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Wieloch, Mattias

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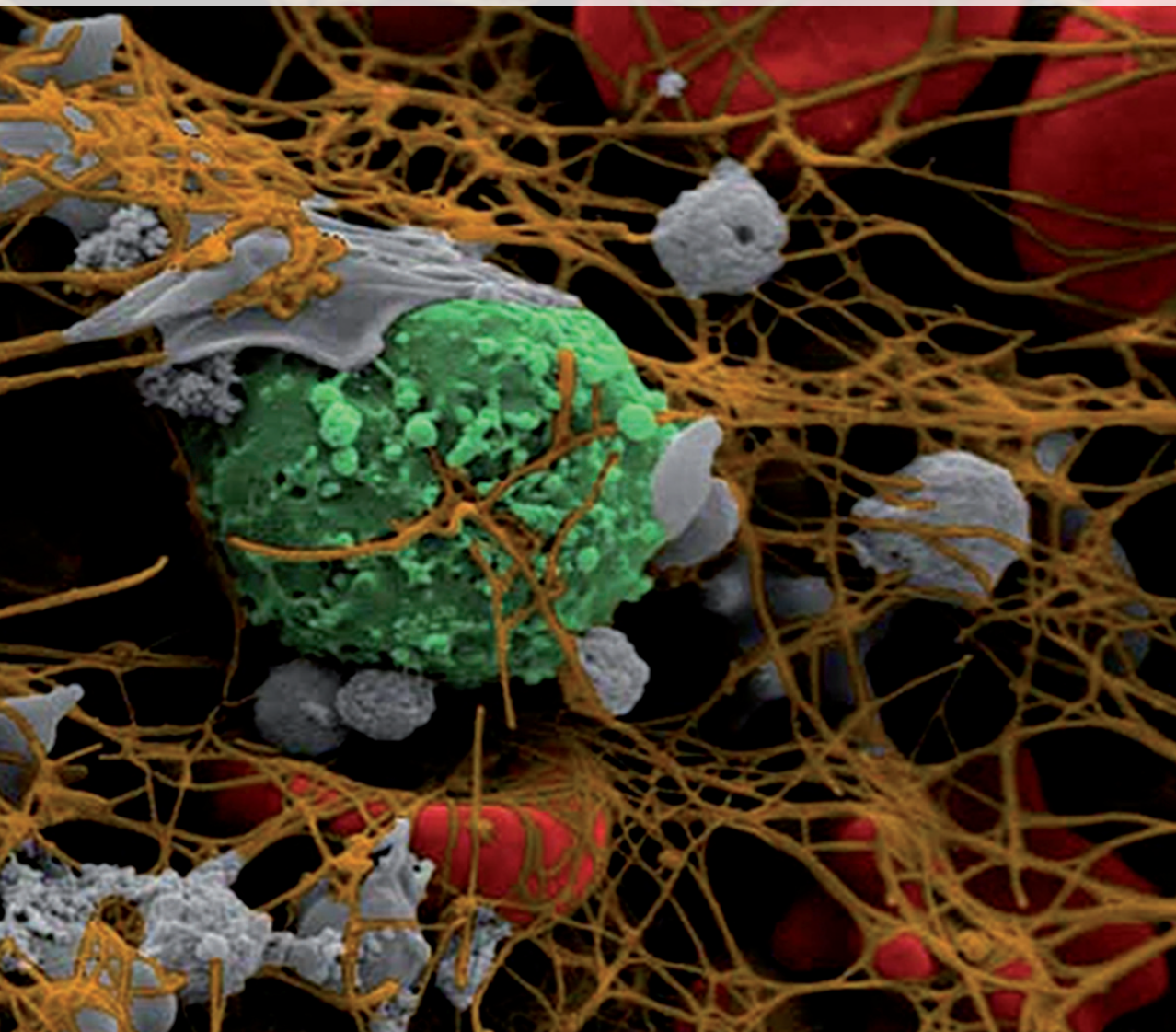
Lund University



Oral Anticoagulation Treatment in Atrial Fibrillation

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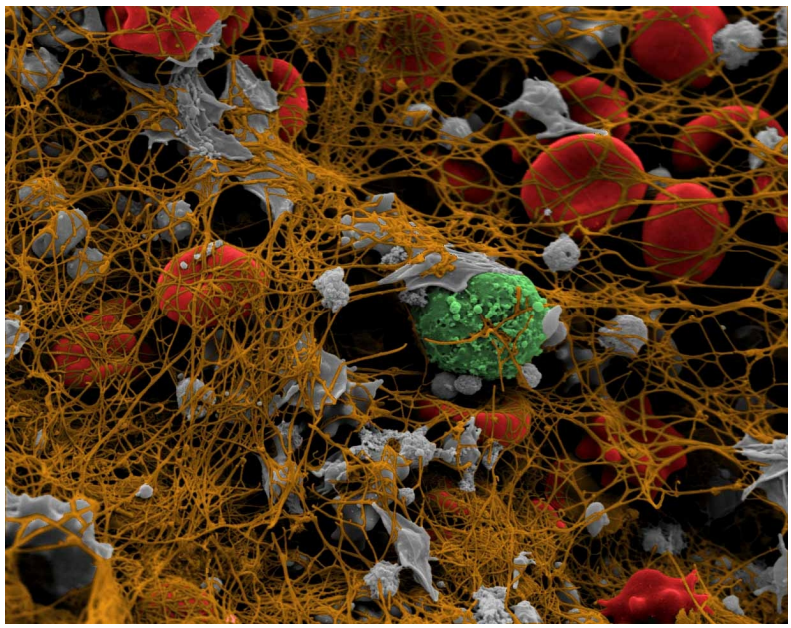

Mattias Wieloch

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Cover. Thrombus formation. Red blood cells in red, white blood cells in green, platelets in grey and fibrin network in orange. Courtesy of John Weisel, PhD, Perelman School of Medicine, University of Pennsylvania, USA

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"A wise man has big ears, but a short tongue,
A wise man knows little, but has great knowledge.
But for the ears, I still have a long way to go…."

-Mattias Wieloch October 31st, 2011

To Annette, Alexandra, and Sanna

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ACE	angiotensin converting enzyme
ADP	adenosine diphosphate
AF	atrial fibrillation
APTT	activated thromoplastin time
AV	atrioventricular
b.i.d.	*bis in die (latin;* in a prescription of medication*)* = twice a day
$CHADS_2$	Stroke risk scheme. Details in Figure 9.
CHA_2DS_2- VASc.	Stroke risk scheme. Details in Figure 10.
CI	confidence interval
CNS	central nervous system
CKD	chronic kidney disease
CV	cardioversion
DC	direct current
DVT	deep vein thrombosis
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EQUALIS	Swedish Committee for External Quality Assurance in Laboratory Medicine
GFR	glomerular filtration rate
GÅS	Gott Åldrande i Skåne (population study)
HAS-BLED	Bleeding risk score. Details in Figure 11.
HMWK	high-molecular weight kininogen
HR	hazard ratio
IDMS	isotope dilution mass spectrometry
INR	international normalized ratio
IQR	inter-quartile range
ISI	international sensitivity index
ISTH	International Society on Thrombosis and Haemostasis
LAA	left atrial appendage
LM	Lund-Malmö
LMWH	low-molecular weight heparin

MDRD	Modification of Diet in Renal Disease
NNT	numbers needed to treat
NSAID	non steroid anti-inflammatory drug
NPT	near-patient testing
OAT	oral anticoagulation treatment/therapy
OR	odds ratio
PCC	prothrombin complex concentrate
p-Cr	plasma creatinine
POC	point-of-care
PT	prothrombin time
RCT	randomized controlled trial
SD	standard deviation
SUS	Skåne University Hospital
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TIA	transitory ischaemic attack
t-PA	tissue plasminogen activator
TTR	time in treatment/therapeutic range
	iTTR - individual time in treatment/therapeutic range
	cTTR - centre time in treatment/therapeutic range
UMAS	University Hospital in Malmö, UMAS
VKA	vitamin K antagonist
VKOR	vitamin K epoxide reductase
VTE	venous thromboembolism
vWF	von Willebrand factor

ORIGINAL PUBLICATIONS

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

I. Anticoagulation control in Sweden: reports of time in therapeutic range, major bleeding, and thrombo-embolic complications from the national quality registry AuriculA. Wieloch M, Själander A, Frykman V, Rosenqvist M, Eriksson N, Svensson PJ. Eur Heart J. 2011 Sep;32(18):2282-9.

II. Glomerular filtration rate in patients with atrial fibrillation on warfarin treatment: A subgroup analysis from the AURICULA registry in Sweden. Jönsson KM, Wieloch M, Sterner G, Nyman U, Elmståhl S, Engström G, Svensson PJ. Thromb Res. 2011 Oct;128(4):341-5.

III. Estimated glomerular filtration rate is associated with major bleeding complications but not thromboembolic events, in patients taking warfarin. Wieloch M, Jönsson KM, Själander A, Lip GYH, Eriksson N, Svensson PJ, submitted.

IV. Comparison and evaluation of a Point-of-care device (CoaguChek XS) to Owren-type prothrombin time assay for monitoring of oral anticoagulant therapy with warfarin. Wieloch M, Hillarp A, Strandberg K, Nilsson C, Svensson PJ. Thromb Res. 2009 Jul;124(3):344-8.

BLOOD COAGULATION

HISTORICAL BACKGROUND

The phenomenon of the formation of solid blood clots from blood in a fluid state after a cut was thought by both Aristotle and Hippocrates, to be related to the cooling of blood [1]. As early as 2600 B.C. a Chinese physician named Huan-Di described how blood clots could affect blood circulation but the modern understanding of thrombosis, blood clot formation, is generally attributed to the work of the German researcher Rudolf Virchow (1821-1902), professor in pathology at the University of Berlin. Today, three main elements, recognized as "Virchow's triad", illustrate the process of thrombosis formation. However, the elements in Virchow's triad of the pathogenesis of venous thrombosis were never proposed by Virchow himself. Instead, it took decades following Virchow's death before a consensus was reached postulating that thrombosis formation is the result of 1) alterations in blood flow, 2) changes in the blood vessel wall, today recognized as vascular endothelial injury, and 3) alterations in the constitution of the blood.

Physiologist Johannes Müller (1801-1858) identified the insoluble thrombus substance "fibrin" and Rudolf Virchow posted the hypothesis of a soluble plasma precursor of fibrin, which he named "fibrinogen". Alexander Schmidt (1831-1894) suggested that the conversion of fibrinogen into fibrin was a "fermentative" (enzymatic) process and named his hypothetical enzyme "thrombin", and subsequently called its presumed plasma precursor "prothrombin" [2]. Nicolas Arthus (1862-1945), discovered the anticoagulant effect of citrate and oxalate in 1890 and demonstrated that there is an absolute requirement for calcium ions in the thrombus formation [3]. Blood platelets, identified in 1865, and their function elucidated by Giulio Bizzozero in 1882 [4], were also suspected of being part of the coagulation process. However, the initiation of the coagulation process was still veiled in mystery. It was presumed that there was some kind of potent material, which was physically prevented from mixing with the blood, either by the blood-vessel wall or by the intact structure of the blood cells/platelets. This substance, or substances, was thought to be capable of hastening clotting and probably initiated the whole process of coagulation. In 1905 Paul Morawitz (1879-1936) named this mysterious substance

"thrombokinase", which today is known as tissue factor (TF). Prothrombin, he hypothesized, was converted into the enzyme thrombin by "thrombokinase" in the presence of calcium. Thrombin then converted fibrinogen into fibrin [5].
Armand Quick, developed the prothrombin time (PT) test in 1935 with the intent of measuring prothrombin [6]. The Quick PT test is, with minor modifications, still the predominant routine plasma method worldwide for screening and monitoring the effects of oral anticoagulation therapy (OAT). Quick's PT test was also instrumental in the discovery of other enzymes (coagulation factors) participating in blood coagulation. Factors V, VII, and X were recognized as a result of Quick's PT test, while other tests, developed during the same period, led to the discovery that activated Factor X (Xa) was the activator of prothrombin. In the 1950's the situation was chaotic with many of the coagulation factors being referred to in the literature by multiple names and subsequently in 1954 the International Committee for the Nomenclature of Blood Clotting Factors was established to promote a common scientific terminology in this field. The usage of Roman numerals rather than eponyms or systematic names was agreed upon during annual conferences between 1957 and 1961 [7]. Assignment of numerals ceased in 1963 after the naming of Factor XIII. Thromboplastin, initially labelled Factor III, was however identified as the combination of phospholipids and tissue factor. Accelerin, initially labelled Factor VI, was found to be activated Factor V. Hence Factors III and VI are today unassigned. The committee has now evolved into the present-day International Society on Thrombosis and Haemostasis (ISTH).

HAEMOSTASIS

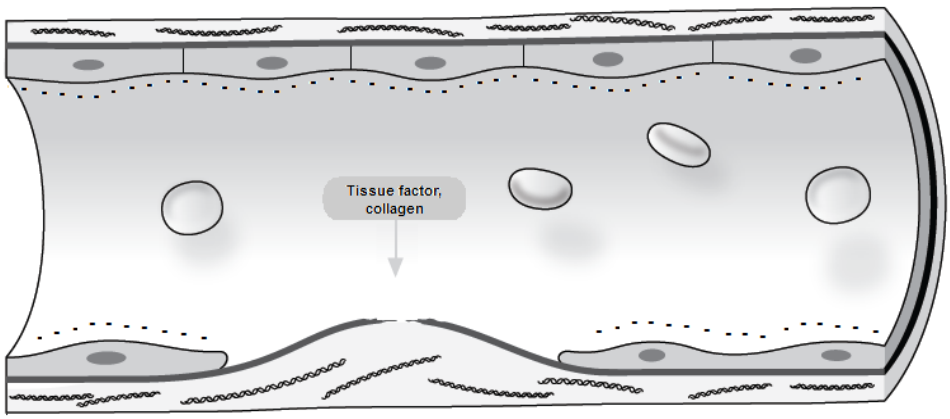
Haemostasis, from the Ancient Greek word for "styptic drug of blood", is by definition the changing of blood from a fluid state to a solid state, a process for keeping blood within a damaged blood vessel. It is one of the body's most important defence mechanisms with its main purpose being to prevent uncontrolled bleeding in conjunction with injury. It is comprised of a balanced system of coagulation and anticoagulation, in a complex cellular process of platelets and endothelial cells, to ensure both sufficient repair of injured blood vessels and to prevent extensive thrombosis formation.
Traditionally there are three main stages in haemostasis:

- Primary haemostasis
  - vasoconstriction, platelet adhesion, aggregation and the formation of a platelet plug.
- Secondary haemostasis
  - plasma coagulation, a series of chain reactions known as the coagulation cascade, ending in the formation of a fibrin network inter-linking with platelets, forming a thrombus.
  - anticoagulation, limiting propagation of thrombus formation, down-regulating and balancing plasma coagulation.
- Fibrinolysis
  - lysis of the thrombus.

Primary haemostasis

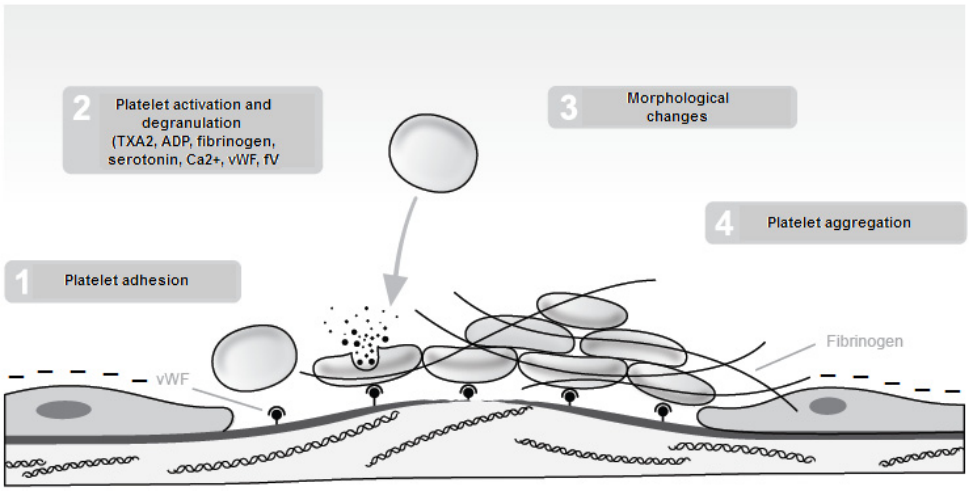
Healthy endothelial cells that line the blood vessel walls are covered by a negatively charged layer of glycocalyx, an endogenous heparin in the form of heparin sulfate which, together with antithrombin produced in the liver, binds to and inactivates circulating coagulation factors. Since platelets are also negatively charged, the endothelial cells and the platelets repel each other. When there is an injury in a blood vessel, local vasoconstriction occurs and the damaged area in the blood vessel is shrunk, thereby reducing the amount of blood leakage. Since the negatively charged endothelial cells are damaged, platelets are less repelled and during vasoconstriction blood flow is slowed down enough to allow platelets to adhere to the vessel wall. Platelets roll over the endothelium and come into contact with collagen and other sub-endothelial thrombogenic components (**Fig.1**), which are exposed in the blood vessel wall. This leads to the activation of platelets, which undergo morphological

Figure 1: Blood vessel damage. Exposure of sub-endothelial thrombogenic components and expression of tissue factor. Healthy endothelium and platelets are negatively charged and repel each other. With permission from Casper Asmussen.



changes. The platelets are altered from a smooth, discoid shape to a more irregular form with pseudo-pods, leading to the emptying of intracellular dense bodies and α-granules and a multi-fold enlargement of the surface of the platelet. The enlarged surface of the platelet, together with an enhanced expression of surface receptors, promotes adhesion and activation of other platelets and coagulation factors. The dense bodies contain ADP, Ca^{2+}, and serotonin, whereas α-granules contain vWF, factor V, Factor XIII and fibrinogen. ADP activates other platelets through ADP-receptors (action sites of the anti-platelet agents clopidogrel, prasugrel and ticagrelor). Ca^{2+} is needed for the activation of coagulation factors and for inter-linkage of platelets, whereas serotonin is a potent vasoconstrictor. The platelet is fixed to the sub-endothelial tissue, through the binding of platelet receptors (GP1b) in the exposed collagen and to collagen-bound von Willebrand factor (vWF) (**Fig.2**). When the surface of the collagen is covered by a mono-layer of platelets, a further aggregation of platelets is maintained by activation through ADP-receptors on platelet surfaces. Thromboxane A_2, released from activated platelets, promotes the expression of GPIIb/IIIa fibrinogen receptors (the site of action for eptifibatid and abciximab), which further promotes platelet aggregation through fibrinogen cross-linking.
Acetylicsalicylic acid, commonly known as aspirin, causes an irreversible inactivation of the cyclooxygenase enzyme required for prostaglandin and thromboxane A_2 synthesis, leading to an inhibitory effect on platelet activation and aggregation. Non-steroidal anti-inflammatory drugs (NSAIDs), such as diclofenac and ibuprofen, are reversible inhibitors of the cyclooxygenase enzyme.

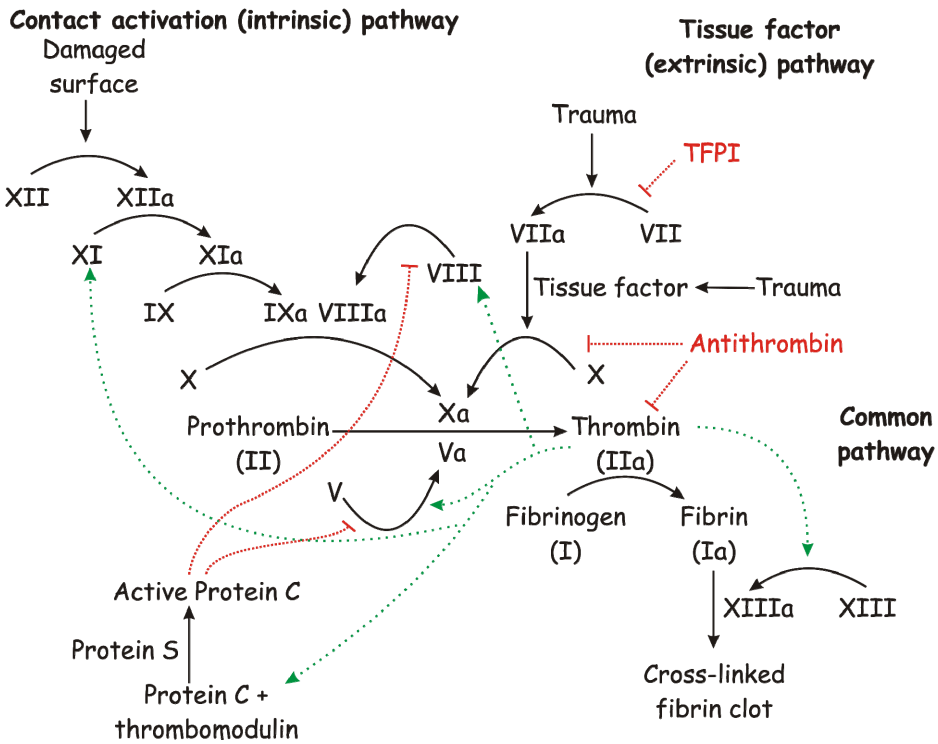
Figure 2: Primary Hemostasis. TXA2 = thromboxane A2, ADP = adenosine diphosphate, vWF = von Willebrand factor, fV = factor V. With permission from Casper Asmussen.



Secondary haemostasis

Since most experiments on coagulation factors have been done in test tubes in laboratory settings (*in vitro*), only mimicking *in vivo* situations it was previously thought that the coagulation cascade consisted of two pathways of equal importance joined in a common pathway leading to fibrin formation. These are the contact activation pathway (intrinsic pathway), and the tissue factor pathway (extrinsic pathway). Deficiencies of any of the active coagulation factors in the different pathways would prolong the coagulation time *in vitro*, prothrombin time (PT), for the extrinsic pathway and activated partial thromboplastin time (APTT) for the intrinsic pathway (**Fig.3**). The coagulation cascade, as a model of the haemostatic process, is however not a map of two different routes to coagulation. Patients deficient in the initial components of the intrinsic pathway (FXII, high-molecular-weight kininogen (HMWK), or prekallikrein) have a prolonged activated partial thromboplastin time (APTT) but no bleeding tendency, indicating that this pathway is redundant. However, components of the intrinsic pathway must play an important role in haemostasis, since patients deficient in Factor VIII [8] or IX [9] have serious bleeding tendencies (Haemohpilia A and B), although the extrinsic pathway is intact. Similarly, patients deficient in FVII also have a serious bleeding tendency [10], although the intrinsic pathway is intact. Thus, the intrinsic and extrinsic pathways cannot operate as independent, redundant pathways *in vivo* as they do in the cascade model.

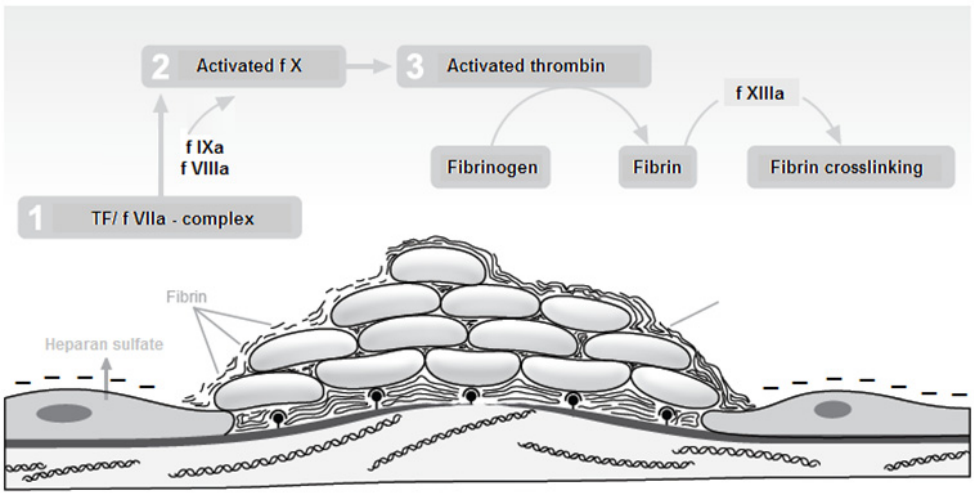
Figure 3. The coagulation cascade demonstrating the contact activation and tissue factor pathway. Routes of inhibitors of active coagulation are marked with red. Positive feedback loops of thrombin are marked in green. TFPI = tissue factor pathway inhibitor.



Instead, the coagulation cascade is a cellular response mechanism involving platelets, endothelial cells and sub-intimal cells. It is now well appreciated that the coagulation cascade does not occur as a consequence of linear activation of different coagulation factors, but rather via a self-augmenting network of simultaneously interacting coagulation factors through a positive feedback mechanism amplifying the output [11]. A positive feedback, in this sense, means that a later enzyme in the clotting cascade either enables or greatly accelerates an earlier step.

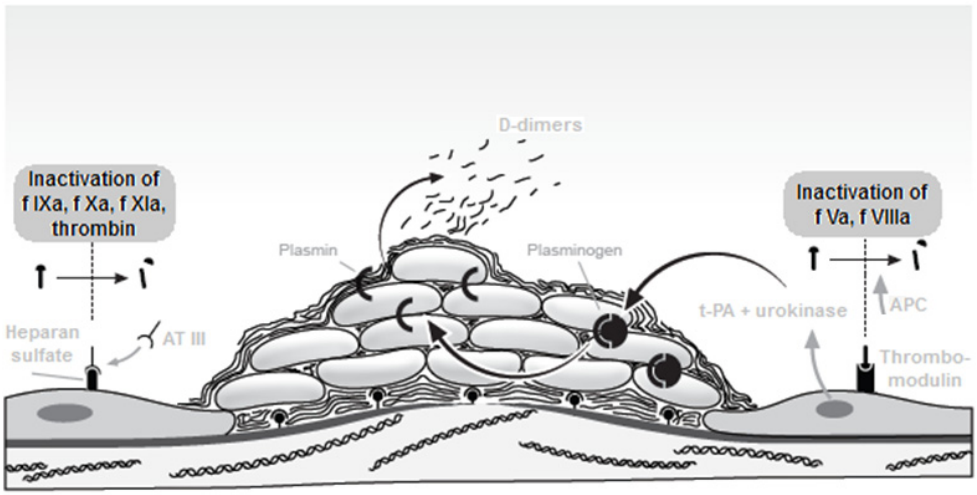
The contact activation pathway (intrinsic pathway), begins with the formation of the primary complex on collagen by HMWK, prekallikrein and FXII which activate FXI. Through activation of FIX, FX is activated, which in turn, in the presence of phospholipids and Ca^{2+}, promotes the formation of thrombin.

Figure 4. Plasma coagulation during secondary hemostasis. TF = tissue factor. With permission from Casper Asmussen.



The primary pathway for the initiation of blood coagulation is the tissue factor pathway. This pathway starts simultaneously with platelet adhesion, when tissue factor (TF) is expressed on the surface of the stromal fibrocytes and leukocytes. TF activates freely-circulating Factor VII (FVII/FVIIa), together forming a TF/FVIIa-complex which in turn activates Factor X (FX/FXa) and Factor V (FV/FVa). The newly formed thrombin-activating FXa/FVa-complex is formed in conjunction with the damaged tissue and converts prothrombin into thrombin (FII/FIIa) (**Fig.4**). This small, initial amount of thrombin is, however, only active adjacent to the damaged endothelium and plays no large role in producing a fibrin network. Instead, thrombin serves more the purpose of further attracting and activating platelets and amplifying the coagulation cascade through the activation of FV and FVIII. This subsequently leads to the activation of FXI, which, in turn, activates FIX. Furthermore, thrombin activates and releases FVIII from being bound to vWF. Through feedback loops, thrombin and FXa are the two main amplifiers of the coagulations cascade (**Fig.3**), and in turn novel mechanisms of anticoagulation (i.e. thrombin inhibitors and factor Xa inhibitors) have targeted these enzymes to prevent coagulation from uncontrollable propagation [12-14].

Figure 5. Mechanisms of fibrinolysis and anticoagulation. AT III = anti-thrombin III, t-PA = tissue plasminogen activator, APC = active protein C. With permission from Casper Asmussen.



Anticoagulation

To prevent the coagulation cascade from propagating through the blood vessels, inhibitors of active coagulation factors are present. Healthy endothelial cells that line the blood vessel walls outside the damaged area are negatively charged and repel platelets. Heparan sulfate on the surface of endothelial cells and antithrombin, bind to and inactivate circulating coagulation factors and thrombin (**Fig.5**). The healthy endothelium also secretes nitric oxide (NO) and prostacyclins that further prevent activation and aggregation of platelets.

The tissue factor pathway inhibitor (TFPI) is a potent reversible inhibitor of mainly FXa but also of thrombin. While FXa is inhibited, the Xa-TFPI complex can further inhibit the FVIIa/TF-complex [15]. A receptor on the healthy endothelial cells (thrombomodulin), binds to thrombin and via activation of the vitamin k-dependent protein C [16] and its co-factor protein S, a complex is formed. This complex cleaves FVa and FVIIIa on the surface of the platelets, thereby sustaining thrombus propagation. Also, as earlier mentioned, the coagulation factors Xa and thrombin are regulated by antithrombin (AT) and inhibition of the coagulation cascade through this mechanism can be greatly enhanced by heparin, which will raise the threshold for coagulation activation. Disorders of these physiological anticoagulation systems, mainly deficiencies in protein C and S, APC-resistance (fV Leiden), and prothrombin gene mutations are well-established causes of thrombophilia [17].

Fibrinolysis

The central purpose of the coagulation system is to generate a platelet plug during blood vessel injury, stabilize this so-called thrombus and seal the injury itself to prevent extensive blood loss. Thrombin produces soluble fibrin monomers by enzymatic cleavage of fibrinogen, which are then assembled side-by-side and end-to-end by FXIII to form a mesh of cross-linked fibrin polymers (**Fig.4**). To further prevent an irreversible expansion of this thrombus, with potential risks of ischaemia and infarction in affected areas distal of the thrombus, additional anticoagulant mechanisms are present. Healthy endothelial cells surrounding the blood vessel injury react to the reduction in blood flow mediated by vasoconstriction and fibrin formation, by releasing tissue plasminogen activator (t-PA) into the blood stream. Fibrin then serves as a cofactor to t-PA for the activation of plasminogen by an enzymatic cleavage, forming plasmin (**Fig.5**). Plasmin mediates fibrin degradation, generating fibrin degradation products [18], such as D-dimers, which can serve as markers for plasmin activation, indicating ongoing fibrinolysis and/or prior thrombus formation.

PROTHROMBIN TIME

The prothrombin time (PT), i.e. the time it takes plasma to clot *in vitro* after the addition of tissue factor, is a measure of the extrinsic pathway of the coagulation cascade. PT is measured in seconds but expressed in international normalized ratio (INR) [19], after correction for the International Sensitivity Index (ISI) (**Fig.6**). The normal range for the INR is 0.8–1.2. The result for a prothrombin time will vary according to the type of analytical system employed, due to differences in tissue factor reagent between manufacturers. Each manufacturer assigns an ISI value for any tissue factor they manufacture, indicating how it compares to an internationally standardized sample. The ISI is usually between 1.0 and 2.0.

The original Quick PT test [6], measuring the activity of vitamin K-dependent coagulation Factors II (prothrombin), VII and X, is the predominant routine plasma method worldwide. However, Factor V and fibrinogen, which are non-vitamin K-dependent coagulation factors, do affect the outcome of the Quick PT. In the Nordic countries, a PT test called Owren PT [20] that only measures the vitamin K-dependent coagulation Factors II, VII and X, is used. This method standardizes concentrations of Factor V, fibrinogen and non-vitamin K-dependent coagulation factors, by adding bovine plasma, free from vitamin K-dependent coagulation factors, along with a citrate buffer, resulting in a final dilution of the original plasma of 1:21 [21, 22]. The prothrombin time can be prolonged as a result of anticoagulation treatment, deficiencies in vitamin K, malabsorption, liver disease, lack of intestinal colonization by bacteria (newborns), and increased consumption during disseminated intravascular coagulation in septicemia.

Figure 6. Calculation of INR for standardization of PT test results [19]. INR = international normalized ratio, PT = prothrombin time, ISI = international sensitivity index.

$$INR = \left(\frac{PT_{test}}{PT_{normal}} \right)^{ISI}$$

ANTICOAGULATION TREATMENT

Early post-surgical complications, such as deep vein thrombosis (DVT), demonstrated the need for a possible way to block the coagulation process and efforts to discover anticoagulants started at the beginning of the 20th century.

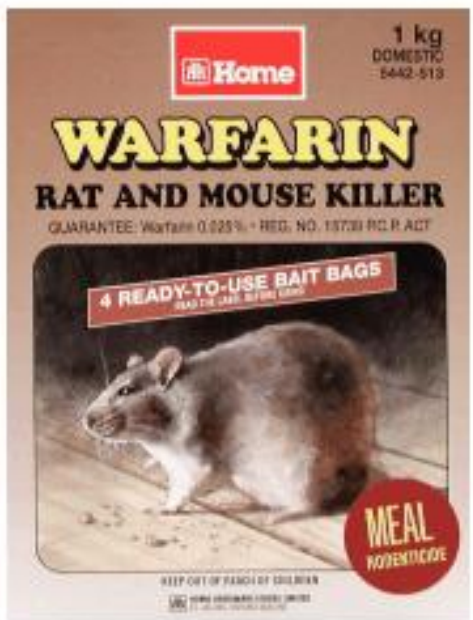
Heparin

In 1916 Jay McLean, a medical student working under William Howell at Johns Hopkins University, isolated a fat-soluble anti-coagulant from canine liver tissue. Howell named anticoagulant heparin (*hepar*; Greek for liver) in 1918. Heparin was however toxic and, in consequence, of no medical value until a non-toxic product became available in 1936. After the Swedish scientist Erik Jorpes published his work on heparin in 1935 [23], the Swedish company Vitrum AB launched the first product for intravenous use. The heparin of today is a highly negatively charged sulfated glucosaminoglycan, which activates antithrombin (AT), and which in turn inactivates thrombin and Factor Xa (**Fig.3**). Besides the use *in vivo*, heparin is also used to prevent blood coagulation outside the body, in test tubes and renal dialysis machines among other things.

Vitamin K antagonist (VKA) therapy

There was an outbreak of a previously unrecognized cattle disease in the United States and Canada in the early 1920's. Cattle were suffering severe spontaneous haemorrhages, and some cattle had died after dehorning and castration. Autopsies demonstrated that all of these animals had bled to death. In 1921, Frank Schofield, a Canadian veterinary pathologist, determined that the cause was ingestion of hay made from spoiled sweet clover. Using tests on rabbits he determined that the spoiled sweet clover functioned as a potent anticoagulant [24]. In 1929 veterinarian L.M. Roderick demonstrated that the bleeding condition after ingestion of spoiled sweet clover was due to a decrease in functioning prothrombin [25]. At the same time the Danish scientist, Henrik Dam, discovered that deficiency in vitamin K ("koagulation") caused a haemorrhagic disease in chickens [26]. These chickens also had deficient plasma levels of prothrombin, the same as in the North American cattle and also, which was later demonstrated, of the other vitamin K–dependent factors (VII, IX, and X). The identity of the haemorrhagic agent in spoiled sweet clover remained however a mystery for another couple of years. In 1933 Karl Paul Link at the University of Wisconsin set out to isolate the haemorrhagic agent from the sweet clover with the intention of making a potent rat poison. It took five years to recover 6 mg of anticoagulant and through degradation experiments it was later established

that the anticoagulant was 3,3'-methylene-bis-(4-hydroxycoumarin), which Link later named dicoumarol. Dicoumarol is a fermentation product from the plant molecule coumarin, which is now known to be present in many plants. Coumarin is responsible for the sweet smell of freshly cut grass or hay and in fact, the original name of "sweet clover" is due to a high content of coumarin in that specific plant. Coumarins have to be fermented by fungi in order to have any anticoagulant properties and a fungal attack of the spoiled sweet clover stalks in large silages explained the presence of dicoumarol. In 1939, Link assigned the patents of dicoumarol to the Wisconsin Alumni Research Foundation and continued working on the development of more potent anticoagulants for use as rat poisons. In 1948 he introduced the most potent substance and named it "warfarin", according to the initials of the foundation (**Picture 1**). Initially thought to be toxic to humans, an unsuccessful suicide attempt in 1952 [27] suggested otherwise and a couple of years later the diverse response in different individuals to a fixed dose of warfarin was reported for the first time [28].



Picture 1. Warfarin as a potent rat poison. www.homehardware.ca

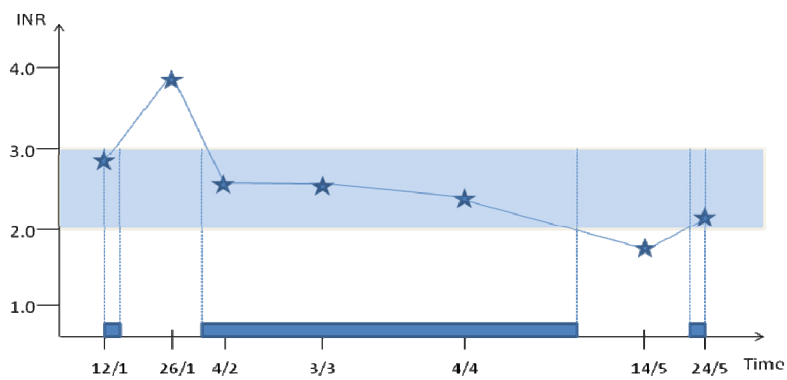
Warfarin, in Sweden sold under the label Waran®, inhibits vitamin K epoxide reductase (VKOR) [29], and especially the subunit VKORC1. VKOR is a "recycling" enzyme that reduces oxidized vitamin K after it has participated in the carboxylation of coagulation factors, mainly Factors II (prothrombin), VII, IX, X, protein C and protein S. Warfarin consists of two isomers, where S-warfarin has five times the potency of the R-isomer with respect to the inhibition of vitamin K reduction. Warfarin is metabolized mainly by the CYP2C9 system. Due to gene polymorphism in VKORC1 [30], making VKOR less susceptible to inhibition by warfarin, and variations in induction of CYP2C9, there is a large individual variation in response to warfarin dosing [31]. Also, patients exhibit a highly variable dose-response that is attributable to disease-related and environmental factors, as well as prescription and non-prescription drugs, dietary vitamin K and alcohol. [32].

The effects of warfarin treatment on blood coagulation is measured in international normalized ratio (INR) using a prothrombin test [6]. The INR target interval of warfarin treatment usually depends on the indication of anticoagulation treatment. The antithrombotic effects of warfarin treatment are not seen directly after administration since previously synthesized vitamin K–dependent plasma clotting factors have to be catabolized and replaced by insufficiently carboxylated molecules. Even though an early prolongation of the INR is seen due to a decline in Factor VII, which has a short half-life, full antithrombotic effect does not take place until a significant reduction in carboxylated Factor II, which has a long half-life, occurs after three to five days. Also, warfarin causes a decline in protein C levels in the first 36 hours which, together with reduced levels of protein S, lead to a shift in the haemostasis system towards a prothrombotic state. Thus, to ensure full protection of thrombus formation or propagation, oral anticoagulation treatment with warfarin can be instituted in conjunction with a more rapidly acting anticoagulant, usually heparin or low-molecular weight heparin (LMWH) [33]. Since the half-life of insufficiently carboxylated thrombin is also long, warfarin treatment must be stopped several days before surgery, while the liver is replenishing the normal vitamin K–dependent factors. In case of bleeding, anticoagulation treatment is stopped and, depending on the severity of bleeding, vitamin K or a concentrate of vitamin K-dependent coagulation factors (i.e. prothrombin complex concentrate, PCC), can be administered repeatedly to provide substrates for thrombus formation.

TIME IN TREATMENT RANGE

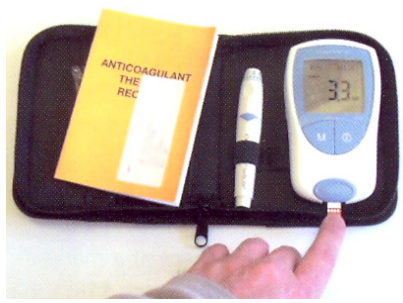
Today, the PT test is the world-wide standardized coagulation test used for monitoring and evaluating the effect of vitamin K antagonist (VKA) therapies. To obtain optimal benefits of anticoagulation control, patients on treatment with VKA therapy need to be maintained within their international normalized ratio (INR) target/reference range, which requires regular monitoring and appropriate adjustment of treatment. The target range depends on the indication of anticoagulation treatment, but since INR <2.0 is associated with an increased risk of thromboembolic events and INR >4.0 is associated with an increased risk of major bleeding events, current recommendations are INR 2.0-3.0 for patients with atrial fibrillation [33, 34] and venous thromboembolism [35], and 2.0-3.5 for patients with mechanical heart valves [34]. The definition of an individual's time in therapeutic range (iTTR) is the percentage of time within the target range, out of the total time of treatment. TTR is calculated with the assumption of a linear increase or decrease between two consecutive INR determinations according to Rosendaal´s method of linear interpolation [36] (**Fig.7**). Meta-analysis of 47 studies of patients with atrial fibrillation on oral anticoagulation treatment with warfarin demonstrated that TTR and the percentage of INRs in range were the most frequently reported measures to determine the therapeutic effectiveness of oral anticoagulation [37], and that TTR had an inversely significant relationship with major bleeding and thromboembolic events, supporting TTR as the optimal measure of INR control.

Figure 7. Calculation of time in therapeutic range (TTR). Blue stars are INR samples at different dates (x-axis). Treatment range in light blue (2.0-3.0). The amount of time in range in dark blue bars on the x-axis. Total treatment time (Jan 12th to May 24th) is 132 days. Days in range 3+91+2=96. TTR 96/132 = 72.7%.



POINT-OF-CARE

Home INR monitoring, so called point-of-care (POC), or near-patient testing (NPT), is becoming increasingly common, especially in Germany where it started, as well as in the UK and the USA. Using methods similar to those patients with diabetes mellitus use for testing blood glucose levels, a drop of capillary blood is obtained using a finger-prick, placed on a test strip in a POC-device and the INR comes up on a display within 30 seconds (**Picture 2**). The procedure is faster and more convenient, usually less painful, and offers the ability for patients to monitor their own INRs closely when required. It is a more flexible procedure which has been shown to improve patients' quality of life [38] compared to scheduled venous blood tests. Testing is used both by patients at home and by anticoagulation clinics, to minimize hospital and primary care visits for regular venous blood sampling. Meta-analysis of 14 studies on patient self-testing with medical support, and patient self-management, where patients adjust their own anticoagulant dose, has also been shown to improve anticoagulation control, demonstrated by TTR, leading to reduced major bleeding and thromboembolic complications [38]. However, a randomized study of 2,922 patients demonstrated that weekly self-testing compared with monthly high-quality clinical testing with TTR, did not delay the time to a first stroke, major bleeding episode, or death to the extent suggested by prior studies, and hence did not support the superiority of self-testing over clinical testing among patients on OAT with warfarin [39]. Using the same principles as the Quick PT, earlier POC-devices have been shown to produce comparable results with traditional Quick PT [40, 41] but have demonstrated differences in mean INR as well as a significant increase in INR difference with increasing INR, compared with Owren-type PT [42]. Difficulties in maintaining precise and reproducible results have subsequently led to some concerns regarding implementation in clinical practice in Sweden [43].

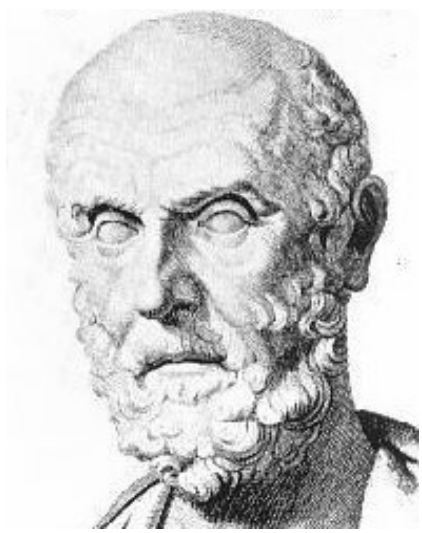


Picture 2. INR measurement test using a POC-device, the CoaguChek S, from Roche Diagnostics.

ATRIAL FIBRILLATION

HISTORICAL BACKGROUND

The typical signs of atrial fibrillation (AF), symptomatic palpitations and a completely irregular pulse, could be very alarming, to a previously asymptomatic person and hence the disease could not pass through medical history without making a footprint. The earliest description of AF may date from ancient China in *The Yellow Emperor's Classic of Internal Medicine* [44]. The authorship of this textbook of medicine has been attributed to the Chinese hero and founder of the Han dynasty, Huang Di (**Picture 3**), but it is recognized today that the original text was altered and revised by many other anonymous authors until the version that is known today arose around 400-200 B.C. The poor prognosis associated with the distinct irregularity of the pulse, was acknowledged by many of the ancient physicians. Hippocrates (**Picture 3**) described a patient with a

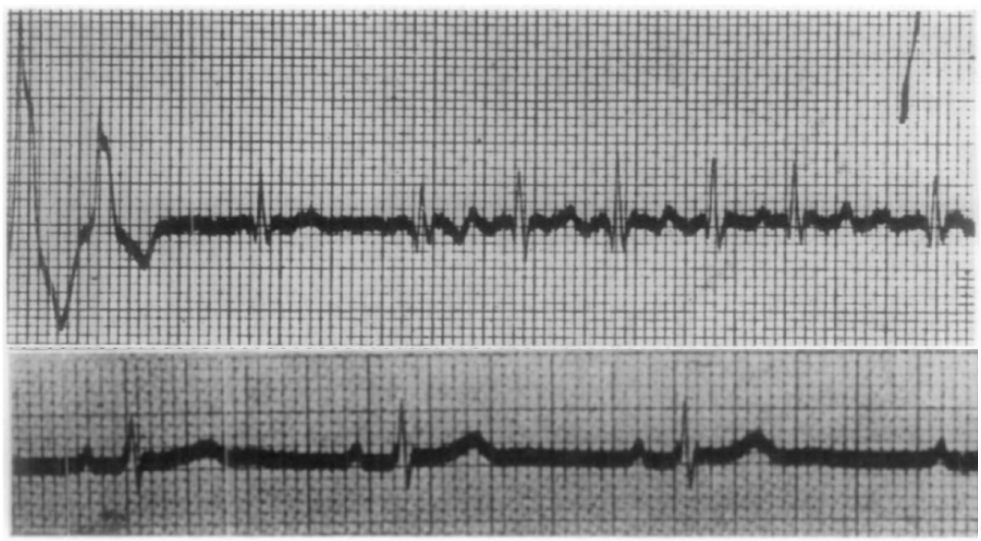


Picture 3. The yellow Emperor Huang-Di (2696-2598 B.C) and Hippocrates (approx 460-370 B.C)

poor prognosis and "violent palpitations of the heart" [45] around the year 400 B.C, although this could also have been another arrhythmia than AF. During the 19th century, the completely irregular pulse associated with AF in humans was associated with diseases such as mitral stenosis and atherosclerosis in the heart. The pulse waves in AF were first recorded using an instrument by C.W.H Nothnagel in 1876. He named this phenomenon "*delirium cordis"* and demonstrated that "*In this form of arrhythmia the heartbeats follow each other in complete irregularity. At the same time, the height and tension of the individual pulse waves are continuously changing*" [46, 47]. H.E Hering, who believed this state of arrhythmia to be permanent, named it *"pulsus irregularis perpetuus"* [48]. J. Mackenzie demonstrated in 1904 that the atrial pulse waves, measured in jugular veins, disappeared at the onset of the persistent irregular arterial pulse and returned when the pulse became regular again [49] and Hering later confirmed these findings [50]. Later, it was generally accepted that the three essential features of the *"pulsus irregularis perpetuus"* or *"the absolutely irregular heart"* were an absolute irregularity of the arterial pulse, the persistence of the rhythm and the absence of demonstrable activity of the atria manifested by the absence of venous atrial pulse waves [46, 51] . The association of electricity and AF was first noted in 1874 when E.F.A Vulpian observed the irregular atrial behaviour that he termed *"fremissement fibrillaire"* in canine hearts *in vivo* [52] after applying a strong electrical current to the atria.

The diagnosis of atrial fibrillation (AF), by today's standards, requires the measurement of the electrical activity in the heart and Willem Einthoven, the inventor of the string galvanometer (the first electrocardiograph), published the first ECG in a human being, showing AF in 1906 [53, 54], without however, recognizing its true nature (**Picture 4**) [46]. In 1910, during electrocardiographic studies Thomas Lewis, working in London, stated that the fine oscillations between the R waves, already noted by others (J. Mackenzie and K.F. Wenckebach) but thought to be distur-bances, were evidence of atrial activity throughout the cardiac cycle [55]. From a detailed study of the chest leads, Lewis demonstrated that these oscillations originated from the atria rather than from the atrioventricular (AV) node, which was until then commonly accepted after J. Mackenzie's research [46]. Also, Lewis noticed that the R wave on the ECG was relatively normal with a preserved electrical vector during irregular pulse and stated that ventricular contraction must therefore originate from its usual starting point. Lewis had the opportunity to observe the phenomenon of heart irregularity *in situ* in horses, where he saw the auricles of the atria trembling, with the same findings of ECG and venous pressure curves, and he named this phenomenon *"auricular fibrillation"* [55, 56]. At almost the same time in Vienna, Rothberger and Winterberg produced similar research and named the arrhythmia *"Vorhofflimmern"* [57].

The mechanism of atrial (auricular) fibrillation has been under debate since the early 20th century and today, electrophysiologists are still not in agreement on the subject. Early theories ranged from an extreme acceleration from a single focus in the atria at speeds of 3,000 impulses per minute [58], to circus movement or reentry, as in atrial flutter [59, 60]. Today, the present understanding of AF is that it involves both processes of multiple self-sustaining reentrant wavelets [61], and enhanced automaticity (triggers), with rapidly firing groups of cells in the atria, especially around the orifices of the pulmonary veins [62, 63]



Picture 4. The first electrocardiograms from 1906 demonstrating atrial fibrillation (top) and a normal sinus rhythm (bottom). From the translation of *Le telecardiogramme* by W. Einthoven [53, 54].

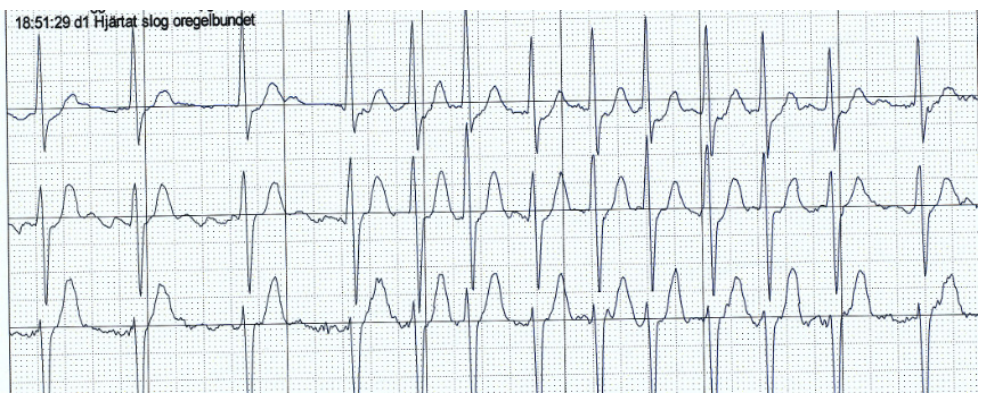
DEFINITION

According to the most recent ESC guidelines for the management of atrial fibrillation, AF is defined as a cardiac arrhythmia with the following characteristics [33] :

- The surface ECG shows 'absolutely' irregular RR intervals (**Picture 5**). AF is therefore sometimes known as *arrhythmia absoluta*, i.e. RR intervals that do not follow a repetitive pattern.

- There are no distinct P waves on the surface ECG. Some apparently regular atrial electrical activity may be seen in some ECG leads, most often in lead V1.

- The atrial cycle length (when visible), i.e. the interval between two atrial activations, is usually variable and <200 ms (>300 bpm).



Picture 5. Atrial fibrillation in 3-lead electrocardiogram. Irregular RR-intervals with no distinct p-waves and a period with enhanced automaticity probably originating from the orifices of the pulmonary veins.

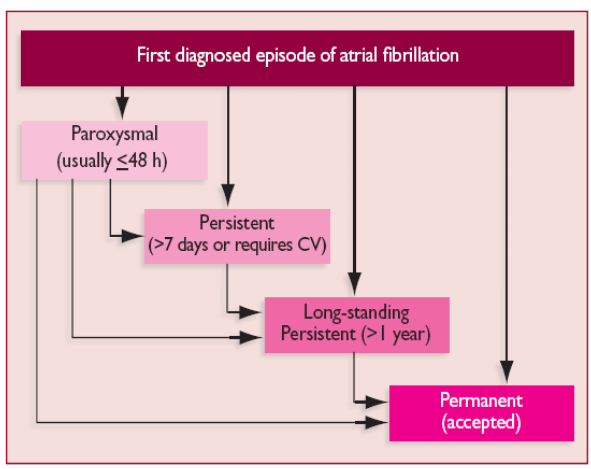
EPIDEMIOLOGY

Atrial fibrillation is the most common cardiac arrhythmia. The prevalence in the general population is age-dependent and estimated at 1-2%, increasing to nearly 10% in those aged over 80 years [33, 64, 65]. In Sweden however, the total prevalence of AF is not known. A study of the prevalence of patients with AF in the Swedish population during 2007 demonstrated that 1.1%, or 100,557 out of 9,182,927 individuals were identified with AF either as a primary or as a secondary diagnosis in hospital care [66]. However, there are additional patients treated in primary health care, and patients with no hospital/primary care contact, the number of which can only be approximated due to a suggested high number of patients with asymptomatic AF. Studies focused on elderly patients, a population with a significant burden of AF, have reported an incidence of asymptomatic AF of between 10% and 40% [33, 67], which is probably underestimating the true incidence, due to low-intensity monitoring. Approximations of up to 140,000-150,000 AF patients in Sweden have recently been proposed [66] . The number of patients with AF is likely to increase in forthcoming years as the proportion of elderly in the population is rising due to improved survival rates in diseases such as cancer, coronary heart disease, stroke, and heart failure [64].

CLASSIFICATION

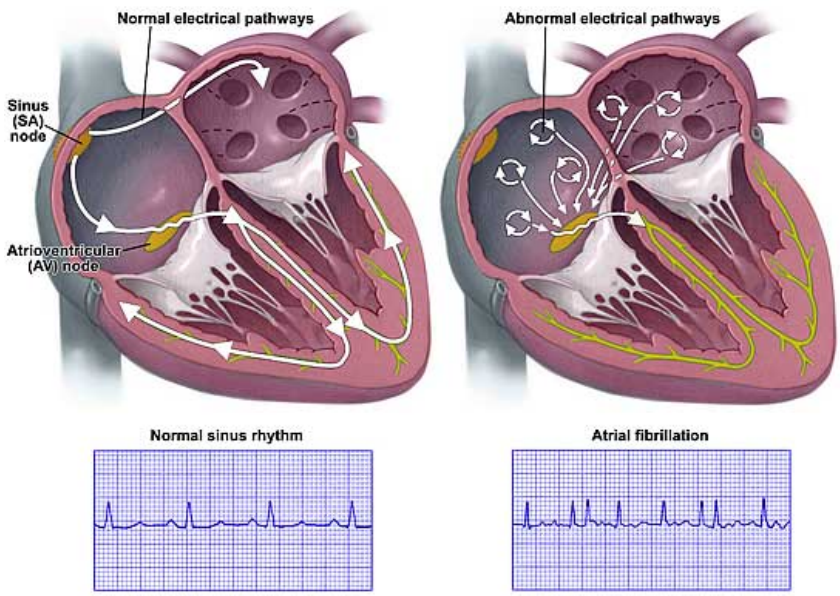
The currently recommended classification scheme of AF [33], is based on the presentation and duration of the arrhythmia at the first time the patient is introduced to the clinic (**Fig.8**). In patients with symptomatic palpitations it is usually an easy task to distinguish the onset and the duration of AF. However, in patients with longstanding tachycardia-mediated symptoms such as fatigue, shortness of breath and mild congestive heart failure, but without palpitations, it is generally not possible to determine the onset of AF with absolute certainty. In addition, in totally asymptomatic patients, it is impossible to determine whether the AF is paroxysmal, persistent or sometimes even long-standing. The term "silent AF", is usually associated with an asymptomatic episode of AF, diagnosed by coincidence during, for example, a yearly visit at the general practitioner's office or in conjunction with another clinical condition. The term "lone AF" is used to describe younger patients (<60 years) with AF and no cardiovascular, cardiopulmonary or co-morbid disease. However, growing evidence of numerous pathogenic mechanisms, environmental and genetic factors related to AF raises the question of whether "lone AF" really does exist at all [68].

Figure 8. Different types of AF. The arrhythmia tends to progress from paroxysmal (self-terminating, usually <48h) to persistent (non-self-terminating or requiring cardioversion (CV)), long-standing persistent (lasting longer than 1 year) and eventually to permanent (accepted) AF. First-onset AF may be the first of recurrent attacks, or already be deemed permanent. AF = atrial fibrillation, CV = cardioversion. Reprinted from *The ESC Guidelines for the management of atrial fibrillation* [33].



MECHANISMS

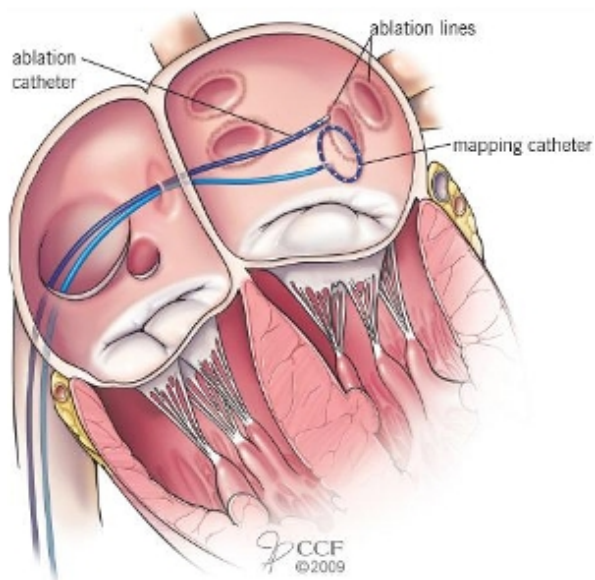
Structural heart disease, such as valve disease and hypertension, triggers a progressive process of structural remodelling in both the ventricles and the atria of the heart [69]. Proliferation and differentiation of fibroblasts into myofibroblasts and subsequent development of fibrosis, leads to electrical dissociation between muscle bundles, creating small electro-anatomical substrates that can facilitate multiple small re-entrant circuits [61, 69] (**Picture 6**). Due to shorter refractory periods, cells around the orifices of the pulmonary veins have a stronger potential to act as triggers and perpetuate atrial fibrillation [63]. Further progression of comorbid diseases, with subsequent structural changes in the atria, can lead to atrial dilatation and progression of AF from paroxysmal to more persistent or permanent forms. Hence, the early detection of AF could provide an opportunity to introduce therapies, such as ACE-inhibitors and statins, treating the underlying disease and subsequently halt or slow progression of AF from a potentially treatable condition, to an utterly refractory and irreversible problem [70].



Picture 6. Electrical pathways in depolarization of the heart in sinus rhythm (left) and in atrial fibrillation (right). Right picture demonstrates reentry wavelets, originating from the orifices of the pulmonary veins in the left atria. www.doctortipster.com.

MANAGEMENT

The medical treatment of AF patients mainly involves treating concomitant cardiovascular diseases, reducing symptoms, and preventing complications associated with AF, especially thromboembolic stroke [33]. It is essential to obtain an adequate control of ventricular rate during AF, especially since high ventricular rates are associated with both acute symptoms, such as shortness of breath, chest pain, fatigue and dizziness, and since long-standing tachycardia can induce tachycardia-mediated cardiomyopathis. The treatment of hypertension, anemia, heart failure, thyreotoxicosis, underlying infectious diseases and poorly-controlled diabetes mellitus, can alleviate symptoms, decrease ventricular rate, and have an effect on both the enhanced automaticity in the atrias, as well as long-term effects on remodelling. Hence, a patient cannot be evaluated regarding the symptoms of AF itself until an adequate rate control is achieved. Additional symptom relief may however require rhythm control therapy, by cardioversion (CV), antiarrhythmic drugs, invasive ablation therapy (**Picture 7**), or open heart surgery (Maze).



Picture 7. Pulmonary vein ablation. Femoral vein approach and trans-septal puncture to access the left atria and the pulmonary veins. Ablation using high radiofrequencies induces a small transmural ring of necrosis around the orifices of the pulmonary veins to stop propagation of rapid depolarizations from cells with enhanced automaticity, acting as triggers of atrial fibrillation. From the Cleveland Clinic Journal of Medicine, 2009. 76(9):545.

THROMBOGENESIS

An autopsy study in patients with previous strokes demonstrated the presence of an intracardiac thrombus in 20% of deceased patients with atrial fibrillation [71] and in an autopsy study from 1972, 46/74 patients with long-term AF (>1 month) and 3/19 with short-term AF (<2 weeks) had a thrombus in their left atrial appendage (LAA) [72]. In patients with non-valvular AF 90 % of all atrial thrombi originate from the LAA [73]. The thrombogenesis in AF seems to be related to several underlying pathophysiological mechanisms. During AF there is no coordinated contraction of the atria and subsequently only passive diastolic ventricular filling of blood. Stasis in the left atrium, with an abnormal blood flow seen as spontaneous echocontrast, is generally mimicking more of a venous blood flow rather than an arterial. Anatomical and structural defects, such as atrial dilatation, endocardial denudation, and fibroelastic infiltration of the extracellular matrix, lead to abnormal changes in atrial walls. Additionally, haemostatic and platelet activation, inflammation, and growth factor changes contribute to thrombogenesis. All these changes result in the fulfilment of Virchow's triad for thrombogenesis and, in accordance with the hypercoagulable state in this arrhythmia [74], predisposes for thrombus formation, especially in the LAA, and a subsequent risk for systemic embolism.

The dissociation of a part of the thrombus from the LAA can lead to the most feared complication in AF, thromboembolic stroke. The risk of stroke is increased fivefold in the presence of AF [65], and it is estimated that in one out of every four strokes, AF is the source of thromboembolism. A meta-analysis [75] of different trials of anticoagulation treatment in atrial fibrillation, has demonstrated an average yearly stroke rate of 4.5% for patients without a previous stroke (primary prevention) and 12% per year for patients with a previous history of stroke (secondary prevention) in the placebo/no treatment group. Hence, the most important treatment goal in atrial fibrillation is to reduce thromboembolic complications.

ANTI-THROMBOTIC TREATMENT

Antiplatelet therapy

A meta-analysis of different randomized controlled trials [76-82] of aspirin versus placebo/no treatment in AF, showed that aspirin was associated with a 19% (95% CI, -1% -35%) reduction of stroke [75]. There was an absolute risk reduction of 0.8% per year (number needed to treat (NNT) 125) for primary prevention trials and 2.5% per year (NNT 40) for secondary prevention trials. However, there was a marked variation in the dose of aspirin between the studies (50-1300 mg), and results were not consistent over the individual trials. Hence, no evidence favours one dosage of aspirin over another [75]. However, since an almost complete pharmacological platelet inhibition is achieved with aspirin 75 mg, and bleeding rates are greater with higher doses of aspirin, doses of 75- 100 mg daily are recommended for patients in whom antiplatelet therapy is considered [33]. Dual anti-platelet treatment with clopidogrel and aspirin have demonstrated a small reduction in stroke but also an increased risk of bleeding, compared to mono-therapy with aspirin in patients with AF [83]. An increased risk of bleeding has also been seen in high-risk patients with previous stroke/transitory ischaemic attack (TIA), when adding aspirin to clopidogrel without the benefit of a reduction in recurrent strokes [84]. If anticoagulation therapy is found to be unsuitable, the combination of aspirin and clopidogrel therapy could perhaps be considered as an alternative, but only if anticoagulation therapy is not considered suitable because of a high bleeding risk.

Anticoagulation therapy

Six large randomized trials [76, 77, 79, 85-87], one of which focused on secondary prevention [79], have evaluated adjusted-dose vitamin K antagonists (VKA), such as warfarin and coumadin, for the prevention of thromboembolism in patients with AF. According to meta-analysis [75], treatment with VKA was associated with a 64% (95% CI, 49-74%) reduction in stroke, corresponding to an absolute risk reduction of 2.7% for primary prevention (NNT=37) and 8.4% (NNT=12) for secondary prevention.

Meta-analysis of 12 comparisons of VKA with antiplatelet therapy alone [75], has shown that treatment with adjusted-dose VKA was associated with a 37% (95% CI, 23- 48%) reduction in stroke. In ACTIVE-W [88], VKA therapy with adjusted-dose warfarin was demonstrated to be superior to the combination of anti-platelet therapy of clopidogrel plus aspirin with a 40% reduction in stroke.

In the elderly population, the BAFTA trial [89] demonstrated that VKA therapy with adjusted-dose warfarin (target INR 2.0-3.0), was superior to aspirin 75 mg daily with

a 52% reduction in a combined primary endpoint of stroke, intracranial haemorrhage, and clinically significant arterial embolism. No difference in the risk of major bleeding between warfarin and aspirin was seen.

Novel anticoagulants

Several new anticoagulants have been developed for the prevention of thromboembolic events in patients with AF. Two main classes can be identified, the oral direct thrombin inhibitors (ximelagatran, dabigatran and AZD0837) and the oral factor Xa inhibitors (apixaban, rivaroxaban, edoxaban, betrixaban and YM150).

Thrombin inhibitors

In clinical trials, ximelagatran demonstrated similar rates of thrombo-embolism and lower rates of major bleeding compared to OAT with warfarin [90, 91], but the drug was withdrawn due to hepatotoxicity and because major adverse cardiovascular events were observed in other studies. In the RE-LY trial, dabigatran in a dose of 110 mg b.i.d. demonstrated comparable rates of thromboembolic events with lower rates of major bleeding, whilst dabigatran 150 mg b.i.d. was associated with lower rates of thromboembolic events with similar rates of major bleeding, compared to OAT therapy with warfarin [12]. Mean TTR for the warfarin population was 64%.There were, however, differences between age groups as demonstrated by a subgroup analysis [92], where the higher dose of dabigatran was clearly beneficial in patients <75 years but was associated with an increase of major bleeding events compared to warfarin in patients ≥75 years. A marked and significant reduction in intracerebral bleeding was seen with both doses of dabigatran irrespective of age, but a selective increase in major gastrointestinal bleeding for the lower gastrointestinal tract was seen [92]. Data from a phase II trial of the thrombin inhibitor AZD0837 have demonstrated similar suppression of thrombogenesis at a potentially lower bleeding risk compared with dose-adjusted VKA with warfare [93].

Factor Xa inhibitors

A trial comparing apixaban and acetylsalicylic acid (AVERROES) was stopped early due to a significant reduction in thromboembolic events with apixaban 5 mg b.i.d. compared with aspirin 81–324 mg in patients who were intolerant of/unsuitable for VKA therapy [13]. In the recently published ARISTOTLE-trial, comparing apixaban and OAT with warfarin, apixaban was shown to be non-inferior to warfarin on the combined outcome of thromboembolic events [94]. In addition, apixaban met the secondary endpoints of superiority on efficacy and major bleeding compared with warfarin. The mean TTR in the warfarin-treated population was 62%. The recently published ROCKET-AF [14] trial met its primary efficacy end point of non-

inferiority to OAT with warfarin with regard to thromboembolism with comparable rates of major bleeding. Mean TTR in the warfarin-treated population was 55%. A recent study has proposed the possibility of reversing the anticoagulation effect of rivaroxaban by PCC, but has failed to establish a similar effect on OAT with dabigatran, indicating possible advantages in this aspect for Factor Xa-inhibitors [95].

RISK STRATIFICATIONS

Thromboembolic risk

The risk of stroke varies with age and co-morbidities, where prior stroke/TIA/thromboembolism, age, hypertension, diabetes, and structural heart disease have been identified as important risk factors for thromboembolic events in patients with AF [96]. The simplest and today the most adopted risk score, is the $CHADS_2$-score [33, 96], which is based on a point system in which 1 point each is assigned for cardiac failure, hypertension (treated/untreated), age ≥75 years, diabetes mellitus, and 2 points are assigned for a history of stroke/TIA (**Fig.9**).

The $CHADS_2$-score can be used as a simple measurement of assessing stroke risk, for easy use by general practitioners, and other medical specialists. In patients with a $CHADS_2$-score of ≥2, chronic oral anticoagulation treatment (OAT) with an INR target range of 2.0–3.0, is recommended by the European Society of Cardiology [33], given no contraindications of treatment are present. OAT is recommended in patients with a $CHADS_2$-score of ≥2. Recently, new tools for stroke risk assessment, using a more comprehensive risk factor-based approach, have been developed [97] for use in patients with a $CHADS_2$-score of 0–1, the CHA_2DS_2- VASc –score (**Fig.10**). This scheme is based on a point system in which 2 points are assigned for a history of stroke/transitory ischaemic attack (TIA), or age ≥75; and 1 point each is assigned for cardiac failure, hypertension, diabetes, vascular disease age 65–74 years, and female sex.

Figure 9. Calculation of stroke risk in atrial fibrillation. The $CHADS_2$-score: Cardiac failure, Hypertension, Age, Diabetes Mellitus, Stroke/TIA. Absolute risks of stroke based on a multivariate analysis (assuming no aspirin use) of data from a cohort of 1733 hospitalized AF patients. Reprinted from *The ESC Guidelines for the management of atrial fibrillation* [33] and adapted from Gage et al [96].

$CHADS_2$ score	Patients (n=1733)	Adjusted stroke rate (%/year)[a] (95% confidence interval)
0	120	1.9 (1.2–3.0)
1	463	2.8 (2.0–3.8)
2	523	4.0 (3.1–5.1)
3	337	5.9 (4.6–7.3)
4	220	8.5 (6.3–11.1)
5	65	12.5 (8.2–17.5)
6	5	18.2 (10.5–27.4)

Figure 10. Calculation of stroke risk in atrial fibrillation. The CHA_2DS_2-VASc-score : Cardiac failure, Hypertension, Age, Diabetes Mellitus, Stroke/TIA, Vascular disease, Age 65-75 years, Sex category (i.e female sex). Absolute risks of stroke based on a multivariate analysis from the Euro Heart Survey on atrial fibrillation by Lip et al [97]. Reprinted from *The ESC Guidelines for the management of atrial fibrillation* [33].

Risk factor	Score
Congestive heart failure/LV dysfunction	1
Hypertension	1
Age ≥75	2
Diabetes mellitus	1
Stroke/TIA/thrombo-embolism	2
Vascular disease[a]	1
Age 65–74	1
Sex category (i.e. female sex)	1
Maximum score	**9**

CHA_2DS_2-VASc score	Adjusted stroke rate (%/year)[b]
0	0%
1	1.3%
2	2.2%
3	3.2%
4	4.0%
5	6.7%
6	9.8%
7	9.6%
8	6.7%
9	15.2%

In patients with a score of 0, antiplatelet therapy can be considered, but no therapy is recommended, and in patients with a score of 1, antiplatelet therapy can be considered but anticoagulation therapy is recommended. In patients with a CHA_2DS_2- VASc-score of ≥2, there is an absolute recommendation of anticoagulation therapy.

Patients with paroxysmal AF should be regarded as having a risk of thromboembolic events similar to those with persistent or permanent AF, and the same risk factors apply for risk stratification [78, 98, 99]. Patients with lone AF have a very low cumulative stroke risk, estimated to be 1-2% over 15-30 years [100] and hence anticoagulation treatment is not recommended in these patients [33]. In the Japan Atrial Fibrillation Stroke Trial [82], patients with lone AF were randomized to treatment with aspirin (150– 200 mg/day) or to a control group without antiplatelet or anticoagulant therapy. In this trial treatment with aspirin caused a non-significant increased risk of major bleeding (1.6%) compared with the controls (0.4%), indicating that in these patients antiplatelet therapy confers a substantial risk without a certain benefit of treatment. Lone AF is, however, only lone until it is accompanied by a risk factor and hence the risk of stroke in patients with lone AF is not static. Since the risk of stroke is associated with age, a continuous variable and no on/off phenomenon, the risk of stroke in young patients with lone AF must be reassessed for risk factors for stroke over time. In a study of lone AF, all patients who had a cerebrovascular event during a follow-up period of over 25 years, had developed ≥1 risk factor for thromboembolism during the study period [100].

Bleeding risk

The risk of bleeding during antithrombotic therapy in patients with AF is very heterogeneous, and several clinical risk factors have previously been incorporated into clinical bleeding risk stratification. An algorithm for predicting risks for major bleeding during anticoagulation treatment in atrial fibrillation has recently been proposed, the HAS-BLED-score [101] (**Fig.11**). One point each is assigned for Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly, and concomitant use of Drugs/Alcohol. Abnormal renal function is defined as haemodialysis or plasma creatinine >200 μmol/L. One problem when using risk scores for predicting thromboembolic and major bleeding events is however that many of the risk factors are risk factors for both thromboembolism and major bleeding.

Figure 11. Calculation of bleeding risk in atrial fibrillation. The HAS-BLED-score: Hypertension, Abnormal Renal/Liver Function, Stroke, Bleeding History or Predisposition, Labile INR, Elderly,and concomitant use of Drugs/Alcohol. Absolute risks of major bleeding based on a multivariate analysis from the Euro Heart Survey on atrial fibrillation by Lip et al [101]. Reprinted from *The ESC Guidelines for the management of atrial fibrillation* [33].

Letter	Clinical characteristic[a]	Points awarded
H	Hypertension	1
A	Abnormal renal and liver function (1 point each)	1 or 2
S	Stroke	1
B	Bleeding	1
L	Labile INRs	1
E	Elderly (e.g. age >65 years)	1
D	Drugs or alcohol (1 point each)	1 or 2
		Maximum 9 points

CHRONIC KIDNEY DISEASE

The incidence of AF and chronic kidney disease (CKD) are age-dependent and increase with increasing age [102]. The frequency of AF in patients with end-stage renal failure is 10- to 20-fold higher than in the general population [102, 103]. A commonly used surrogate marker for the estimation of kidney function is the Cockcroft-Gault formula [104], commonly referred to as estimated glomerular filtration rate (eGFR), expressed in mL/min.

Patients with end-stage renal failure are at increased risk for thromboembolic events due to different platelet and coagulation abnormalities [105]. Various comorbidities (hypertension, diabetes, heart failure) may well be contributory to the increased risk seen. In a large prospective cohort study of patients with AF, low eGFR was associated with an increased risk of thromboembolic events with hazard ratios of 1.39 and 1.16 for an eGFR of <45 mL/min and an eGFR of 40-59 mL/min compared with an eGFR of >60 mL/min [106]. Another study of patients on haemodialysis has demonstrated a risk of ischaemic stroke of 4.75 per 100 patient-years among patients

with AF compared to 0.48 per 100 patient-years in patients with sinus rhythm [107]. Patients with severe renal impairment have increased risk factors for bleeding and pathophysiological reasons include platelet abnormalities, uremic toxins, uncontrolled hypertension, and altered blood rheology [105]. These patients are also at greater bleeding risk with oral anticoagulation therapy with warfarin. In a study of 578 patients with AF and impaired kidney function, patients with eGFR <30 mL/min required lower doses of warfarin independent of VKORC1 and CYP2C9 genotypes, spent less time within therapeutic INR target range, and were at higher risk of overanticoagulation (INR>4.0) [108]. The percentages of time within treatment range were 49.7% and 45.6% for eGFR >60 mL/min and <30mL/min, respectively, and patients with severe renal impairment had a 2.4-fold risk of major bleeding compared to patients with lesser degrees of renal dysfunction. Impaired kidney function has also been shown to be associated with a greater need for warfarin dose adjustment [109].

There are no randomized controlled trials that have assessed the risk/benefit of full anticoagulation treatment in patients with severely impaired kidney function. Algorithms for oral anticoagulation in atrial fibrillation and chronic kidney disease have been proposed [101, 105] and the recognition of a significant bleeding risk with impaired renal function has led to a debate over the risk-benefit balance for using warfarin in chronic kidney disease patients, particularly if they need dialysis [110-112]. Guidelines are controversial [105], since our current risk stratification schemes are based on studies that have actively excluded end-stage renal failure patients [76, 77, 79, 85, 86, 89]. In recent trials of the novel anticoagulants, the apixaban (ARISTOTLE) [13] and rivaroxaban (ROCKET-AF) [14] and trials also employed a renal function exclusion criteria of <20 and <30 mL/min, respectively. The latter (GFR<30 mL/min) was also used in the RE-LY-trial (dabigatran) [12]. However, the rivaroxaban and apixaban trials also applied lower doses of the study drugs to patients with moderately impaired renal function. A subgroup analysis of the ROCKET-AF trial patients with GFR 30-49 mL/min demonstrated higher rates of stroke and bleeding in these patients, compared with patients with normal renal function [113]. In this subgroup analysis rivaroxaban was still non-inferior to warfarin.

AIMS OF THE THESIS

- **Paper I:** To report patient characteristics, individual (iTTR) and centre (cTTR) times in therapeutic range, for the participating centres in AuriculA, and, in a subgroup of two centres, the correlation between iTTR, major bleeding and thromboembolic complications during 2008.

- **Paper II**: To study the prevalence of impaired kidney function in AF patients on anticoagulation treatment with warfarin in comparison to a healthy reference group, using two different equations of eGFR.

- **Paper III:** To investigate the relationship between iTTR, eGFR, major bleeding and thromboembolic complications in a cohort of patients on OAT with warfarin.

- **Paper IV:** To compare and evaluate capillary INR results from a POC-device, as a more convenient method of monitoring, with regular venous INR analyzed using Owren PT.

MATERIAL AND METHODS

All studies in this thesis are based on patients on OAT with warfarin in the Anticoagulation Clinic at Skåne University Hospital Malmö, formerly known as the University Hospital in Malmö, UMAS. This hospital serves a regional catchment area of approximately 300,000 inhabitants and is one of the largest hospitals in Sweden. All patients on OAT with warfarin in the Anticoagulation Clinic are included in the internet-based Swedish national quality register AuriculA (Atrialt flimmer och Antikoagulation). AuriculA, created in 2006, is a register of patients with atrial fibrillation, which includes key patient characteristics, information on risk factors for thromboembolism, current treatment, concurrent illnesses, and previous investigations of cardiac function. However, AuriculA also has a separate part for warfarin dosing regardless of treatment indication, which was created with the intent to improve the quality of anticoagulation treatment and to evaluate the benefits of modifications. This integrated dosing algorithm suggests the appropriate dosage of warfarin based on the last two INR results. Key outcome measures for patients on anticoagulation treatment in AuriculA are thromboemolic events and major bleeding according to ISTH (International Society on Thrombosis and Haemostasis) definitions [114, 115]. All studies in AuriculA comply with the Declaration of Helsinki and research using this register has been approved by the Ethics Committee at Lund University.

PAPER I

Data on age, gender, treatment indications, dosage of warfarin, number of INR tests and TTR was extracted from the national database AuriculA for all 18,391 patients listed during the period 1st January 2008 to 31st December 2008. A follow-up of all 4,273 patients registered during the same time period at the Skåne University Hospital, Malmö and the General Hospital in Sundsvall, regardless of indication of anticoagulation treatment, was also performed. Although data on complications has been collected prospectively in AuriculA, through routine follow-up telephone calls, a review of all hospital records of every patient has assured that no complications were missed.

PAPER II

Out of a total of 4,298 patients, data on age, gender, and treatment indications were extracted from the national database AuriculA for all 2,671 patients with AF on OAT with warfarin, eligible on June 1st, 2009 at Skåne University Hospital in Malmö. A database containing all laboratory results of blood analysis in the region's catchment area was used to collect levels of plasma creatinine (p-Cr). As a reference group, subjects from the ongoing, longitudinal population-based project, "Good Ageing in Skåne" (GÅS), part of the Swedish National Study on Ageing and Care [116], were included. The GÅS study includes 2,931 subjects aged ≥59 years, recruited from February 2001 to July 2004, and selected for being representative of the Swedish general population with respect to age, gender distribution and marital status. Six hundred and seventy subjects in this reference group treated with warfarin and/or diagnosed with AF were excluded, leaving a total of 2,261 subjects eligible for the study. Two different formulas were used for calculating eGFR:

The IDMS-traceable four-variable Modification of Diet in Renal Disease (MDRD) Study equation [117]: $175 \times (\text{p-Cr}/88.4)^{-1.154} \times \text{age}^{-0.203} \times 0.742$ (if female) $\times$ 1.212 (if Afro-American).

The Lund-Malmö (LM) equation, derived and internally validated at the present University Hospital [118] : $e^{X - 0.0124 \times \text{age} + 0.339 \times \ln(\text{age}) - 0.226 \text{ (if female)}}$

$X = 4.62 - 0.0112 \times \text{p-Cr}$ if p-Cr <150 μmol/L,
$X = 8.17 + 0.0005 \times \text{p-Cr} - 1.07 \times \ln(\text{p-Cr})$ if p-Cr ≥150 μmol/L.

Ethnicity was, however, not taken into consideration using the MDRD formula since AuriculA contains no such information. Patients were divided into groups, with a pre-specified eGFR cut-off at 30 ml/min/1.73 m^2, corresponding to CKD stage 1-3 and 4-5, respectively [119]. Also, GFR <30 ml/min/1.73 m^2 is common as a relative contraindication or recommendation of dose adjustment for different pharmaceuticals eliminated by the renal route [12]. Moreover, pre-specified eGFR levels of 45 and 60 ml/min/1.73 m^2 were used as secondary cut-off points, representing the suggested boundaries between CKD stages [120].

PAPER III

Data on age, gender, treatment indications and iTTR were extracted from the national database AuriculA for 3,536 patients listed between 1st January, 2008 and 31st December, 2008 at the University Hospital in Malmö. A follow-up of all registered patients in AuriculA during 2008 was made, regardless of any indication of anticoagulation treatment with warfarin. Events were adjudicated by one of the authors. The indications for anticoagulation treatment were grouped as atrial fibrillation and other. A review of all the hospital records of every patient assured that no complications were missed. A database containing all laboratory results of previous blood analysis in the region was used to collect levels of p-Cr. The last p-Cr registered between 1st January, 2007 and 31st December, 2008 was used. For analysis of renal function, the MDRD and the LM equation were used for calculating eGFR. In patients with complications, p-Cr levels at the time of the event and at least one month before the event were listed in order to rule out any effect of bleeding on the p-Cr levels. Patients were divided into groups, with pre-specified eGFR cut-offs at 30, 45, and 60 ml/min/1.73 m^2, representing the suggested boundaries between CKD stages [120].

PAPER IV

At the start of the study in February 2008, 3,200 patients were registered in AuriculA in the Anticoagulation Clinic at Malmö University Hospital. During the enrolment period, which was March-May 2008, 1,214 consecutive patients scheduled for INR tests, regardless of anticoagulation treatment indication, who had presented INRs of 2.0-3.0 for at least three months prior to screening, were sent a written invitation to participate in the study, and 397 patients responded to the invitation. Written consent was obtained from all patients. During a routine scheduled test of INR at the Department of Clinical Chemistry at Malmö University Hospital, additional capillary blood samples were taken. Two different Coaguchek XS POC PT systems (Roche Diagnostics) were used for capillary whole blood analysis. In 245 out of 397 patients one capillary blood sample was analyzed and 152 patients had two capillary blood samples analyzed, from two separate pricks on two different fingers. From 100 consecutive patients, and 52 patients in whom the first CoaguChek XS INR was ≥3.0, capillary samples were taken twice. Capillary whole blood was obtained using an Accu-check Softclix (Roche Diagnostics) and one drop of blood was applied to the Coaguchek XS test strips. Calibration of the system was provided by the manufacturer and stored in a lot-specific microchip code included in every vial of test

strips. Five professional laboratory technicians performed all capillary and venous blood sampling for INR analysis.

In all patients venous blood was drawn into evacuated tubes containing 0.129 mol/l sodium citrate (Becton Dickinson). The venous blood samples were drawn within 5 minutes of the capillary samples and were centrifuged within 60 minutes at 2000 x g to obtain platelet-deprived plasma. Analysis of the venous blood samples were performed within a total of 3-4 hours from blood sampling, using the standard Owren PT test at the Department of Coagulation Disorders, Malmö University Hospital, Malmö. The Owren PT test was the SPA Prothrombincomplex assay (Diagostica Stago) measured on BCS-XP (Siemens). The Owren PT test was calibrated in a procedure recommended by the Swedish Committee for External Quality Assurance in Laboratory Medicine (EQUALIS). The local ISI was 1.02 and the mean normal PT was 23.2 s. The total imprecision of different instruments with day-to-day and lot-to-lot variation, calculated as coefficient of variation, was 3.1 % at INR 1.1, and 5.0 % at INR 2.6.

STATISTICS

For Papers I and III age was defined as the age of the patient at the time of the first INR test in 2008. TTR was calculated according to F.R. Roosendaal's algorithm with linear interpolation [36]. The mean TTR of the separate indications of anticoagulation treatment was calculated as the mean of the iTTR of patients with that indication. Patients could have more than one indication of OAT with warfarin. Age in patients with a complication was defined as the age of the patient at the time of the event. If a patient had more than one event, only the first in each separate category (i.e major bleeding/thromboembolism) was used for statistical analysis. The "days at risk" were extracted from AuriculA for each patient and complication frequencies were converted to rates (percent per patient-year) and reported with appropriate 95% CI for a rate. In patients with complications, only INR values and "days at risk" before the event were used for statistical analysis.
Variables were generally expressed as means, reported with standard deviations (SD), as medians, reported with interquartile ranges (IQR) or as proportions (%), unless otherwise specified. Skewness was calculated for continuous data to assess the normal distribution. All statistical tests were two-sided and the *P*-value threshold for significance was <0.05.

PAPER I

AuriculA general population

All 18,391 patients from 67 centres in AuriculA were included in an analysis of age, gender, dosage of warfarin, number of INR samples and indications of treatment. A total of 15,601 patients with anticoagulation treatment with warfarin >1 week and INR target range 2.0-3.0 were included in the analysis of TTR [33] and as a result 2,242 patients with other target ranges and 548 patients without enough INR results to calculate TTR, were excluded. In every participating centre the mean TTR (cTTR) was calculated, based on the mean of the TTR of every patient (iTTR) in that centre during 2008 and was reported with 95% CI. Due to the skew distributions of TTR

and mean weekly warfarin dose, the associations between them and age (as categories) were analyzed using Kruskal-Wallis-test.

AuriculA subgroup

A total of 4,273 patients from two centres (Malmö 3,555 patients, Sundsvall 718 patients) were included in the analysis. Three thousand six hundred and nineteen patients on anticoagulation treatment with warfarin >1 week and target INR 2.0-3.0 were included in the analysis of TTR for the different indications in the subgroup and subsequently 611 patients with other INR target ranges, and 43 patients without enough INR values to calculate TTR, were excluded in the analysis of TTR. Complications were tested for differences in patient characteristics. Differences in age were tested using Wilcoxon's test, and differences in gender and treatment indications using Pearson's test. For statistical analyses, R version 2.10.1(R foundation for statistical computing, Vienna, Austria) and SAS version 9.2 (SAS Institute INC, Cary, NC, USA), were used.

PAPER II

Age was defined as the age of the patient on the 31st of December 2008. Differences between groups were tested using Student's t-test for parametric variables and Mann-Whitney for non-parametric variables. To adjust for age and gender, a binary logistic regression analysis was used. For statistical analyses SPSS software, version 17.0 (SPSS, Inc, Chicago, IL) was used.

PAPER III

iTTR in all patients was defined as the time in treatment range within each individual's target range. Patients on anticoagulation treatment with warfarin >1 week were included in the analysis of iTTR. Subsequently, 17 patients without enough INR results to calculate iTTR, were excluded in the analysis of iTTR. Differences in means were tested using Student's t-test. Fisher's exact test was used to test if differences in proportions were appropriate. Odds ratios were calculated using binary logistic regression. Log Rank was used to test the equality of cumulative incidence distribution for the different levels of eGFR and Cox regression was used to calculate the adjusted hazard ratios. The risks per patient year were calculated using the Person Time module in OpenEpi, version 2.3.1 (www.openepi.com). For all

other statistical analyses, the IBM SPSS Statistics software, version 19.0 (SPSS, Inc, Chicago, IL) was used.

PAPER IV

The age of each individual patient was defined as the age on the day of the INR testing. Differences between capillary and venous INR values were tested using Student's paired t-test and a Pearson's correlation coefficient was calculated. Differences in age and gender between the study population and the AuriculA population were tested with Student's t-test and χ^2-test respectively. Imprecision of the CoaguChek XS test strips was calculated from the double capillary whole blood tests and expressed as a coefficient of variation (CV) (**Fig.12**). For statistical analyses SPSS software, version 16.0 for Windows (SPSS, Inc, Chicago, IL) was used.

Figure 12. Demonstration of INR imprecision by calculation of CV. sd = standard deviation, INR = international normalized ratio, CV = coefficient of variation

$$sd = \sqrt{\frac{1}{2n}\sum_{i=1}^{n}\left(INR_{1i} - INR_{2i}\right)^2}$$

$$\text{and} \quad CV(\%) = \frac{sd \cdot 100}{\text{mean INR}}$$

RESULTS

PAPER I

A total of 250,142 INR values from 18,391 patients in 67 different centres were registered in AuriculA during 2008 (**Fig.13)**. The main indications of OAT with warfarin are listed in **Table 1.** The mean age (SD) of the whole population of 18,391 patients was 70 (12) years. The mean age (SD) was higher in women, 73 (12) than in men, 69 (12). In patients with a target INR of 2-3, after exclusion of the first week of therapy, the adjusted mean TTR (n=15601) was 76.2 % (**Fig.14**). A significant correlation between TTR and increasing age (P<0.001) was seen (**Fig.15**). The mean weekly dose of warfarin decreased with increasing age, from 43 mg/week in patients of age 41-50, to 24 mg/week in patients of age 81-90 (**Fig.16**, P<0.001). In the subgroup of the two centres of Malmö and Sundsvall (n=4,273) the mean TTR was 74.9 % and a total of 87 bleeding events and 58 thromboembolic events were detected during a total of 3,377 treatment years (**Table 2**). There were 14 CNS (16%), 32 gastrointestinal (37%) and 41 other (47%) bleeding events according to ISTH guidelines and a total of 47 arterial (81%) and 11 venous (19%) cases of thromboembolism. TTR (SD) was generally lower in patients who had had a bleeding event compared to patients who had not (69.4% (24.5) vs. 75.0% (20.2); P=0.09). In patients with thrombosis, results were similar with trends towards lower TTR (SD) compared with patients without thrombosis (67.9% (27.3) vs. 74.9% (20.2); p=0.16). Patients with a bleeding event had a higher mean percentage of time >3.0 INR (17.2% compared to 11.4%; P=0.001) and a trend towards an increased mean percentage of time <2.0 INR in patients with thrombosis than in patients with no thrombosis (22.5% vs. 13.5%; P=0.08), was seen.

Dividing complications in age categories (**Fig.17**) demonstrated a significant increase in the incidence of major bleeding events with increasing age (P <0.001). As expected, due to higher life expectancy in women, a significant age difference was seen between the sexes (P <0.001). However, there was no statistical difference in the risk of bleeding (P=0.46) or thrombosis (P =0.61) between the sexes.

Figure 13. Distribution of INR values (n=250142) in 18,391 patients in AuriculA during 2008. 18.9% of INR values were <2.0, 0.63 % were ≥5.0 and <0.01 % were ≥8.0.

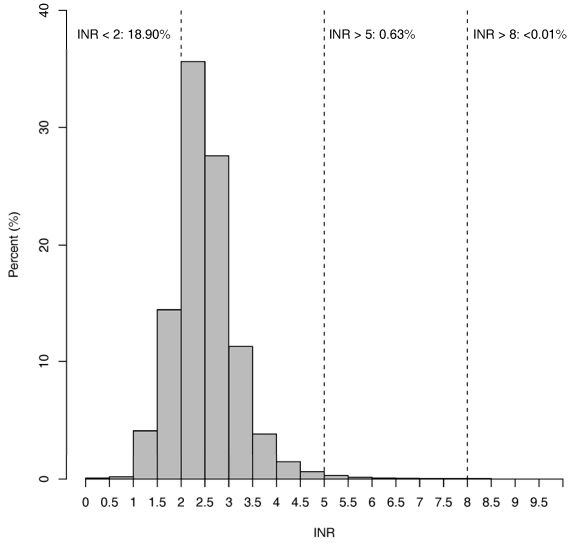


Figure 14. Time in therapeutic range (TTR), 95% CI, in 49 different centres in AuriculA. 18 centres with <10 patients are not shown in the graph. TTR was calculated in patients on treatment with warfarin >1 week and target INR 2.0-3.0; Mean TTR (SD) 76.2% (20.8). n=15601. The mean TTR was 75.7% in hospital-based centres and 80.3% in primary care centres.

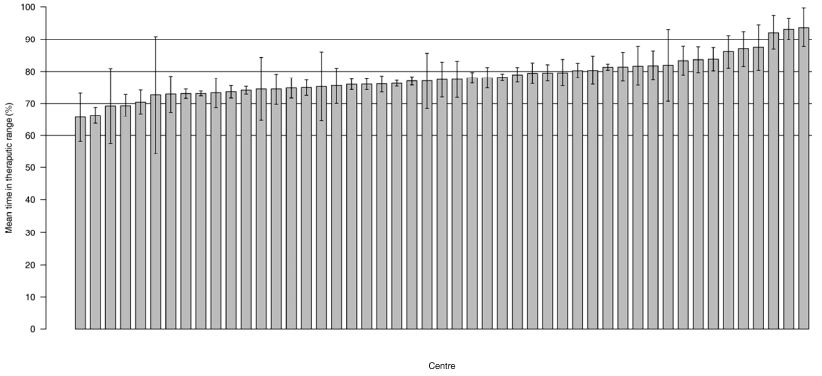


Table 1. Patient characteristics of 18,391 patients enrolled in AuriculA during the year 2008. Patients can have more than one indication of anticoagulation treatment with warfarin. The mean ages (SD) of men and women in the whole AuriculA population were 69 (12) and 73 (12) years respectively. Time in therapeutic range (TTR) was calculated in patients with treatment with warfarin >1 week and target INR 2.0-3.0; n=15601.

Indication	Total	Men	Women	Mean age (SD)	Mean dose (mg/week)	nINR/ patient	Mean TTR (%)
Whole AuriculA population	n=18391	n=11097	n=7294	70 (12)	30.9	13.6	76.2
Atrial fibrillation	64%	65%	64%	73 (10)	29.2	13.5	76.5
-Primary prevention	-89%	-90%	-87%	73 (10)	29.5	13.5	76.4
-Stroke+TIA	-10%	-10%	-12%	76 (9)	27.7	13.1	77.6
-Arterial embolism	-1%	-1%	-1%	79 (9)	24.1	13.6	73.2
Heart valve dysfunction	13%	15%	11%	66 (13)	34.4	15.8	78.2
-Mechanical valve	-85%	-87%	-82%	65(13)	35.7	16.3	79.9
-Biological valve	-9%	-8%	-11%	73(10)	25.6	12.7	69.4
-Mitral stenosis	-3%	-2%	-5%	74(10)	26.2	13.0	77.2
-Other	-3%	-3%	-2%	68(10)	27.8	13.1	65.6
Venous thromboembolism	19%	16%	22%	67 (16)	33.5	12.6	73.6
Other	9%	9%	8%	67 (14)	31.5	12.1	77.6
DC cardioversion	7%	8%	5%	67 (10)	31.6	16.3	68.6

Figure 15. Box plot of time in therapeutic range (TTR) of the AuriculA population divided in age categories. n=15601; *P*<0.001 for differences between age groups. The horizontal line indicates the median, the box covers the 25–75% percentiles and the maximum length of each whisker is 1.5 times the interquartile (IQR) range. Points outside this range show up as outliers.

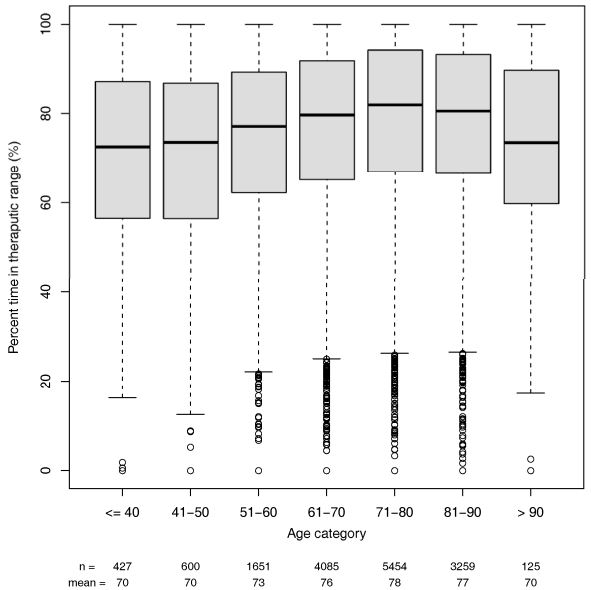


Figure 16. Box plot of mean weekly dose of warfarin by 10-year age categories. n=18353; *P*<0.001 for differences between age groups. The horizontal line indicates the median, the box covers the 25–75% percentiles and the maximum length of each whisker is 1.5 times the interquartile range. Points outside this range show up as outliers.

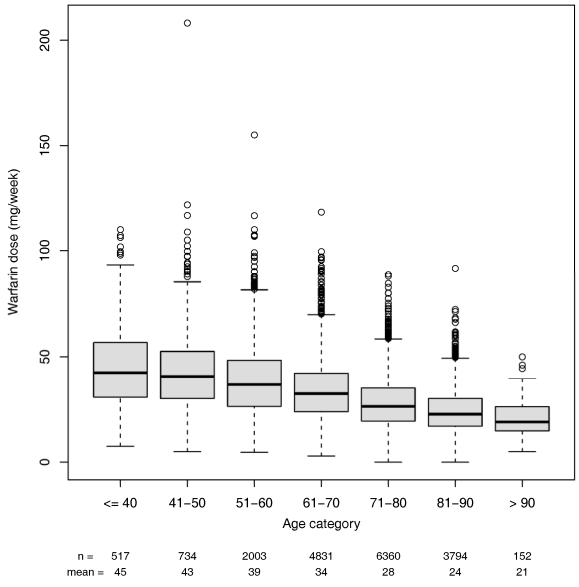
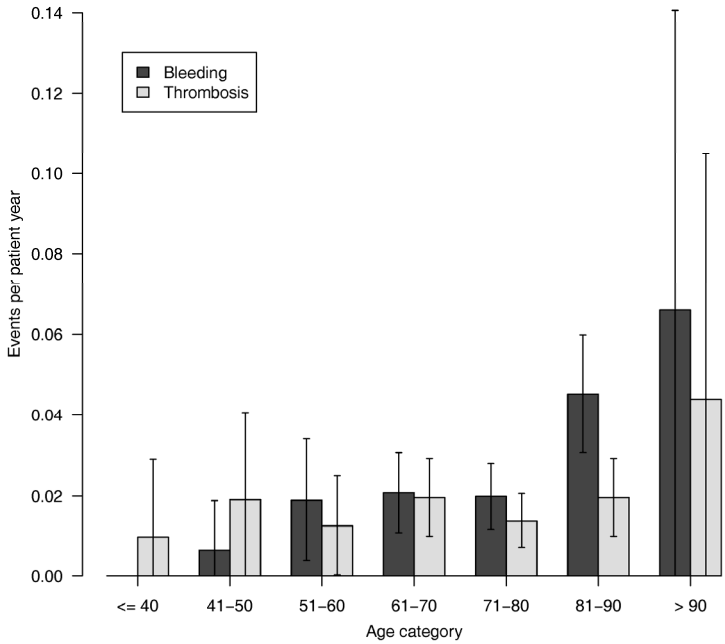


Table 2. Complication frequencies and estimated risk per patient year in 4,273 patients from the AuriculA subgroup with 95% CI in parenthesis. Patients can have more than one indication of treatment. *A significant increase in risk for thrombosis was seen in the group consisting of patients with heart valve dysfunctions, compared to other indications of treatment; *P*=0.03. Mean TTR was calculated from adjusted data (patients with target INR 2.0-3.0 with >1 week of warfarin therapy); n=3619. Patients with the indication DC conversion (n=95 with 4 bleeding and 2 thromboembolic complications), are not listed due to too few treatment years.

Indication	Total (n)	Mean age	Treatment years	Bleeding (n)	Thrombosis (n)	Bleeding risk/ patient year (%)	Thrombosis risk/ patient year (%)	Mean TTR (%)
Whole population	4273	70	3377	87	58	2.6 (2.0-3.1)	1.7 (1.3-2.2)	74.9
#men	2425	69	1906	46	31	2.4 (1.7-3.1)	1.6 (1.1-2.2)	74.9
#women	1848	73	1471	41	27	2.8 (1.9-3.6)	1.8 (1.1-2.5)	74.8
Atrial fibrillation	2491	74	2043	53	29	2.6 (1.9-3.3)	1.4 (0.9-1.9)	75.8
Heart valve dysfunction	597	67	519	12	14	2.3 (1.0-3.6)	2.7 (1.3-4.1) *	76.0
Venous thromboembolism	1146	66	802	21	14	2.6 (1.5-3.7)	1.8 (0.8-2.7)	72.6
Other	267	65	213	4	2	1.9 (0.0-3.7)	0.9 (0.0-2.2)	74.7

Figure 17. Events per patient year by age categories in the whole AuriculA subgroup with 87 major bleeding events according to ISTH definitions and 58 thromboembolic events. A significant correlation between age and major bleeding (P<0.001) is seen but no correlation between age and thromboembolic events (P=0.147).



PAPER II

The characteristics of the 2,603 AF patients and the 2,261 reference subjects are presented in **Table 3**. The mean age in the AF group and the reference population was 75.4 ±10.2 and 70.8 ±9.6 years and the proportions of women were 42.6% and 54.4%, respectively. The proportion of women differed significantly for subjects 59-69, 70-79 and 80-89, whereas the mean age difference was very small for subjects 59-69, 70-79, 80-89 and ≥90 years. Mean eGFR did not differ significantly between study and reference groups for any of the age groups. Mean eGFR according to the LM formula was generally lower compared with eGFR calculated using the MDRD formula.

The prevalence of subjects with eGFR <30 ml/min/1.73 m^2 differed significantly between AF and reference groups for both equations tested (P <0.001) (**Table 4**). The prevalence of subjects with eGFR <30 ml/min/1.73 m^2 increased with age in both the AF and reference groups (P <0.001). In AF patients aged ≥75 years, the age cut-off in $CHADS_2$ [31], 11.4% of patients had eGFR <30 ml/min/1.73 m^2 according to the LM and 5.6% according to the MDRD equation, respectively. The differences in proportions of eGFR <30 ml/min/1.73 m^2 between AF and reference groups were significant in all age groups, except for subjects ≥90 years. Differences in the prevalence of impaired kidney function between the AF and reference groups were also significant using an eGFR cut-off of 45 ml/min/1.73 m^2, which, consistent with the 30 ml/min/1.73 m^2 cut-off, demonstrated an age-related decrease in eGFR (**Table 4**; **Fig. 18**). The age of AF patients was positively correlated to the proportion of patients with eGFR <30, <45 and <60 ml/min/1.73 m^2 (**Figure 18**). After adjustment for age and gender, the odds ratios of having an eGFR <30 or <45 ml/min/1.73 m^2, were higher in the AF group compared with the reference group, except in subjects ≥90 years.

Table 3. Characteristics of study participants with respect to age, gender and kidney function. *P*-value refers to difference between groups.

		Controls	AF	P-value
All	Number	2261	2603	
	Mean age (years)	70.8 ±9.6	75.4 ±10.2	<0.001
	Women (%)	54.4	42.6	<0.001
	Mean p-Cr	88.1 ±27.2	99.2 ±51.9	<0.001
	Mean eGFR, LM	61.1 ±13.7	56.2 ±17.4	<0.001
	Mean eGFR, MDRD	67.6 ±16.0	64.7 ±21.2	<0.001
<59	Number	0	182	
years	Mean age (years)	NA	51.9 ±7.7	NA
	Women (%)	NA	25.8	NA
	Mean p-Cr	NA	86.7 ±34.6	NA
	Mean eGFR, LM	NA	75.5 ±15.6	NA
	Mean eGFR, MDRD	NA	81.8 ±21.0	NA
59-69	Number	1246	489	
years	Mean age (years)	63.2 ±3.0	64.9 ±3.1	NS
	Women (%)	50.7	25.4	<0.001
	Mean p-Cr	83.6 ±23.1	92.8 ±61.5	0.001
	Mean eGFR, LM	67.5 ±10.7	67.7 ±15.7	NS
	Mean eGFR, MDRD	72.6 ±14.1	75.6 ±20.7	0.004
70-79	Number	469	937	
years	Mean age (years)	74.7 ±3.0	75.0 ±2.9	NS
	Women (%)	55.4	41.3	<0.001
	Mean p-Cr	89.7 ±30.3	98.7 ±47.4	<0.001
	Mean eGFR, LM	58.2 ±12.0	56.1 ±15.1	0.005
	Mean eGFR, MDRD	65.6 ±15.5	64.3 ±19.5	NS
80-89	Number	449	909	
years	Mean age (years)	83.5 ±2.4	83.8 ±2.7	0.040
	Women (%)	61.2	54.0	0.012
	Mean p-Cr	95.8 ±30.2	104.0 ±53.2	<0.001
	Mean eGFR, LM	50.2 ±12.1	48.5 ±14.4	0.019
	Mean eGFR, MDRD	58.9 ±15.5	57.9 ±19.1	NS
≥90	Number	97	111	
years	Mean age (years)	90.8 ±1.3	91.6 ±2.0	<0.001
	Women (%)	64.9	61.3	NS
	Mean p-Cr	103.0 ±31.2	109.9 ±44.3	NS
	Mean eGFR, LM	43.4 ±11.3	41.6 ±14.3	NS
	Mean eGFR, MDRD	52.7 ±14.5	52.4 ±19.7	NS

AF: Atrial fibrillation; eGFR: estimated glomerular filtration rate in ml/min/1.73 m^2; LM: Lund-Malmö equation; MDRD: Modification of Diet in Renal Disease Study equation; NA: not analyzed; NS: non-significant; p-Cr: serum creatinine in µmol/L

Figure 18. Proportion of atrial fibrillation patients with eGFR <30, <45 and <60 ml/min/1.73 m², with respect to two different equations of eGFR. eGFR = estimated glomerular filtration rate; LM = Lund-Malmö equation; MDRD = Modification of Diet in Renal Disease Study equation

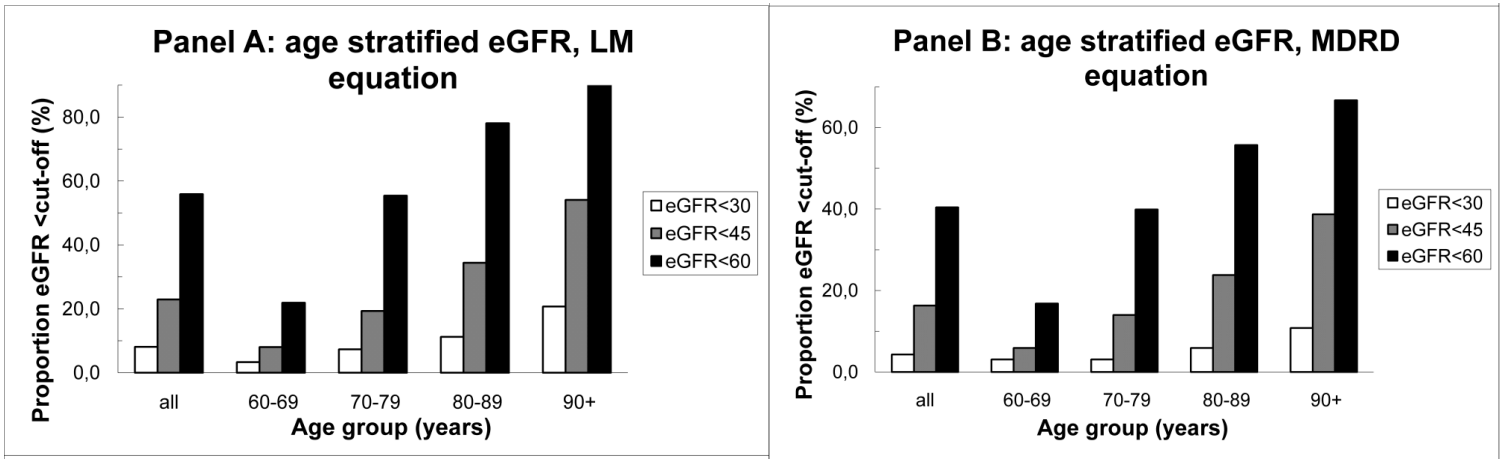


Table 4. Odds ratios for patients (OR) with atrial fibrillation also having an increased prevalence of GFR <30, <45 and <60 ml/min/1.73 m² compared to controls in the different age groups. The two equations for eGFR are shown separately. *Adjusted for age and gender using logistic regression. Odds ratio for atrial fibrillation in relation to controls. 95% CI in brackets. *P*-value refers to difference between groups. Non-significant values in italic.

Age group	eGFR <30 ml/min/1.73 m² (%)				eGFR <45 ml/min/1.73 m² (%)				eGFR <60 ml/min/1.73 m² (%)			
(years)	Controls	AF	*P*-value	Adjusted OR*	Controls	AF	*P*-value	Adjusted OR*	Controls	AF	*P*-value	Adjusted OR*
All subjects	n=2261	n=2603			n=2261	n=2603			n=2261	n=2603		
LM	2.6	8.1	<0.001	5.4 (2.1-13.9)	11.6	22.9	<0.001	2.7 (1.6-4.6)	39.5	55.9	<0.001	*0.9 (0.7-1.2)*
MDRD	1.2	4.3	<0.001	6.1 (2.2-16.8)	7.3	16.3	<0.001	2.9 (1.6-5.3)	28.5	40.4	<0.001	*1.0 (0.8-1.4)*
59-69	n=1246	n=489			n=1246	n=489			n=1246	n=489		
LM	0.6	3.3	<0.001	4.9 (1.9-13.0)	2.2	8.0	<0.001	2.6 (1.5-4.5)	19.0	21.9	*0.18*	*0.9 (0.7-1.2)*
MDRD	0.5	3.1	<0.001	5.5 (1.9-15.5)	1.7	5.9	<0.001	2.8 (1.5-5.2)	14.8	16.8	*0.20*	*1.0 (0.8-1.4)*
70-79	n=469	n=937			n=469	n=937			n=469	n=937		
LM	3.2	7.3	0.002	2.2 (1.2-3.8)	11.1	19.3	<0.001	1.9 (1.4-2.7)	47.5	55.4	0.007	1.4 (1.1-1.8)
MDRD	1.3	3.1	0.045	*2.4 (0.97-5.7)*	7.2	14.0	<0.001	2.1 (1.4-3.2)	34.1	39.9	0.036	1.4 (1.1-1.7)
80-89	n=449	n=909			n=449	n=909			n=449	n=909		
LM	5.6	11.2	0.001	2.0 (1.3-3.1)	29.4	34.4	*0.065*	*1.2 (0.96-1.6)*	76.4	78.1	*0.49*	*1.1 (0.8-1.4)*
MDRD	2.7	5.9	0.007	2.2 (1.2-4.2)	17.4	23.8	0.008	1.5 (1.1-2.0)	52.1	55.7	*0.22*	*1.2 (0.9-1.5)*
90 and older	n=97	n=111			n=97	n=111			n=97	n=111		
LM	11.3	20.7	*0.090*	*1.6 (0.7-3.7)*	52.6	54.1	*0.89*	*0.9 (0.5-1.6)*	93.8	91.9	*0.79*	*0.7 (0.2-2.0)*
MDRD	4.1	10.8	*0.12*	*2.1 (0.6-7.2)*	33.0	38.7	*0.47*	*1.1 (0.6-2.0)*	69.1	66.7	*0.77*	*0.8 (0.4-1.5)*

AF: atrial fibrillation; eGFR: estimated glomerular filtration rate; LM: Lund-Malmö equation; MDRD: Modification of Diet in Renal Disease Study equation; OR: odds ratio

PAPER III

A total of 3,536 patients (1,925 male (54%); 1,611 female (46%); mean age 71.6 (SD 13.1) years) were included in the analyses. The mean age was higher in women than in men (**Table 5**), and patients with atrial fibrillation were generally older than patients with other indications for anticoagulation treatment. After exclusion of the first week of therapy, the adjusted mean iTTR (n=3519) was 76.1 %. An iTTR of >70 % was consistent for all indications of anticoagulation treatment with target interval of INR 2.0-3.0. Mean iTTR was lower in patients with atrial fibrillation and target INR of 2.0-4.0 than in other indications of warfarin treatment with the same target interval. A total of 75 bleeding and 51 thromboembolic events were registered during a total of 2,875 treatment years (**Table 6**).

Bleeding events

There were 12 CNS (16%), 28 gastrointestinal (37%) and 35 other (47%) bleeding events. The mean INR (SD) at the bleeding event was 3.5 (1.7), and the mean iTTR was lower in patients who had a major bleeding event when compared to patients who had not (70.6% vs. 76.2%;*P*=0.02). These patients also had an increased proportion of time with INR>3.0 (*P*<0.001) but not of INR<2.0 (*P*=0.96). There was a correlation between age and bleeding events (*P*<0.001), even when the age groups of <75 years and ≥75 years were considered (**Table 6**). A trend towards lower iTTR in patients <75 years who had suffered a bleeding event (*P*=0.051) was seen.

Thromboembolic events

A total of 41 arterial (80%) and 10 venous (20%) cases of thrombo-embolism were registered. The mean INR (SD) at thrombosis was 2.3 (1.0). There was no significant difference in iTTR in patients with thromboembolic events in the whole cohort (*P*=0.19) although a significant difference in mean iTTR in patients <75 years with thromboembolic events (*P*=0.05) was seen, when compared to patients without a thromboembolic event.

Effect of renal function

In patients with a bleeding event, there was a significant difference in mean eGFR at the time of the event, compared to patients without an event; *P*=0.003 (**Table 7**). Differences in eGFR between these patients were similar using both the Lund-Malmö equation (8.6 ml/min/1.73 m^2), and the MDRD equation (8.1 ml/min/1.73 m^2). There were higher proportions of patients with a major bleeding event, who had eGFRs of <30 and <45 ml/min/1.73 m^2, with odds ratios of 2.7 and 2.1 respectively, adjusted for age and gender, when compared to the rest of the population. No

differences in mean eGFR or in the proportions of eGFR <30 and <45 ml/min/1.73 m^2 were seen in patients with thromboembolic events. There was an inverse correlation between the risk for major bleeding and eGFR with a bleeding risk/patient year of 7.7% in patients with eGFR <30, 5.2% in patients with eGFR<45, 3.7% in patients with eGFR <60 and 1.7% in patients with eGFR >60 ml/min/1.73 m^2 (**Fig.19**). No correlation between the risk for thromboembolic events and eGFR was seen.

The risks of thromboembolic events/patient year were 1.7% in patients with eGFR <30, 2.1% in patients with eGFR <45, 1.9% in patients with eGFR <60 and 1.8% in patients with eGFR >60 ml/min/1.73m^2 (data not shown). Patients ≥ 75 years seemed to have similar risks for major bleeding as patients <75 years given the same renal function, although eGFR levels <30 ml/min/1.73m^2 were associated with high risks of bleeding in the elderly patients aged ≥75 years (**Table 8**). There was no difference in mean age, or time of INR >3.0, between different levels of eGFR in patients with major bleeding events. Also, there was no difference in mean age or time of INR<2.0 between different levels of eGFR in patients with thromboembolic events.

The mean p-Cr at the time of any event and at >1 month before the event, was 111 μmol/L and 111 μmol/L respectively. The median (IQR) numeral difference between the two p-Cr values was 2 (-9-12) μmol/L for all patients, 4 (-8-15) in patients with major bleeding and 0 (-9-10) in patients with thromboembolic events.

Indications for anticoagulation

Data were consistent in patients with atrial fibrillation, where an inverse correlation of major bleeding and eGFR was seen, with no difference in mean age or time of INR >3.0 between different levels of eGFR (**Table 9**). Patients with other indications for anticoagulation treatment had a higher absolute risk of major bleeding, but also a greater percentage of time of INR >3.0.

Mean eGFR (SD) calculated using the LM equation in patients with major bleeding were 48.5 (22.0) in atrial fibrillation, and 54.1 (26.3) in patients with other indications of anticoagulation treatment; *P*=0.32. Also, in patients with major bleeding events, the total percentage of time INR >3.0 (SD) was 14.5 (12.3) for atrial fibrillation, and 30.9 (23.6); *P*=0.001, for other indications. The mean ages (SD) for the atrial fibrillation and other indication groups were 79 (9) and 75 (12) years, respectively (*P*=0.19).

Table 5. Patient characteristics, complication frequencies and estimated risk per patient year in 3,536 patients from AuriculA with 95% CI in parenthesis. Patients can have more than one indication of anticoagulation treatment with warfarin. iTTR was calculated in patients with treatment with warfarin >1 week (n=3519). iTTR and risk of complications were not listed for some indications and target intervals due to too few treatment years.

	Total (n)	Mean age (years)	Treat-ment (years)	Major Bleeding (n)	Throm-bosis (n)	Bleeding risk/ patient year (%)	Thrombosis risk/ patient year (%)	Mean iTTR (%)
Whole population	3536	72	2875	75	51	2.6 (2.0-3.2)	1.8 (1.3-2.3)	76.1
- Men	1925	70	1561	37	27	2.4 (1.6-3.2)	1.7 (1.1-2.3)	75.9
- Women	1611	74	1314	38	24	2.9 (2.0-3.8)	1.8 (1.1-2.5)	76.3
- INR 2.0-3.0	2894	72	2355	60	39	2.5 (1.9-3.1)	1.7 (1.2-2.2)	74.5
- INR 2.0-4.0	543	67	431	13	8	3.0 (1.4-4.6)	1.9 (0.6-3.2)	89.3
- INR Other	99	71	88	2	4	--	--	--
Atrial fibrillation	2118	75	1790	45	27	2.5 (1.8-3.2)	1.5 (0.9-2.1)	76.6
- INR 2.0-3.0	1837	76	1603	41	25	2.6 (1.8-3.4)	1.6 (1.0-2.2)	75.9
- INR 2.0-4.0	242	69	151	4	1	2.6 (0.1-5.1)	0.6 (0.0-1.8)	84.7
- INR Other	39	79	36	0	1	--	--	--
Other	1603	67	1247	33	26	2.6 (1.9-3.7)	2.1 (1.4-3.0)	75.5
- INR 2.0-3.0	1185	68	862	21	15	2.4 (1.5-3.7)	1.7 (1.0-2.8)	72.0
- INR 2.0-4.0	350	67	326	10	7	3.1 (1.5-5.5)	2.1 (0.9-4.2)	92.9
- INR Other	68	67	59	2	4	--	--	--

Table 6. Comparison of individual percentage of time in treatment range (iTTR) and of time >3.0 INR and <2.0 INR; patients with bleeding and thromboembolic complications compared with patients without an event in 3,536 patients; subgroups of ≥75 years and <75 years of age. iTTR was calculated in patients with treatment with warfarin >1 week (n=3519) for each individual target range.

	No bleeding	Bleeding	p-value	No bleeding ≥75years	Bleeding ≥75years	p-value	No bleeding <75years	Bleeding <75years	p-value
no of patients	3461	75	-	1708	50	--	1753	25	--
mean age	71.5 ±13.1	77.2 ±10.4	<0.001	81.5 ±4.4	83.4 ±4.5	0.002	61.7 ±11.3	64.8 ±7.1	0.04
iTTR (%)	76.2 ±20.9	70.6 ±24.7	0.02	76.8 ±19.8	74.0 ±21.9	0.34	75.7 ±21.8	63.6 ±28.8	0.051
T-INR >3.0	13.9 ±17.2	21.2 ±19.5	<0.001	11.7 ±14.9	18.7 ±16.4	0.001	16.2 ±18.9	26.4 ±24.1	0.009
T-INR <2.0	13.6 ±17.6	13.7 ±23.7	0.96	13.9 ±17.4	11.7 ±22.1	0.39	13.3 ±17.7	17.8 ±26.8	0.41

	No thrombosis	Thrombosis	p-value	No thrombosis ≥75years	Thrombosis ≥75years	p-value	No thrombosis <75years	Thrombosis <75years	p-value
no of patients	3485	51	-	1728	30	--	1757	21	--
mean age	71.6 ±13.1	73.5 ±13.7	0.29	81.5 ±4.4	82.6 ±5.4	0.20	61.8 ±11.3	60.2 ±11.4	0.64
iTTR (%)	76.2 ±20.8	70.8 ±28.5	0.19	76.7 ±19.8	77.2 ±25.6	0.88	75.7 ±21.8	61.4 ±30.4	0.05
T-INR >3.0	14.1 ±17.3	12.1 ±18.0	0.41	11.9 ±15.0	10.2 ±16.7	0.55	16.3 ±19.0	14.8 ±19.8	0.72
T-INR <2.0	13.5 ±17.5	20.9 ±27.5	0.067	13.8 ±17.4	16.2 ±26.1	0.62	13.2 ±17.7	27.6 ±28.8	0.04

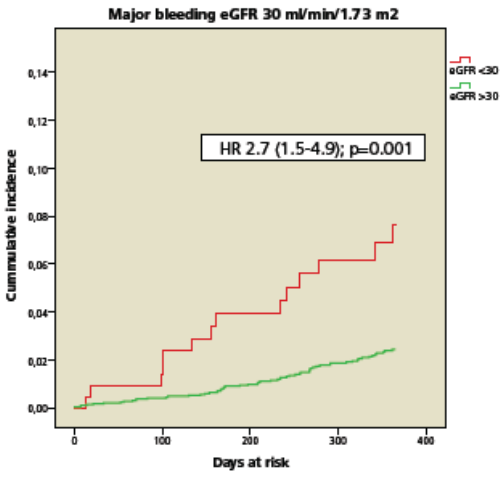
Table 7. Mean eGFR in patients with major bleeding and thromboembolic complications; prevalence of patients with eGFR <30 and 45 ml/min/1.73 m²; subgroups of ≥75 years and <75 years of age. The two equations for eGFR are shown separately. eGFR calculated using the LM-equation in 3,349/3,536 patients. Odds ratios for eGFR adjusted for age and gender using logistic regression, 95% CI in brackets. Two-tailed *P*-value with level of significance <0.05.

	No bleeding	Bleeding	OR	p-value	No bleeding ≥75years	Bleeding ≥75years	OR	p-value	No bleeding <75years	Bleeding <75years	OR [b]	p-value
number of patients	3461	75	--	--	1708	50	--	–	1753	25	--	–
mean age	71.5 ±13.1	77.2 ±10.4	--	<0.001	81.5 ±4.4	83.4 ±4.5	--	0.002	61.7 ±11.3	64.8 ±7.1	--	0.04
mean eGFR (LM)	59.4 ±18.5	50.8 ±23.8	–	0.003	50.5 ±14.7	42.8 ±18.1	--	0.005	68.5 ±17.6	67.5 ±26.1	–	0.85
mean eGFR (MDRD)	67.8 ±23.4	59.7 ±31.1	–	0.003	59.3 ±19.4	50.8 ±23.1	--	0.002	76.4 ±24.0	78.3 ±37.4	–	0.81
[a] eGFR <30 ml/min/1.73 m2²	6.5 %	18.9%	2.7 (1.4-4.9)	0.002	9.7 %	26.0 %	2.9 (1.5-5.6)	0.002	3.2 %	4.2 %	1.2 (0.2-9.2)	0.85
[a] eGFR <45 ml/min/1.73 m2²	20.2%	40.5%	2.1 (1.3-3.4)	0.005	31.4 %	52.0 %	2.1 (1.2-3.7)	0.01	8.9%	16.7%	1.2 (0.5-2.8)	0.27

	No thrombosis	Thrombosis	OR	p-value	No thrombosis ≥75years	Thrombosis ≥75years	OR	p-value	No thrombosis <75years	Thrombosis <75years	OR	p-value
number of patients	3485	51	--	--	1728	30	--	–	1757	21	--	–
mean age	71.6 ±13.1	73.5 ±13.7	--	0.29	81.5 ±4.4	82.6 ±5.4	--	0.20	61.8 ±11.3	60.2 ±11.4	--	0.64
mean eGFR (LM)	59.2 ±18.7	59.0 ±18.4	–	0.92	50.2 ±14.9	51.5 ±14.2	--	0.63	68.5 ±17.6	70.2 ±18.5	–	0.67
mean eGFR (MDRD)	67.6 ±23.6	68.5 ±23.0	–	0.80	59.0 ±19.6	61.1 ±19.1	--	0.56	76.4 ±24.1	79.5 ±24.4	–	0.58
[a] eGFR <30 ml/min/1.73 m²	6.7 %	6.0 %	0.8 (0.2-2.7)	1.00	10.2 %	6.7 %	0.6 (0.1-2.4)	0.42	3.1 %	5.0 %	1.8 (0.2-13.7)	0.60
[a] eGFR <45 ml/min/1.73 m²	20.6 %	24.0%	1.1 (0.6-2.2)	0.60	32.1 %	33.3 %	1.0 (0.4-2.1)	0.91	8.9 %	10.0 %	1.3 (0.3-5.6)	0.76

Figure 19. Cumulative incidence rates for major bleeding events according to estimated glomerular filtration rate (LM) cut-offs of 30, 45 , and 60 ml/min/1.73 m². The bleeding risk/patient year was 7.7% in patients with eGFR <30 (**A**), 5.2% in patients with eGFR <45 (**B**), 3.7% in patients with eGFR <60, and 1.7% in patients with eGFR >60 ml/min/1.73 m^2(**C**). Hazard ratios for eGFR, adjusted for age and gender using Cox regression, with 95% CI in brackets; two tailed *P*-value with level of significance <0.05.

A.



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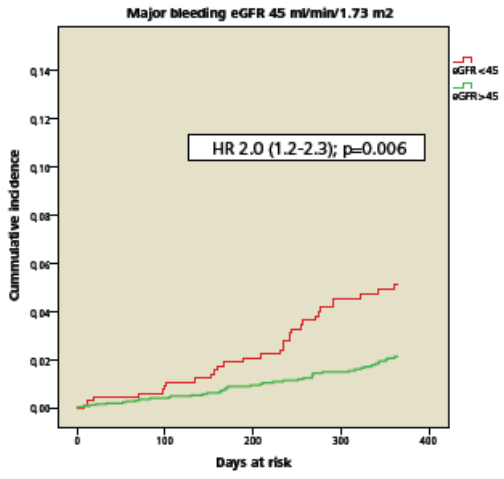


C.

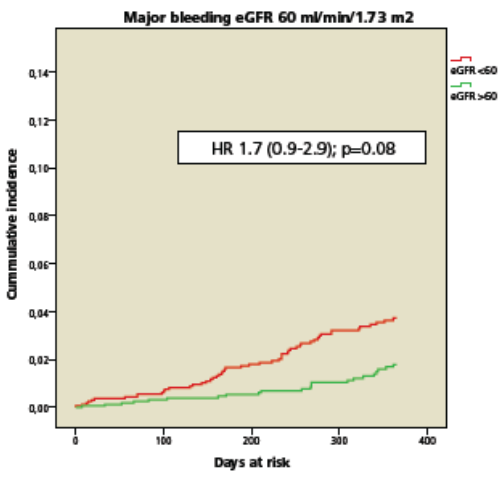


Table 8. Absolute risks of major bleeding (A) and thromboembolic (B) events in patients aged ≥75 and <75 years with respect to kidney function in ml/min/1.73m². Percentage of time in INR >3.0 listed for major bleedings, and time in INR <2.0 listed for thromboembolic complication. Risks in percent/patient year with 95% CI in brackets. eGFR calculated using the LM-equation in 3,349/3,536 patients.

	Major Bleeding						Thromboembolic events					
	(n)	Mean age	Patient years	Events	Risk/patient year (%)	T-INR >3.0	(n)	Mean age	Patient years	Events	Risk/patient year (%)	T-INR <2.0
All patients	3536	72	2875	75	2.6 (2.0-3.2)	14.2	3536	72	2875	51	1.8 (1.3-2.3)	13.6
eGFR>60	1686	66	1320	22	1.7 (1.0-2.5)	15.0	1689	66	1323	24	1.8 (1.2-2.7)	14.1
eGFR 45-60	970	78	809	22	2.7 (1.7-4.1)	12.6	968	78	808	14	1.7 (1.0-2.8)	13.4
eGFR 30-45	466	80	399	16	4.0 (2.4-6.4)	13.4	469	80	400	9	2.3 (1.1-4.1)	12.5
eGFR<30	227	79	181	14	7.7 (4.2-13.0)	15.5	224	79	180	3	1.7 (0.3-4.9)	15.5
Age ≥75 years	1758	82	1487	50	3.4 (2.5-4.4)	11.9	1758	82	1487	30	2.0 (1.4-2.8)	13.8
eGFR>60	466	80	384	8	2.1 (1.0-4.0)	11.2	465	80	384	9	2.3 (1.1-4.3)	15.2
eGFR 45-60	691	82	578	16	2.8 (1.6-4.4)	11.9	690	81	577	11	1.9 (1.0-3.3)	13.3
eGFR 30-45	371	83	326	13	4.0 (2.2-6.6)	12.2	373	83	328	8	2.4 (1.1-4.6)	12.7
eGFR<30	174	83	145	13	9.0 (5.0-15.0)	13.8	173	83	145	2	1.4 (0.2-4.6)	14.9
Age <75 years	1778	62	1388	25	1.8 (1.2-2.6)	16.3	1778	62	1388	21	1.5 (1.0-2.3)	13.3
eGFR>60	1220	60	937	14	1.5 (0.9-2.4)	16.5	1224	60	939	15	1.6 (0.9-2.6)	13.7
eGFR 45-60	279	68	231	6	2.6 (1.1-5.4)	14.1	278	68	231	3	1.3 (0.3-3.5)	13.7
eGFR 30-45	95	69	72	3	4.1 (1.1-11.3)	18.2	96	69	72	1	1.4 (0.1-6.9)	11.9
eGFR<30	53	66	36	1	2.8 (0.1-13.7)	21.3	51	66	36	1	2.8 (0.1-13.7)	17.5

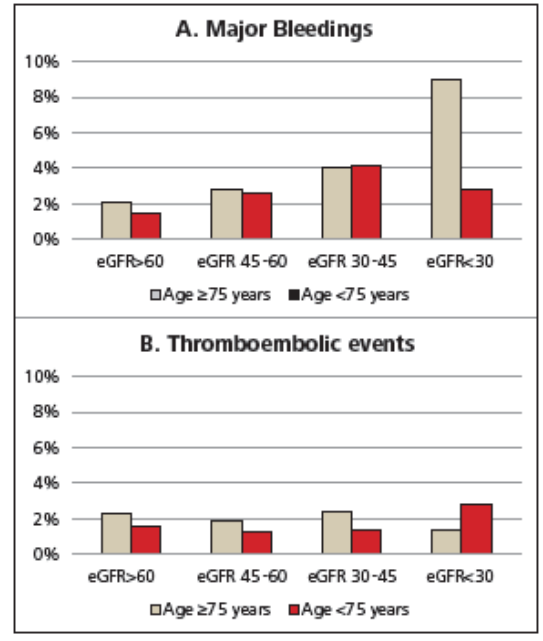


Table 9. Absolute risks of major bleeding in patients with atrial fibrillation and other indications of anticoagulation treatment, with respect to kidney function in ml/min/1.73m². Percentage of time INR >3.0 listed for major bleedings. Risks in percent/patient year with 95% CI in brackets. eGFR calculated using the LM-equation in 3,349/3,536 patients. eGFR=estimated glomerular filtration rate; T-INR = time in international normalized ratio.

	(n)	Mean age	Patient years	Bleeding events	Risk/patient year (%)	T-INR >3.0
Atrial fibrillation	2118	75	1790	45	2.5 (1.9-3.3)	11.5
eGFR>60	883	70	726	11	1.5 (0.8-2.6)	11.9
eGFR 45-60	697	78	590	16	2.7 (1.6-4.3)	10.9
eGFR 30-45	319	80	285	9	3.2 (1.5-5.8)	11.5
eGFR<30	154	79	130	8	6.2 (2.9-11.7)	12.2
Other	1418	67	1084	30	2.8 (1.9-3.9)	17.9
eGFR>60	803	61	595	11	1.8 (1.0-3.2)	18.5
eGFR 45-60	273	76	219	6	2.7 (1.1-5.7)	16.8
eGFR 30-45	147	79	114	7	6.1 (2.7-12.2)	17.6
eGFR<30	73	78	51	6	11.8 (4.8-24.5)	22.4

PAPER IV

Baseline characteristics of the 397 patients are listed in **Table 10**. The age difference between men (68.9) and women (65.0) was significant; $P<0.001$, and there was a difference in the distribution of gender between the two populations (χ^2-test; $P<0.001$). Only data on median age was available in the whole AuriculA population so no statistical comparison could be made between the study population and the whole AuriculA population.

A comparison of INR values from 397 patients measured using the Coaguchek XS POC-device and venous Owren PT demonstrated a correlation(r) of 0.94; $P<0.001$ (**Fig.20**). When dividing in results in ranges of INR <2.0; 2.0-3.0; and >3.0 there was a concordance of 88.2%. The mean INR (SD) was 2.52 (0.64) with the Coaguchek XS and 2.50 (0.62) with Owren PT (**Fig.21**). There was a positive correlation (r=0.99, $P<0.001$) between the 152 double capillary blood samples analyzed with the CoaguChek XS. The imprecision demonstrated as the coefficient of variation (CV) (**Fig.22**) was 2.24%.

Table 10. Baseline characteristics of the study population compared to the whole AuriculA population in Malmö. * Difference between study population and AuriculA population χ^2-test; $P<0.001$. ** Patients can have several indications of anticoagulation treatment.

Baseline charcteristics	Study population (n = 397)	Whole population (n = 3200)
Male*	66%	55%
Female*	34%	45%
Median age	69.0	75
Indications		
–atrial fibrillation	56%	62%**
–valve prosthesis	14%	13%**
–venous thromboembolism	27%	26%**
–others	3%	4%**

Figure 20. Scattered plot with line of regression demonstrating correlation of INR values measured by Coaguchek XS PT and Owren PT. The Pearson's coefficient of correlation was 0.94; *P*<0.001; n=397.

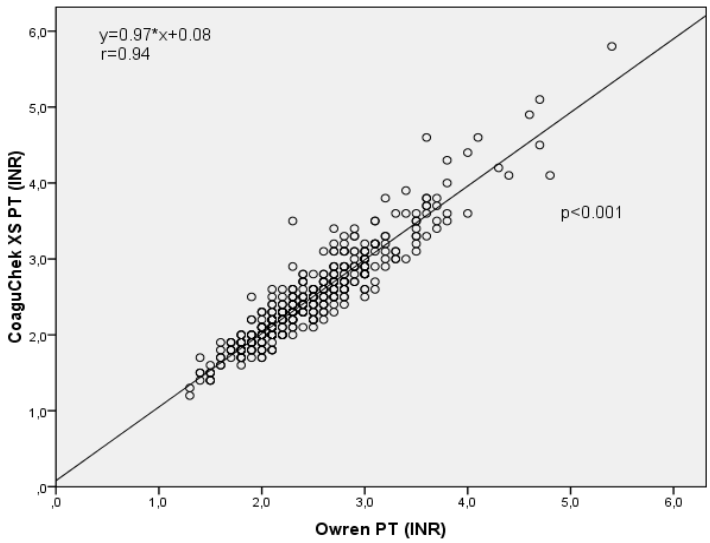


Figure 21. Bland-Altman plot demonstrating the correlation between the difference of the results, and the mean of the results. The lines indicate the mean difference (0.02) ±2 SD (0.44); n=397

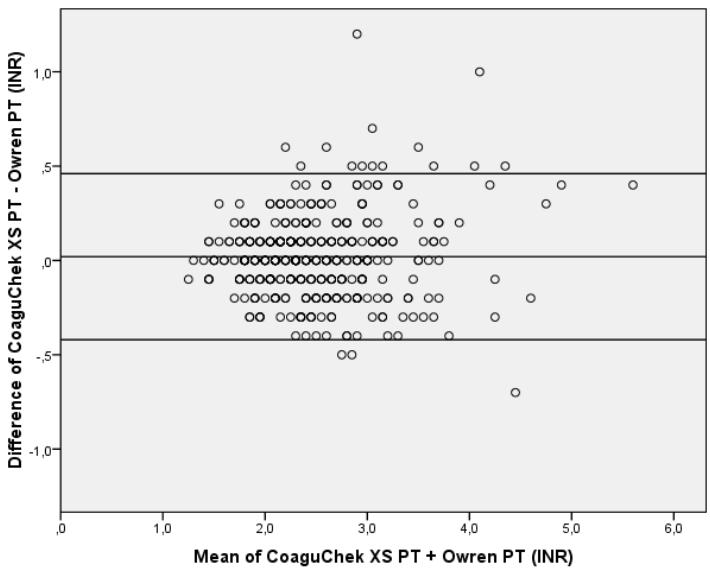
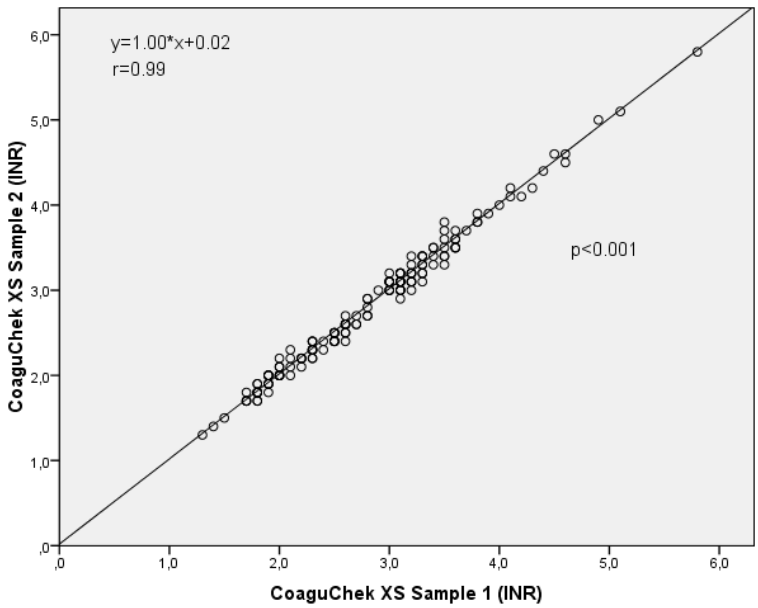


Figure 22. Scattered plot with line of regression demonstrating the correlation of double capillary INR values measured using the Coaguchek XS. The Pearson's coefficient of correlation (r) was 0.99; *P*<0.001. The coefficient of variation (CV) was 2.24%; n=152.



DISCUSSION

TIME IN THERAPEUTIC RANGE

In patients with AF on OAT with warfarin, a strong inverse correlation has been shown between TTR and a reduction in complications such as major bleeding and thromboembolic events [37]. Also, randomized controlled trials (RCT) have been shown to be superior to retrospective studies (TTR 64.9 % versus 56.4 %; *P*=0.01) [37]. However, in order to have a "clean" comparison of treatments, RCTs have systematically excluded patients with bad compliance, cognitive difficulties, and multiple co-morbidities, especially severely impaired renal function, whereas in clinical practice these patients present substantial challenges with respect to interaction between different types of medications, and in adherence to treatment. Hence, TTR has usually been lower in clinical cohorts compared with organized trials, due to less selection bias. Differences in cTTR have also been demonstrated in a meta-analysis of warfarin-treated patients in the United States where patients treated in anticoagulation clinics demonstrated a mean TTR of 63 % compared to 51% in patients in community practice [121]. In a study from Sweden, these differences between anticoagulation clinics and community care were not present [122], indicating a potential difference in treatment regimens or patient selection between countries.

Paper I, the first report from the Swedish national quality register for anticoagulation and atrial fibrillation, AuriculA, demonstrates that in a large, unselected clinical population of nearly 20,000 patients, the quality of OAT with warfarin is high, with a mean cTTR of 76.2 % (**Table 1**). The mean iTTR in Paper III was 76.1% for all target intervals of INR, and 74.5% for INR 2.0-3.0 without consideration given to target interval (data not shown). Follow-up data from two centres in Paper I identify a low risk of major bleeding and thromboembolic complications at 2.6% and 1.7% per treatment year, respectively. In patients with atrial fibrillation, the risks of complications were 2.6% and 1.4% respectively (**Table 2**).

There was a difference in mean TTR between hospital-based centres (cTTR=75.7%) and primary care centres (cTTR=80.3%) in Paper I. A probable cause for this difference in cTTR is that primary care centres in Sweden treat a somewhat healthier

population, whereas patients with multiple co-morbidities and medications, with subsequent difficulties of INR-control (i.e. alcoholics, chronic heart failure patients, etc) are overrepresented in anticoagulation clinics. These data were consistent with earlier data from Sweden [122] which, quite the opposite of American studies [121], demonstrate that primary care centres can produce high quality anticoagulation control.

The AuriculA population is representative of a clinical setting, at least in Sweden, and the high TTR reflects an organization of specialized anticoagulation centres that seems to be in good control of anticoagulation treatment with warfarin. Data on TTR in Paper I and III also support earlier data [37] that TTR is an excellent prognostic marker of the quality of anticoagulation treatment given in a clinical setting, where a high cTTR is correlated to a low incidence of both thromboembolic and major bleeding events. The dosing algorithm in AuriculA could have contributed to the results by eliminating human error to some extent and keeping dosing regimens consistent over centres. However, future reports of AuriculA, with complication frequencies in more centres and a longer follow-up period will be needed in order to see if the trends reported in Papers I and III are reproducible.

HEART VALVE DYSFUNCTION

The risk of bleeding was low for all treatment indications of warfarin in Paper I, but there was a somewhat higher frequency of thromboembolic events in patients with heart valve dysfunction. These patients, with an INR target interval 2.0-3.0, were mainly from the Sundsvall centre. The risk of thromboembolic events in these patients with heart valve dysfunction was 2.7% per patient/treatment year compared to 1.7% in all patients in Malmö and Sundsvall regardless of treatment indication (**Table 2)**. In data from Paper III, where mechanical valve replacements in Malmö, made up most of the group labelled "Other" with a target interval of 2.0-4.0 (**Table 5**), a lower incidence of thromboembolic events was seen at 2.1% per treatment year. However, a risk of major bleeding of 3.1 % per patient year was also seen in the Malmö patients with target interval of 2.0-4.0 in Paper III (**Table 5**), greater than in the Sundsvall patients in Paper I, with target intervals of 2.0-3.0 (**Table 2**) who had a bleeding risk of 2.3 % per patient year. The number of complications in Paper III, both major bleeding and thromboembolic, was lower in patients with AF, than in patients with other indications of anticoagulation treatment and target interval INR 2.0-4.0 (**Table 5**).

The higher incidence of thromboembolic events (**Table 2+5**) in patients with heart valve dysfunction compared with patients with AF could be due to differences in co-

morbidities between the groups, but is most probably due to different mechanisms of thrombogenesis. The noted differences in risk of thromboembolic events between patients with heart valve dysfunction in Papers I and III could be due to differences in mean age, and co-morbidities but could also reflect the need of a mean INR target greater than INR 2.5 or a lower boundary of the target interval, greater than INR 2.0. However, a target interval of 2.0-4.0 in Paper III seems to be associated with an increased risk of bleeding which could indicate the need for a lowered upper limit of the designated target interval. Since the iTTR in both populations was very high, there is probably no gain in obtaining a higher adherence. Whether a target interval of INR 2.5-3.5 is more optimal than current recommendations of INR 2.0-3.0 or 2.0-3.5, remains to be seen, however.

POINT-OF-CARE

INR self-management in Sweden is only used in about 1,200 patients out of approximately 150,000 patients on anticoagulation treatment with warfarin [43]. None of these patients participated in AuriculA in 2008 and subsequently it is not certain that the high quality results on TTR and complications from Paper I can be applied to this population, although previous meta-analysis has demonstrated a reduced incidence of major bleeding and thromboembolic complications with patient-assisted self testing [38]. Even though the POC-device CoaguChek XS had earlier been validated against Quick PT, Paper IV was the first study of the correlation with Owren PT and demonstrated a high correlation (r=0.94) and a mere 0.02 mean difference in INR. Assuming that Owren PT, used in Sweden, has had a stable calibration between 2004 and 2008, the CoaguChek XS seems to correlate better with Owren PT (r=0.94) than its predecessor the CoaguChek S (r=0.81) [42]. The strength of Paper IV, compared to previous studies which could not evaluate the reproducibility of their results [42], was the highly significant correlation of 0.99 with a CV of 2.23% in the double CoaguChek XS samples, ruling out any major preanalytical error.

Although the results from Paper IV cannot be applied on self-testing, a project has started at the Department of Clinical Chemistry, Skåne University Hospital Malmö, in 2010 where patients are trained in self-testing and measure their own INR in a hospital setting. After testing, the barcode on the back of the patient's drivers licence or identification card is scanned, the INR result is forwarded into AuriculA and a dosing scheme arrives by mail to the patient the following day.

IMPAIRED RENAL FUNCTION

Patients with end stage renal disease are at high risk for both bleeding and thrombosis [123, 124], and even a moderate decrease in glomerular filtration rate (GFR) is associated with thromboembolic [125] and bleeding complications [126, 127]. Data from Paper II demonstrate a significant difference in the prevalence of impaired renal function in patients with AF on OAT with warfarin, compared to a healthy reference population (**Table 4**). Almost 50% of AF patients in Paper II had an eGFR <60 mL/min/1.73 m^2, the level defined as CKD [119]. One in five AF patients on OAT with warfarin had an eGFR of <45 mL/min/1.73 m^2 (the border between CKD stage 3a and 3b) [120], associated with an increased risk of mortality and of progression to ESRD and CKD stage 4. Most importantly, the results also suggest that approximately one-tenth of AF patients on OAT with warfarin had severely impaired renal function (eGFR <30 mL/min/1.73 m^2) corresponding to CKD stage 4. This data is of high clinical significance as renal function slowly decreases with age. With rapid fluctuations in GFR caused by dehydration, anemia, heart failure, infection and hypotension, patients with moderately impaired renal function can temporarily progress into severely impaired renal function (eGFR <30 mL/min/1.73 m^2), a level associated with drug accumulation. A study exploring the pharmacokinetics of the thrombin inhibitor dabigatran etexilate demonstrated a more than six-fold larger area under the plasma concentration-time curve (AUC) and doubled elimination half-time (T½) for the drug if eGFR was <30 mL/min/1.73 m^2 [128].

Paper III is probably the first report of an association between decreased kidney function, as evaluated by eGFR, and the marked increased incidence of major bleeding events in a large prospective clinical cohort of patients on OAT. These data are unique since iTTR in Paper III is much higher than in most randomized controlled trials of warfarin [12-14, 90, 91, 129], and previous prospective studies of decreased kidney function [108], indicating that even in patients with high iTTR, eGFR is a greater risk factor for major bleeding than age.

Reduced kidney function has earlier been demonstrated to affect warfarin dosage, lead to poorer anticoagulation control and a more than two-fold risk of bleeding with eGFR <30 ml/min/1.73m^2 [108]. In that particular study by Limdi et al, TTR (INR 2.0-3.0) ranged from 40.1% to 49.7%, and percentages of INRs >3.0 were 24.2% and 18.0%, in patients with eGFR <30 and >60 mL/min/1.73m^2, respectively. The authors concluded that there is a correlation between low eGFR and the quality of anticoagulation treatment, where patients with severely impaired renal function are difficult to manage. In corresponding data from Paper III, TTR of INR 2.0-3.0 (not only patients with target range 2.0-3.0) ranged from 69.0% to 70.9% and

percentages of INRs >3.0 were 15.5% and 15.0% in patients with eGFR<30 and >60 mL/min/1.73m^2, respectively. Of special note, however, is that one out of seven patients in Paper III had an INR target interval of 2.0-4.0 and hence spends a larger proportion of time in INR >3.0 than patients with target intervals of INR 2.0-3.0 (**Table 5**). Subsequently, data from Paper III suggest that the high incidence of bleeding in patients with eGFR <30 mL/min/1.73m^2 seen by Limdi et al, could partly be related to poor anticoagulation control. Also, data indicate that anticoagulation control per se does not correlate to impaired renal function, in the larger, prospective clinical cohort in Paper III. In concordance with earlier data [108], there was a strong correlation in Paper III (**Fig.19**) between the incidence of major bleeding events and low eGFR with a very high yearly risk (95%CI) of major bleeding events of 7.7% (4.2-13.0). These data have now been reproduced, but for the first time in patients with a high mean percentage of iTTR.

There is a variation in the results in Papers II and III depending on which equation was used to calculate eGFR. Globally, the MDRD equation is a well-established equation for estimating relative GFR [117]. The MDRD formula was derived and validated in groups of patients with CKD, with a mean eGFR <40 mL/min/1.73 m^2 [130] However, the MDRD equation is considered to underestimate GFR when applied to patients with GFR >60 mL/min/1.73 m^2 [118, 131]. In a study from southern Sweden, the regionally developed LM equation performed better than the MDRD formula at predicting GFR in groups of patients with mean GFR of 55 mL/min/1.73 m^2, especially in patients with an eGFR <30 mL/min/1.73 m^2 [118]. In Papers II and III, eGFR values calculated using the LM equation are generally lower than eGFR according to the MDRD equation. There is an inherent problem in applying any eGFR equation to a patient group with different characteristics than the population used for derivation and validation of the equation [132]. However, when mean age, gender and mean eGFR are taken into consideration, the AF groups in Papers II and III are more similar to study subjects in the LM study than in the MDRD study. This could suggest that the LM formula possibly presents more accurate GFR estimations compared to the MDRD equation in these specific populations.

THE ELDERLY

Age is a risk factor for thromboembolism in $CHADS_2$ and CHA_2DS_2-VASc scores [97], and as a risk factor for bleeding in HAS-BLED [101]. Since there is progression of disease and co-morbidities with increasing age, the fact that the risk of stroke

increases with increasing age is inarguable. The main objective of OAT is to reduce these thromboembolic complications. However, the increased risk of bleeding seen with increasing age in RCTs of OAT can be multifactorial, since a part of the bleeding risk is something that we provide these patients with, namely pharmaceutical agents for OAT. Hence, factors that affect the quality of OAT treatment with warfarin, subsequently affect the bleeding risk in these patients, for example liver metabolism, concurrent medications, adherence/compliance to treatment and of course the organization and dosing of the OAT treatment given.

Age strongly correlates with the need for a lower warfarin dose to reach therapeutic INR in Paper I. This could be the result of less enzymatic activity in the liver, but the increased use of concurrent medications in the elderly, for example statins, probably affects the results. Although concurrent medications were not listed in Paper I, hopefully data could assist physicians, when initiating warfarin therapy, to start with and aim for lower doses in their elderly patients (**Fig.16**). Data in Paper I (**Fig.15**) also indicate that elderly patients manage their warfarin therapy at least as well as, or even better than younger patients and that age itself should not affect the decision to start a patient on anticoagulation therapy, given no other contraindications are present. However, in spite of the high TTR values in the elderly, the increase in rates of major bleeding with increasing age was still significant (**Fig.17+Table 6**).

In accordance with previous studies from Sweden [122, 133], the elderly AuriculA population in Papers I and III were expected to have more major bleeding events, compared to RCTs of warfarin treatment in which patients were younger, and still the risk of major bleeding was very low. As expected there was a correlation between age and major bleeding in Paper I (**Fig.17**; Wilcoxon test; $P<0.001$) but no correlation between age and thromboembolic events (**Fig.17**; Wilcoxon test; $P=0.147$), indicating that elderly patients have at least the same, and probably greater, benefit of OAT treatment as younger patients.

Even though results were not significant there was a trend towards lower iTTR in patients with events compared to those without events in Paper I. In Paper III there was a significant correlation of low TTR and the risks of major bleeding events and a trend towards low TTR in patients with thromboembolic events. As expected, there was a very strong relationship between age, the percentage of time INR >3.0 and major bleeding, demonstrated in both Papers I and III; $P=0.001$ (**Table 6**). Although there was a significant correlation between low iTTR and major bleeding in Paper III , only a correlation between low iTTR and major bleeding events was seen in patients aged <75 years and not in the elderly (**Table 6**). The mean iTTR in patients aged ≥75 years with major bleeding events was 74.0% and comparable ($P=0.34$) with patients of the same age without major bleeding events. Importantly, the prevalence of moderately impaired renal function (eGFR <45mL/min/1.73m^2) and severely

impaired renal function (eGFR <30 mL/min/1.73m^2) in patients aged ≥75 years with major bleeding in Paper III was 52 % and 26 % with odds ratios of 2.1 (P<0.01) and 2.9 (P<0.002) respectively (**Table 7**). These data implicates that in centres with high TTR (at least in Sweden), other factors may have greater influence on the risk of major bleeding in patients ≥75 years than iTTR, whereas iTTR is of greater importance for complications in patients aged <75 years with fewer co-morbidities.

Since reduced GFR appears to be common among AF patients on anticoagulation treatment with warfarin as demonstrated in Paper II, and because the size and mean age of this patient group are anticipated to grow [64], it seems conceivable to suggest regular monitoring of eGFR, especially if the patients in the future are on OAT with substances eliminated by renal route. The simplicity of regular controls of p-Cr and the calculation of eGFR is an appealing, simple, inexpensive and commonly available method, which could easily be done by a general practitioner. Data from Paper III indicate that elderly patients (≥75 years) do not have an increased risk of major bleeding if their kidney function, as evaluated by eGFR, is >60 mL/min/1.73m^2 (**Table 8+9**). This could be of great importance in clinical practice, since many physicians are reluctant to prescribe warfarin to elderly patients due to a perceived high risk of major bleeding. Whereas a normal eGFR in an elderly patient would constitute a very low risk of major bleeding events in the presence of high iTTR, a patient with an eGFR of <30mL/min/1.73m^2 has a very high yearly risk of major bleeding events, especially if there is evidence of over-anticoagulation and frequent time >INR 3.0. In these patients a serious evaluation of the risk of thromboembolic complications is recommended, using validated risk stratification schemes ($CHADS_2$ and CHA_2DS_2-VASc) [97] in patients with atrial fibrillation. In patients with low risk scores, anticoagulation should perhaps be avoided if severely impaired kidney function is present, given the high risk of major bleeding events.

ATRIAL FIBRILLATION AND NOVEL ANTICOAGULANTS

Patient selection

The results on TTR in Papers I and III are in line with, or, in some cases, even better compared to prospective randomized clinical trials of anticoagulation treatment with warfarin [12-14, 90, 91, 129] (**Table 10**). However, compared to RCTs, the AuriculA population represents a clinical cohort of older patients, where it is up to each individual clinician to assess the risk-benefit for every single patient before referring them for

Table 10. Comparison of OAT with warfarin in randomized trials of atrial fibrillation and the AuriculA AF subgroup. TTR= time in treatment range. *median age. ACTIVE-W (warfarin vs clopidogrel +aspirin); SPORTIF (warfarin vs ximelagatran); ROCKET-AF (warfarin vs rivaroxaban); ARISTOTLE (warfarin vs apixaban); RE-LY (warfarin vs dabigatran)

Study name	Sample size	Mean age	TTR	Event rates (% / patient-year)	
	(n)	years	%	Thromboembolic	Major bleeding
ACTIVE-W	3371	70	64	1.6	2.2
SPORTIF-III	1703	70	66	2.9	1.8
SPORTIF-V	1962	72	68	1.9	2.8
ROCKET-AF	7133	73*	55	2.4	3.4
ARISTOTLE	9081	70	62	1.6	3.1
RE-LY	6022	71	64	1.7	3.4
AuriculA	2491	74	76	1.4	2.6

anticoagulation treatment. Although there are no data on $CHADS_2$ and CHA_2DS_2-VASc-scores and other co-morbidities, given the higher mean age in the AuriculA population in Papers I and III and the absence of distinct exclusion criteria for OAT treatment, one can presume that the AuriculA population probably reflects a clinical cohort on OAT treatment with warfarin better, than the populations of RCTs.

Patients in the ROCKET-AF, ARISTOTLE and RE-LY trials were not allowed to have co-morbid conditions with life expectancies ≤1 year, prosthetic valve disease, and patients with severely impaired renal function were actively excluded at screening [12, 14, 94]. These exclusion criteria are of upmost importance since the selected populations in these RCTs are probably healthier and definitely younger than clinical cohorts of anticoagulated patients (**Table 10**). It is evident that a decrease in kidney function is seen with increasing age [96] and since >60% of bleeding and thromboembolic events in Papers I and III, were observed in patients over the age of 75, where the prevalence of severely impaired kidney function was around 10% (Paper II), a systematic exclusion of elderly patients with the highest risk for bleeding events has been done in these RCTs. Dabigatran (80%), rivaroxaban (33%) and apixaban (25%) are eliminated by renal route and besides the fact that these novel anticoagulants cannot be used to the same extent in real life as in the RCTs due to the high prevalence of concomitant valve disease, and severely impaired kidney function in AF patients, results from Paper III indicate that their use in patients with moderately impaired kidney function must be carefully monitored, especially in elderly patients.

TTR, eGFR and complications

Trials comparing novel anticoagulants with warfarin are dependent on the quality of the management of the warfarin cohort. Even though RCTs generally have a high patient adherence to protocol, it is still obvious that compliance varies. The RELY-trial, comparing two different doses of dabigatran to warfarin in patients with AF, demonstrated similar event rates in the warfarin group, as expected by data from meta-analysis by Wan and coworkers [37], with a TTR of 64%. Dabigatran, at the higher dose of 150 mg b.i.d., was shown to be statistically superior to warfarin in reducing thromboembolic complications, and non-inferior in reducing major bleeding events. The lower dose of 110 mg b.i.d.was statistically non-inferior to warfarin in reducing thromboembolic event and statistically superior in reducing major bleeding events [12]. In the ROCKET-AF trial, rivaroxaban was proven to be non-inferior to OAT with warfarin with a TTR of 55% [14], and in the ARISTOTLE trial apixaban was shown to be non-inferior to warfarin in reducing thromboembolic events and superior in reducing major bleeding events with a TTR of 62% [94]. The problem is that the interpretation of non-inferiority and superiority in a given trial may depend both on the homogeneity and treatment accuracy of the control group, which in these trials reflects the $CHADS_2$-score, and the TTR of OAT treatment with warfarin.

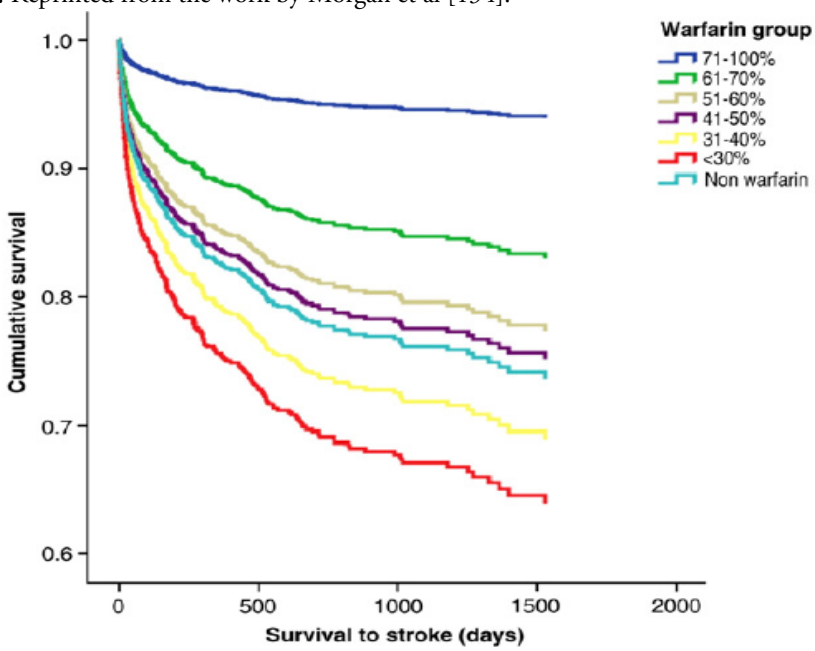
There were differences between age groups in the RE-LY trial as demonstrated by a subgroup analysis, where the higher dose of dabigatran was clearly beneficial in patients <75 years but was associated with an increase of major bleeding events compared to warfarin in patients ≥75 years [92]. A more than two-fold higher risk of major bleeding was evident in patients on both warfarin and dabigatran, with a creatinine clearance <50 mL/min compared with those who had a clearance >80 mL/min [92]. However, no correlation between eGFR and major bleeding was seen after adjustment for age in the RE-LY substudy, results which stand in contrast to data from Paper III (**Table 8**). Data from Paper III indicate that there is no difference in the incidence of major bleeding between different age groups at the same levels of eGFR. Data were also consistent in patients with atrial fibrillation (**Table 9**). Since patients with eGFR <30 mL/min/1.73m^2 were excluded from the RE-LY trial, the absence of these patients, with their high prevalence of bleeding events as demonstrated in **Table 8+9**, could in part explain these differences in results. Also, the mean TTR (INR 2.0-3.0) in the RE-LY trial was 64% whereas the adjusted mean iTTR (INR 2.0-3.0) was 74.5% in Paper I, indicating other potential causes for differences in results. No data were available from the RE-LY trial on differences in management of OAT treatment between different age groups, similar to data from Paper I (**Fig.15**) and subsequently no correlation between iTTR and complications in

the elderly have been made. Given the strong correlation between eGFR and major bleeding events in patients on anticoagulation treatment demonstrated in Paper III, caution is advised in patients with impaired renal function in the upcoming era of new oral anticoagulants with elimination by renal route, especially in the elderly.

ORGANIZATION OF ANTICOAGULATION TREATMENT

In a study of 1,749 patients with AF and $CHADS_2$-risk score of ≥2, anticoagulation control with >70% of time within therapeutic range has been demonstrated to significantly improve outcomes in terms of stroke compared to treatment without warfarin [134] (**Figure 23**). A near significant trend was also seen in patients with TTR >60%, but TTR <60% was not associated with any benefits in stroke reduction. Evidence is clear that poorly controlled OAT with warfarin is potentially harmful and there is a general acceptance that if good anticoagulation control cannot be achieved, perhaps the therapy should be stopped. However, what percentage of TTR can be definitively regarded as good, what is acceptable and what can in fact be harmful?

Figure 23. Cox proportional hazards model for survival to post atrial fibrillation stroke in 1,749 patients at moderate or high risk of stroke $CHADS_2$ ≥2 by level of warfarin control. Reprinted from the work by Morgan et al [134].



In the RELY-trial, Sweden had the highest TTR of 77% and other Nordic countries such as Finland and Denmark had TTRs of 74 and 72%. Also, Sweden has in several RCTs [88, 90, 129] previously demonstrated high percentages of TTR that could in part be due to the organization of anticoagulation treatment in Sweden and not entirely to the fact that these were RCTs. Sweden has an excellent tradition of good adherence to anticoagulation treatment with an organization of anticoagulation centres both in primary care, and hospital settings. The results in this thesis confirm these previous data. In Papers I and III, the algorithm for dose-adjustment of warfarin dosing in AuriculA could in part explain these high quality results, eliminating human error to some extent and keeping the dosing of warfarin consistent throughout different centres. With this in mind, the question is whether the percentage of TTR in some trials of novel anticoagulants is to be regarded as too low for an adequate comparison of warfarin treatment? Or does the low TTR in some of these trials just mirror the current problems with OAT with warfarin and the need of better alternatives, and/or the need of improved organizations of anticoagulation treatment in centres with low percentages of TTR?

A retrospective subgroup analysis of the RE-LY trial has shown that differences in thromboembolic and major bleeding events were markedly reduced in centres with cTTR >72.4% [135] (**Table 11**), although the results were statistically consistent with the trial as a whole. Also, centres

Table 11. Comparing rates of complications (percent per treatment year) between the RELY-population, the subgroup of cTTR >72.4%, and the AuriculA subgroup (cTTR=75%) in patients with atrial fibrillation. AF=atrial fibrillation; cTTR=centre time in treatment range;; Dabi=dabigatran b.i.d; ICH=intracranial haemorrhage

		n	Thrombo-embolism	Major bleeding	ICH
RELY	Warfarin	6022	1.69%	3.36%	0.74%
TTR=64%	Dabi 110 mg	6015	1.53%	2.71%	0.23%
	Dabi 150 mg	6077	1.11%	3.11%	0.30%
RELY	Warfarin	1509	1.34%	3.11%	0.77%
cTTR	Dabi 110 mg	1482	1.23%	2.81%	0.21%
>72.4%	Dabi 150 mg	1514	1.27%	3.60%	0.30%
AuriculA	AF Subgroup	2492	1.40%	2.57%	0.39%

with a cTTR >72.4% had a significantly higher percentage of treatment with ACE-inhibitors, beta-blockers, statins and less concomitant use of aspirin and amiodarone [135], which could reflect better adherence to clinical guidelines, better patient adherence to treatment and a more structured organization of the healthcare setting and of anticoagulation clinics. In addition, $CHADS_2$-scores were generally lower in these centres with mean iTTR>72.4%, which could reflect both exclusion of indentified individuals with a high risk of major bleeding events, and a prominent healthcare setting in primary prevention of cardiovascular disease.

While awaiting the upcoming era of new oral anticoagulation therapy, the data in this thesis support the need for an improved organization of specialized anticoagulation centres and treatment regimens in centres with low levels of TTR. At the same time, we need to be prepared to quickly introduce the new anticoagulants to patients who benefit the most, for example patients who are intolerant to warfarin due to side effects or allergies, patients with presumably good compliance and large variations in INR, and patients who previously have refused warfarin therapy and only take antiplatelet agents.

LIMITATIONS

GENERAL

Since Papers I to III are observational register studies, although prospective, some limitations can easily be acknowledged. Confounders can be present since there were no data on $CHADS_2$/CHA_2DS_2-VASc scores in patients with atrial fibrillation, nor have concomitant illnesses or medications been listed in Papers I-III. Also, the prevalence of cardiovascular death and all-cause mortality has not been listed in Papers I and III. Subsequently, with the exception of gender, age (Papers I and III) and renal function (Paper III), no evaluations of risk factors for major bleeding or thromboembolism have been made. Only data from the year 2008 and complications from two centres in Paper I and one centre in Paper III have been studied. Consequently, in some cases, patient numbers and treatment years were low. Data in Paper II is also from just one centre, cross-sectional and consequently only demonstrates an epidemiological link between AF and impaired renal function. In Paper III only an epidemiological association between low eGFR and major bleeding events can be established. Hence, data in this thesis are merely hypotheses-generating.

MISCLASSIFICATIONS

Indication of OAT treatment

Indication of OAT with warfarin was extracted from AuriculA. AF diagnosis had previously been documented on electrocardiography upon initiation of anticoagulation treatment by the referring physician. There was no adjudication of the diagnosis of atrial fibrillation as an indication of anticoagulation treatment. In addition, although there are data indicating that paroxysmal AF has the same risk of thromboembolic events as chronic AF [78, 98, 99], no distinction as to whether the AF was chronic, persistent or paroxysmal was made.

Endpoints

Continuous follow-up is done prospectively in AuriculA through routine telephone calls and major bleeding and thromboembolic events are registered in AuriculA. For patients who had not suffered an event or who had not denied such complications during follow-up, a systematic review of hospital records was made in Papers I and III by four different nurses at the Department of Coagulation Disorders in Malmö and by a physician in the General Hospital in Sundsvall. Major bleeding events were defined according to ISTH Guidelines, and thromboembolic events according to the AuriculA program. No separate adjudication of major bleeding or thromboembolic events was made by a physician in Paper I, which, of course, could reflect both an overestimation and an underestimation of events. However, adjudication of events was made in Paper III, mirroring a large proportion of events in paper I and no large numeral differences were seen in complication frequencies. Only hospital records from the Skåne University Hospital and in the General Hospital in Sundsvall were however used in the review and it cannot be ruled out that some patients suffered an event but were treated at another hospital, leading to an underestimation of events.

Renal function

Data in Paper II and III lacked information about height and weight, preventing a more accurate calculation of body surface area and absolute eGFR. Relative eGFR was used instead which is not ideal to assess the appropriate dosing of drugs in relation to renal function, where an absolute eGFR, independent of body surface area, gives more accurate information about renal clearance. Hence, the findings in this thesis need to be reproduced in different international settings, and in future studies of AuriculA, using other methods/equations of estimating GFR.

GENERALIZABILITY

In order to obtain a uniform, high quality treatment for all patients on OAT, international guidelines are issued by the major international cardiology societies, and national guidelines are issued by the Swedish National Board of Health and Wellfare. Adherence to these guidelines by physicians is probably growing but to what extent is largely unknown. Recently, the RHYTHM-AF study was presented demonstrating large variations between countries regarding patient co-morbidities, risk factors for stroke, and use of medical treatment [136]. AuriculA was created for one of these reasons, to be able to observe the treatment of AF patients in respect to population characteristics, guideline adherence and outcome.

The general population in AuriculA is heterogeneous and there is a difference in cTTR between hospitals. If the quality of OAT differs between hospitals, there are probably also differences in patient selection, co-morbidities and adherence to guidelines. Once again, the major deficiency of Papers I to III is the lack of data on CHA_2DS_2-VASc -score to establish that warfarin is prescribed on the correct indication of treatment. It could be that patients in Sweden on OAT with warfarin have low CHA_2DS_2-VASc –scores, which at least to some extent could explain the low numbers of complications. It is also not certain that patients in Malmö and Sundsvall on OAT reflect the general Swedish population and that these patients do not receive treatment according to established guidelines. Subsequently, the cohorts in Paper I-III could reflect a healthier population with a lower incidence of stroke and other thromboembolic events. However, in Papers I and III, patients with atrial fibrillation had a mean age of 74 and 75 years respectively, which is 3-4 years higher than that of recent randomized controlled trials of warfarin [12]. Taking into account the age-associated co-morbidities such as hypertension, diabetes and heart failure, this could in fact reflect a population with a higher CHA_2DS_2-VASc-score than those of randomized controlled trials and a subsequent increased risk of both major bleeding and thromboembolic events. Of course, this is only speculation. Hopefully, in the future, AuriculA can be used to establish how well different centres/hospitals in Sweden perform, compared to each other, and on a more international level, to different hospitals in different countries.

In Paper IV, the patients did not do the blood tests themselves so we can not apply our results to patient self-testing. Also, we have not evaluated lot-to-lot or instrument variation. Supporting multi-centre trials have still not been made to this date, but since Paper IV was accepted, other studies have demonstrated a satisfactory level of concordance in patient self-testing [137] and children [138], in centres that practice Quick PT.

REPRESENTATIVITY

The foundation of the organization of anticoagulation treatment in Sweden is built on anticoagulation centres, both in primary care and in hospital-based settings. Patients enrolled in AuriculA are representative of the whole patient community treated with anticoagulants in Sweden, with both large urban centres as well as small primary care centres. Although there may be differences in demographics between centres, especially between hospital-based centres and primary care centres, there is no selection bias of patients in AuriculA. Since every anticoagulation centre that participates in AuriculA enrolls all their patients, and entire regions in Sweden

participate, the population is well representative of a clinical population in Western Europe. Numbers are growing with more than 67,000 patients enrolled as of August 2011.
The Anticoagulation Clinic at Skåne University Hospital Malmö serves a population of 300,000 inhabitants in the third largest city of Sweden. In AuriculA the mean age for all indications OAT was 70 years, and in atrial fibrillation, 73 years. The mean age of all patients on OAT in Malmö in Paper III was 72 years, and in atrial fibrillation, 75 years, indicating a population with more co-morbidities and risk factors for major bleeding events as well as thromboembolism than in the general AuriculA population. The General Hospital in Sundsvall serves a population of 148,000 inhabitants and the mean age of all patients on OAT was 60 years, and in atrial fibrillation 68 years, indicating a population with the opposite profile. To what extent our results in Paper I, on risks of major bleeding and thromboembolic events, were affected by these regional differences in patient profiles and health is unknown. However, when comparing **Table 2** and **Table 5** only a very subtle effect on the difference in complication frequencies is demonstrated.
In Paper II, the mean eGFR in patients with AF was 65 ml/min/1.73 m^2 according to the MDRD equation. Some cohort studies with similar age profiles demonstrate higher mean eGFR among AF patients, reporting baseline eGFR of 76, 90 and 109 ml/min/1.73 m^2, respectively [139-141]. One explanation for the lower eGFR in Paper II and III could be the exclusion of AF patients without anticoagulation treatment with warfarin, (i.e. $CHADS_2$-score 0-1) who are probably healthier However, the "true" mean eGFR could also be underestimated since a lot of elderly patients, with subsequently lower eGFR, do not receive anticoagulation therapy due to an increased risk of bleeding. Hence, the study population in Paper II and III represents a different selection of AF patients, feasibly displaying other co-morbidity patterns.

SELECTION BIAS

In the analysis of eGFR in Papers II and III, 63 of 2,671 and 187 of 3,536 patients respectively, did not have a p-Cr measured during the study period, and two patients with complications in Paper III did not have a p-Cr measured at the time of the event. This bias in patient selection could affect the results especially in Paper III where these patients constitute more than 5% of the study population. However, since patients with known impaired kidney function usually have regular contact with specialized and primary care to monitor their kidney function, the lack of these results during a two-year period probably reflects that we have systematically excluded

healthier individuals. If this is the case, this would have overestimated our results in Paper II and underestimated our results in Paper III.
In Paper III, 331 patients with an indication of anticoagulation treatment other than atrial fibrillation had a mechanical valve replacement and hence, the high incidence of bleeding events seen in the group with INR target interval 2.0-4.0 could reflect a selection bias (**Table 5**). Patients with mechanical valves probably continue treatment if a bleeding event is not so severe (non-CNS), but in patients with AF there is a higher probability that warfarin treatment would be withdrawn.

REFERENCE POPULATION

In Paper II the study and control groups differed in terms of mean age and gender (i.e. the proportion of women), although the difference in mean age was non-significant or very small when dividing patients in age groups (**Table 3**). Adjustment for differences in age and gender was made using logistic regression when calculating odds ratios and by using the present formulas for calculating eGFR. After adjustment for age and gender, the demonstrated difference in eGFR between study groups and reference groups remained significant (**Table 4**). Hence, these differences between the AF population and the reference population will therefore, most likely, not explain the differences in eGFR between the populations. Data would, however, have been more easily accepted if the AF and the reference population were matched with regards to age and gender.

CONFOUNDING

TTR is an established marker of the quality of anticoagulation control and correlates inversely to both major bleeding and thromboembolic events [37]. The absence of a more thorough patient profile in Papers I to III with co-morbidities, risk factors for bleeding and thromboembolic events, medications, smoking status and alcohol consumption severely limits the interpretations of the results. Although interesting, data in Paper III only demonstrate that other factors apart from iTTR, such as renal function, may influence the risk of major bleeding in patients ≥75 years, whereas iTTR is of greater importance for complications in patients aged <75 years, who have less co-morbidities. Hence, data are just indicative and only demonstrate an epidemiological link between major bleeding events and impaired renal function where other risk factors probably play an important role.

CONCLUSIONS

- The quality of OAT with warfarin in Sweden is high and comparable to prospective randomized trials of warfarin treatment. Complications with OAT are low, probably due to the organization of anticoagulation treatment in Sweden.
- Use of the AuriculA dosing program might have contributed to the results by keeping dosing regimens consistent over centres, while eliminating human error to some extent.
- Severe renal impairment is common among AF patients on anticoagulant treatment with warfarin, especially at higher ages. Hence, many AF patients are at risk of drug accumulation, which implies caution in the upcoming era of new anticoagulants, eliminated by renal route.
- Other factors apart from iTTR, may be of greater importance for the risk of major bleeding in patients ≥75 years, whereas iTTR is of greater importance for complications in patients aged <75 years who have fewer co-morbidities.
- With high quality anticoagulation control, measured by iTTR, elderly patients ≥75 years seem to have similar risks for major bleeding as younger patients, if consideration is given to renal function.
- Severely impaired kidney function (eGFR <30ml/min/1.73m^2) is associated with a very high yearly risk of major bleeding events, especially if the percentage of time in INR >3.0 is high. In patients who belong to this group, and in whom low risks of thromboembolism are present, withdrawal of anticoagulation treatment should perhaps be considered.
- The POC-device CoaguChek XS presents reproducible results, highly comparable with Owren PT at therapeutic levels of INR, offering a more convenient method of monitoring, compared to regular venous INR measurement.

FUTURE CONSIDERATIONS

It seems conceivable to implement regular monitoring of renal function in AF patients on anticoagulation treatment in clinical practice, since reduced GFR appears to be common among AF patients on anticoagulation treatment with warfarin. This is also important since the size and mean age of this patient group is anticipated to grow [64]. The clinical relevance of the results in Paper II, where almost a fifth of all AF patients on warfarin present an eGFR of <45 mL/min/1.73m^2 has already been acknowledged in the editorial of Thrombosis Research [142]. The strict inclusion criteria and three month follow-up that are applied in RCTs of new anticoagulants cannot be applied in the general healthcare of these patients, should they receive these new pharmaceuticals. Monitoring of renal function in this patient group is, however, indicated upon initiation of these anti-coagulants, especially in adjunction to hospitalizations where marked fluctuations in renal function can be seen in infectious disease, congestive heart failure, dehydration, and surgical procedures, both during hospital stay and at follow-up after discharge. Also, the monitoring of renal function is of additional importance upon initiation of ACE-inhibitors, ARB, NSAIDs, and other medications that can affect renal function. An initial glance at these clinical challenges may cause some reluctance, and perhaps these novel anticoagulants, eliminated by renal route should not be presented to this patient category (eGFR <45 mL/min/1.73m^2) at first.

Compliance is another issue, where patient adherence to treatment with the novel anticoagulants will be put to the test. Where patient adherence to warfarin treatment can, at least to some extent, be monitored using the present day INR testing (Even though my father-in-law taught me that a patient who presents an INR of 2.5 at testing can be far from adherent to the current prescription and regulations of warfarin treatment), failure to comply with treatment of new anticoagulants can go by relatively unnoticed. The only way to probably monitor adherence to treatment with these new anticoagulants is to closely follow-up these patients and look for an increase in cases of thromboembolism as a surrogate marker of bad compliance. One of the benefits of the new anticoagulants, that have been proposed, is the lack of the need of INR monitoring and repeated blood tests. Data in this thesis are, however, indicative

of a further need of monitoring and blood tests in patients on oral anticoagulation treatment. In the upcoming era of new anticoagulants, the present organization of anticoagulation clinics with their long experience and knowledge of anticoagulation treatment, and the AuriculA register, can be used to monitor eGFR, both in patients on warfarin, but especially in patients starting new anticoagulants eliminated by renal route.

The question of whether anticoagulation therapy with warfarin in countries/centres with high levels of TTR will be comparable to new oral anticoagulation treatments outside randomized controlled trials is still to be answered. Central registers comparing complication frequencies between different oral anticoagulation treatments in a clinical setting, in older patients with more co-morbidities, will be needed to give further information of any differences in clinical benefit in Sweden. To establish the full risk/benefit of different oral anticoagulation treatments in clinical cohorts of patients with impaired renal function, with respect to both thromboembolic, and major bleeding events, a more careful assessment of risk factors (i.e CHA_2DS_2-VASc and HAS-BLED), as well as a more thorough estimation of GFR, have to be made. A register considering all these aspects will be started in AuriculA in the Skåne University Hospital Malmö and Lund. Hopefully, in a couple of years we will have answers to some of these questions.

Eventually, the time will come for an evaluation, to see if warfarin can be replaced once and for all and then only one issue remains. Will dabigatran, rivaroxaban and apixaban provide us with even better rat poisons….?

"Hold it, I wonder if I might try the warfarin again?"

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POPULÄRVETENSKAPLIG SAMMANFATTNING

Uppskattningsvis 140–180 000 patienter i Sverige har förmaksflimmer. Den totala förekomsten är dock okänd eftersom vissa patienter också helt saknar symtom och därför inte har kännedom om sin sjukdom. Förmaksflimmer, som både kan vara kroniskt eller komma i attacker, innebär att förmaken inte aktivt pumpar ner blodet i hjärtats kammare. Istället sker mer okoordinerade sammandragningar av förmaken, vilket leder till blodstockning med risk för att blodet levrar sig och bildar blodproppar framför allt i förmaksöronen (auricula). Den mest allvarliga komplikationen vid förmaksflimmer är när en blodpropp lossnar från förmaken och hamnar i hjärnan, vilket kan leda till stroke.

Ålder över 65 år, hjärtsvikt, diabetes, högt blodtryck, tidigare stroke, kärlsjukdom, kvinnligt kön och förmaksflimmer är riskfaktorer vid stroke. Patienter med förmaksflimmer och med ytterligare minst en riskfaktor för stroke bör enligt nationella och internationella riktlinjer behandlas med blodförtunnande behandling. Den största risken med blodförtunnande behandling är allvarliga blödningar, framför allt hjärnblödningar eller blödningar i mag- och tarmkanalen. Man måste därför värdera patientens följsamhet av behandlingen samt blödningsrisken som påverkas av ett antal kända faktorer, däribland ålder och njursjukdom.

Stora studier har visat att blodförtunnande behandling med warfarin (Waran) minskar risken för stroke med 65 % jämfört med att inte behandla patienterna. Behandling med acetylsalicylsyra (Magnecyl, Trombyl, Albyl) kan dock vara aktuell när Waranbehandling av olika anledningar inte är lämplig, men denna behandling är inte lika effektiv för att minska risken för blodproppar. Det är viktigt att Waranbehandlingen är välkontrollerad eftersom läkemedlet ska skydda mot proppar utan att öka risken för blödningar. Waranets effekt mäts med ett blodprov (INR) och målsättningen är att blodet ska vara två till tre gånger tunnare än normalt blod (INR 2,0-3,0). På grund av stora individuella variationer i patienternas svar på Waranbehandlingen måste patienterna genomgå regelbundna blodprov, vanligen var fjärde till åttonde vecka. I Sverige finns etablerade verksamheter med mångårig erfarenhet av blodförtunnande behandling, s.k antikoagulationsmottagningar, som ansvarar för INR-kontroller och ordinationen av Waran. Behandlingseffekten med Waran kan mätas med TTR vilket är en slags kvot som i procent anger hur stor del av

den totala behandlingstiden som patientens blod är lagom tunt och där patientens INR-värden ligger mellan INR 2,0–3,0. TTR påverkas av doseringsjusteringar av Waran men framför allt av patientens följsamhet och ett högt TTR (>60 %) har visat sig vara starkt kopplad till minskad risk för både stroke och blödningar för patienten.

För vissa patienter är de täta blodprovskontrollerna under Waran-behandling besvärande. Ett annat problem är att Waran interagerar med en del vanliga mediciner vilket kan påverka INR-värdet. Kost (t.ex kål, broccoli och jordgubbar) och alkohol kan även ge en viss påverkan av INR-värdet. Därför har nya läkemedel, s.k. trombinhämmare och faktor Xa-hämmare utvecklats och kommer snart att lanseras i sjukvården. Fördelen med dessa är en fast dosering där levringsförmågan av patienternas blod inte behöver kontrolleras, och att läkemedlen saknar interaktioner med andra läkemedel. Dessa nya läkemedel har i stora internationella studier visat sig vara minst likvärdiga och i vissa fall bättre än Waran med avseende på minskad risk för både stroke och blödningar.

I denna avhandling studeras framför allt patienter med förmaksflimmer under behandling med Waran, i den svenska nationella databasen och kvalitetsregistret AuriculA. Syftet med avhandlingen är att ge en bild av den svenska Waranbehandlingen med avseende på patienternas TTR, risk för stroke och blödningar. Vidare vill avhandlingen utvärdera möjligheten till kapillär istället för venös blodprovstagning på Waranbehandlade patienter, samt förekomsten av nedsatt njurfunktion hos Waran-behandlade patienter med förmaksflimmer och undersöka hur detta är kopplat till förekomsten av stroke och blödningar.

I delarbete 1 beskrivs alla 18391 Waranbehandlade patienter i databasen AuriculA under 2008, och där medelvärdet för patienternas TTR-värde var mycket högt, ca 76 % av tiden. I två centrum (Malmö och Sundsvall) såg man att det höga TTR-värdet var kopplat till en låg förekomst av både stroke, blodproppar och stora blödningar. Dessa resultat kan tolkas bero på Sveriges välutvecklade organisation med antikoagulationsmottagningar.

I delarbete 2 studeras förekomsten av sänkt njurfunktion hos 2603 Waranbehandlade förmaksflimmerpatienter i Malmö under 2009. Studien visar att uppemot en femtedel av patienterna har en kliniskt relevant sänkning av njurfunktionen vilket är viktigt att känna till då nya trombinhämmare och vissa faktor Xa-hämmare utsöndras via njurarna, och därmed riskerar att ansamlas i kroppen vid bland annat infektioner, uttorkning och kirurgi.

Delarbete 3 är en studie av samtliga 3536 patienter som behandlades med Waran i Malmö under 2008. Studien visar på en stark koppling mellan nedsatt njurfunktion och risken för stora blödningar, trots att patienternas TTR är högt. Risken för stor blödning verkar vara mindre beroende av ålder och mer kopplad till njurfunktionen än vad man tidigare trott. Risken för stor blödning var ca 7-10% per år för de med kraftigt nedsatt njurfunktion. Däremot sågs ingen ökad risk för stroke med ökad ålder

eller nedsatt njurfunktion hos patienterna med Waranbehandling vilket tyder på en god behandlingseffekt.

Delarbete 4 är en jämförelse av kapillär (stick i fingret) blodprovstagning jämfört med traditionell venös (stick i armvecket) på ca 400 patienter i AuriculA. Studien visade att den kapillära analysmetoden är likvärdig den venösa provtagningen och skulle kunna bana väg för en större användning av kapillär blodprovstagning i svensk sjukvård.

Avhandlingens slutsats är att Waranbehandlingen vid antikoagulations-mottagningar i Sverige är av hög kvalitet och risken för stroke och stora blödningar under Waranbehandling är, i ett internationellt perspektiv, mycket låg. En stor del av förmaksflimmerpatienterna som behandlas med Waran har sänkt njurfunktion och man kan förutse ett större behov att följa njurfunktionen framöver då det både finns en koppling till ökad förekomst av stora blödningar, men även eftersom många av de nya trombinhämmarna och faktor Xa-hämmarna utsöndras via njurarna. Då Waranbehandling av patienter med förmaksflimmer i Sverige verkar vara mer effektiv än vad som tidigare visats i studier från andra länder väcker det frågan huruvida de nya läkemedlen verkligen kommer minska risken för stroke och blödningar i Sverige. Kontrollerna av INR i Sverige kan dessutom komma att förenklas med hjälp av den nya kapillära provtagningen. Patienter som skall behandlas med de nya läkemedlen bör därför införas i AuriculA så att dessa patienters njurfunktion kan följas på samma sätt som idag sker med INR-värden, för att om möjligt justera behandlingsdosen vid försämrad njurfunktion. Införandet i AuriculA kommer i framtiden även att möjliggöra en utvärdering av dessa nya behandlingar i jämförelse med dagens Waranbehandling för att se om de verkligen är bättre.

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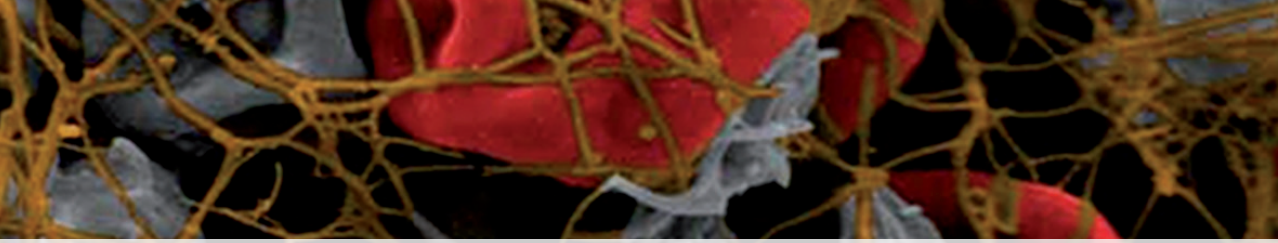

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