.49–0.63)	1.05 (0.93–1.16)	0.50 (0.42–0.57)
Other	2.17 (1.94–2.40)	0.85 (0.77–0.94)	1.79 (1.63–1.94)	0.71 (0.62–0.81)
Any thromboembolism	**4.41 (4.09–4.73)**	**2.37 (2.23–2.51)**	**3.48 (3.27–3.69)**	**2.46 (2.29–2.63)**
Arterial	2.52 (2.28–2.76)	1.41 (1.30–1.53)	1.98 (1.82–2.14)	1.51 (1.38–1.65)
Myocardial infarction	1.90 (1.69–2.11)	0.98 (0.88–1.07)	1.53 (1.39–1.67)	0.96 (0.85–1.07)
Venous	0.24 (0.16–0.31)	0.09 (0.06–0.12)	0.16 (0.12–0.21)	0.11 (0.07–0.14)

Table 3. Annual rates of complications for atrial fibrillation patients started on warfarin subdivided in level of individual time in therapeutic range (iTTR) and level of international normalized ratio (INR) variablity. Presented in complication per treatment year, with 95% confidence interval (CI). High INR variability equals INR variability ≥ mean INR variablity and low INR variability equals < mean INR variablity. Table published with permission from paper IV.

In the subgroup of AF patients with an iTTR of 70% or higher, the cumulative incidences of complications were not statistically significantly altered despite degree of INR variability (Figure 6).

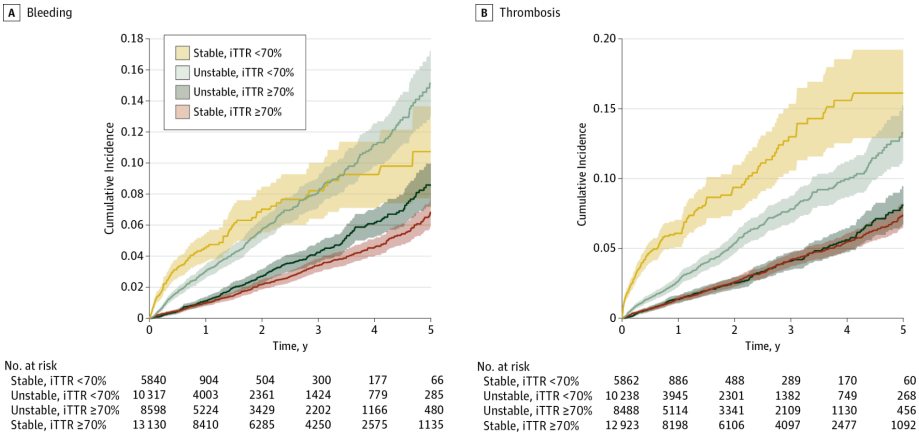


Figure 6. Complications for warfarin-treated patients with atrial fibrillation, subgrouped according to control of the international normalized ratio (INR). Bleedings (A) and thrombosis (B) related to the individual time in therapeutic range (iTTR) and degree of INR variability. Solid lines indicate cumulative incidence. Shaded areas indicate 95% confidence interval. Numbers of patients at risk are included below the graphs. Stable equals low INR variability (≥ mean INR variability) and unstable equales high INR variability (< mean INR variability). Graphs published with permission from paper IV.

Persistence to warfarin treatment

Persistence to warfarin treatment for patients with AF was studied in study II and III. For patients started on warfarin after stroke or TIA (study II) the overall proportion of persistence to warfarin was 0.78 (CI 0.76–0.80) after one year of therapy, 0.69 (CI 0.67–0.71) after 2 years treatment and 0.47 (CI 0.43–0.51) after 5 years (Figure 7). Even higher proportion of persistence to treatment was found for the local AF cohort in study III, with 0.91 (CI 0.89–0.93) after one year, 0.85 (CI 0.81–0.89) after two years and 0.73 (CI 0.69–0.77) after four years (Figure 8).

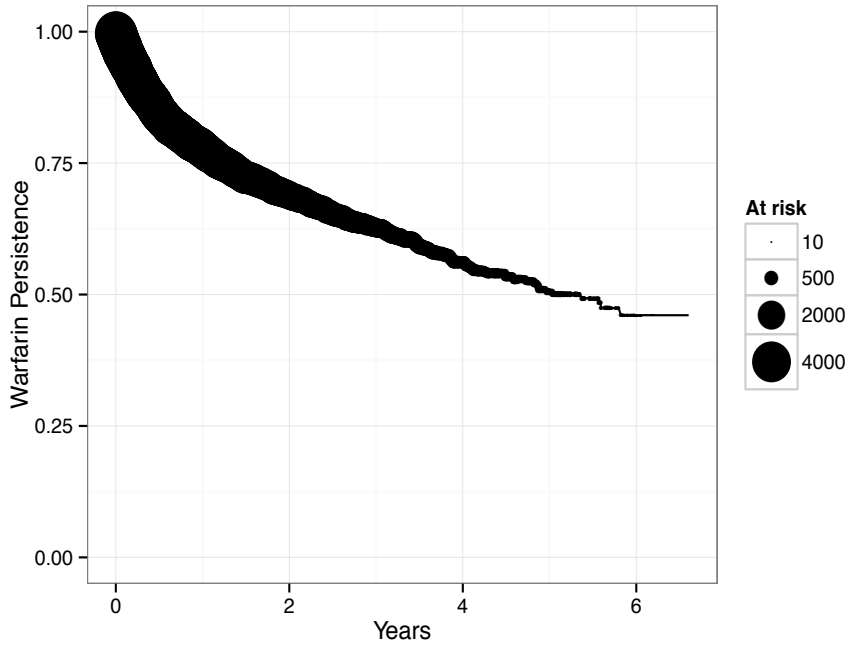
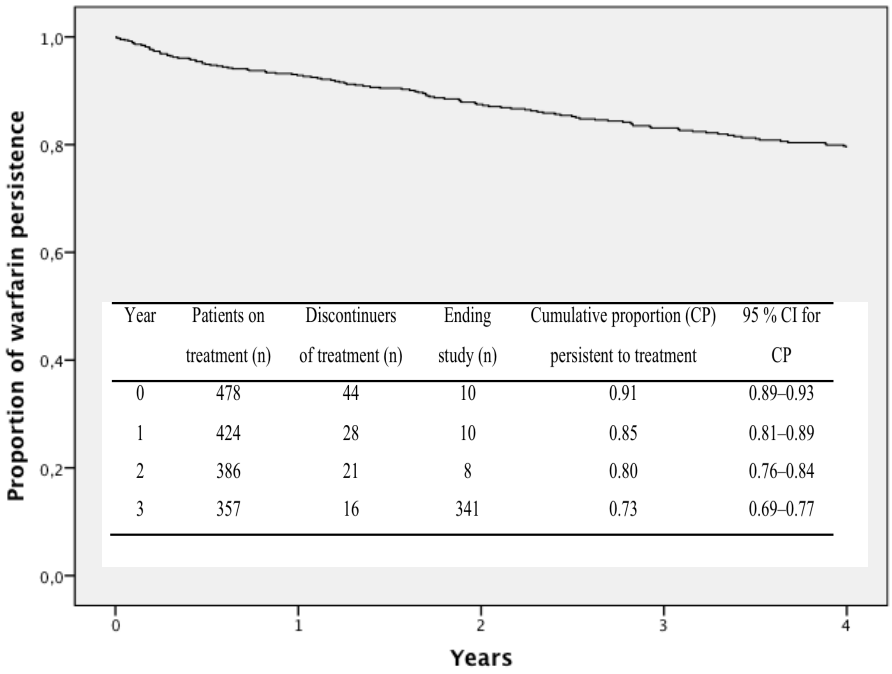


Figure 7. Cox regression plot of overall proportion of persistence to warfarin treatment in relation to time from treatment start, for stroke/TIA patients with atrial fibrillation. Number of patients at risk indicated in the plot. Figure published with permission from paper II.



Year	Patients on treatment (n)	Discontinuers of treatment (n)	Ending study (n)	Cumulative proportion (CP) persistent to treatment	95 % CI for CP
0	478	44	10	0.91	0.89–0.93
1	424	28	10	0.85	0.81–0.89
2	386	21	8	0.80	0.76–0.84
3	357	16	341	0.73	0.69–0.77

Figure 8. Cox regression plot of overall proportion of persistence to warfarin treatment, in relation to time from study start, for patients with atrial fibrillation. Life table is included in the figure. Adapted from paper III.

Warfarin treatment discontinuation

Predictors of discontinuation

In study II and III we examined predictors for treatment discontinuation. For patients on warfarin due to stroke or TIA in addition to AF (study II), those with diagnosed dementia at baseline were most likely for discontinuation of treatment. These patients were more than two-times likely of discontinuation of warfarin than others (hazard ratio (HR) 2.22, CI 1.51–3.27). Patients with excessive alcohol use had 66% higher risk of discontinuing treatment than others (HR 1.66, CI 1.19–2.33). We also found that chronic obstructive pulmonary disease (COPD), cancer and chronic heart failure (CHF) were baseline diagnoses each associated with over 20% increased risk of treatment discontinuation (HR 1.28, CI 1.08–1.51, HR 1.27,

CI 1.09–1.49 and HR 1.23, CI 1.09–1.39). The risk of warfarin discontinuation increased significantly with treatment start-age of the patients. For every year this risk increased with 1.5% (HR 1.01, CI 1.01–1.02). Stroke/TIA patients with a TTR < 60% had a higher risk of treatment discontinuation as compared to patients with TTR ≥ 60%, odds ratio 1.93 (95% CI 1.69–2.20).

When the patients from study II were sorted in CHA_2DS_2-VASc score of 2–3, 4–5, 6–7 and 8–9, a Kaplan-Meier analysis showed that higher CHA_2DS_2-VASc score significantly lead to lower persistence to warfarin treatment (log-rank test, $p<0.001$) (Figure 9).

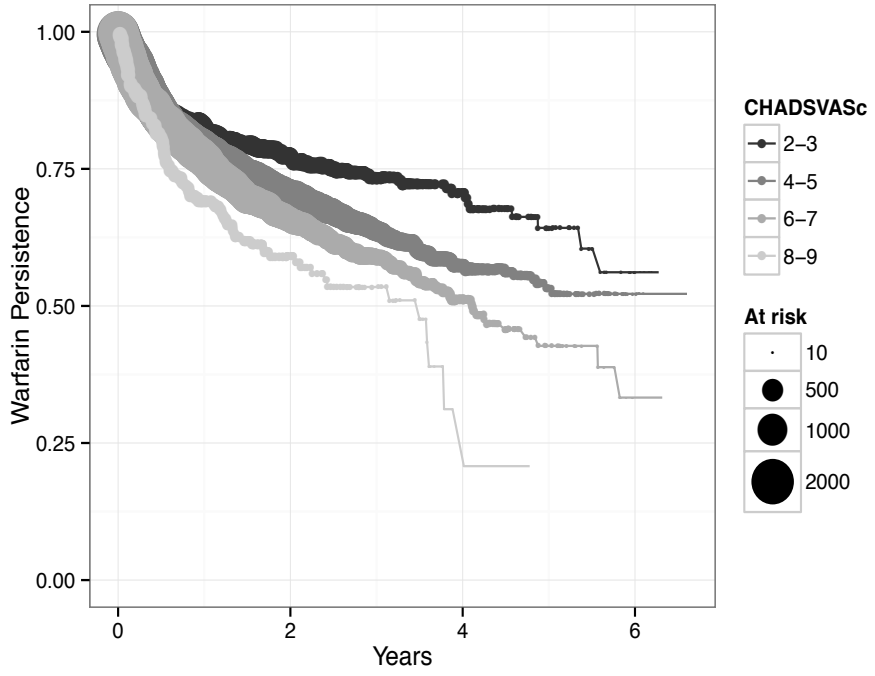


Figure 9. Kaplan-Meier plot of proportion of persistence to warfarin treatment in relation to time from treatment start, for stroke/TIA patients with atrial fibrillation, sub-grouped according to CHA_2DS_2-VASc score 2–3, 4–5, 6–7 and 8–9. Number of patients at risk indicated in the plot. Figure published with permission from paper II.

In the smaller AF-cohort (study III), where the majority of patients had not yet suffered stroke or TIA, we found that those who had had a previous intracranial bleeding were most likely to discontinue warfarin treatment. They had more than five times higher risk of discontinuation (HR 5.66, CI 2.23–14.36), than others. Patients with excessive alcohol use, anemia or pulmonary or peripheral emboli had more than two times higher risk of treatment discontinuation, compared to other patients (HR 2.54, CI 1.48–4.37, HR 2.40, CI 1.38–4.17, and HR 2.13, CI 1.02–4.46). Women and patients with a history of stroke or TIA were more likely to persist on warfarin (HR 0.50, CI 0.31–0.81, and HR 0.44, CI 0.23–0.82). In this cohort we found no significant association between CHA2DS2-VASc score and warfarin treatment discontinuation.

Reasons for discontinuation

In study III we found regained sinus rhythm to be the most common addressed cause of discontinuation of warfarin treatment (31.2%), followed by problematic monitoring (16.5%) and bleedings (14.7%). We estimated that nearly half (49.5%) of the treatment discontinuations were clinically well motivated (Table 4).

Alternative medical thromboembolic prophylaxis was provided for 59.6% of the AF patients (study III) discontinuing warfarin. The most commonly obtained agent was ASA 43.1%, while only 3.7% were prescribed NOACs. For 40.4% of the AF patients taken off warfarin, no other thromboembolic prophylactic treatment was initiated.

	n (%)
Clinically motivated discontinuations	**54 (49.5)**
Bleeding	16 (14.7)
Comorbidity	12 (11.0)
Problematic monitoring	
Instable INR	12 (11.0)
Excessive alcohol use	4 (3.7)
Cognitive impairment	2 (1.8)
Acute need for antiplatelet therapy	
Acute myocardial infarction + Percutaneous coronary intervention	3 (2.8)
Percutaneous coronary intervention	2 (1.8)
No indication (CHA_2DS_2-VASc = 0)	3 (2.8)
Patient's demand	**11 (10.1)**
Clinically questionable discontinuations	**44 (40.4)**
Sinus rhythm	34 (31.2)
Risk of fall	7 (6.4)
Fall	2 (1.8)
Normal echocardiography	1 (0.9)

Table 4. Documented main cause of discontinuation for the 109 patients stopping warfarin treatment during the study period in paper III.

Discussion

These observational studies mainly based on large real life representable cohorts, show that Swedish warfarin treatment quality in initiated stroke prevention is high. With generally low rates of complications, high TTRs and consistent results both in ACC and PHCC warfarin still is a valid alternative to NOACs in Sweden.

Although persistence to warfarin treatment for patients with AF seems reasonable and better than previous reports, there is still room for improvement since many discontinuations of treatment depend on clinically questionable causes.

Complication rates

The relatively low complication rates found in our studies (I and IV) tell us that well-managed warfarin treatment, such as in Swedish settings, is safe and effective. These findings should be representative since the studied cohorts were large (77 423 and 40 449 patients) and taken from real life data with no or minimal exclusion. To set these rates in context comparison with the pivotal NOAC-studies [62-65] is inevitable. The cohort in study IV, represented by patients with a mean $CHADS_2$ score of 2.1 starting warfarin due to non-valvular AF, is somewhat comparable with those smaller ones (where mean $CHADS_2$ scores ranged from 2.1 to 3.46) in the pivotal NOAC-studies [62-65]. Complication rates from study IV was lower or comparable than those presented in the NOAC-studies. We found an annual incidence of all-cause mortality of 2.19 %. This is lower than shown in the NOAC-studies, both compared to the warfarin-cohorts and the NOAC-cohorts (3.9–4.9% vs. 3.5–4.5%) [62-65]. The annual incidence of intracranial bleeding was 0.44% in study IV. For comparison this incidence was 0.70–0.85% in the warfarin control groups in the randomised trials, while the rate with NOACs in the trials was approximately 0.3%.

Results from study I show that Swedish complication rates do not significantly differ between treatments monitored in ACC compared with in

PHCC, why centralisation of warfarin treatment doesn't seem to be necessary when using AuriculA in clinical reality.

Study IV highlights patients with concomitant ASA use as an important subgroup of patients on warfarin treatment. Complication rates found support previous findings of higher risk of major bleeding among warfarin treated patients recieving additional ASA [32, 33]. We found ASA-users to have significantly higher annual incidence of *any major bleeding, gastrointestinal bleeding* and *other major bleeding,* compared with patients on no additional antiplatelet drugs. Since indication for additional treatment with ASA for patients on warfarin is newly performed coronary stenting, one can question the call for additional ASA in the majority of the cases of our cohort, when only 2.6 % of them had this indication.

Level of INR control

TTR

With study I and IV, we show that warfarin treatment quality measured in TTR is high in Sweden. For the largest cohort, including 77 058 patients (study I), we found a mean TTR as high as 76.5%, with consistently high TTR no matter treatment in ACC or PHCC. For comparison, specialist clinics in the United States have shown a TTR of 63% and American public health centers only 51% [35]. These national differences are probably due to Swedish longstanding tradition in anticoagulation therapy, including specialised nurses and support of a computerised dosing system, AuriculA, where aids such as a dosing algorithm are available [47]. Interestingly we found in study I significantly higher TTR in PHCC compared to ACC (79.6% vs. 75.7%, $p<0.001$) for all patients. The lower TTR found in ACC could be partly due to more frequent comorbidities in the population monitored in these clinics. There was for instance a higher proportion of the patients with heart valve disease (9.5% vs. 5.4%) and AF with planned DC conversion (14.0% vs. 5.3%) in ACC compared to PHCC. On the other hand, patients monitored at PHCC were generally older (73.4 vs. 69.8 years) and more often diagnosed with previous stroke (18.8% vs. 14.0%). A more probable

explanation for the TTR differences found is however, a higher proportion of warfarin experienced patients in PHCC, since warfarin not seldom is initiated in ACC and patients then are subsequently transferred to PHCC for continued monitoring. Notable is that despite those TTR differences found between ACC and PHCC, no differences were found in actual complication rates.

In study IV the mean TTR was 68.6%, which also can be classified as high. Since this cohort was composed of patients with non-valvular AF that *during the study period* were started on warfarin, this result can be compared with results from the international pivotal NOAC-studies (who had similar cohorts) where mean TTR ranged from 55.2% to 64.9% [62-65].

TTR vs. INR variability

Our findings of overall significantly lower incidence of treatment complications for AF patients who have achieved iTTR 70% or above, compared with those patients with iTTR below 70%, is in line with European guidelines for warfarin treatment, where iTTR ≥70% is considered "good anticoagulation control" [68], and highlights the importance of striving for high individual TTRs. We show that warfarin treated AF patients who have low INR variability, that is having stable INR-levels, have generally lower complication rates, compared with AF patients with high INR variability. This supports previous findings [34-36, 38-40] and highlights the importance of good INR-control in warfarin treatment, however does not answer the question of which cut-point to use for classifying on-going patients as stable or unstable.

By comparing cumulative incidences of general complications for patients started on warfarin due to AF, with subgroupings depending on degree of iTTR *and* INR variability, we show that patients with iTTR ≥70% have the lowest incidence. In this well managed subgroup of AF patients, with iTTR ≥70%, the degree of INR variability did not seem to affect the results. We conclude that iTTR better predicts treatment complications than INR

variability, which contradicts previous findings of Lind et al [40]. When managing warfarin treatment focus should therefore lie on achieving individual TTR over 70%. Interestingly, those AF patients with poor iTTR (below 70%) have fewer complications if having high INR variability compared with low INR variability. Worst-case scenario is therefore, a patient who's INRs are stabile outside the therapeutic range.

Persistence to warfarin treatment

Persistence to treatment is of fundamental importance for initiated anticoagulation to be effective in stroke prevention. With study II and III we show that persistence to warfarin is high in Sweden.

In study II, with a cohort of stroke/TIA patients started on warfarin due to AF, we found a one-year persistence of 78%, despite no exclusion in the cohort, aiming to describe real life figures. Similar one-year persistence (> 75%) have been described for stroke/TIA patients on secondary preventive treatment in studies based on patients' self-reporting [56, 69], a method known to overestimate persistence. In these comparative studies there were exclusion of patients due to treatment by centres with low follow-up rate [56], or due to patients being lost to follow-up and/or death of patient [69], both thereby risking false high persistence results.

We found a 2-year treatment persistence of 69%, which is higher than previously reported in Sweden [59], where Glader et al reported a 2 year persistence of only 45%. This difference in results is probably due to methodological differences in the calculation of persistence. We measured persistence by using exact treatment time registered in AuriculA, while Glader et al calculated persistence indirectly by registration of patient's prescription refills within fixed time periods. In the latter method patients who accumulate pills and therefore not need refill, but still are on warfarin treatment, falsely fall in the category of non-persisters and rendering underestimation of persistence.

In our local smaller cohort of warfarin treated patients with AF in study III, even higher persistence to treatment was found, compared to study II. However, since this cohort included both treatment naïve *and* warfarin experienced patients, this is unsurprising.

Warfarin treatment discontinuation

Predictors of discontinuation

We found dementia and excessive alcohol use as the strongest predictors for poor persistence to secondary warfarin treatment, which is in line with previous observations [57, 70], highlighting subgroups of patients whom in everyday praxis are challenging for adherence and persistence to medical treatment. Our finding that high age is related to lower persistence to warfarin among stroke patients contradicts earlier observations [69]. This is probably explained by difference in the studied cohorts. We analysed a cohort of stroke patients with a mean age of 76.5 years for non-persisters and 75.1 years for persisters, while comparative figures from Sappok et al were 62.2 years vs. 66.7 years [69]. Our cohort, representing real life background characteristics for stroke patients, to a greater extent included patients from 'the very old' (> 90 years), whom are known to have lower persistence compared with younger patients [57]. Degree of persistence to warfarin after stroke was not depending on sex, which contradicts results in some previous studies [55, 59].

Interestingly we found cancer, COPD and CHF to be related to lower persistence to warfarin among stroke/TIA patients, results that to our knowledge have not been earlier described. A probable explanation is that stroke patients with additional diagnoses of cancer, COPD and/or CHF are more vulnerable than other stroke patients, rendering greater risk for adverse side effect of warfarin and/or ending up in palliative treatment care.

Both these scenarios lead to higher rate of warfarin discontinuation, which naturally might be clinically appropriate.

Results from study II clearly point to lower persistence to warfarin for stroke patients with high CHA_2DS_2VASc scores compared to those with low scores at baseline. This is probably explained by the fact that a high CHA_2DS_2VASc score equals greater comorbidities and thereby also higher risk for bleedings. It has previous been shown that patients with high bleeding risk more often discontinue their warfarin treatment [71]. In study III, however, we found no such association between CHA_2DS_2VASc scores and degree of persistence to warfarin treatment. This is actually no surprise since the cohort in study III consisted of AF patients in general, not only stroke and TIA patients. For AF patients in general it has previously been shown the opposite relation from our study II; persistence to warfarin treatment tend to be lower for those with low thromboembolic risk (CHA_2DS_2VASc 0–1) compared to those with higher thromboembolic risk (CHA_2DS_2VASc 2–9) [55, 57, 69].

As in study II, excessive alcohol use was unsurprisingly found to be a strong predictor of warfarin treatment discontinuation in the smaller local AF cohort in study III. Excessive alcohol use is known to be linked to poorer adherence to anticoagulation treatment [70]. In study III 92% of all patients with excessive alcohol use were male, which might explain some of the lower persistence found for men compared to women.

Other predictors found for warfarin discontinuation in study III were intracranial bleeding, anemia and pulmonary or peripheral emboli. The finding of the strongest one of them, history of intracranial bleeding, is somewhat supported by previous knowledge of higher warfarin discontinuation rates for AF patients with recent bleeding events [72]. Though not previously shown, the finding of anemia as a predictor of warfarin discontinuation seems reasonable, when anemia clinically is often linked to feared or proven bleeding events, questioning the net clinical benefit of anticoagulants.

Reasons for discontinuation

Even though our studies overall shows high Swedish warfarin treatment quality in initiated stroke prevention, with low rates of complications and high TTRs, there are concerns when analysing reasons for warfarin treatment discontinuation. Since we found, in study III, that over half of these discontinuations were due to a medically questionable cause or patients demand, there is room for improvement.

We found regained sinus rhythm to be the most common cause of discontinuation, which corresponds with previous findings for AF patients younger than 80 years [71]. Since long-term anticoagulation is required for AF patients with identified high risk for thromboembolism even after sinus rhythm has been restored [73], regained sinus rhythm as a cause of discontinuation is questioned. There were 9 patients (8.3%) in our cohort who stopped treatment due to fall or risk of fall, which should be classified as medically questionable reasons to discontinue, since the risk of stroke almost always outweighs the risk of intracranial bleeding in AF patients on warfarin [74]. When it comes to patients demand as a cause of ending warfarin, which was found to be the main cause in 10.1%, it is difficult to classify this reason as medically correct or not. Even though these patients have a clear medical indication for anticoagulant treatment due to AF, they are, of cause, free to choose not to continue treatment. But, if so, they should receive extensive information about the risk-benefit ratio with anticoagulant in AF. Alternative treatment like NOACs could be considered if patient's reluctance to continuing warfarin treatment is based on practical issues, such as INR monitoring and dosage.

In study III we found that the AF patients discontinuing their warfarin treatment, for whatever reason, in the majority of the cases (83.5%) received no alternative effective stroke prophylactic treatment. This included no treatment at all and ASA in mono-therapy, which has been shown to lack protective effect as stroke prophylaxis in AF patients [75].

Limitations and strengths

All studies in this thesis have a retrospective observational design, with the strength of reflecting medical every day practice.

Study I, II and IV are based on data retrieved from medical records and registries. These data, as in all register based research, are limited by the accuracy and completeness of documentation. Performed validation of the NPR, however, points to high validity of this register when it in somatic care only lacks information of primary diagnosis in 0.5–0.9% of hospital admissions. A diagnosis in the NPR has an overall high positive predictive value (85–95%), but the sensitivity is varying. For more severe diagnoses like stroke and myocardial infarction, the sensitivity is high (above 90%), but for less severe diagnoses such as hypertension, the sensitivity is rather low (8.8–13.7%) [76]. Under-diagnosis of hypertension in studies I, II and IV, is therefore likely, risking falsely lower $CHADS_2$ and CHA_2DS_2-VASc scores. Study III, with data not taken from registers, but meticulously retrieved directly from medical journals, does not share this limitation why its background data more likely are even more accurate.

When analysing such differences in background characteristics due to methodological differences, the comparison on data in study III and IV shown in Table 1 is useful as an internal validation on data accuracy. As expected, for the more severe diagnoses like stroke and myocardial infarction there were no great differences in prevalence, indicating high data accuracy. Moreover, the findings of higher prevalence of hypertension (84.7% vs. 59.8%) and excessive alcohol use (7.5% vs. 2.0%) in the AF cohort with data derived from medical journals, compared to the cohort derived from the NPR, points to the known phenomena with lower sensitivity of less severe diagnosis in the NPR, indicating more “true” prevalence values found in study III. Since the complications for the large cohorts presented in the NPR-based studies I and IV (Table 3) are compilations of *severe* diagnosis like stroke, myocardial infarctions and intracranial bleeding, sensitivity of these data is expected to be high.

In study I and IV there were lack of baseline characteristics for patients treated purely in PHCC and therefore not included in the NPR. Even if these patients could be healthier than those with hospital visits, underestimation of complications rates is unlikely, since events registered in these studies equates to diseases requiring hospital admission, if not leading to death.

Our studies are based on cohorts derived from Sweden, including patients mostly with a white European background. The stroke incidence is decreasing in Sweden, as in other high income-countries, while increasing in low income-countries [77]. Thus, generalization of our findings should be done with caution for low income-countries and other ethnic groups than European whites.

Since the PDR does not include data of over-the-counter used drugs, such as non-steroidal anti-inflammatory drugs, bleeding results in study IV may be affected.

Conclusions

Quality of Swedish warfarin treatment in initiated stroke prevention is high, based on generally low rates of complications and high TTRs, no matter treatment in ACC or PHCC, including high long time persistence to warfarin, both in primary and secondary stroke prevention. Warfarin is in Sweden still a valid alternative to NOACs for stroke prevention in patients with AF.

For better outcome in future warfarin treatment for patients with AF clinicians should aim for iTTRs above 70%, avoid additional ASA therapy, support fragile patients like those with excessive alcohol use and dementia, and base decisions on treatment discontinuations on solid medical arguments.

Future perspective

In Swedish stroke prophylactic treatment with anticoagulants, there is a need for greater knowledge of real life outcomes when using NOACs. This includes both crude complication rates and long time persistence, compared to results with warfarin. For this kind of evaluation and future research, ideally *every* patient on any anticoagulant, warfarin *or* NOACs, is included in *one* nationwide register.

In the clinicians perspective the overall strive in this field of research is the finding of the most suitable treatment applicable for each patient, based on treatment indication, estimated treatment risks, structure of available social and medical networks and patients preference. The following questions could ideally be answered with such research:

- Are NOACs better than warfarin in low risk patients?
- Are there differences between NOACs and warfarin depending on treatment time?
    - Why bother initiation of warfarin if treatment periods are short?
    - How to secure and measure crucial long time persistence for NOACs?
- Are some NOAC better than others?

In a national economic perspective there is a need for further cost/benefit analyses of NOACs vs. warfarin, based on real life results to answer questions like:

- Why use expensive NOACs if cheap warfarin still work?
- Why use warfarin, with its monitoring costs, when NOACs need no monitoring?
- Are anticoagulation clinics still motivated?

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