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Anticoagulant and antiarrhythmic agents for atrial fibrillation

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Abstract

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia. AF treatment involves management of precipitating factors, rate- and rhythm control and anticoagulation for prevention of stroke and systemic thromboembolism.

The aims of this thesis were to describe clinical practice in prescription of anticoagulation therapy and trends in ischemic stroke incidence among AF patients, to report plasma concentrations of anticoagulant dabigatran at 110 mg bid under concomitant treatment with antiarrhythmic agent dronedarone in real-life patients and to assess ECG-derived indices of AF organization as predictors of cardioversion with vernakalant.

A considerable proportion of AF patients do not receive adequate stroke prevention therapy with oral anticoagulation, despite increased guideline adherence. Efforts to reduce under-treatment should particularly be targeted on female patients < 65 years with additional stroke risk factors and elderly > 84 years. The increased use of oral anticoagulants between 2011 and 2013 in patients with incident AF is associated with decline in the cumulative incidence of ischemic stroke in Skåne County. Dronedarone and dabigatran are often indicated in the same patient population. Trough plasma concentration of dabigatran at 110 mg bid dose with dronedarone was comparable to plasma dabigatran concentration at the dose of 150 mg bid without concomitant dronedarone in RE-LY study with reportedly low rates of major bleeding and thrombosis. Larger trials on efficacy and safety of this treatment strategy might refute the present contraindication. ECG-derived markers of atrial remodelling failed to predict treatment response in acute cardioversion of AF with vernakalant.

Key words anticoagulants, atrial fibrillation, dabigatran, dronedarone, stroke, vernakalant

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Anticoagulant and antiarrhythmic agents for atrial fibrillation

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To my son Michael J. Hambiliki

Content

List of abbreviations

AAD	anti-arrhythmic drugs
ACT-trial	Atrial Arrhythmia Conversion trial
AEs	adverse events
AF	atrial fibrillation
AFR	atrial fibrillatory rate
APPT	activated partial thromboplastin time
ASA	acetylsalicylic acid
AV	Atrioventricular
AVRO-trial	Amiodarone in Subjects with Recent Onset Atrial Fibrillation trial
b.i.d.	*bis in die* (*latin*; in a prescription of medication) = twice daily
BMI	body mass index
CI	confidence interval
CHA_2DS_2-VASc	stroke risk score in atrial fibrillation
DOAC	direct-acting oral anticoagulant
ECG	electrocardiography or electrocardiogram
eGFR	estimated glomerular filtration rate
EMEA	European Medicines Agency
ESC	European Society of Cardiology
FDA	Food and Drug Administration
fpm	fibrillations per minute
F-wave	fibrillatory wave

GARFIELD-AF	Global Anticoagulant Registry in the FIELD Atrial Fibrillation
HAS-BLED	bleeding risk score in atrial fibrillation
ICD	International Classification of Diseases
INR	international normalized ratio
IQR	inter-quartile range
ISTH	International Society on Thrombosis and Haemostasis
i.v.	Intravenous
LADD	left atrial end-diastolic diameter
LVEF	left ventricular ejection fraction
NOAC	non-vitamin K antagonist oral anticoagulation
NSAID	non-steroidal anti-inflammatory drugs
NYHA	New York Heart Association
PAI-1	plasminogen activator inhibitor 1
PITX2 gene	paired like homeodomain 2
P-gp	P-glycoprotein
PT	prothrombin time
OAC	oral anticoagulation
OR	odds ratio
ORBIT-AF	The Outcome Registry for Better Informed Treatment of Atrial Fibrillation
RAAS	renin-angiotensin-aldosterone system
RCT	randomized controlled trial
RELY-trial	Randomized Evaluation of Long Term Anticoagulation Therapy trial
SD	standard deviation
SHR	Skåne Healthcare Register

SR	sinus rhythm
TAFI	thrombin activatable fibrinolysis inhibitor
TF	tissue factor
TFPI	tissue factor pathway inhibitor
TIA	transitory ischaemic attack
t-PA	tissue plasminogen activator
TTR	time-in-therapeutic range
TXA2	thromboxane A2
u-PA	urokinase-type plasminogen activator
VKA	vitamin K antagonist
VTE	venous thromboembolism
vWF	von Willebrand factor
ZFHX3	zinc finger homeobox 3

Original publications

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

I. Mochalina N, Jöud A, Carlsson M, Sandberg M.E, Själander A, Juhlin T, Svensson P.J. Antithrombotic therapy in patients with non-valvular atrial fibrillation in Southern Sweden: A population-based cohort study. Thromb Res, 2016; 140:94-9

II. Mochalina N, Isma N, Svensson PJ, Själander A, Carlsson M, Juhlin T, Wieloch M. Ischemic stroke rates decline in patients with atrial fibrillation as anticoagulants uptake improves: a Swedish cohort study. Thromb Res, 2017; 158:44-5

III. Mochalina N, Juhlin T, Platonov P.G, Svensson P.J, Wieloch M. Concomitant use of dabigatran with dronedarone in patients with atrial fibrillation in clinical practice. Thromb Res, 2015; 135 (6) 1070-4

IV. Mochalina N, Juhlin T, Öhlin B[1], Carlson J, Holmqvist F, Platonov P.G. Predictors of successful cardioversion with vernakalant in patients with recent-onset atrial fibrillation. Ann Noninvasive Electrocardiol, 2015; 20 (2) 140-7

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[1] Deceased in November 2015

Haemostasis

Haemostasis is the body's normal physiological response in conjunction to injury in order to prevent uncontrollable bleeding and safeguard the patency of the vasculature and the surrounding tissue. The term is derived from Ancient Greek roots "haimo" (blood) and "stasis" (stagnation).

Haemostasis includes following stages:

Primary haemostasis

– vasoconstriction, platelet adhesion on injured endothelium and platelet plug formation.

Secondary haemostasis

– activation of the coagulation cascade leading to formation of cross-linked fibrin for plug reinforcement.

Anticoagulation

– a process limiting propagation of the thrombus.

Fibrinolysis

– dissolution of the thrombus.

Primary haemostasis

Blood vessels are lined with endothelial cells with negatively charged layer of glycocalix. Healthy endothelial cells repel negatively charged platelets and prevent blood clot formation by inactivating circulating coagulation factors. Injury to blood vessel results in immediate local vasoconstriction that minimizes blood leakage but also slows down the platelets allowing them to adhere to exposed collagen and other sub-endothelial thrombogenic components.

Circulating von Willebrand factor (vWF) attaches to the exposed collagen and serves as a bridge between the tissue and the GPIb-V-IX receptor on the platelets.

The platelets undergo subsequent morphological changes leading to surface enlargement and development of pseudo-pods. They release alpha-granule contents (vWF, factor V, factor XIII and fibrinogen) and the dense bodies contents (adenosine diphosphate (ADP), calcium and serotonin) that enhance further coagulation. Highly activated platelets also release thromboxane A2 that facilitates GPIIb/IIIa receptor expression. GP IIb/IIIa receptor promotes aggregation of the platelets inducing fibrinogen cross-linking (Fig.1)

Acetylsalicylic acid inhibits platelet aggregation by the irreversible inactivation of the cyclooxygenase enzyme that facilitates synthesis of prostaglandin and thromboxane A2.
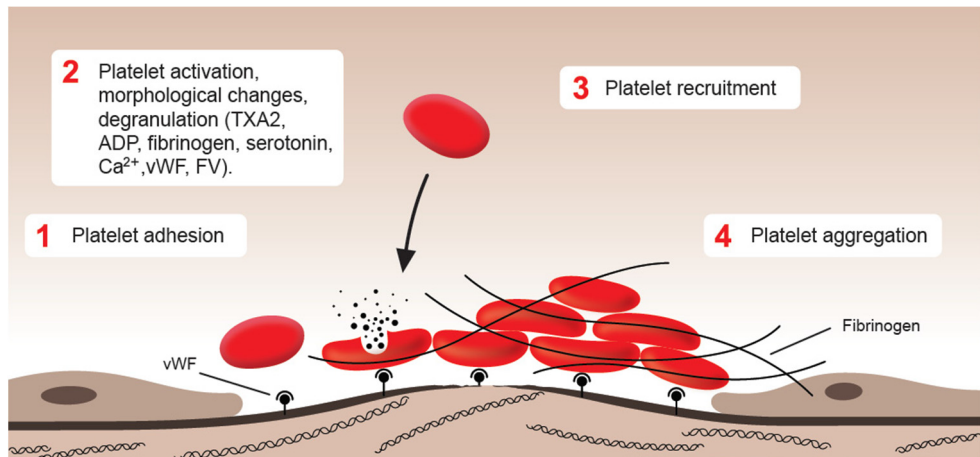
Figure 1 Primary hemostasis
Thromboxane A2 (TXA2), Adenosine diphosphate (ADP), von Willebrand factor (vWF). With permission from Casper Asmussen.

Secondary haemostasis

The cascade model where one clotting factor leads to activation of another by the contact activation pathway (also known as intrinsic pathway) or the tissue factor (TF) activation pathway (also known as extrinsic pathway) was proposed by researchers after *in vitro* experiments (1, 2). These pathways ultimately combine into a common pathway leading to the formation of thrombin that in turn converts fibrinogen to fibrin (Fig. 2). Factor Xa (a=activated) and thrombin are two major amplifiers of the coagulation cascade through feedback loops. Direct-acting oral anticoagulants (DOAC) also known as non-vitamin K oral anticoagulants (NOAC) inhibit either thrombin or factor Xa.

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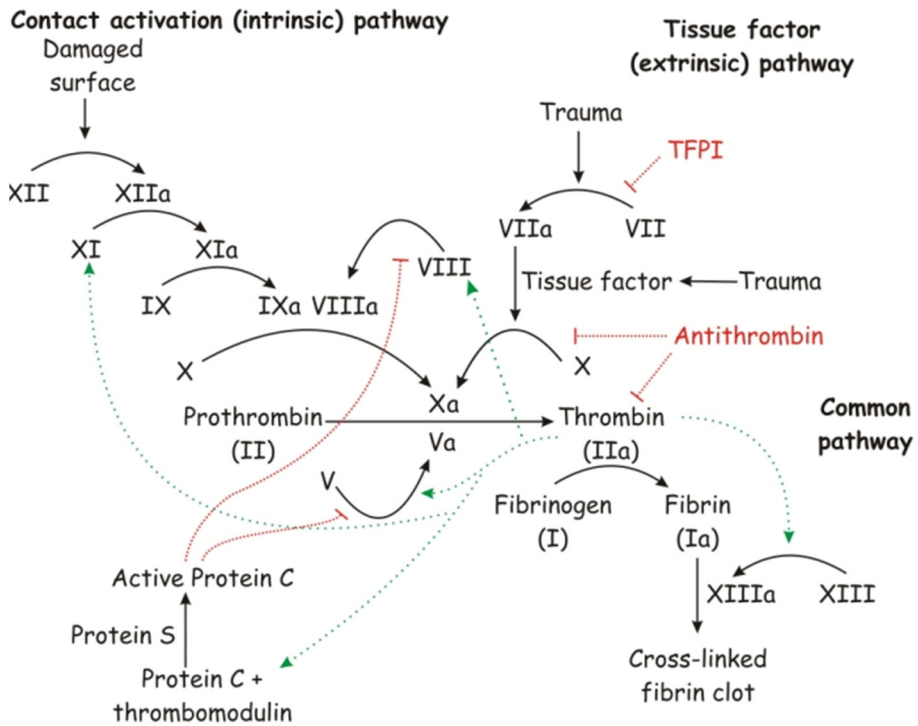
Figure 2. The cascade model.
TFPI=tissue factor pathway inhibitor. Negative feedback loops are marked in red. Positive feedback loops are marked in green. With permission from Casper Asmussen.

The prothrombin time (PT) and the activated partial thromboplastin time test (APTT) measure the integrity of the extrinsic and the intrinsic pathway respectively.

This separation of coagulation into two parallel pathways is however artificial. Current evidence supports that the intrinsic and extrinsic pathways is an interdependent network of reactions *in vivo* (3). Patients deficient in the initial factors of the intrinsic pathway (such as FXII, prekallikrein or high-molecular weight kininogen) do not exhibit any clinical bleeding tendency. However, patients deficient in FVIII (Haemophilia A) or FIX (Haemophilia B) in the intrinsic pathway have serious bleeding disorders despite the intact extrinsic pathway (4, 5). Also, patients deficient in FVII in the extrinsic pathway have serious bleeding tendencies in spite of efficient intrinsic pathway (6).

Fig. 3 shows the plasma coagulation during secondary haemostasis. A contemporary cell-based model of haemostasis proposed by Hoffman and Monroe

involves three overlapping phases (3). *The initiation phase* takes place on the surface of extravasal TF-bearing cells exposed to circulating FVII after damage of the vessel wall. FVII binds to TF in the presence of calcium, leading to activation of FX and FIX and formation of small amounts of thrombin. During *the amplification phase,* taking place on the platelets' surface, thrombin activates FV, FVIII and FXI. During *the propagation phase,* large-scale thrombin generation takes place on the surface of activated platelets. FVIII and FIX form the tenase complex activating FX. Activated factors X and V form the prothrombinase complex that converts prothrombin to thrombin. Thrombin then causes conversion of the soluble fibrinogen to the insoluble fibrin, leading to formation of a thrombus. Thrombin also activates factor XIII that stabilises the thrombus by cross-linking the fibrin clot.
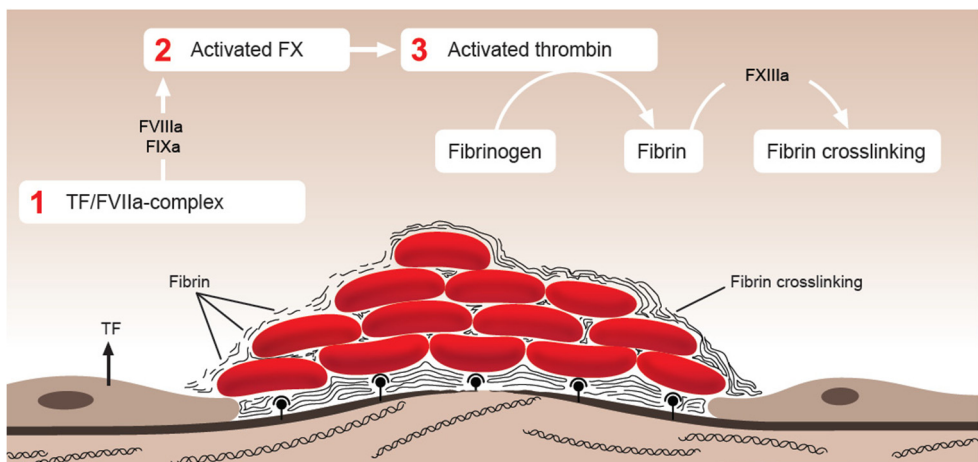
Figure 3. Secondary hemostasis.
Tissue factor (TF). With permission from Casper Asmussen.

Anticoagulation

Three major mechanisms balance the effect of coagulation in order to prevent excessive intravasal thrombus propagation and restrict plasma clotting to the area of the injury. The tissue factor pathway inhibitor (TFPI), a protein secreted by the endothelial cells, binds FXa and thrombin. Furthermore, the FXa-TFPI complex can inhibit TF/FVIIa complex (7). Secondly, antithrombin inhibits thrombin, factor IXa, Xa, XIa and XIIa. The inhibition of coagulation cascade by antithrombin can be reinforced by heparin administration (8) or heparin-like molecules on the surface of the endothelial cells. Finally, vitamin K-dependent activated protein C (APC) and its cofactor protein S cleave FVa and FVIIIa (9).

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Dysfunctions of these anticoagulation mechanisms (such as APC resistance, protein C-, protein S- or antithrombin deficiencies) result in predisposition to venous thromboembolism, also known as thrombophilia (10).

Fibrinolysis

After the haemostatic clot has served its purpose of sealing the injured vessel wall and the vessel damage is healed, the process of dissolving the fibrin network begins (Fig. 4) Healthy endothelial cells secret tissue-plasminogen activator (t-PA) and urokinase type plasminogen activator (u-PA) (11). These proteases convert plasminogen to plasmin that lyses intravascular fibrin. Fibrin serves as a cofactor to t-PA and thus potentiates its own breakdown. The d-dimer is a product of fibrin degradation that serves as clinical marker of fibrinolysis and ongoing/prior thrombus formation (12).

There are several factors that can counteract fibrinolysis. One of them is plasminogen activator inhibitor 1 (PAI-1) that inhibits the conversion of plasminogen to plasmin (13). Another factor is thrombin activatable fibrinolysis inhibitor (TAFI) that down-regulates fibrinolysis by decreasing the rate of plasmin generation (14)
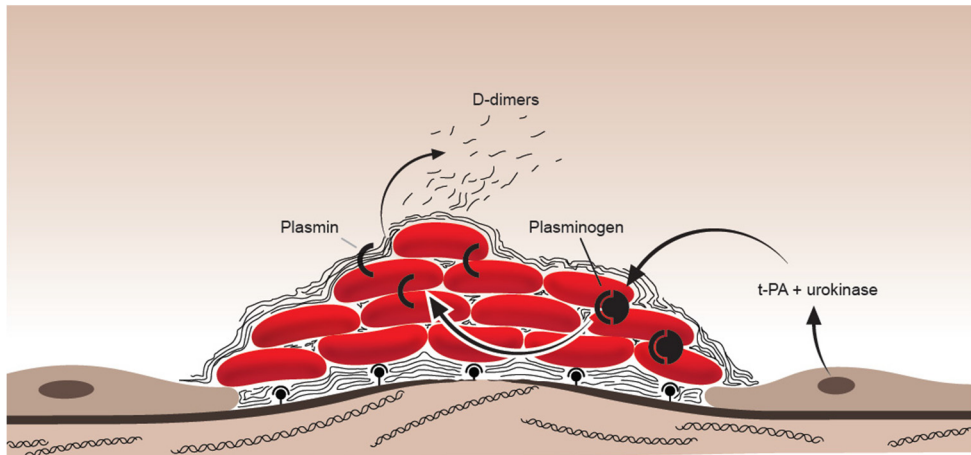
Figure 4. Mechanisms of fibrinolysis.
Tissue plasminogen activator (t-PA). With permission from Casper Asmussen.

Atrial fibrillation

Atrial fibrillation (AF) is characterised by chaotic activity in the atria with totally irregular ventricular response, resulting in the absence of p-waves on the electrocardiogram (ECG) (15) (Figure 5).
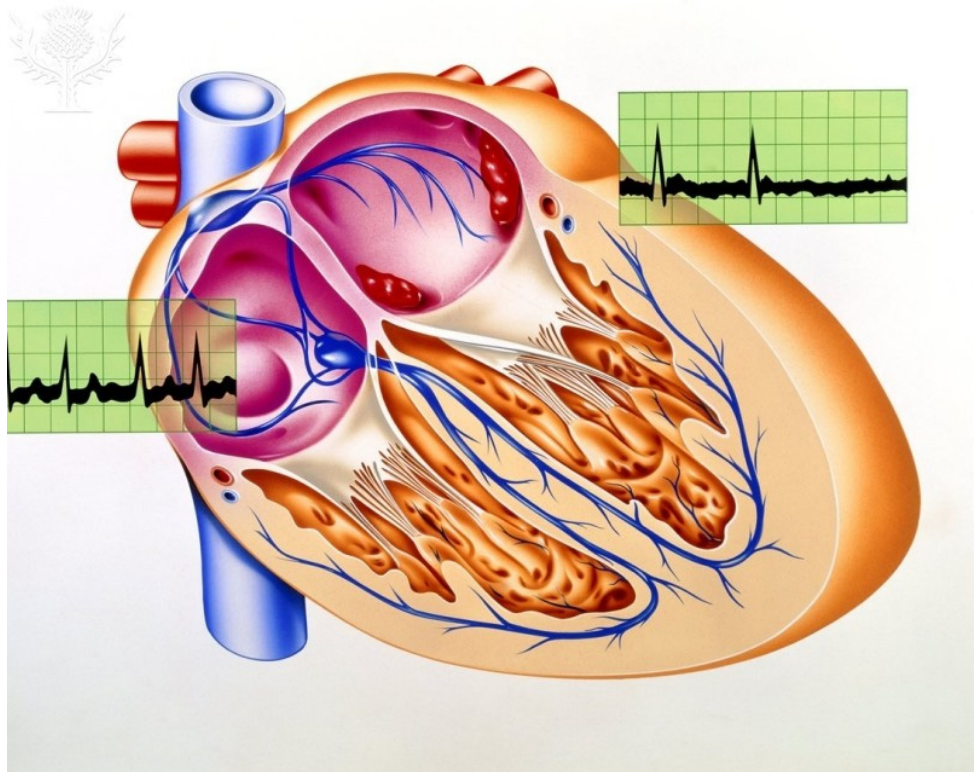
Figure 5. Atrial fibrillation.
Source: Atrial fibrillation, artwork. Photography. Britannica ImageQuest, Encyclopædia Britannica, 25 May 2016.
quest.eb.com/search/132_1265772/1/132_1265772/cite. Accessed 10 May 2017

Historical background

Many notable physicians were involved in the development of the AF concept over the centuries. The legendary Chinese emperor Huangdi described chaotic irregular pulse as early as 2600 BC (16). French physician Jean Baptiste de Senác (1693-1770) assumed correlation between "rebellious palpitations" and mitral stenosis (15). German internist C.W.H. Nothnagel (1841-1905) recorded AF pulse waves and named the disease *"delirium cordis"* (17). Sir James MacKenzie recognized the loss of atrial contraction in AF after recording atrial pulse waves in the jugular vein in 1904 (18). Dutch physiologist W. Einthoven invented electrocardiography (ECG) in 1903 (Fig. 6) and received the Nobel Prize in Medicine in 1924 for his discovery. He recorded the first ECG demonstrating AF in 1906 (19). Sir Thomas Lewis described the connection between the electrical and anatomical manifestations of AF and coined the term *"auricular fibrillation"* in 1909, establishing AF as a clinical entity.
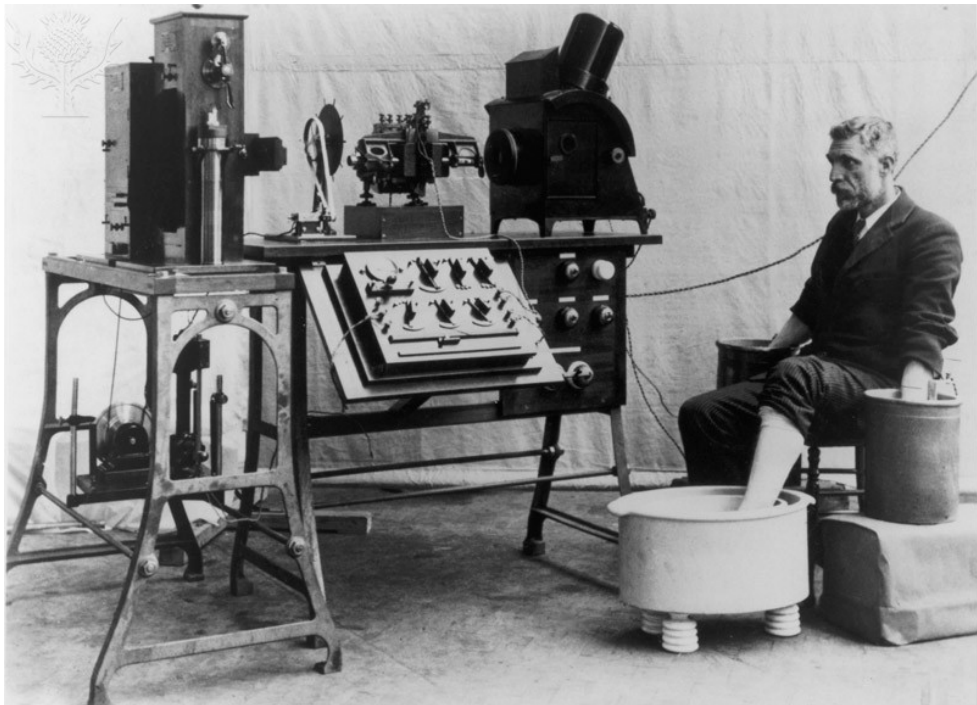
Figure 6. Early electrocardiograph recorder.
Britannica ImageQuest, Encyclopædia Britannica, 25 May 2016.
quest.eb.com/search/115_2749180/1/115_2749180/cite. Accessed 10 Jul 2017. Accessed 10 May 2017.

Epidemiology

AF is the most common sustained cardiac arrhythmia that affects approximately 3% of the adult population (20). This arrhythmia is one of the major causes of stroke and heart failure (21, 22). AF is also associated with frequent hospitalizations (23), reduced quality of life (24), cognitive decline and vascular dementia (25). Twenty-five per cent of all adults over 40 will develop AF during their lifetime (26), with a five-fold increase of stroke compared to non-AF population (27). Females with AF are older, have more comorbidities (28) and demonstrate higher AF-associated mortality rates compared to males (29). Women with AF are often more symptomatic, but are still less likely to receive rhythm control therapy (30). AF prevalence is age–dependent rising to 10-17% in those over 80 years of age (31). AF is a consequence of structural disease of the atria and hence more common in patients with hypertension, heart failure, coronary artery disease, obesity, diabetes mellitus and valvular heart disease (32, 33). The incidence of AF is increasing worldwide due to the rising prevalence of these predisposing conditions in the ageing population (34).

Classification and mechanisms

AF is traditionally divided into first diagnosed, paroxysmal, persistent, long-standing persistent and permanent based on presentation, duration and termination pattern of the disease. AF usually progresses from short and often self-terminating episodes, typically lasting for less than 48 hours but sometimes up to 7 days (paroxysmal AF), to longer attacks lasting for over 7 days and/or requiring cardioversion (persistent AF). Continuous AF lasting $\geq$ 1 year is termed long-standing persistent AF, when a rhythm-controlling strategy still is pursued. If the patient and physician agree not to pursue a rhythm-controlling strategy of the AF, the condition is called permanent AF.

The underlying mechanisms of AF vary depending on AF type and are often multi-factorial in the same patient. Multiple electrical re-entry wavelets in the atria cause loss of atrial synchronization (35). The size of the functional re-entry depends on wavelength, which is a product of conduction velocity, and refractoriness in conducting atrial cells. Shorter wavelengths allow for multiple simultaneous re-entry circles (36). Thus, large atria with short refractory periods and decreased conduction velocities are more prone to sustained AF.

The pathophysiology of AF often involves ion channel dysfunction, Ca^{2+}-handling abnormalities, structural remodelling and autonomic neural dysfunction (37, 38).

In patients with mitral stenosis or prosthetic valves, the increased atrial pressure and/or regurgitation volume load leads to atrial enlargement and structural remodelling (39). Similarly, AF in structural heart disease (such as long-standing hypertension with heart failure or left ventricular hypertrophy) is characterized by increased atrial pressure with atrial remodelling as well as activation of sympathetic- and renin-angiotensin systems (40). In these patients AF is often a cause of hospitalization and a predictor of poor prognosis (41, 42). AF can also arise due to acute factors such as atrial oxidative stress (43), high sympathetic tone (44), inflammation (45), electrolyte changes and volume overload (46). Since these triggers are common after surgery, approximately 30 % patients develop AF after cardiac surgery (47), possibly in combination with pre-existing substrate.

AF can arise in structurally normal hearts. Younger patients with frequent short episodes of paroxysmal AF can have local ectopic triggers, in most cases originating from pulmonary veins, left atrium or crista terminalis (a smooth muscular ridge in the right atrium) (48, 49) in the absence of left atrial enlargement. Also, AF in endurance athletes may be caused by increased atrial volume and vagal tone (50). Monogenic or polygenic mutations in ion channels are a relatively rare cause of AF, and can be associated with early AF onset (51).

Management

AF treatment involves rate control, rhythm control in symptomatic patients, management of precipitating factors and ischemic stroke prevention. Rhythm control for symptom improvement can be achieved with antiarrhythmic drugs, cardioversion, catheter ablation or AF surgery.

Thromboembolism in patients with AF

AF is associated with loss of organized atrial contraction and blood flow stagnation. Alternation in blood flow, together with atrial remodelling with dilatation and fibro-elastic infiltration, predispose to thrombus formation in the left atrial appendage with a subsequent risk for systemic embolism (52).

AF accounts for at least 15% of all ischemic strokes and up to 36% of ischemic strokes in the elderly (53). Strokes in AF patients tend to be more severe with greater risk of recurrence, disability and death (54).

The CHA_2DS_2-VASc score (55) is a well-established tool for estimation of ischemic stroke risk. The score has been validated in numerous cohorts of AF

patients (56, 57). One point each is given for congestive heart failure, hypertension, age over 65 years, diabetes mellitus, vascular disease and female sex. Hypertension is defined as current antihypertensive treatment or blood pressure at rest $\geq$ 140/90 on at least two occasions. Vascular disease is defined as previous myocardial infarction, presence of peripheral arterial disease or aortic plaque. Prior ischemic stroke, transitory ischemic attack (TIA) or a thromboembolic event and age $\geq$ 75 years are strong risk factors rendering two points each. The scoring system and the absolute ischemic stroke risk are outlined in Table 1.

Treatment with oral anticoagulation (OAC) is recommended in all patients with AF and a CHA_2DS_2-VASc score $\geq$ 2 and should be considered in patients with CHA_2DS_2-VASc score = 1 according to European Society of Cardiology (ESC) Guidelines from 2012 (58). The latest ESC Guidelines from 2016 (59) recommend OAC treatment in men with AF and CHA_2DS_2-VASc score $\geq$ 2 and in women with CHA_2DS_2-VASc score $\geq$ 3. OAC treatment should also be considered in patients with only one risk factor for stroke (CHA_2DS_2-VASc score of 1 in men and 2 in women). Thus, the majority of patients with AF should receive OAC with the exception of those without any known risk factors for systemic thromboembolism.

Table 1. CHA_2DS_2-VASc score for AF stroke risk (55).

Risk factor	Points assigned	CHA2DS2-VASc score	Adjusted stroke rate (%/year)
		0	0
Congestive heart failure	1	1	1.3
Hypertension	1	2	2.2
Age 65-74 years	1	3	3.2
Age ≥ 75 years	2	4	4.0
Diabetes mellitus	1	5	6.7
Stroke, TIA or thromboembolism	2	6	9.8
Vascular disease	1	7	9.6
Sex category (female)	I	8	6.7
Maximum score	9	9	15.2

Anticoagulant treatment

Warfarin reduces risk of ischemic stroke by approximately two-thirds (60). In 1933 Karl Link in the University of Wisconsin discovered the precursor to warfarin (named after Wisconsin Alumni Research Foundation) in the attempt to

develop an effective rat poison (Figure 7). The substance was approved for medical use in 1954 (61).

Warfarin is a vitamin K antagonist (VKA) that blocks vitamin K epoxide reductase which is necessary for synthesis of vitamin K dependent coagulation factors II, VII, IX and X (62). Patients exhibit variable dose-response to warfarin due to interactions with concomitant medications, alcohol and dietary vitamin K as well as genetic polymorphism altering warfarin metabolism (63, 64). Warfarin treatment requires regular monitoring of international normalized ratio (INR) with prothrombin time (65). For patients with mechanical valve prosthesis or rheumatic mitral stenosis warfarin is currently the recommended option for prevention of systemic thromboembolism (66, 67).

Direct-acting oral anticoagulants (DOAC), such as apixaban, dabigatran, rivaroxaban and edoxaban, are superior to warfarin for prevention of stroke or systemic embolism with a similar risk for major bleeding or non-inferior with a lower risk of major bleeding, depending on the dosage (68-72). Apixaban, edoxaban and rivaroxaban act as factor Xa inhibitors, whereas dabigatran is a direct thrombin inhibitor (73). DOAC are given at fixed dose, do not require routine monitoring of coagulation and have fewer food and drug interactions compared to warfarin (74). They are preferred to warfarin when AF therapy is initiated in AF patient eligible for DOAC according to current ESC guidelines (59).

Patient treated with oral anticoagulants are prospectively followed up in the Swedish national quality register AuriculA, which contains information about anticoagulation treatment, patient's INR values for warfarin, comorbidities and complications (75).
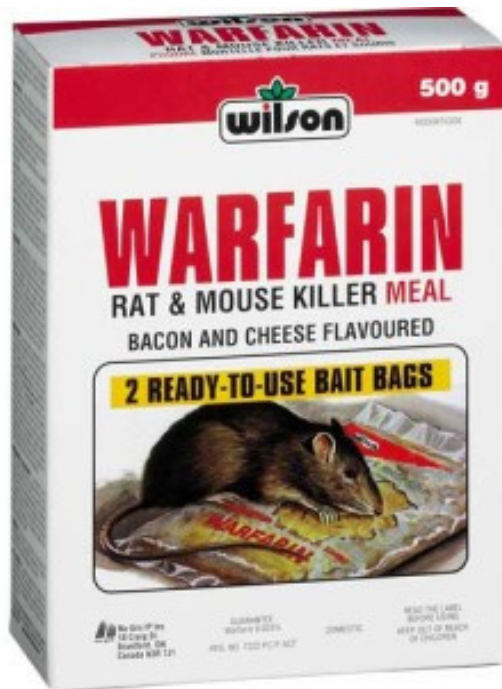
Figure 7. Warfarin.
Source: Britannica ImageQuest, Encyclopædia Britannica, Accessed the 9th of May 2017.

Acetylsalicylic acid (ASA) should not be used for stroke prevention in AF patients since it is not effective (76, 77) and carries the same bleeding risks as OAC treatment (78).

Bleeding risk in AF patients can be assessed using HAS-BLED score where points are given for hypertension, renal- or liver disease, stroke history, prior major bleeding or predisposition to bleeding (such as anaemia, platelet or coagulation defect), age > 65 years, labile INR during warfarin treatment, medication usage predisposing to bleeding (antiplatelet agents or non-steroidal anti-inflammatory drugs/NSAID) or alcohol abuse (79).

Risk scores for bleeding and ischemic stroke share some common components such as prior history of stroke, hypertension and old age. The HAS-BLED score should not be used to exclude patients from OAC treatment since considerable stroke risk in patients without OAC treatment often outweighs the bleeding risk on OAC treatment (59). Bleeding risk scores should rather be used to structure the management of modifiable bleeding risk factors (hypertension treatment, identification and correction of bleeding source, reduction of DOAC dosage or closer INR monitoring, avoidance of alcohol and prevention of falls).

Rhythm control

Acute restoration of sinus rhythm can be achieved with antiarrhythmic drugs (such as amiodarone, flecainide, propafenone, ibutilide (80) or vernakalant (81)) or with electrical cardioversion (82). Electrical cardioversion is a first-line treatment of AF in case of hemodynamic instability. Sinus rhythm after cardioversion can be maintained with dronedarone, amiodarone, flecainide, propafenone or sotalol (83). The choice of the antiarrhythmic drug depends upon comorbidities, risk of drug-induced pro-arrhythmia, symptom burden and patient's preferences. Recurrent AF can also be treated by catheter ablation (84), AF surgery (85) or hybrid therapy (that is combination of antiarrhythmic drugs with ablation or surgery) in selected patients (86).

Sustained AF is more likely to persist in large atria with a short refractory period (87). Antiarrhythmic agents act either by changing the conduction velocity or prolonging the refractory period in order to reduce the amount of electric wavelets (88).

Vernakalant is an atrial-selective antiarrhythmic agent that acts as a mixed sodium- and potassium channel blocker and supresses re-entry by prolonging atrial refractoriness (89). Na-channel blockage is rate- and voltage depended and occurs mainly in rapidly depolarizing atria during AF (90). Ventricular conduction velocity and refractoriness are thus only minimally affected and pro-arrhythmic potential is relatively low (91, 92). The reported conversion rate for new-onset AF with vernakalant is 52%, with median time to conversion of 11 minutes among responders (93).

Dronedarone maintains sinus rhythm and reduces mortality and hospitalisation due to cardiovascular events in patients with paroxysmal and persistent AF (94). Dronedarone can be used in patients with stable coronary artery disease (95), but is contraindicated in patients with heart failure NYHA class III-IV (96) and in permanent AF (97).

Treatment with DOAC and dronedarone are often indicated in the same patient population. P-glycoprotein (P-gp) transporter is involved in re-secretion of dabigatran (98), apixaban (99) and edoxaban (100) after absorption in the gut and probably in renal clearance of rivaroxaban (101). Dronedarone is a strong P-gp-inhibitor with a potential to increase bioavailability of DOAC if given concomitantly. Competitive inhibition of the P-gp pathway may increase the bioavailability of DOAC (by 70-100% for dabigatran and by 85% for edoxaban, no data is available for apixaban and rivaroxaban) (102).

In a study on 16 healthy volunteers (age 18-45 years and 81.3% males) trough concentration of dabigatran was 1.7-fold higher when dabigatran was co-administered with dronedarone than when it was administered alone (103, 104).

Retrospective cohort studies using claim databases has not shown any increased risk of major bleeding with concomitant treatment with dabigatran and dronedarone, compared to dabigatran alone (104, 105). Hence, the clinical significance of dabigatran and dronedarone interaction is unknown. The European Medicines Agency (EMEA) has decided that concomitant use of dabigatran and dronedarone should be contraindicated based on pharmacokinetic data from the above-mentioned study on healthy volunteers (105). No prospective study had previously evaluated the safety of the concomitant treatment in AF patients to whom both drugs are indicated.

Since dabigatran is eliminated by 80% via renal route (106), the impaired renal function can lead to increased bleeding risk due to dabigatran accumulation (107).

Non-invasive indices of atrial remodelling

Previous research has established a correlation between fibrillatory wave (f-waves) characteristics obtained from surface-ECG and a degree of electrical remodelling of the atria (108).

Atrial fibrillatory rate (AFR) measured in fibrillations per minute (fpm) and assessed from surface ECG reflects the average refractory period of the atria and may be used to predict the ability to restore and maintain sinus rhythm (109, 110). AFR < 360 fpm has been correlated to favorable therapeutic response to ibutilide (111) and flecainide (112).

Exponential decay (ED) derived by a signal processing technique called time-frequency analysis (108, 113-115) is a marker of greater degree of atrial signal organization. Organized atrial activity such as sinus tachycardia results in a very low ED, whereas disorganized input signal from a great number of AF wavelets results in a high ED. Lower ED during AF was reported to correlate with higher likelihood of sinus rhythm maintenance following AF cardioversion (116).

High fibrillatory wave (F-wave) amplitude predicted a success of catheter ablation (117) as well as SR maintenance after catheter ablation (118) and electrical cardioversion (119).

Aim of the studies

Paper I: To describe the prescription pattern of oral anticoagulation therapy in clinical practice in patients diagnosed with incident AF during 2011-2014 in the Skåne County

Paper II: To assess the uptake of OAC treatment and trends in incidence of ischemic stroke among patients diagnosed with incident AF during 2011-2013 in the Skåne County

Paper III: To report plasma concentrations of dabigatran at 110 mg bid during concomitant treatment with dronedarone, in real-life patients with AF

Paper IV: To assess ECG-derived indices of AF organization as predictors of cardioversion with vernakalant in recent-onset AF

Materials and methods

Paper I

The study of a population-based cohort of 13 837 adults with incident non-valvular AF and flutter, diagnosed between the 1st of January 2011 and 31st of December 2014 in primary and secondary care in Skåne County and identified in Skåne Healthcare register (SHR) by International Classification of Disease (ICD) code I 48. Diagnosis of AF was defined as incident if there was no occurrence of ICD code I 48 during the preceding 10 years in order to differentiate between prevalent and incident AF cases.

Comorbidities for calculation of CHA_2DS_2-VASc and HAS-BLED scores were assessed 10 years prior to AF diagnosis using ICD-codes registered in the SHR.

The outcome was treatment with warfarin, a DOAC or ASA dispensed within 3 months from AF diagnosis. The prescribed treatment was identified using the Skåne County's Prescribed Drug Database.

Potential undertreatment was defined as ASA or no treatment in patients with CHA_2DS_2-VASc score ≥ 2. Overtreatment was defined as ASA or OAC in patients with CHA_2DS_2-VASc $= 0$ without other indications for OAC (such as venous thromboembolism (VTE)) 6 months retrospectively or 3 months prospectively from AF diagnoses or recurrent VTE (≥ 2 VTE within 10 years prior to AF diagnosis) or cardioversion).

ESC guideline adherent treatment in 2011-2013 was defined as treatment with OAC in patients with CHA_2DS_2-VASc ≥ 2, OAC or no treatment in patients with CHA_2DS_2-VASc score 1, and no treatment of patients with CHA_2DS_2-VASc score 0.

Paper II

The study of a population based cohort of 11 500 adults diagnosed with incident non-valvular AF or flutter between the 1st of January 2011 and the 31st of December 2013 in primary or secondary care and identified using the Skåne Healthcare Register (SHR) by the International Classification of Diseases (ICD 10) code I 48.

Comorbidities for CHA_2DS_2-VASc score were assessed in SHR for the 10 years preceding the AF-diagnosis using ICD-10 codes in positions 1 to 8.

Treatment with ASA, warfarin or a DOAC dispensed within 3 months from AF diagnosis and prior to outcome was assessed using the Skåne County's Prescribed Drug Database.

The study outcome was the occurrence of ICD-10 code I63 for ischemic stroke in first position in the SHR within 365 days from AF diagnosis. An episode of ischemic stroke registered during the same admission as the first AF diagnosis was classified as a comorbidity.

Paper III

AF patients treated concomitantly with dabigatran 110 mg b.i.d and dronedarone 400 mg b.i.d at the discretion of the patient's cardiologist at Skåne University Hospital during the period of January 2012 to July 2013 were followed up prospectively in the internet-based Swedish national quality registry AuriculA.

The outcome was trough plasma concentrations of dabigatran at one week and one month after the start of concomitant treatment. Plasma concentration of dabigatran was measured at Department of Clinical Chemistry, Skåne University Hospital. Trough venous samples at steady state, between 08:00 and 08:30 in the morning before patients had taken their morning dabigatran dose, were collected at pre-specified time points at one week and one month after the initiation of the concomitant treatment.

Plasma concentrations of dabigatran were obtained using the diluted thrombin time calibrated with a dabigatran standard (Hemoclot thrombin inhibitor assay, HYPHEN BioMed) (120) in accordance with recommendations of International Society of Thrombosis and Homeostasis (ISHT) (121). The total imprecision, calculated as coefficient of variation, was 9.85% at 100 ng/ml and 4.59% at 400 ng/ml.

A review of all hospital records of every patient with concomitant treatment was performed in May 2014 to assess concomitant medications and to assure that no comorbidities or treatment complications were missed. Baseline CHA_2DS_2-VASc and HAS-BLED scores were calculated.

Rates of major bleeding (according to ISTH definition (122)) and rates of ischemic stroke or systemic embolism during the time of concomitant treatment were also assessed.

Assessment of other drugs that can alter P-gp listed in Food and Drug Administration (FDA) Guidance for Industry Drug Interaction Studies (123) was performed. Concomitant treatments with cardiovascular drugs and medications that could affect bleeding risk (antiplatelet agents, NSAID, proton pump inhibitors and corticosteroids) were also assessed.

Dabigatran is eliminated predominantly via renal route, and hence renal function was monitored at treatment initiation, at three, six and twelve months and thereafter annually (124). The Lund-Malmö equation was used for calculation of estimated glomerular filtration rate (eGFR), which was derived and internally validated at the present University Hospital (125).

Paper IV

The study population consisted of patients ≥ 18 years with symptomatic AF < 48 hours duration, undergoing pharmacological conversion with vernakalant at Skåne University Hospital between December 2010 and December 2012. Patients receiving at least part of the recommended drug dose were included in the study.

The initial infusion of vernakalant was administered as a 3 mg/kg dose over 10 minutes, followed by a 15-minute observation period. A second infusion at a 2 mg/kg dose over 10 minutes was administered if the AF had not been terminated by the first infusion.

The primary endpoint, defining a patient as a treatment responder, was conversion to sinus rhythm within 90 minutes after the start of the first vernakalant infusion. ECG-derived indices of AF organization (AFR, exponential decay, and F-wave amplitude) were estimated using a 10-second recording of lead V1 using AFRtracker software (CardioLund Research AB, Lund, Sweden).

Statistics

The statistical analyses were performed using SPSS (version 21.0 and 22.0, Armonk, NY: IBMCorp).

Normally distributed data were expressed as means and reported with standard deviations (SD). Otherwise, medians reported with interquartile ranges (IQR) or ranges were used. Categorical variables were expressed as numbers and percentages.

All statistical tests were two-sided and p-values < 0.05 were considered as statistically significant.

Paper I

Descriptive analysis of baseline characteristics was performed. Chi-2 test was used to test differences in proportions between different treatment groups. Differences among groups in age, CHA_2DS_2-VASc and HAS-BLED scores were assessed with Kruskal-Wallis test (for four-groups comparisons) and Mann-Whitney test (for two-groups comparisons).

Binary logistic regression with calculation of odds ratio (OR) was used to assess association between the independent stroke risk factors and use of OAC in patients with CHA_2DS_2-VASc score ≥ 2.

Multiple logistic regression model included variables of CHA_2DS_2-VASc score (congestive heart failure, hypertension, age, diabetes mellitus, ischemic stroke, unspecified stroke, TIA, peripheral arterial embolism, myocardial infarction, peripheral arterial disease and gender). Variables with non-significant p-values were removed stepwise. The adjusted odds ratios and associated 95% intervals for OAC prescription were determined. Goodness-of-fit of the final model was assessed using Hosmer-Lemeshow test.

Paper II

The endpoint was diagnosis of ischemic stroke identified by ICD-10 code in the first position within 365 days from AF diagnosis. First, we calculated cumulative rates of ischemic stroke for the whole study population according to the given treatment (OAC, ASA or none)

Then we divided the study population into three cohorts according to the year of AF diagnosis (2011, 2012 and 2013). Cumulative incidence was calculated in each of the three cohorts for the whole population, by gender and by risk subgroups (CHA_2DS_2-VASc score 0-1; 2-4 and 5-9) to assess trends in ischemic stroke incidence.

Finally, we have calculated the proportion of patients treated with OAC in each of the three cohorts and performed linear regression to assess correlation between OAC uptake and stroke incidence.

Paper III

Only descriptive analyses of the baseline characteristics were performed. Plasma concentrations of dabigatran were expressed as median and range at one week and one month after the start of concomitant treatment with dronedarone.

Paper IV

Baseline characteristics and ECG-derived indices of AF organization were compared between responders and non-responders. Student's t-test was performed to assess differences in age and ECG-derived indices of AF organization between responders and non-responders to vernakalant treatment. Mann-Whitney test was performed on nonparametric data such as time to ECG and median duration of current AF episode.

Categorical variables were analysed using chi-2 test. Binary logistic regression was performed to assess association between gender and treatment response.

Results

Paper I

A total of 13,837 patients (mean age 76 ± 11 and 52.6% men) were diagnosed with incident non-valvular AF and flutter between the 1st of January 2011 and 31st of December 2014 in primary and secondary care in Skåne County.

Demographics and selected baseline characteristics of the study population and patients with CHA_2DS_2-VASc score ≥ 2 are outlined in Table 2.

Table 2. Baseline characteristics of the study population.
(** p<0.001 and * p<0.05)

Measure	Study population (n=13837)				Patients with CHA$_2$DS$_2$-VASc score ≥ 2 (n=12421)	
	DOAC N=1272 (9.2%)	Warfarin N=5949 (43.0%)	ASA N=2941 (21.3%)	None N=3675 (26.6%)	DOAC or Warfarin N=6529 (52.6%)	ASA or none N=5892 (47.4%)
Age, median (IQR)	74 (67-81)**	76 (69-82)**	81 (72.5-88)**	77 (67-85)**	76 (69-82)**	79 (69-87)**
Male, n (%)	692 (54.4)**	3350 (56.3)**	1455 (49.5)**	1782 (48.5)**	3413 (52.3)**	2669 (45.3)**
CHA$_2$DS$_2$-VASc score, median (IQR)	3 (2-4)**	4 (3-5)**	4 (3-5)**	3 (2-5)**	4 (3-5)**	4 (3-5)**
HAS-BLED score, median (IQR)	2 (1-2)**	2 (2-3)**	2 (2-3)**	2 (1-3)**	2 (1-3)**	2 (1-3)**
Heart failure, n (%)	229 (18.0)**	1298 (21.8)**	845 (28.7)**	757 (20.6)**	1489 (22.8)**	1588 (27.0)**
Hypertension, n (%)	919 (72.2)**	4378 (73.6)**	2213 (75.2)**	2355 (64.1)**	5098 (78.1)**	4404 (74.7)**
Diabetes mellitus, n (%)	229 (18.0)**	1303 (21.9)**	702 (23.9)**	688 (18.7)**	1515 (23.2)	1369 (23.2)
Ischemic stroke, n (%)	123 (9.7)**	858 (14.4)**	398 (13.5)**	305 (8.3)**	981 (15.0)**	703 (11.9)**
Vascular disease, n (%)	261 (20.5)**	1418 (23.8)**	1147 (39.9)**	704 (19.2)**	1660 (25.4)**	1848 (31.4)**
Liver disease, (%)	16 (1.3)**	81 (1.4)**	48 (1.6)**	103 (2.8)**	86 (1.3)*	125 (2.1)*
Renal disease, n (%)	47 (3.7)**	421 (7.1)**	314 (10.7)**	353 (9.6)**	453 (6.9)**	644 (10.9)**
Intracranial bleeding, n (%)	15 (1.2)**	53 (0.9)**	51 (1.7)**	118 (3.2)**	63 (1.0)**	157 (2.7)**
Gastric/duodenal bleeding, n (%)	17 (1.3)**	86 (1.4)**	69 (2.3)**	119 (3.2)**	99 (1.5)**	175 (3.0)**
Other severe bleeding, n (%)	41 (3.2)**	236 (4.0)**	197 (6.7)**	334 (9.1)**	259 (4.0)**	485 (8.2)**
Anaemia, n (%)	121 (9.5)**	638 (10.7)**	516 (17.5)**	764 (20.8)**	730 (11.2)**	1205 (20.5)**
Dementia, n (%)	23 (1.8)**	93 (1.6)**	297 (10.1)**	213 (5.8)**	112 (1.7)**	504 (8.6)**

The proportion of patients with CHA_2DS_2-VASc score ≥ 2 receiving OAC was 52.6%. The uptake of warfarin and DOAC was 43.8% and 8.8% respectively.

Adherence to the ESC guidelines regarding OAC treatment increased from 47.6% in 2011 to 66.1% in 2014. This was mostly due to a decrease in undertreatment (Fig. 8). The uptake of ASA decreased from 29.9% to 14.7% and the uptake of OAC increased from 42.2% to 62.8% in patients to whom OAC were indicated by the guidelines (Fig.9). Prescription of DOAC among these patients increased from 2.1% in 2012 to 25.1% in 2014.

The use of ASA increased with increasing CHA_2DS_2-VASc and HAS-BLED scores (Fig. 10 and 11).

Age < 84 years (with the highest OR between 65 and 74 years), male gender, history of ischemic stroke and hypertension were statistically significant predictors of OAC prescription (Table 3). Undertreatment was more common in the elderly (65.3% in women and 62% in men over 84 years) and in women < 65 years (55.8%)(Fig. 12).

Uptake of ASA and OAC in patients with no other indication for OAC was 35.9% among men and 36.4% among women.

We found similar prescription patterns in all provider specialties (primary care, emergency medicine, cardiology, internal medicine and other secondary care).

Table 3. Factors associated with prescription of OAC in patients with CHA$_2$DS$_2$-VASc score≥2.
Hosmer-Lemeshow goodness-of-fit test p=0.763.

	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age:		
< 65 years (reference)	1	1
65-74 years	1.52 (1.31-1.76)	1.48 (1.28-1.72)
75-84 years	1.36 (1.18-1.57)	1.36 (1.18-1.57)
>84 years	0.54 (0.47-0.62)	0.54 (0.47-0.63)
Ischemic stroke	1.31 (1.18-1.45)	1.55 (1.39-1.74)
Male gender	1.32 (1.23-1.42)	1.26 (1.17-1.35)
Hypertension	1.20 (1.11-1.31)	1.25 (1.14-1.36)
Diabetes mellitus	1.00 (0.92-1.09)	0.90 (0.83-0.98)
Peripheral arterial disease	0.78 (0.70-0.87)	0.78 (0.69-0.88)
Myocardial infarction	0.76 (0.70-0.83)	0.74 (0.68-0.82)
Unspecified stroke	0.69 (0.58-0.81)	0.56 (0.47-0.67)

Figure 8. Guideline adherence in 2011-2014.

Figure 9. Trends in antithrombotic drug prescription in patients with CHA$_2$DS$_2$-VASc score > 2.
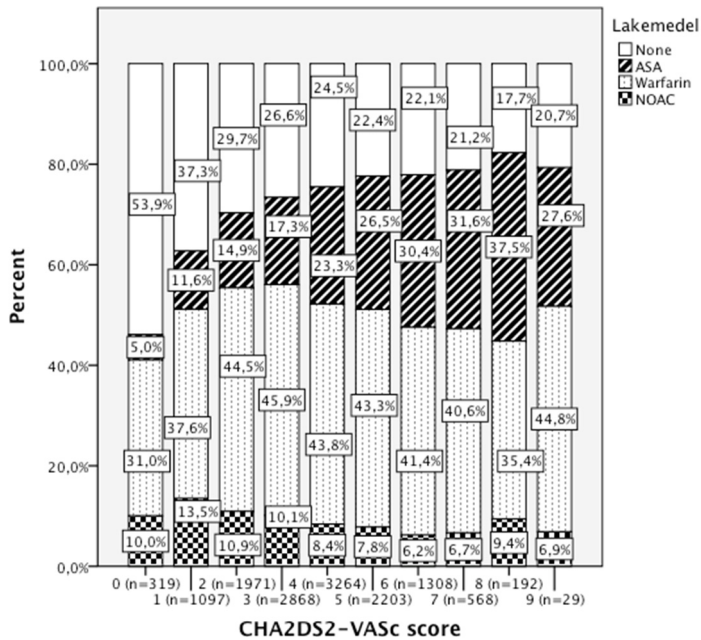
Figure 10. Treatment patterns according to ischemic stroke risk score.
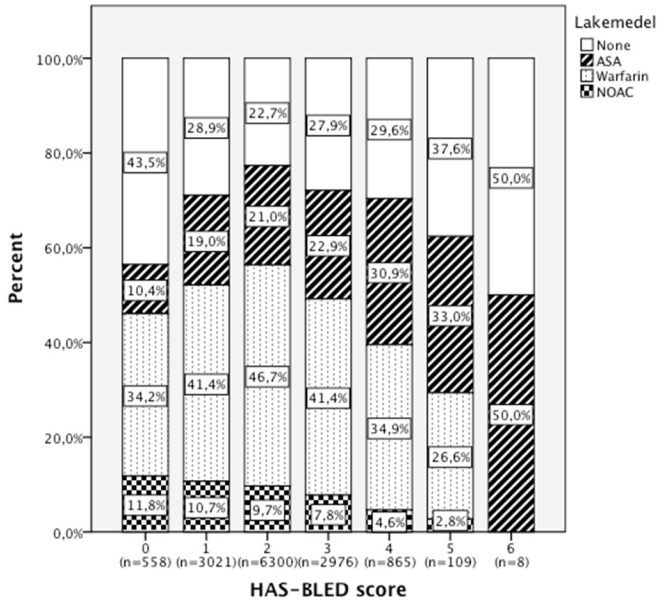
Figure 11. Treatment patterns according to bleeding risk score.
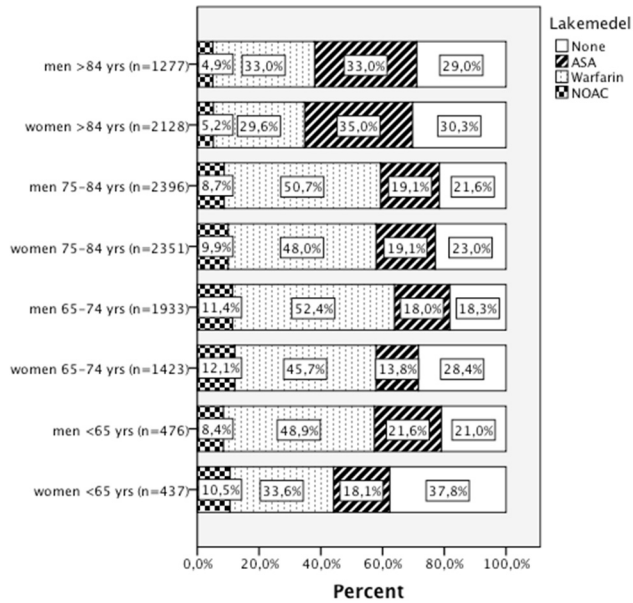
Figure 12. Impact of age and gender on treatment strategy in patients with CHA$_2$DS$_2$-VASc score ≥ 2.

Paper II

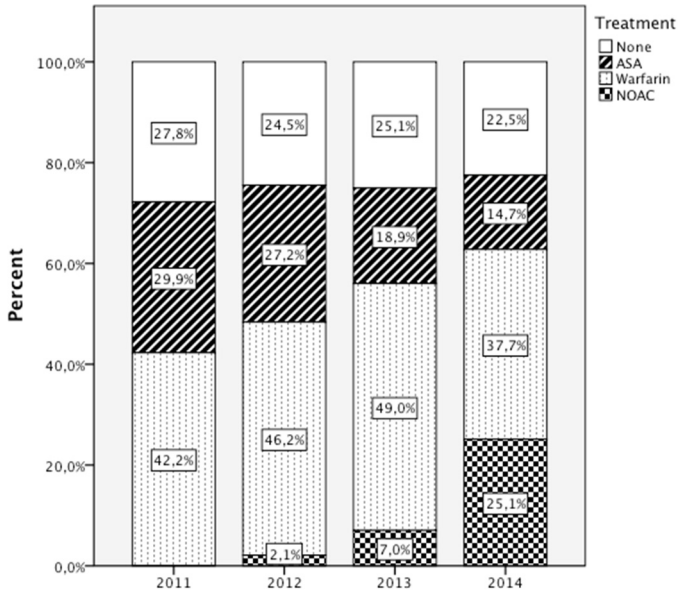A population-based cohort of 11 500 patients with incident AF (mean age 77 ± 11 years and 51.5% men) diagnosed between the 1st of January 2011 and the 31st of December 2013 was followed up during a total of 10116 patient-years (mean observation time 321 days).

Table 4 outlines the baseline characteristics of the study cohort. OAC treatment uptake increased from 36.6% to 48.3%, whereas uptake of ASA decreased from 28,8% to 19,7% (Figure 13). Use of OAC increased in all age subgroups, all CHA_2DS_2-VASc score subgroups and in both genders (Table 5).

Cumulative incidence of ischemic stroke among patients with CHA_2DS_2-VASc score ≥ 2 receiving OAC, ASA or no treatment were 1.54% (95% confidence interval (CI) 1.22-1.95%), 3.43% (95% CI 2.81-4.19%) and 3.02% (95% CI 2.49-3.66%) respectively.

The cumulative incidence of ischemic stroke decreased from 2.87% (95% CI 2.37-3.45%) in 2011 to 2.33% (95% CI 1.90-2.85%) in 2012 and 1.93% in 2013 (95% CI 1.54-2.41%) (Figure 14). Patients with CHA_2DS_2-VASc score 5 through 9 demonstrated a greater reduction in stroke incidence compared with those with CHA_2DS_2-VASc score 0 through 1 (Figure 15).

Incidence of ischemic stroke decreased in both sexes, but female patients had higher ischemic stroke rates compared to males (Figure 16). Women with AF in our cohort were older than men (mean age ± SD 79 ± 11 years vs. 75 ± 11 years in men). Female patients with AF had twice as large proportion of individuals with high stroke risk compared to the male patients (CHA_2DS_2-VASc score 5 through 9 in 43.1% of women vs. 22.8% of men in the study population).

Linear regression confirmed an association between decline in ischemic stroke rate and increase in OAC uptake (regression coefficient -0.08; 95% CI, -0.09 to -0.07, $p < 0.001$) (Figure 17).

Table 4.

Baseline characteristics of the study population

	2011	2012	2013	Total
	(n=3700)	(n=3907)	(n=3892)	(n=11500)
Age, mean ± SD	77 ± 11	77 ± 11	77 ± 11.	77 ± 11
Male, n (%)	1868 (50.5)	2024 (51.8)	2032 (52.2)	5924 (51.5)
CHA$_2$DS$_2$-VASc score				
• 0-1	357 (9.6)	376 (9.6)	362 (9.3)	1095 (9.5)
• 2-4	2143 (57.9)	2270 (58.1)	2235 (57.4)	6648 (57.8)
• 5-9	1200 (32.4)	1261 (32.2)	1296 (33.3)	3757 (32.7)
Heart failure, n (%)	888 (24.0)	928 (23.8)	896 (23.0)	2712 (23.6)
Hypertension, n (%)	2484 (67.1)	2615 (66.9)	2738 (70.3)	7837 (68.1)
Diabetes, n (%)	743 (20.1)	825 (21.5)	794 (20.4)	2362 (20.5)
Ischemic stroke, n (%)	435 (11.8)	457 (11.7)	500 (12.8)	1392 (12.1)
Unspecified stroke, n (%)	158 (4.3)	160 (4.1)	149 (3.8)	467 (3.8)
TIA, n (%)	249 (6.7)	271 (6.9)	301 (7.7)	821 (7.1)
Myocardial infarction, n (%)	687 (18.6)	720 (18.4)	749 (19.2)	2156 (18.7)

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Table 5. Proportion of patients receiving OAC by gender, age and stroke risk.

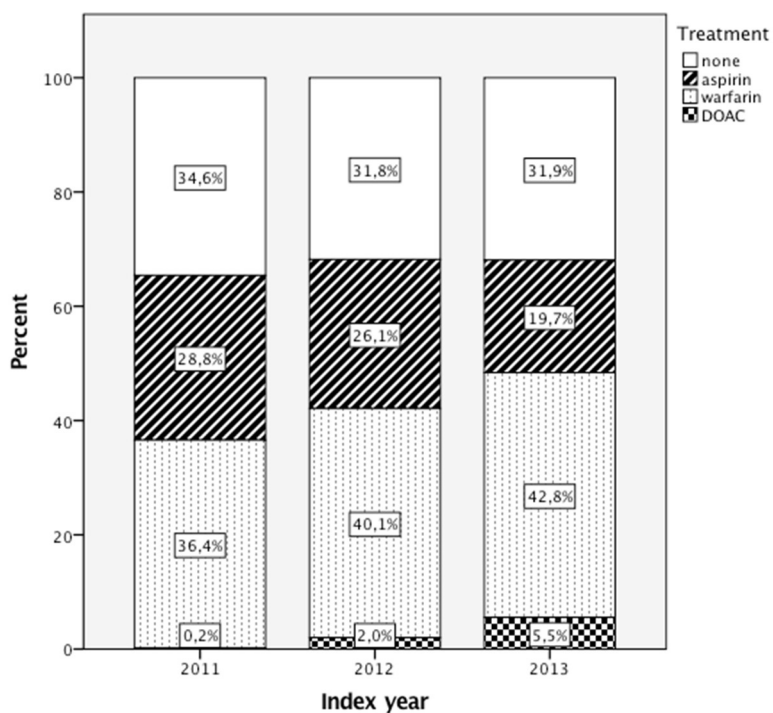|	Index year		
	2011	2012	2012
Total, n (%)	1354 (36.6)	1646 (42.1)	1884 (48.4)
Female, n (%)	591 (32.3)	707 (37.5)	834 (44.8)
Male, n (%)	763 (40.8)	939 (46.4)	1050 (51.7)
Age			
• **< 65 years**	181 (37.5)	239 (44.8)	243 (47.1)
• **65-74 years**	446 (48.0)	500 (52.7)	589 (59.4)
• **75-84 years**	526 (42.4)	636 (48.2)	728 (56.2)
• **> 84 years**	201 (19.2)	271 (24.5)	324 (29.7)
CHA$_2$DS$_2$-VASc score			
• **0-1**	129 (36.1)	167 (44.4)	174 (48.1)
• **2-4**	842 (39.3)	990 (43.6)	1121 (50.2)
• **5-9**	383 (31.9)	489 (38.8)	589 (45.4)

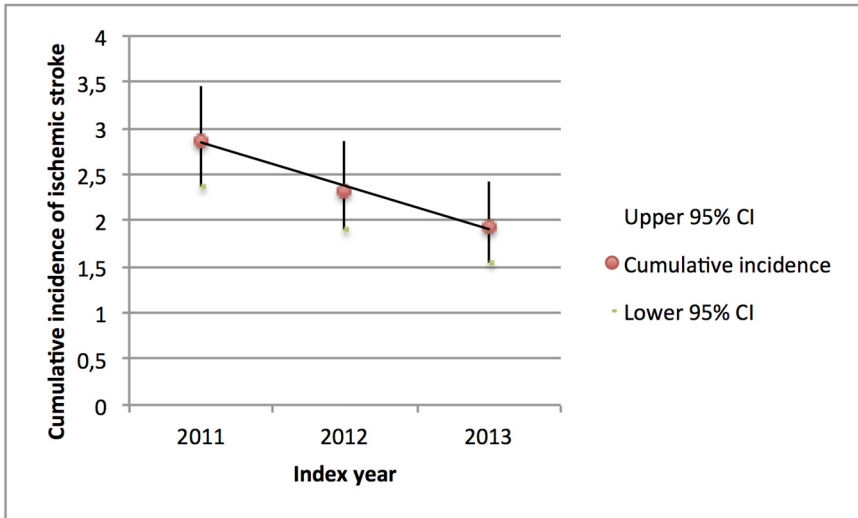**Figure 13. Treatment trends.**

Figure 14. Cumulative incidence of ischemic stroke per index year.
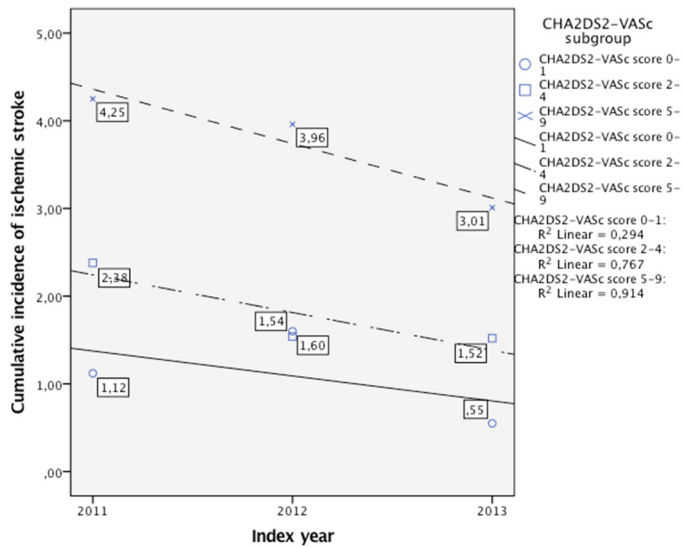
Figure 15. Cumulative incidence of ischemic stroke per index year in different CHA₂DS₂-VASc subgroups.

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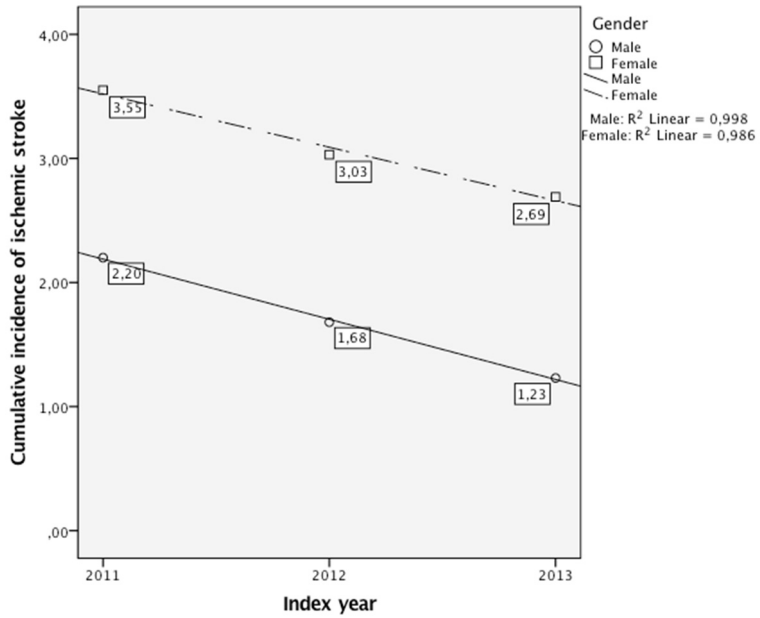
Figure 16. Cumulative incidence of ischemic stroke per index year by gender.
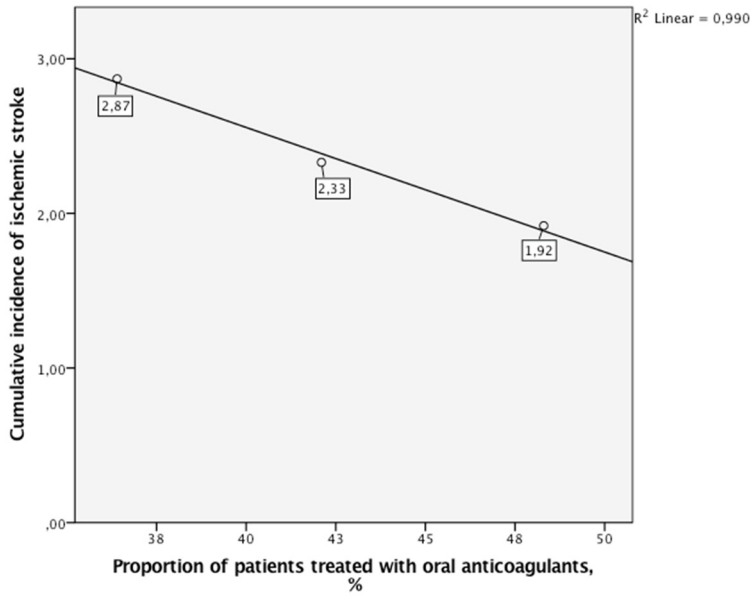
Figure 17. Cumulative incidence of ischemic stroke vs. OAC uptake.

Paper III

A total of 33 patients (mean age 64 years and 48.5% men) treated concomitantly with dabigatran 110 mg b.i.d and dronedarone were followed up prospectively. Median treatment length was 13 months (range 1-27 months) and the total follow-up time was 35.5 patient-years. The most common reason for discontinuation of concomitant treatment was switching to another antiarrhythmic drug. Since all patients on OAC treatment are reported to the AuriculA registry, none of the potentially eligible study patients was missed or lost to follow-up. The mean CHA_2DS_2-VASC score was 2.3 ± 1.3 and mean HAS-BLED score was 1.6 ± 0.9.

Table 6 outlines the baseline characteristics of the study population.

Trough plasma concentrations of dabigatran were measured at one week (n=29) and at one month (n=29) after the initiation of concomitant treatment with dronedarone. At least one plasma concentration sample of dabigatran was collected from each patient in our study.

Median concentrations of dabigatran at one week and at one month after the initiation of the concomitant treatment was 102.0 (10th to 90th percentile 48-238, range 8-251) and 84 (10th to 90th percentile 38-255; range 27-302) ng/ml respectively (Fig. 18). The highest plasma concentration of dabigatran was 302 ng/ml due to kidney failure in a 74-year-old woman, leading to discontinuation of the drug.

Since data from the RE-LY sub-study demonstrated that the 10th percentile trough concentration in 110 bid subgroup was 28.2 ng/ml (126), we considered an indirect estimation of patient compliance through p-dabigatran concentrations. Two patients in our study had plasma concentrations of dabigatran less than 20 ng/ml (8 and 14 ng/ml one week after the concomitant treatment start). In these two presumably non-compliant patients plasma dabigatran concentrations were 64 and 34 ng/ml at one month after the start of concomitant treatment.

No cases of ischemic stroke or systemic embolism occurred during the follow-up. There was one major bleeding event in the cohort (2.8% per patient-year) with hematochezia at eleven month after the start of concomitant treatment. The patient had a similar adverse event during treatment with warfarin 2,5 years earlier.

Table 6. Baseline characteristics of the study patients and patients in RELY study.

* according to the RELY substudy (126)

	Our study	RELY study Dabigatran 150 mg bid (72)
Treated patients, (n)	33	6076
Age, mean (SD), years	64.0 (8.7)	71.5 (8.8)
Males, n (%)	16 (48.5)	3840 (63.2)
eGFR, mean (SD), ml/min/1.73m2	66.0 (11.2)	N/A
• **< 50**	3 (9)	1126 (18.9)*
• **50-79**	29 (88)	2898 (48.6)*
• **>80**	1 (3)	1945 (32.5)*
Medical history:		
• **Heart failure, n (%)**	2 (6.1)	1934 (31.8)
• **Hypertension, n (%)**	23 (69.7)	4795 (78.9)
• **Vascular disease, n (%)**	6 (18.2)	N/A
• **Diabetes, n (%)**	3 (9.1)	1402 (23.1)
• **Prior stroke or TIA, n (%)**	4 (12.1)	1233 (20.3)
• **Prior systemic or peripheral** • **arterial embolism, n (%)**	2 (6.1)	N/A
• **Renal disease, n (%)**	0 (0)	N/A
• **Abnormal liver function, n (%)**	0 (0)	N/A
• **Prior intracranial bleeding, n (%)**	0 (0)	N/A
• **Prior other bleeding, n (%)**	1 (3.0)	N/A
• **Labile INR, n (%)**	3 (9.1)	N/A
• **Alcohol abuse, n (%)**	3 (9.1)	N/A
CHA$_2$DS$_2$-VASC score		
• **0-1, n (%)**	9 (27.3)	1958 (32.2)
• **2, n (%)**	11 (33.3)	2137 (35.2)
• **3-6, n (%)**	13 (39.4)	1981 (32.6)
HAS BLED score		N/A
• **0-2, n (%)**	29 (87.9)	
• **3-4, n (%)**	4 (12.1)	
Concomitant medications at baseline:		
• **Other P-gp-inhibitors/inducers, n (%)**	1 (3.0)	N/A
• **Proton pump inhibitors, n (%)**	4 (12.1)	847 (13.9)
• **Antiplatelet agents, n (%)**	0 (0)	2352 (38.7)
• **Non-steroidal anti-inflammatory drugs,** • **n (%)**	0 (0)	N/A
• **Angiotensin converting enzyme inhibitor or angiotensin II antagonists,** • **n (%)**	19 (57.6)	4053 (66.7)
• **Beta-blocking agents,** • **n (%)**	28 (84.8)	3872 (63.7)
• **Statins, n (%)**	12 (36.4)	2667 (43.9)
• **Corticosteroids, n (%)**	2 (6.1)	N/A

Figure 18. Plasma dabigatran concentration at one week and one month after the start of concomitant treatment.

Paper IV

A total of 113 patients (median age 62 years, 69 men) received vernakalant on 148 treatment occasions. Only the first treatment outcome was included in statistical analysis. Successful cardioversion with vernakalant was achieved in 75 patients (66%) with median time to conversion of 10 minutes. The conversion rate was higher in females (80%) than in males (58%)(Figure 19). Female gender was a significant predictor of cardioversion in logistic regression analysis (OR 2.82, 95% CI 1.18–6.76, P = 0.02).

ECG-derived study variables could not be assessed in five of the study patients. No significant differences in AFR, exponential decay of F-wave amplitude were observed between responders and non-responders (Table 7).

Adverse events occurred in 14 patients, leading to drug discontinuation in seven patients (mostly due to hypotension). Pro-arrhythmic events were observed in seven patients, the most common being atrial flutter (n = 4). One patient developed 1:1 conducted atrial flutter.

Table 7. Baseline characteristics and electrocardiographic parameters of the study patients.

	Study population (n=113)	Responders (n=75)	Non-responders (n=38)	P-value
Female/male	44 /69	35/40	9/29	0.024
Age, median yrs. (range)	63 (23-87)	64 (23-87)	62.5 (37-85)	0.932
Height, cm	176±9	174±10	180±7	0.014
Weight, kg	82±13	81±14	83±12	0.344
BMI	26±3	27±4	26±3	0.323
Time to ECG, h [IQR]	3.1 [1.4-9.9]	2.8 [1.4-9.5]	5.5 [2.0-12.8]	0.223
Median duration of current AF, h [IQR]	8.2 [4.7-16.3]	8 [4.4-16.2]	9.1 [5.7-16.7]	0.400
New-onset AF, n (%)	32 (28.3)	25 (33.3)	7 (18.4)	0,123
AF ablation earlier, n (%)	7 (6.2)	4 (5.3)	3 (7.9)	0.686
Lone AF, n (%)	49 (43.4)	35 (46.7)	14 (36.8)	0.422
Hyperlipidemia	30 (26.5)	17 (22.7)	13 (34.2)	0.259
Hypertension	57 (50.4)	37 (49.3)	20 (52.6)	0.843
Ischemic heart disease	18 (15.9)	9 (12.0)	9 (23.7)	0.172
Diabetes mellitus	8 (7.1)	5 (6.7)	3 (7.9)	1.000
Congestive heart failure	3 (2.7)	1 (1.3)	2 (5.3)	0.261
Concomitant medications				
• **Beta-blockers, n (%)**	88 (77.9)	59 (78.7)	29 (76.3)	0.813
• **Calcium channel blockers, n (%)**	12 (10.6)	7 (9.3)	5 (13.2)	0.534
• **RAAS-inhibitors, n (%)**	35 (31.0)	21 (28.0)	14 (36.8)	0.391
• **Class I or III AAD, n (%)**	7 (6.2)	4 (5.3)	3 (7.9)	0.686
ECG parameters				
• **AFR, fpm**	350±60	350±60	348±62	0.893
• **Exponential decay**	1.32±0.42	1.30±0.42	1.35±0.42	0.376
• **F-wave amplitude, µV**	87±47	86±33	88±67	0.852

Figure 19. Correlation between gender and conversion to sinus rhythm.

Discussion

Uptake of anticoagulants

Whereas adherence to ESC guidelines on stroke prevention in AF improved in Skåne County, a large proportion of AF patients still received suboptimal anticoagulation treatment.

Over 47 % of the patients in our cohort in Paper I with significant risk of ischemic stroke did not receive OAC treatment as recommended by the ESC guidelines. Also, 35% of patients at low stroke risk with no other indications to anticoagulation were overtreated and thus exposed to unnecessary bleeding risks. Similar findings were reported in the Stockholm AF cohort study conducted a decade ago (127). The use of anticoagulants was lower in our study compared to recent Swedish (128) and European (129) reports, probably due to the exclusion of patients with valvular AF in our study .

Only three out of seven stroke risk factors in CHA_2DS_2-VASc score (hypertension, prior ischemic stroke and age 65-84 years) increased the odds of OAC prescription, whereas some important stroke risk factors (female gender, age over 84 years, vascular disease and diabetes) decreased the odds of receiving anticoagulants.

This finding can be due to the fact that some of the risk indicators in CHA_2DS_2-VASc score carry stronger predictive values than others. Friberg et al conducted a study validating CHA_2DS_2-VASc score in the Swedish AF cohort, where a stronger association was found between thromboembolic events and history of ischemic stroke (hazard ratio (HR): 2.81, 95% CI 2.68–2.95), age between 65 and 74 years (HR: 2.97, 95% CI 2.54–3.48) and age over 74 years (HR: 5.28, 95% CI 4.57–6.09) compared to the weaker association between thromboembolic events and vascular disease (HR: 1.14, 95% CI 1.06–1.23), diabetes (HR: 1.19, 95% CI 1.13–1.26) or female gender (HR: 1.17, 95% CI 1.11–1.22) (57).

The uptake of ASA in Paper I increased with increasing age and bleeding risk score, probably due to the false perception that ASA is a safer alternative to OAC in frail patients with AF, with regards to bleeding risk. Even though warfarin has been demonstrated to be more effective in reducing stroke risk compared to ASA

in elderly patients (78, 130) and the bleeding risks are similar (78), it seems that the historically bad reputation of anticoagulant treatment is persistent.

The use of DOAC in our population has increased twelve-fold three years from the introduction. DOAC can be a valuable alternative to warfarin in patients with presumed good compliance or labile INR values and those who refuse warfarin due to inconvenience of frequent monitoring and dose adjustments. DOAC are also preferred to a warfarin in eligible patients when OAC therapy is initiated according to the recent ESC guidelines for AF management(131).

Similar prescription patterns of ASA, warfarin and DOAC were found regardless of if the AF was diagnosed in primary care, emergency medicine, cardiology, internal medicine and other secondary care. It is reasonable to assume that the health provider that diagnosed AF also decided upon antithrombotic treatment strategy.

Suboptimal treatment could be initiated due to misjudgement of the risk-and-benefit ratio for the particular patient. Discordance between provider-assessed risk and empirical stroke- and bleeding risk scores in AF patients was previously reported in ORBIT-AF study [28]. Efforts to improve guideline awareness should be made to optimize the dissemination of the current stroke prevention recommendations in AF within the physician community.

Trends in ischemic stroke incidence

The cumulative incidence of ischemic stroke in patients with incident AF in Skåne County decreased from 2.87% to 1.93%, whereas use of anticoagulants increased from 36.6% to 48.3% between 2011 and 2013 (regression coefficient -0.08; 95% CI, -0.09 to -0.07, p <0.001).

Declining rates of ischemic have been reported in AF cohorts from Sweden (132) and Denmark (133) as well as in the Framingham Heart Study (34). The incidence rates of ischemic stroke in Paper II are consistent with those previously reported in the contemporary Swedish AF cohort (134). However, the findings in Paper II are unique in the sense that we have demonstrated the correlation between the decreased incidence of ischemic stroke and the increased use of anticoagulants in an AF cohort.

Meanwhile, a recent American study did not find any decrease in ischemic stroke incidence in AF patients over the last decade. A plausible explanation could be the fact that the use of anticoagulants did not change over time in the studied cohort (135).

OAC treatment in AF reduces ischemic stroke risk by approximately two-thirds (60), which is consistent with the findings in Paper II. Patients with CHA_2DS_2-VASc score ≥ 2 treated with ASA had a higher stroke incidence compared to those treated with anticoagulants in Paper II. According to Paper I, the use of ASA in this cohort was more common among elderly as well as in patients with higher risk of ischemic stroke and bleeding. ASA is not recommended by the current ESC guidelines since it does not protect against AF-associated ischemic stroke (59). The higher stroke incidence seen in the ASA subgroup might be explained by the presence of high-risk individuals receiving inadequate treatment.

Since OAC treatment decreases the risk of ischemic stroke by 64% (60), patients with the highest baseline risk receive the greatest absolute risk reduction. The greatest decline in ischemic stroke incidence was observed in patients with highest baseline ischemic stroke risk (CHA_2DS_2-VASc score 5 through 9) in Paper II. Since the absolute benefit from a very low stroke risk at baseline is numerically low with OAC treatment, there was no clear trend in reducing ischemic stroke incidence among patients with CHA_2DS_2-VASc score 0 through 1.

The use of anticoagulants increased even in patients without clinical stroke risk factors, which might indicate a trend towards overtreatment. It is unlikely that elective cardioversion or pulmonary vein isolation requiring OAC were performed in a frequency that could explain these results in these patients in 2013 compared to 2011.

There was no decrease in comorbidity burden in the study cohort that could explain the declining trend of ischemic stroke in 2011 through 2013 (Table 4). The increased uptake of OAC and decreased uptake of ASA provides a plausible explanation for stroke rate reduction in the cohort

If the findings in Paper II can be extrapolated to the prevalent total AF population, we can anticipate a large proportional decrease in ischemic stroke burden. About 400 ischemic strokes per year could be prevented by reducing the cumulative stroke incidence from 2,87% to 1,93% events, given an AF prevalence of 3% among the 1,3 millions inhabitants of Skåne County.

Female gender

Gender-related differences in comorbidities, age of onset, treatment patterns and drug-induced events in AF have been long recognized (136-139). Women with AF are older and have more comorbidities (28, 140, 141).

Female patients with AF have higher stroke risk compared to men in the presence of additional stroke risk factors (142, 143) and thus derive greater benefits from anticoagulation. Of concern, we found a considerable undertreatment of women < 65 years with additional risk factors for ischemic stroke in Skåne County in Paper I (Figure 12). Underuse of OAC in female AF patients is consistent with Swedish Council on Health Technology Assessment (SBU) report from 2013 (144), despite the fact that there are no reported sex differences in major bleeding risks (139).

Women in Paper II had higher ischemic stroke incidence than men, probably due to the higher prevalence of high-risk individuals (CHA$_2$DS$_2$-VASc 5-9), older age and lower OAC uptake. Similar differences in age and comorbidities among men and women with AF were previously reported in the Euro Heart Survey on Atrial Fibrillation (145) and higher incidence of ischemic stroke among female patients was also previously demonstrated in Swedish nationwide retrospective AF cohort (75).

The decline in cumulative incidence of ischemic stroke in women in Paper II was similar to that in men. The proportion of patients treated with OAC increased in both genders, but women started from a lower OAC uptake of 32.3% compared to 36.6% in men in the beginning of our study.

Sixty-one per-cent patients receiving vernakalant in Paper IV were men despite that women were more likely to respond to the treatment in our study. The higher proportion of men in the study population in Paper IV probably cannot entirely be contributed to the higher incidence of AF in men. Since AF is more prevalent among elderly, and women have a longer lifespan, the absolute number of AF in males and females is however similar (146), and since women have greater incidence of recurrence and experience more AF-related symptoms they are more likely to seek medical care than men (147).

Whereas women with AF are more symptomatic and have lower life quality, they are still less likely to receive treatment with antiarrhythmic agents or to be referred for catheter ablation (139, 140). Moreover, our data confirms findings from previous studies, that women still are less likely to receive OAC treatment for ischemic stroke prevention (144, 148).

Antiarrhythmic drugs

The markers of atrial electrical remodeling derived from a surface ECG did not predict AF termination with vernakalant. According to a previous study with implantable loop recorders, AFR initially increases and then reaches a plateau within 3 hours from the start of the AF episode (149). Mean time to ECG in our study was 3.1 hours, which allows AFR stabilize and be reliably used for analysis.

The size of our study population is comparable with population sizes in previous reports, where AFR was used as a predictor of sinus rhythm restoration in other clinical contexts.

Drug effects may be dependent on other factors than electrical remodeling of the atria. Individual variations in drug metabolism ("poor vs. extensive metabolizers") may affect the treatment effect without altering the electrical properties of the atria. Moreover, the affinity of vernakalant to sodium channels becomes greater as the atrial rate increases (91), perhaps making vernakalant more effective in patients who are otherwise less likely to restore sinus rhythm.

Dronedarone is indicated for long-term rhythm control in patients paroxysmal or persistent AF. It is well tolerated (150) with a low risk of pro-arrhythmia (94), and reduces mortality and hospitalization due to cardiovascular events (94). Many of patients treated with dronedarone also have indications for OAC treatment and according to the current ESC guidelines, DOAC should be preferred to warfarin in eligible patients when oral anticoagulation is initiated (131). Dronedarone may increase bioavailability of all DOAC through P-gp inhibition and could theoretically increase DOAC concentrations with a subsequent risk of bleeding. As of September 2017, dabigatran is the only DOAC that has a specific antidote and it is of benefit to be able to reverse the anticoagulation effect in case of life-threatening bleeding or indication for urgent surgery.

The current contraindication against concomitant treatment with dabigatran and dronedarone is based on a small study on 16 healthy volunteers at a conventional dabigatran dose 150 mg bid (103). Our study in Paper III is performed in twice as many real-life AF patients using the lower dabigatran dose of 110 mg bid.

Dabigatran is eliminated mostly by renal route. The trough plasma concentration of dabigatran is thus largely determined by renal function. There were more individuals with impaired renal function (eGFR <80) in our study compared to RE-LY.

The median trough plasma concentrations in Paper III were comparable to the median trough concentration of 93 (10th to 90th percentile 39.8-215) ng/ml of dabigatran at the 150 mg bid dose without concomitant dronedarone treatment in RE-LY sub-study (151).

The outcomes of dabigatran treatment at a conventional dose 150 mg are well studied and the incidence of adverse events such as thrombosis and major bleeding is low (72, 124, 152).

It is unlikely that the patients failed to adhere to the study treatment. Two patients in Paper III can be assumed to have compliance problems since they demonstrated plasma concentrations below 10% percentile in RE-LY. There might however be a selection bias towards patients with better compliance compared with general AF

population in our study, where TTR in warfarin treated patients in the Swedish national registry AuriculA is 76.2% (75).

Limitations

Baseline patient characteristics in **Paper I** were assessed using the ICD-codes retrieved from a healthcare registry. Thus, we could not address some important factors affecting the choice of treatment for ischemic stroke prevention in Paper I such as patients' preferences or lack of compliance.

We did not adjust for pulmonary vein isolation as potential indication for OAC and did not account for warfarin treatment over 3 months prior to cardioversion in patients with labile INRs. That could cause some degree of overestimation of the unnecessary treatment in our study. Since we did not have data on all components of the HAS-BLED score (such as alcoholism, use of NSAID or history of labile INR), the true bleeding risk could be underestimated.

In **paper II** we assumed that the initial therapeutic strategy (oral anticoagulation, ASA, or no treatment) remained unchanged throughout the follow-up year, which may not always be the case. The generalizability of our findings for oral anticoagulants might be limited, since we have no data on compliance and TTR in this study. Overall, the mean TTR in Sweden is 76.2%, which is considerably higher than TTR of 55-65% in warfarin arm of key RCTs treatment of non-VKA trials (69, 71, 72, 75) or TTR of 55% in meta-analysis of 14 centers in the US (153). The prevalence of the stroke risk factors did not differ significantly between different index years apart from hypertension becoming somewhat more prevalent. The improved control of the modifiable stroke risk factors impacts on the incidence of the ischemic stroke in the community. A key limitation of Paper II is that we have no clinical data on how these stroke risk factors were managed.

Paper I and II studied population-based cohorts. On the contrast, patients in **paper III and IV** were assigned to the study at the discretion of a cardiologist. This may introduce selection bias despite the real-life setting of the study. We did not perform sample size calculation in **paper III and IV** and did not adjust for multiple comparisons in **paper IV.**

Paper III was conducted in real-life setting and aimed at measuring trough plasma concentrations of dabigatran. No other pharmacokinetic measurements (peak concentration, time to peak concentration and estimation of cumulative exposure) were performed. However, according to RELY sub-study with 30% of the cohort on concomitant P-gp-inhibitors, there were no advantages measuring peak

concentrations compared with trough concentrations (154). We did not have any data on baseline through plasma concentration of dabigatran prior to the start of concomitant treatment with dronedarone. Thus, the magnitude of the increase in p-dabigatran concentration after the start of dronedarone treatment could not be estimated. As with any pharmacological study, the measured dabigatran concentrations could be impacted by non-compliance. However, in a real-life setting, it is impossible to control medication intake twice daily by all patients during the entire follow-up period.

Conclusions

- A considerable proportion of AF patients diagnosed in different clinical settings in Skåne County still do not receive adequate stroke prevention therapy with OAC, despite increased adherence to ESC Guidelines among physicians.

- Efforts to further improve adherence to ESC Guidelines on stroke prevention in AF should particularly be targeted on female patients < 65 years with additional risk factors and elderly patients > 84 years, since OAC are underused in these subgroups.

- The increased use of oral anticoagulants between 2011 and 2013 in patients with incident AF is associated with decline in the cumulative incidence of ischemic stroke in Skåne County.

- Dronedarone and dabigatran are often indicated in the same patient population. Trough plasma concentration of dabigatran using the 110 mg b.i.d dose with dronedarone was comparable to RCT plasma dronedarone concentrations at the dose of 150 mg bid without concomitant dronedarone. Larger trials on efficacy and safety of this treatment strategy might refute the present contraindication.

- Signal processing of surface ECG using time-frequency analysis could predict effect of various rhythm-control interventions in previous studies. However, ECG-derived markers of atrial remodelling failed to predict treatment response in acute cardioversion of AF with vernakalant in our study.

Future aspects

A considerable proportion of AF patients do not receive adequate ischemic stroke prevention, whereas some low-risk patients still are over-treated. Notably, many women under the age of 65, with additional risk factors do not receive any stroke prevention. The reason for this is unclear and need to be addressed by education and future studies. The impact of patients' preferences, compliance history and socioeconomic status on likelihood of receiving anticoagulation should be assessed by future research.

The increased use of anticoagulants between 2011 and 2013 was associated with a decrease in the incidence of ischemic stroke in patients with incident AF in Skåne County. Less than 5 % of patients in this study were treated with DOAC. Since there was only one ischemic event in the DOAC-cohort, we were not able to assess the impact of DOAC on ischemic stroke incidence in real life.

The uptake of DOAC in AF patients is rapidly increasing. The main drawback of DOAC trials is a poor-quality of warfarin management, with TTR 55-65% compared to 76.2% in the Swedish AF population. Even though the benefits seen in these trials to some extent have been validated by studies of DOAC cohorts against well-managed warfarin (155), head-to-head comparisons of different DOAC to each other are still needed. In order to improve drug selection in some clinical situations, we might need to assess individual response to a particular DOAC, through measurement of drug concentrations or other tests.

Since concomitant treatment with dronedarone and dabigatran at a lower dose of 100 mg bid can offer potential benefits, larger future trials on efficacy and safety of co-administration are needed. Due to large variability in trough concentrations it might be feasible to monitor individual dose-response to dabigatran.

Svensk populärvetenskaplig sammanfattning

Förmaksflimmer är den vanligaste rubbningen av hjärtrytmen, som drabbar ca 3 % av befolkningen och är vanligare hos äldre. Förmaksflimmer medför att hjärtats förmak drar ihop sig på ett icke-koordinerat sätt, vilket ökar risken för blodstockning i förmaksörat och proppbildning. Blodpropparna kan lossna och täppa till blodkärlen i andra viktiga organ. Den mest fruktade komplikationen av förmaksflimmer är stroke som orsakas av att proppen sätter sig i hjärnans blodkärl.

Behandling av förmaksflimmer syftar dels på att normalisera hjärtats rytm och dels på att förhindra proppbildning i hjärtat med hjälp av blodförtunnande läkemedel.

Huvudsyftet med arbetet var att undersöka hur man kan behandla förmaksflimmer med läkemedel som minskar risken för stroke, återställer normal sinusrytm och förhindrar flimmerrecidiv.

Det **första arbetet** beskriver nuvarande praxis vid insättning av blodförtunnande läkemedel (antikoagulantia) vid nydebuterat förmaksflimmer (FF) och undersöker vilka faktorer som påverkar terapivalet. Huvudresultatet är att en betydande andel av patienterna i Skåne fortfarande får suboptimal behandling trots ökad följsamhet till de europeiska behandlingsriktlinjerna.

Det **andra arbetet undersöker** trender i förekomsten av blodproppar i hjärnan (ischemisk stroke) hos samtliga 11500 patienter diagnostiserade med förmaksflimmer mellan 2011 och 2013. Studien visar ett samband mellan minskad förekomst av stroke och ökad förskrivningen av blodförtunnande i Skåne.

Dabigatran, som finns i två doser, är ett blodförtunnande läkemedel och dronedaron är ett rytmreglerande läkemedel som ofta används till samma patienter. Dronedaron har visat sig att fördubbla blodkoncentrationen av dabigatran vid en tidigare studie på 16 friska försökspersoner. Risken med detta är att en ökad ansamling av blodförtunnande dabigatran i blodet kan leda till blödning. Det **tredje arbetet** undersöker om koncentrationen av dabigatran påverkas hos patienter som använder dabigatran i den lägre dosen tillsammans med dronedaron samt om interaktionen medför kliniskt betydelsefulla blödningskomplikationer. Den genomsnittliga koncentrationen av dabigatran i studien var jämförbar med

den genomsnittliga koncentrationen av dabigatran i den högre dosen utan samtidig behandling med dronedaron i tidigare studier med rapporterad låg förekomst av blodproppar och blödning. Slutsatsen blir att vår studie inte stödjer nuvarande uppfattning om att man inte skall behandla patienter med dessa två läkemedel samtidigt, men att man behöver fler större studier för att vara helt säker.

Vernakalant är ett läkemedel som används vid för att återställa den normala sinusrytmen hos patienter som haft attackvis påkommet förmaksflimmer i mindre än 48 timmar. Lite mer än hälften av patienterna förväntas att svara på behandling med vernakalant, medan över 95 % patienterna kan återfå normal rytm med hjälp av elstöt (elkonvertering). För elkonvertering behöver man dock söva patienten (narkos), vilket kräver tillgång till narkosläkare och kan medföra risker för patienten. Därför är det angeläget att kunna välja patienter som kan förväntas att svara på behandling med vernakalant och som därmed kan slippa elkonvertering. Vid tidigare studier har olika parametrar framtagna från ett vilo-EKG visat sig vara ett effektivt prognostiskt instrument för att förutse framgångsrik behandling av arytmier. Det **fjärde arbetet** undersöker om markörer från EKG kan hjälpa till att förutse effekten vid behandling med vernakalant. Studien visar att dessa parametrar (atrial fibrillation rate, exponential decay och medel flimmervågsamplitud) inte kan användas som prediktorer för att välja ut patienter som kan erbjudas konvertering med vernakalant.

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Paper I

Full Length Article

Antithrombotic therapy in patients with non-valvular atrial fibrillation in Southern Sweden: A population-based cohort study

CrossMark

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ARTICLE INFO

ABSTRACT

Introduction: Oral anticoagulants in patients with atrial fibrillation (AF) with moderate-to-high stroke risk are strongly recommended by the current guidelines.
Materials and methods: Population-based register study of all 13,837 patients with incident non-valvular AF diagnosed during 2011–2014 in primary and secondary care (including all in- and outpatient visits) in Skåne County, Sweden. The outcome was the prescription of direct-acting oral anticoagulants (DOAC), warfarin or acetylsalicylic acid (ASA).
Results and conclusion: Guideline adherence increased from 47.6% in 2011 to 66.1% in 2014, mostly due to decrease in undertreatment. In patients with CHA_2DS_2-VASc score ≥ 2, ASA uptake decreased from 29.9% to 14.7% and DOAC uptake increased from 2.1% to 25.1%. The use of ASA was more common among elderly and with increasing stroke- and bleeding risk. Overall, 47.4% of patients with CHA_2DS_2-VASc score ≥ 2 did not receive oral anticoagulants. Undertreatment was particularly common in women < 65 years (55.8%) and in patients > 84 years (65.3% in women and 62% in men). Overtreatment of patients at low stroke risk was 35.9% in men and 36.4% in women. Provider speciality affected the choice of treatment only to a minor degree. Despite increasing guideline adherence, there is a suboptimal use of antithrombotic therapy in a large proportion of AF patients diagnosed in different clinical settings. Efforts to further improve guideline adherence should particularly be targeted on women < 65 years, elderly > 84 years and patients at low stroke risk.

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1. Introduction

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia associated with increased morbidity and mortality from stroke and systemic thromboembolism [1].

The overall burden, prevalence, incidence and AF-associated mortality are progressively increasing worldwide [2]. Twenty-five per cent of all adults over 40 years of age will develop AF during their life-time [3] with a five-fold increased risk of stroke compared to a non-AF population [4]. Atrial fibrillation accounts for at least 15% of all strokes and as many as 36% of strokes in patients over 80 years of age [5]. Strokes associated with AF are generally more severe with increased risk of death,

disability, complications and recurrence compared to non-AF strokes [6].

Warfarin reduces stroke risk in patients with non-valvular AF by 64% [7]. Direct-acting oral anticoagulants (DOAC), such as rivaroxaban, dabigatran and apixaban, are non-inferior to warfarin in stroke prevention without increasing the risk of major bleeding [8].

CHA_2DS_2-VASc score [9] is used as risk stratification criteria and has been validated in multiple cohorts [10,11]. Oral anticoagulation (OAC) (warfarin or DOAC) is recommended by European Society of cardiologists (ESC) guidelines from 2010 [12] and 2012 [13] for prevention of thromboembolism for patients with CHA_2DS_2-VASc score ≥ 2 and should be considered for patients with CHA_2DS_2-VASc score of 1 [13]. For women under 65 with lone atrial fibrillation no anticoagulation should be considered [13]. The ESC 2010 guidelines recommended use of ASA or OAC in patients with CHA_2DS_2-VASc score of 1 (with OAC as preferred option) and ASA or no antithrombotic treatment in patients

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with CHA_2DS_2-VASc score of 0 (with no antithrombotic treatment as preferred option) [12]. The role of ASA was de-emphasized in the 2012 focused update of the ESC guidelines, since the evidence for stroke prevention in AF with acetylsalicylic acid (ASA) is weak and the risk of bleeding is similar to warfarin [13].

Patients with a high bleeding risk according to HAS-BLED score [14] had even better net clinical benefits with warfarin [10] and therefore HAS-BLED score *per se* should not be used to exclude patients from anticoagulation therapy [13]. Contraindications to anticoagulants are present in about 15–20% of AF patients [15,16].

Current treatment practice does not seem to follow the guidelines. Underuse of anticoagulants in high risk patients was reported in multiple observational studies with treatment levels below 60% (range: 19–81.3%) for patients with previous stroke and below 70% (range: 39–92.3%) for patients with CHADS score ≥ 2 [17]. Recent data from 17,000 patients enrolled in Global Anticoagulant registry in the Field – Atrial Fibrillation (GARFIELD-AF) reports that over 35% of patients with CHA_2DS_2-VASc score ≥ 2 did not receive OAC, while over 41% of patients at low stroke risk were treated [18].

According to Swedish Council on Health Technology Assessment (SBU) report from 2013 only 42% of AF patients in Sweden were treated with anticoagulants and undertreatment was more common in women and patients over 80 years of age [19]. The proportion of patients with CHA_2DS_2-VASc score ≥ 2 receiving OAC varies between 56 and 71% in different county councils of Sweden [20].

The present study aims to provide a detailed description of current clinical practice of anticoagulation therapy in newly diagnosed non-valvular atrial fibrillation in Skåne County of Southern Sweden and assess the impact of the components of CHA_2DS_2-VASc score on the treatment choice.

2. Methods

2.1. Study population

All adult patients (>18 years old) diagnosed with their first non-valvular atrial fibrillation or flutter between the 1st of January 2011 and the 31st of December 2014 were identified in the Skåne Healthcare register (SHR) by the International Classification of Diseases (ICD 10) code I48 and included in the study. The SHR contains detailed information (including date of visit and ICD-10 diagnostic codes) about hospital admissions and ambulatory health care visits from all health care providers (cardiology, emergency medicine, internal medicine, other secondary care and primary care) in Skåne Region (total population 2010, n = 1,243,329). Validity of diagnoses in SHR has been confirmed in previous studies [21,22].

Valvular heart disease (identified by ICD code I05-09 or I33-39), death before the study's end-point, or not being a resident of the Skåne County the entire 10 years preceding the AF diagnosis (for assessing comorbidities) were cause for exclusion.

2.2. Assessment of risk factors

CHA_2DS_2-VASc score [9] (congestive heart failure, hypertension, age over 65 or 75 years, diabetes mellitus, thromboembolic event (ischemic stroke, unspecified stroke, transient ischemic attack (TIA) or peripheral arterial embolism), vascular disease (prior myocardial infarction or peripheral arterial disease) and female gender) and HAS-BLED score [14] (hypertension, renal disease, liver disease, prior stroke, prior major bleeding (intracranial, gastro-duodenal or other) or predisposition to bleeding (anaemia, platelet or coagulation defect), age over 65 years, alcoholism) were calculated to assess the risk of ischemic stroke and bleeding respectively. Since we did not have any information on NSAID use or history of labile INR (international normalised ratio), no points were given for these components of HAS-BLED. Comorbidities relevant for the calculation of CHA_2DS_2-VASc and HAS-BLED scores

were assessed during the 10 years (for cancer; 3 years) preceding the AF-diagnosis, using the ICD-10 codes listed in Table A.1 in the Appendix.

2.3. Outcome

Potential undertreatment was defined as ASA or no treatment in patients with CHA_2DS_2-VASc score ≥ 2. Overtreatment was defined as treatment with ASA or OAC in patients with CHA_2DS_2-VASc score = 0 without any other indications to OAC (cardioversion within 3 months from the AF diagnosis date, venous thromboembolism (VTE) 6 months backwards and 3 months forward from the AF diagnosis date or recurrent VTE (defined as ≥2 VTE diagnoses 10 years backwards from the AF diagnosis date). Treatment with OAC in patients with CHA_2DS_2-VASc ≥ 2, OAC or no treatment in patients with CHA_2DS_2-VASc score 1 and no treatment of patients with CHA_2DS_2-VASc score 0 was considered guideline adherent treatment.

The ESC guidelines update from 2012 recommends that no anticoagulant treatment should be considered to women < 65 years with lone AF. Therefore, the proportion of women diagnosed with AF 2012–2014 with CHA_2DS_2-VASc score = 1 receiving treatment with OAC or ASA (without other indications for OAC) was also assessed.

The outcome of this study was ASA, DOAC or warfarin dispensed within 3 months after the index date and identified in Skåne Region's Prescribed Drug Database. Detailed information of every dispensed prescription linked to the individual patient is automatically collected from all pharmacies. The database in Skåne receives information for all inhabitants in Skåne. Patients receiving combined therapy with OAC and ASA were classified as treated with OAC, since ASA was likely prescribed for other indications than atrial fibrillation.

2.4. Statistical analysis

Proportions of patients receiving DOAC, ASA, warfarin or no treatment were assessed per age and gender category in patients with CHA_2DS_2-VASc score ≥ 2. Prescription patterns in patients with CHA_2DS_2-VASc score ≥ 2 and 0 respectively were analysed in regard to the medical specialties where AF was initially diagnosed. Categorical variables were reported as percentages. Among-group comparisons were made using Chi-2 test. Continuous variables were reported as median and interquartile range. Among group-comparisons were made using Kruskal-Wallis test and Mann-Whitney test when appropriate. Prescription trends and guideline adherence through 2011–2014 were assessed.

For patients with CHA_2DS_2-VASc score ≥ 2 odds ratios (OR) were calculated to estimate the association between the independent stroke risk factors and the use of OAC. Multiple logistic regression model included variables of CHA_2DS_2-VASc score (congestive heart failure, hypertension, age, diabetes mellitus, ischemic stroke, unspecified stroke, TIA, peripheral arterial embolism, myocardial infarction, peripheral arterial disease and gender). Variables with P-value > 0.10 were removed stepwise. Variables with P-value < 0.05 were considered to be significant contributors and retained in the final model. The adjusted odds ratios and associated 95% intervals for OAC prescription were determined. Goodness-of-fit was tested with Hosmer-Lemeshow test.

All data analyses were performed using IBM SPSS Statistics for Macintosh, Version 22.0.

The study complies with the Declaration of Helsinki and was approved by the Ethics Committee at the Lund University, Sweden (EPN 2015/308).

3. Results

3.1. Study population

Overall, 17,790 patients were newly diagnosed with AF between the 1st of January 2011 and the 31st of December 2014. Patients with

valvular heart disease (n = 1543), dead within 3 months after the index date (n = 1834), or moving out of the Skåne County during 2001–2014 (n = 896) were excluded. The final study sample thus consisted of 13,837 patients, since some patients had more than one reason for exclusion. Mean age was 76.1 ± 11.1 and 52.6% were men.

Demographics and selected baseline characteristics of the study population and patients with CHA_2DS_2-VASc score ≥ 2 are outlined in Table 1 (the full version is presented in Table A.2 in the Appendix). The proportion of patients with CHA_2DS_2-VASc score ≥ 2 receiving anticoagulation was 52.6% (43.8% received warfarin and 8.8% received DOAC).

3.2. Guideline adherence and treatment trends

Guideline adherence increased from 47.6% to 66.1% mostly due to decrease in undertreatment (Fig. 1).

The uptake of antithrombotic therapy in patients with CHA_2DS_2-VASc score ≥ 2 remained almost constant (around 75%) since 2011 (Fig. 2). However, there was a large decrease in ASA (from 29.9% to 14.7%) and increase in OAC (from 42.2% to 62.8%). Prescription of DOAC in this group increased from 2.1% to 25.1% since 2012.

3.3. OAC prescription per risk category

Antithrombotic therapy uptake increased with increasing CHA_2DS_2-VASc score, but the uptake of ASA increased from 14.9% till 37.5% and uptake of OAC decreased from 55.4% to 44.8% across CHA_2DS_2-VASc score 2–8 (Fig. 3). Increased ASA uptake is even more pronounced with increasing HAS-BLED scores (Fig. 4).

3.4. Predictors of OAC prescription in patients with CHA_2DS_2-VASc score ≥ 2

Statistically significant positive predictors of OAC prescription were age < 84 years (with the highest OR between 65 and 74 years), male gender, history of ischemic stroke and hypertension (Table 2). Patients over 84 years and those with history of unspecified stroke, vascular disease and diabetes mellitus were less likely to receive OAC. History of heart failure, TIA and peripheral systemic embolism did not affect the treatment choice.
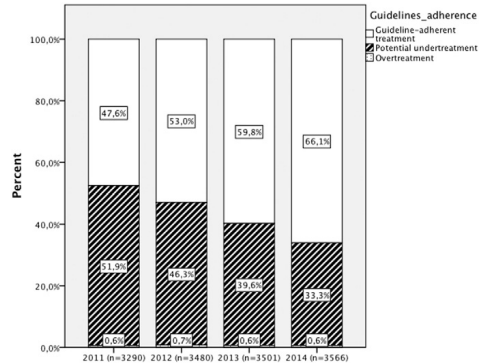

Fig. 1. Guideline adherence 2011–2014.

3.5. Impact of gender and age

Undertreatment was particularly common in women < 65 years (55.8%) and in patients > 84 years (65.3% in women and 62% in men) (Fig. 5). The proportion of women of menstruating age (<50 years) and thus at risk of potential menorrhagia among undertreated women in the age group < 65 years was 14.3%. Older patients received more ASA (34–35%) and less DOAC. Men received somewhat more OAC than women in the same age group.

3.6. Overtreatment of patients at low stroke risk

Uptake of ASA and OAC in patients with no other indication for OAC was 35.9% among men and 36.4% among women (Table 3).

3.7. Impact of the provider specialty

Treatment patterns were similar for AF diagnosed in all provider specialties (cardiology, internal medicine, emergency medicine, other secondary care and primary care) with some marginal variations. The
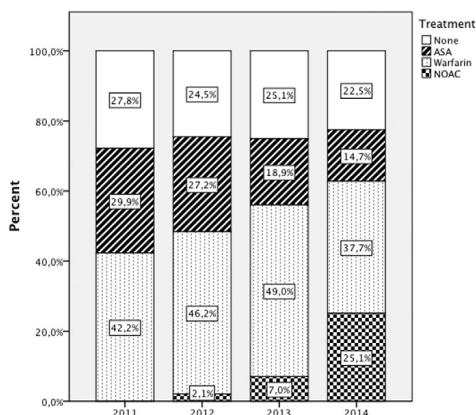
Table 1
Selected baseline characteristics of the study patients.

Measure	Study population (n = 13,837)				Patients with CHA_2DS_2-VASc score ≥ 2 (n = 12,421)	
	DOAC N = 1272 (9.2%)	Warfarin N = 5949 (43.0%)	ASA N = 2941 (21.3%)	None N = 3675 (26.6%)	DOAC or warfarin N = 6529 (52.6%)	ASA or none N = 5892 (47.4%)
Age, median (IQR)	74 (67–81)**	76 (69–82)**	81 (72.5–88)**	77 (67–85)**	76 (69–82)**	79 (69–87)**
Male, n (%)	692 (54.4)**	3350 (56.3)**	1455 (49.5)**	1782 (48.5)**	3413 (52.3)**	2669 (45.3)**
CHA_2DS_2-VASc score, median (IQR)	3 (2–4)**	4 (3–5)**	4 (3–5)**	3 (2–5)**	4 (3–5)**	4 (3–5)**
HAS-BLED score, median (IQR)	2 (1–2)**	2 (2–3)**	2 (2–3)**	2 (1–3)**	2 (1–3)**	2 (1–3)**
Heart failure, n (%)	229 (18.0)**	1298 (21.8)**	845 (28.7)**	757 (20.6)**	1489 (22.8)**	1588 (27.0)**
Hypertension, n (%)	919 (72.2)**	4378 (73.6)**	2213 (75.2)**	2355 (64.1)**	5098 (78.1)**	4404 (74.7)**
Diabetes mellitus, n (%)	229 (18.0)**	1303 (21.9)**	702 (23.9)**	688 (18.7)**	1515 (23.2)	1369 (23.2)
Ischemic stroke, n (%)	123 (9.7)**	858 (14.4)**	398 (13.5)**	305 (8.3)**	981 (15.0)**	703 (11.9)**
Vascular disease, n (%)	261 (20.5)**	1418 (23.8)**	1147 (39.9)**	704 (19.2)**	1660 (25.4)**	1848 (31.4)**
Liver disease (%)	16 (1.3)**	81 (1.4)**	48 (1.6)**	103 (2.8)**	86 (1.3)*	125 (2.1)*
Renal disease, n (%)	47 (3.7)**	421 (7.1)**	314 (10.7)**	353 (9.6)**	453 (6.9)**	644 (10.9)**
Intracranial bleeding, n (%)	15 (1.2)**	53 (0.9)**	51 (1.7)**	118 (3.2)**	63 (1.0)**	157 (2.7)**
Gastric/duodenal bleeding, n (%)	17 (1.3)**	86 (1.4)**	69 (2.3)**	119 (3.2)**	99 (1.5)**	175 (3.0)**
Other severe bleeding, n (%)	41 (3.2)**	236 (4.0)**	197 (6.7)**	334 (9.1)**	259 (4.0)**	485 (8.2)**
Anaemia, n (%)	121 (9.5)**	638 (10.7)**	516 (17.5)**	764 (20.8)**	730 (11.2)**	1205 (20.5)**
Dementia, n (%)	23 (1.8)**	93 (1.6)**	297 (10.1)**	213 (5.8)**	112 (1.7)**	504 (8.6)**

** p < 0.001.
* p < 0.05.

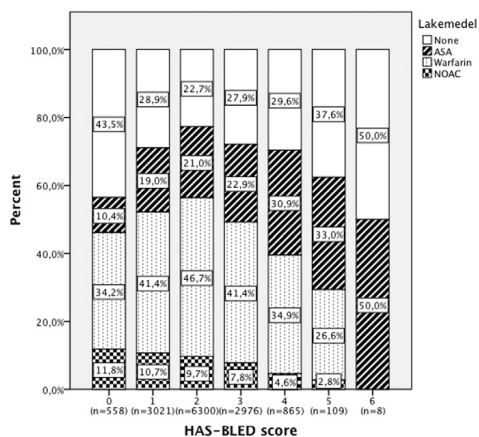**Fig. 2.** Trends in antithrombotic drug prescriptions in patients with CHA2DS2-VASc score ≥ 2.

Fig. 4. Treatment patterns according to bleeding risk score.

uptake of ASA in patients with CHA2DS2-VASc score ≥ 2 was still over 20% in all medical specialties. Undertreatment was more common in other secondary care and overtreatment was more common in primary care and internal medicine clinics compared to other specialties (Figs. A.1 and A.2 in the Appendix).

4. Discussion

In this study we found suboptimal treatment of AF patients despite increasing guideline adherence. Overall, 47.4% of the patients with high risk of stroke to whom OAC therapy is indicated according to the ESC guidelines did not receive it.

Over 35% of patients at low stroke risk and no other indications to anticoagulation were treated with ASA or OAC and thus exposed to unnecessary bleeding hazard. Our findings are similar to the Stockholm cohort study conducted a decade ago with reported under- and

overtreatment rates of 54% and 25% respectively [15]. The uptake of OAC was lower in our study compared to recent Swedish [20] and European [23] reports, probably due to exclusion of patients with valvular heart disease.

OAC prescription did not follow stroke risk assessment. Of seven stroke risk factors in CHA2DS2-VASc score, only three (ischemic stroke, hypertension and age 65–84 years) increased the odds of OAC prescription. There was no association between the treatment choice and heart failure, TIA or peripheral arterial embolism. Some of the important stroke risk factors (age > 84 years, vascular disease, diabetes and female gender) decreased the odds of receiving adequate stroke prevention.

This can be due to the fact that some of the risk factors are considered to carry stronger predictive values than others. On multivariate analysis, stronger association was found between thromboembolic events and history of ischemic stroke (hazard ratio (HR): 2.81, 95% CI 2.68–2.95), age between 65 and 74 years (HR: 2.97, 95% CI 2.54–3.48) and age over 74 years (HR: 5.28, 95% CI 4.57–6.09) compared to association between thromboembolic events and vascular disease (HR: 1.14, 95% CI 1.06–1.23), diabetes (HR: 1.19, 95% CI 1.13–1.26) and female gender (HR: 1.17, 95% CI 1.11–1.22) in the Swedish AF cohort study [11].

Paradoxically, the use of ASA but not OAC increased with the increasing stroke risk. CHA2DS2-VASc score and HAS-BLED score share some components such as hypertension, age and history of stroke. The uptake of ASA in our study increased with increasing age and bleeding risk
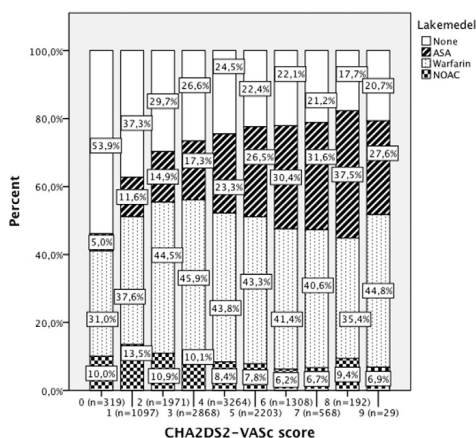

Fig. 3. Treatment patterns according to stroke risk score.

Table 2
Factors associated with prescription of OAC in patients with CHA2DS2-VASc score ≥ 2.[*]

|	Univariate OR (95% CI)	Multivariate OR (95% CI)
Age		
<65 years (reference)	1	1
65–74 years	1.52 (1.31–1.76)	1.48 (1.28–1.72)
75–84 years	1.36 (1.18–1.57)	1.36 (1.18–1.57)
>84 years	0.54 (0.47–0.62)	0.54 (0.47–0.63)
Ischemic stroke	1.31 (1.18–1.45)	1.55 (1.39–1.74)
Male gender	1.32 (1.23–1.42)	1.26 (1.17–1.35)
Hypertension	1.20 (1.11–1.31)	1.25 (1.14–1.36)
Diabetes mellitus	1.00 (0.92–1.09)	0.90 (0.83–0.98)
Peripheral arterial disease	0.78 (0.70–0.87)	0.78 (0.69–0.88)
Myocardial infarction	0.76 (0.70–0.83)	0.74 (0.68–0.82)
Unspecified stroke	0.69 (0.58–0.81)	0.56 (0.47–0.67)

[*] Hosmer-Lemeshow goodness-of-fit test p = 0.763.
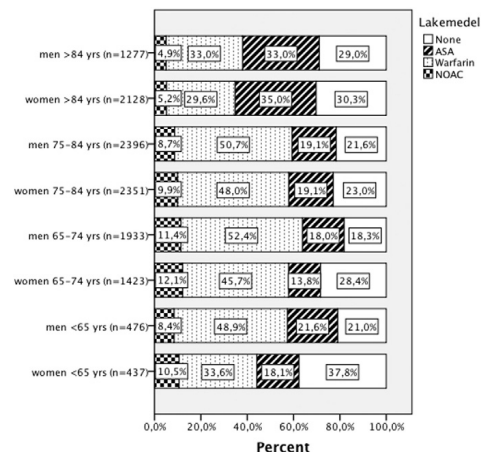
Fig. 5. Impact of age and gender on treatment strategy in patients with CHA$_2$DS$_2$-VASc score ≥ 2.

scores, potentially due to a misconception that ASA is a safer option than OAC. However, warfarin is more effective in reducing stroke risk compared to ASA in elderly patients with no difference in major hemorrhage [24] or with significantly less adverse events, including severe bleeding [25]. Some studies indicate that ASA offers no benefit in stroke protection compared to no treatment [26,27] and that ASA may even increase the incidence of ischemic stroke in the elderly [27].

Of concern, this study found undertreatment of women < 65 years. It is unlikely that they had a higher bleeding risk compared to the older age groups apart from menorrhagia in fertile women.

DOAC uptake increased twelve-fold in three years. DOAC requires less monitoring and can be a valuable alternative in patients who are reluctant to use warfarin due to inconvenience of dose adjustments and regular INR checks.

Different medical specialities had similar prescription patterns. We cannot be certain that the antithrombotic therapy was prescribed by the clinic that diagnosed atrial fibrillation, but it is reasonable to assume that in the majority of cases. Suboptimal treatment could be initiated due to unawareness of the guidelines or misjudgement of risk-and-benefit ratio. The ORBIT-AF study revealed the discordance between provider-assessed risk and empirical stroke- and bleeding risk scores in AF patients [28].

The potential limitation of our study is that it is based on register data. Some important factors affecting treatment decisions, such as patient's preferences and compliance, could not be assessed.

Overtreatment could have been overestimated since we did not adjust for lung vein isolation as a potential indication for warfarin and did not allow for warfarin treatment over 3 months prior to cardioversion in patients with labile INR. We did not have any information on NSAID

uptake or labile INR, which may predispose to underestimation of the bleeding risk. The important strength of our study is that it comprises a large cohort reflecting current clinical practice in different healthcare settings, including both primary and secondary care (hospital admissions as well as special ambulatory care).

5. Conclusion

Guidelines adherence has increased since 2011, but a substantial proportion of AF patients diagnosed in different clinical settings still does not receive the adequate anticoagulation treatment. Efforts to further improve guideline adherence should particularly be targeted on women < 65 years, elderly > 84 years and patients at low stroke risk.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2016.02.023.

Potential conflict of interest

Professor Peter J Svensson, Anders Själander and Tord Juhlin have advisory board assignments for Boehringer Ingelheim, Bayer and BMS/Pfizer.

Table 3
Treatment of AF patients with low stroke risk and no other indications for OAC.

	Men with CHA$_2$DS$_2$-VASc score of 0 (2011–2014) N = 245	Women with CHA$_2$DS$_2$-VASc score of 1 (2012–2014) N = 151
No treatment, n (%)	157 (64.1)	96 (63.6)
ASA, n (%)	16 (6.5)	12 (7.9)
Warfarin, n (%)	59 (24.1)	26 (17.2)
DOAC, n (%)	13 (5.3)	17 (11.3)

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Paper II

Full Length Article

Ischemic stroke rates decline in patients with atrial fibrillation as anticoagulants uptake improves: A Swedish cohort study

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ABSTRACT

Introduction: The impact of the increased anticoagulants uptake on incidence rate of ischemic stroke is largely unknown. We assessed time trends in rates of ischemic stroke in patients with incident atrial fibrillation (AF) diagnosed between 2011 and 2013.
Materials and methods: Population-based retrospective registry study of all 11,500 adults diagnosed with incident non-valvular atrial fibrillation in 2011–2013 in primary and secondary care and receiving oral anticoagulants ($n = 4847$), aspirin ($n = 2850$) or no treatment ($n = 3766$) in Skåne County, Sweden. The primary outcome was the rate of ischemic stroke within 365 days after AF diagnosis.
Results and conclusion: Cumulative incidence of ischemic stroke decreased from 2.87% (95% confidence interval (CI) 2.37–3.45%) to 1.93% (95% CI 1.54–2.41%) while the uptake of oral anticoagulants increased from 36.6% to 48.4% between 2011 and 2013 (regression coefficient − 0.08; 95% CI, − 0.09 to − 0.07, $p < 0.001$). The increased uptake of oral anticoagulants in the community is associated with decreased incidence of ischemic stroke in AF patients.

1. Introduction

Stroke prevention is crucial in the management of patients with atrial fibrillation (AF), since non-valvular AF increases the risk of ischemic stroke five-fold [1]. AF related strokes are associated with greater mortality, disability and recurrence [2].

Oral anticoagulation (OAC) with direct oral anticoagulants (DOAC) or warfarin is recommended in European Society of Cardiology (ESC) guidelines [3] for all patients with AF, except in those patients who are at low risk (aged < 65 years and lone AF), or with contraindications. Aspirin is not effective in ischemic stroke prevention in AF and the risk of major bleeding is comparable to that of OAC [4]. ESC guidelines adherence increased from 47.6% in 2011 to 66.1% in 2014 in Southern Sweden [5], where the present study was carried out. The impact of increased oral anticoagulants (warfarin or DOAC) uptake on incidence rate of ischemic stroke is largely unknown. We aimed to assess time trends in OAC uptake and ischemic stroke rates among patients

diagnosed with incident AF in Southern Sweden between 2011 and 2013.

2. Methods

2.1. Study population

All adult patients (> 18 years old) diagnosed with their first episode of non-valvular atrial fibrillation or flutter between the 1st of January 2011 and the 31st of December 2013 were identified in the Skåne Healthcare register (SHR) by the International Classification of Diseases (ICD 10) code I48 and included in the study. The register contains detailed information about ambulatory health care visits and hospital admissions from all health care providers in the Skåne Region (total population 2010, $n = 1,243,329$). Previous studies have confirmed validity of diagnoses in the register [6,7].

We excluded all patients with valvular heart disease (identified by

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ICD code I05-09 or I33-39) and those who had not been a resident of the Skåne County the entire 10 years preceding the AF diagnosis (to ensure correct assessment of baseline comorbidities).

The present study complies with the Declaration of Helsinki and was approved by the Ethics Committee at the Lund University, Sweden (EPN 2015/308).

2.2. Assessment of risk factors

CHA_2DS_2-VASc score [8] was calculated to assess ischemic stroke risk. Points were given for congestive heart failure, hypertension, age over 65 or 75 years, diabetes mellitus, history of a thromboembolic event (ischemic stroke, unspecified stroke, transient ischemic attack (TIA) or peripheral arterial embolism), vascular disease (prior myocardial infarction or peripheral arterial disease) and female sex. Comorbidities relevant for the calculation of CHA2DS2-VASc score were assessed during the 10 years preceding the AF-diagnosis, using the ICD-10 codes in positions 1 through 8 listed in Supplement Table A.1.

2.3. Baseline medication

The Skåne Region's Prescribed Drug Database contains detailed information of every dispensed prescription linked to the individual patient for all inhabitants in the Skåne County. The information is automatically collected from all pharmacies. Baseline medication was defined as warfarin, DOAC (direct oral anticoagulants) or aspirin collected at a pharmacy within 3 months from the AF diagnosis and prior to the outcome. OAC treatment was defined as treatment with warfarin or DOAC. Patients receiving combined therapy with OAC and aspirin were classified as treated with OAC, since aspirin was likely prescribed for some other indications than atrial fibrillation.

2.4. Outcome

The endpoint was ischemic stroke (ICD-10 code I63 in the first position) within 365 days from AF diagnosis. Diagnoses of ischemic stroke registered under the same admission as the first AF diagnosis were considered as comorbidities and not as new events.

2.5. Statistical analysis

The study population was divided into three cohorts (2011, 2012 and 2013) according to the year of AF diagnosis. The uptake of aspirin, warfarin and DOAC was assessed in each of the three cohorts.

Cumulative incidence rate of ischemic stroke within 365 days from AF diagnosis was calculated. We have also assessed stroke rates in patients with CHA_2DS_2-VASc score ≥ 2 receiving OAC, aspirin or no treatment. Incidence trend of ischemic stroke was assessed in the whole population, then in male and female patients and finally in different risk groups (CHA_2DS_2-VASc score 0 through 1; 2 through 4 and 5 through 9).

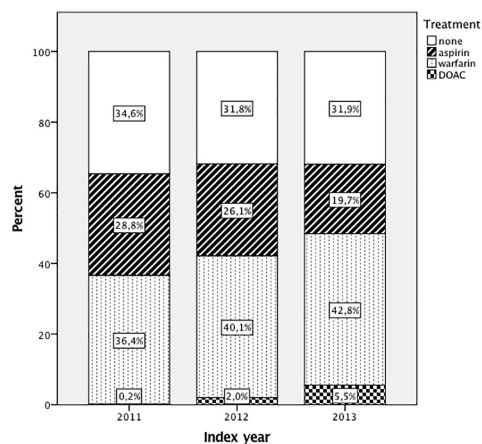Correlation between OAC uptake and stroke incidence was assessed by linear regression.

All data analyses were performed using IBM SPSS Statistics for Macintosh, Version 22.0.

3. Results

Overall, 13,219 patients were newly diagnosed with AF between the 1st of January 2011 and the 31st of December 2013. Patients with valvular heart disease ($n = 1118$) or moving out of the Skåne County during 2001–2013 ($n = 655$) were excluded. The final study population consisted of 11,500 patients, since 64 patients fulfilled both exclusion criteria. The mean age was 77 ± 11 years and 51.5% were men. Mean observation time was 321 days and total observation time was 10,116 patient-years.

Table 1
Baseline characteristics of the study population.

	2011 ($n = 3700$)	2012 ($n = 3907$)	2013 ($n = 3893$)	Total ($n = 11,500$)
Age, mean ± SD	77 ± 11	77 ± 11	77 ± 11.	77 ± 11
Male, n (%)	1868 (50.5)	2024 (51.8)	2032 (52.2)	5924 (51.5)
CHA$_2$DS$_2$-VASc score				
0–1	357 (9.6)	376 (9.6)	362 (9.3)	1095 (9.5)
2–4	2143 (57.9)	2270 (58.1)	2235 (57.4)	6648 (57.8)
5–9	1200 (32.4)	1261 (32.2)	1296 (33.3)	3757 (32.7)
Heart failure, n (%)	888 (24.0)	928 (23.8)	896 (23.0)	2712 (23.6)
Hypertension, n (%)	2484 (67.1)	2615 (66.9)	2738 (70.3)	7837 (68.1)
Diabetes, n (%)	743 (20.1)	825 (21.5)	794 (20.4)	2362 (20.5)
Ischemic stroke, n (%)	435 (11.8)	457 (11.7)	500 (12.8)	1392 (12.1)
Unspecified stroke, n (%)	158 (4.3)	160 (4.1)	149 (3.8)	467 (3.8)
TIA, n (%)	249 (6.7)	271 (6.9)	301 (7.7)	821 (7.1)
Myocardial infarction, n (%)	687 (18.6)	720 (18.4)	749 (19.2)	2156 (18.7)

Fig. 1. Treatment trends.

Baseline characteristics of the study patients are outlined in Table 1.

The proportion of newly diagnosed patients receiving OAC increased from 36.6% during the first year to 48.4% the third year, while uptake of aspirin decreased from 28,8% to 19,7% (Fig. 1). Overall, aspirin uptake increased with increasing CHA_2DS_2-VASc score, while OAC uptake was highest among patients with CHA_2DS_2-VASc score 2 through 3 (Fig. 2).

OAC uptake increased in both sexes, all age subgroups and in all CHA_2DS_2-VASc score subgroups (Table 2).

Cumulative incidence of ischemic stroke among patients with CHA_2DS_2-VASc score ≥ 2 receiving different treatments (none, aspirin or OAC) was 3.02% (95% confidence interval (CI) 2.49–3.66%), 3.43% (95% CI 2.81–4.19%) and 1.54% (95% CI 1.22–1.95%).

Cumulative incidence of ischemic stroke decreased from 2.87% (95% CI 2.37–3.45%) in 2011 to 2.33% (95% CI 1.90–2.85%) in 2012 and 1.93% (95% CI 1.54–2.41%) (Fig. 3). The stroke rate reduction was more pronounced in patients with CHA_2DS_2-VASc score 5 through 9 compared with those with CHA_2DS_2-VASc score 0 through 1 (Fig. 4).

Ischemic stroke incidence decreased in both sexes, but women had higher ischemic stroke rates compared to men (Fig. 5). Women in our population were older than men (mean age ± SD 79 ± 11 years vs. 75 ± 11 years) and 43.1% of women had CHA_2DS_2-VASc score 5
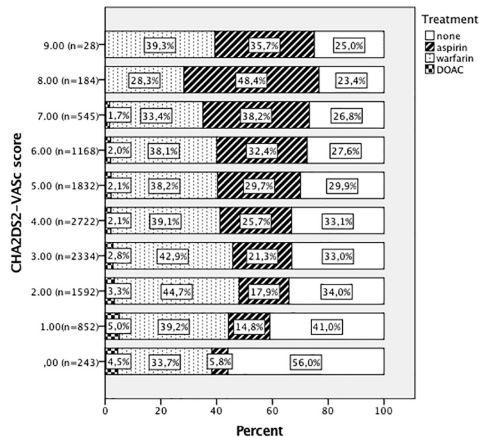
Fig. 2. Treatment patterns according to stroke risk score.

Table 2
Proportion of patients receiving OAC by sex, age and stroke risk.

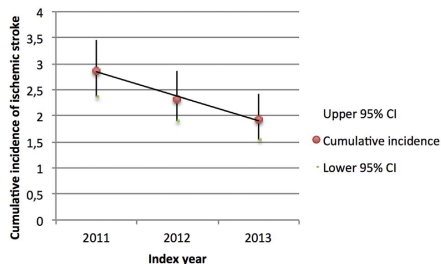|	2011 (n = 3700)	2012 (n = 3907)	2012 (n = 3893)
Total, n (%)	1354 (36.6)	1646 (42.1)	1884 (48.4)
Sex			
Female, n (%)	591 (32.3)	707 (37.5)	834 (44.8)
Male, n (%)	763 (40.8)	939 (46.4)	1050 (51.7)
Age			
< 65 years	181 (37.5)	239 (44.8)	243 (47.1)
65–74 years	446 (48.0)	500 (52.7)	589 (59.4)
75–84 years	526 (42.4)	636 (48.2)	728 (56.2)
> 84 years	201 (19.2)	271 (24.5)	324 (29.7)
CHA_2DS_2-VASc score			
0–1	129 (36.1)	167 (44.4)	174 (48.1)
2–4	842 (39.3)	990 (43.6)	1121 (50.2)
5–9	383 (31.9)	489 (38.8)	589 (45.4)

Fig. 3. Cumulative incidence of ischemic stroke per index year.

through 9 compared to 22.8% of men (Supplementary Table A.2).

Linear regression demonstrates decline in cumulative incidence of ischemic stroke with increasing OAC uptake (regression coefficient − 0.08; 95% CI, − 0.09 to − 0.07, $p < 0.001$) (Fig. 6).

4. Discussion

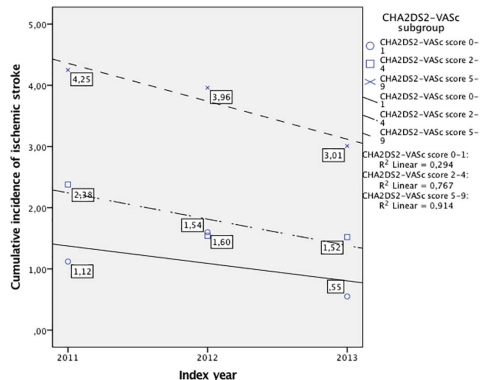In the present study we found that cumulative incidence of ischemic

Fig. 4. Cumulative incidence of ischemic stroke per index year in different CHA_2DS_2-VASc subgroups.
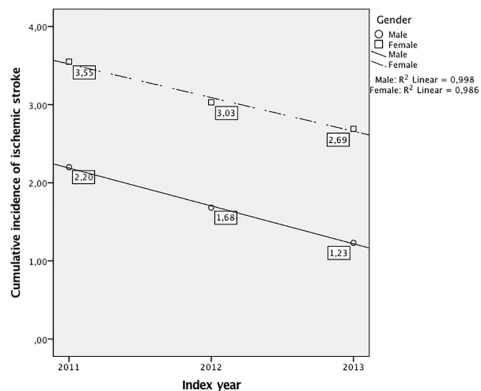

Fig. 5. Cumulative incidence of ischemic stroke per index year in different sexes.
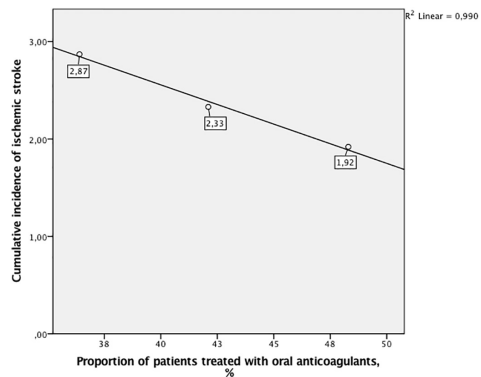

Fig. 6. Cumulative incidence of ischemic stroke vs. OAC uptake.

stroke in patients with newly diagnosed AF decreased from 2.87% to 1.93% while uptake of OAC increased from 36.6% to 48.4% between 2011 and 2013 (regression coefficient − 0.08; 95% CI, − 0.09 to − 0.07, $p < 0.001$). Decreasing incidence rate of ischemic stroke in an AF population was previously reported in studies from Sweden [9], Denmark [10] and in the Framingham Heart Study [11]. The incidence rates of ischemic stroke in our study are consistent with those reported in the Swedish atrial fibrillation cohort [12]. However, our study is unique since we have demonstrated the correlation between increased use of OAC and a decreased incidence of ischemic stroke.

A recent study from USA did not find any decline in ischemic stroke following incident AF over the last decade [13]. This can be due to the fact that the uptake of anticoagulants did not change over time in the studied American cohort.

OAC uptake was lower in patients with high CHA_2DS_2-VASc scores, probably due to frailty associated with multiple comorbidities. Patients with CHA_2DS_2-VASc score ≥ 2 treated with aspirin had a higher stroke incidence compared to those receiving OAC. We have previously demonstrated that the use of aspirin was more common among elderly and patients with higher risk of ischemic stroke and bleeding in the present cohort [5]. Aspirin does not provide protection against stroke in patients with AF (14) and is not recommended by the current guidelines [14].

The high ischemic stroke incidence in this group might be explained by the presence of high-risk individuals receiving inappropriate treatment. Treatment with oral anticoagulants such as warfarin decreases the ischemic stroke incidence by approximately 64% [15], which is in line with our findings.

Since OAC decreases risk of ischemic stroke by approximately two-thirds [15], patients with high baseline risk achieve the greatest absolute risk reduction. Ischemic stroke incidence declined most in patients with high baseline ischemic stroke risk (CHA_2DS_2-VASc score 5 through 9) in our cohort. There was no clear incidence trend in patients with low baseline risk (CHA_2DS_2-VASc score 0 through 1) since their low stroke risk cannot be significantly further reduced by OAC treatment.

Notably, OAC uptake increased even in this subgroup (Table 2), which might indicate overtreatment. OAC in patients with low ischemic stroke risk is indicated before elective cardioversion or pulmonary vein isolation. However, it is unlikely that these procedures were performed more frequently in 2013 compared to 2011.

Women in our study had higher ischemic stroke incidence than men, probably due to higher CHA_2DS_2-VASc score, older age and lower OAC uptake. Similar sex differences in age and comorbidities in AF patients were previously demonstrated by Euro Heart Survey on Atrial Fibrillation [16]. Higher ischemic stroke incidence in female patients was also found in Swedish nationwide retrospective AF cohort [17]. The rate of reduction in ischemic stroke incidence in women was similar to that in men in our cohort. OAC uptake increased in both sexes, but women started from a baseline level of 32.3% compared to 36.6% in men.

The decline in ischemic stroke incidence cannot be explained by decreased comorbidity burden in the study population. There was no significant difference in baseline stroke risk factors 2011 through 2013, apart from the increase in prevalence of hypertension. The increased uptake of OAC and decreased uptake of aspirin provides a plausible explanation for decreased rates of ischemic stroke in our study.

If our findings can be extrapolated to patients with prevalent AF, we can anticipate a large decrease in ischemic stroke burden in Skåne County. Reducing stroke incidence from 3,27 to 2,17 events per 100 patient-years corresponds to over 400 events per year, assuming AF prevalence of 3% among 1,3 millions of Skåne County inhabitants.

Since our study had a retrospective observational design based on data retrieved from the Skåne Healthcare register by the International Classification of Diseases codes there are several important limitations. First, we have assumed that the initial treatment strategy was unchanged throughout the follow-up year. Second, we did not assess treatment compliance for DOAC and time-in-therapeutic range (TTR) for OAC treatment with warfarin during the follow-up, which might limit the generalizability of the result on the DOAC and warfarin. According to a previous report from Swedish national registry for anticoagulation and AF TTR in Sweden was 76.2% [18] compared to 55% in meta-analysis from 14 centres in the USA [19]. Third, we may have missed some events that were miscoded. Fourth, since data on hereditary thrombophilia were not registered, it was not feasible to assess its possible contributions to the incidence of ischemic stroke in our population. Fifth, since we do not have data on mortality we cannot exclude competing risks. Finally, we have no clinical data on how the modifiable stroke risk factors such as hypertension were managed. Since this study mostly included patients treated with warfarin and aspirin, we cannot draw any conclusions whether the increased use of DOAC for the treatment of AF reduces ischemic stroke incidence, even though clinical data supports this [20]. Nevertheless, our study represents the real world outcomes from a large population-based cohort according to attention-to-treat principle.

In conclusion, our study suggests that the increased uptake of oral anticoagulants in the community is associated with decreased incidence of ischemic stroke in AF patients.

Source of funding

Disclosure of conflict of interest

Professor Peter J Svensson, Anders Själander and Tord Juhlin have advisory board assignments for Boehringer Ingelheim, Bayer and BMS/Pfizer.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.thromres.2017.08.004.

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Paper III

CrossMark

Regular Article

Concomitant use of dronedarone with dabigatran in patients with atrial fibrillation in clinical practice ☆

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ARTICLE INFO

ABSTRACT

Introduction: Dronedarone is a strong P-glycoprotein inhibitor with a potential to increase bioavailability of dabigatran. We sought to measure and report plasma concentrations of dabigatran in patients with atrial fibrillation (AF) on concomitant dronedarone treatment.
Materials and methods: A cohort of 33 patients (mean age 64 years, 16 men) concomitantly treated with dabigatran at a dose of 110 mg twice a day (bid) and dronedarone at a dose of 400 mg bid at the discretion of the patient's cardiologist were followed prospectively.
Results: Median trough plasma concentration of dabigatran at one week and one month after the concomitant treatment start was 102.0 (range 8-251) ng/ml and 84 (range 27-302) ng/ml respectively. Median treatment length was 13 (range 1-21) months. There was one major bleeding event (2,8% per patient-year) and no thrombotic events during a total of 35.5 patient-years.
Conclusions: Median trough plasma concentration of dabigatran in our study was observed to be similar to median trough plasma concentration of dabigatran at a dose of 150 mg bid without concomitant dronedarone in earlier studies with low reported rate of bleeding and thrombosis. Since concomitant treatment offers potential benefits to patients with AF, larger future trials that might refute the current contraindication are warranted.

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Introduction

Dabigatran etexilate is a novel oral direct thrombin inhibitor approved as alternative to warfarin for prevention of stroke and systemic thromboembolism in patients with non-valvular atrial fibrillation (AF). Unlike warfarin, dabigatran is given at a fixed dose and does not require dietary restrictions or regular coagulation monitoring.

The Randomized Evaluation of Long Term Anticoagulation Therapy (RE-LY) trial compared the use of dabigatran with warfarin in patients with atrial fibrillation [1]. Dabigatran at a dose of 150 mg twice a day (bid) was associated with lower risk of stroke and systemic thromboembolism without an increase in the overall rate of major bleeding. Dabigatran at a dose of 110 mg bid was non-inferior in reducing stroke and systemic thromboembolism at a lower rate of major bleeding.

Dabigatran elimination occurs predominantly (80%) via renal route [2] and impaired renal function can result in drug accumulation. Dabigatran etexilate is a substrate for the efflux transporter P-glycoprotein (P-gp)

in the intestine [3]. About 48% of patients with atrial fibrillation that use vitamin K antagonists take drugs that affect Pg-p [4] and thus can potentially alter bioavailability of dabigatran.

Dronedarone is an antiarrhythmic drug for maintenance of sinus rhythm that was shown to reduce the incidence of death or hospitalisation due to cardiac events in patients with paroxysmal or persistent atrial fibrillation [5]. Dronedarone is a strong P-gp-inhibitor with a potential to increase bioavailability of dabigatran if given concomitantly. Although dronedarone and dabigatran are often indicated in the same patient population, no previous study has addressed the safety and clinical endpoints of the concomitant treatment in AF patients. Co-administration of these two drugs has only been prospectively studied in 16 healthy volunteers (age 18-45, 81.3% males) and the conclusion of the study was that the trough concentration of dabigatran was 1.7-fold higher when dabigatran 150 mg bid was co-administered with dronedarone than when dabigatran was administered alone [6,7]. Retrospective cohort studies using claim databases has not demonstrated any increased risk of major bleeding with concomitant use of dabigatran and dronedarone compared to dabigatran alone [7,8] and hence the clinical significance of this drug interaction remains uncertain. However, the European Medicines Agency (EMEA) has decided that concomitant use of dabigatran and dronedarone should be contraindicated

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based on pharmacokinetic data from the Sanofi-Aventis study on healthy volunteers, using the dose of dabigatran 150 mg bid [8].

In this study we sought to measure and report plasma concentrations of dabigatran at a lower dose of 110 mg bid on concomidant dronedarone treatment from a real-life setting in patients with atrial fibrillation.

Materials and Methods

Patients treated concomitantly with dabigatran 110 mg bid and dronedarone 400 mg bid at the discretion of the patient's cardiologist at Skåne University Hospital were referred to the anticoagulation clinic during the period of January 2012 to July 2013 and prospectively followed up in the internet-based Swedish national quality registry AuriculA. The patients discussed the risks and benefits of the treatment with their cardiologists. Plasma levels of dabigatran were reported to the cardiologist, responsible for the treatment. The registry contains key patient characteristics, information on anticoagulation treatment, comorbidities and complications to atrial fibrillation as quality indicators [9].

Concomitant treatment with dabigtran and dronedarone was introduced as an alternative to warfarin and dronedarone by local consensus and guidelines at Skåne University Hospital before the present contraindication. Given the strong inhibition of Pg-p by dronedarone, hospital cardiologists and coagulation experts agreed on guidelines using the dabigatran 110 mg bid dose concomitantly with dronedarone and, as a safety measure, measuring dabigatran levels in these patients. Hence, measurement of dabigatran concentrations and review of the patients' hospital records was a part of a quality control and assurance program aiming to follow up the introduction of this new therapeutic strategy.

The study outcome was plasma trough concentration of dabigatran at one week and one month after the start of concomitant treatment. The analysis of dabigatran was performed at Department of Clinical Chemistry, Skåne University Hospital. Trough venous samples at steady state, between 08:00 and 08:30 in the morning before patients had taken their morning dabigatran dose, were collected at pre-specified time points at one week and one month after the initiation of the concomitant treatment, to assess patient compliance. The patients did not receive any specific instructions about the timing of dronedarone and dabigatran intake other than that they should take both medicines twice daily. Plasma concentrations of dabigatran were obtained using the diluted thrombin time calibrated with dabigatran standard (Hemoclot thrombin inhibitor assay, HYPHEN BioMed) [10] in accordance to recommendations from International Society of Thrombosis and Homeostasis [11]. The total imprecision calculated as coefficient of variation was 9.85% at 100 ng/ml and 4.59% at 400 ng/ml.

Rate of major bleeding (according to International Society of Homeostasis and Thrombosis (ISHT) definition) [12] and rate of ischemic stroke or systemic embolism during the time of concomitant treatment were calculated. A review of all hospital records of every patient was performed in May 2014 to assess concomitant medications and to assure that no comorbidities or treatment complications were missed. The list of *in vivo* P-gp inhibitors and inducers was obtained from Food and Drug Administration (FDA) Guidance for Industry Drug Interaction Studies [13] in order to assess the use of other drugs that can alter P-gp. CHA$_2$DS$_2$-VASc [14] and HAS-BLED [15] scores were calculated to estimate the risk of stroke and bleeding. Concomitant use of cardiovascular drugs and medications that can affect bleeding risk (antiplatelet agents, non-steroidal anti-inflammatory drugs, proton pump inhibitors and corticosteroids) was also assessed.

Since dabigatran is eliminated predominantly via kidneys, estimated glomerular filtration rate (eGFR) was calculated using the Lund-Malmö equation (derived and internally validated at the present University Hospital) [16]. Renal function was monitored at treatment initiation, after 3, 6 and 12 months and thereafter annually [17].

Using AuriculA in routine health care complies with the Declaration of Helsinki and the Ethics Committee at the Lund University has approved research using this registry.The assignment of the medical

intervention was not at the discretion of the investigators. The investigators did not have any relationship with the treating cardiologists other than reporting dabigatran levels and were not involved in the medical care of the patients. The investigators were responsible for development of the follow-up program in January 2012 and theretrospective review of the patients' records in May 2014. This paper only reports observational data of current clinical practice. Patients were not subjected to any additional hazards by the above-described follow-up of their treatment and therefore informed consent was not obtained by the authors.

Statistical analysis was performed using SPSS (version 21.0, Armonk, NY: IBM Corp). Median (IQR 25-75%) plasma concentration of dabigatran and median treatment length were calculated.

Results

Study Population

All patients treated concomitantly with dabigatran and dronedarone are reported to AuriculA registry for follow–up and thus none of potentially eligible patients were missed. None was lost to follow-up. Baseline characteristics of the study population (n = 33) are presented in Table 1. The mean age of the patients was 64 years and 48.5% were men.

The mean CHA$_2$DS$_2$-VASC score was 2.3 ± 1.3, range 0-6. One patient with CHA$_2$DS$_2$-VASC score 0 was treated with dabigatran prior to elective electrocardioversion.

Table 1
Baseline characteristics.

	Our study	RELY study Dabigatran 150 mg bid [1]
Treated patients, (n)	33	6076
Age, mean (SD), years	64.0 (8.7)	71.5 (8.8)
Males, n (%)	16 (48.5)	3840 (63.2)
eGFR, mean (SD), ml/min/1.73 m^2	66.0 (11.2)	N/A
<50	3 (9)	1126 (18.9)[*]
50-79	29 (88)	2898 (48.6)[*]
>80	1 (3)	1945 (32.5)[*]
Medical history:		
Heart failure, n (%)	2 (6.1)	1934 (31.8)
Hypertension, n (%)	23 (69.7)	4795 (78.9)
Vascular disease, n (%)	6 (18.2)	N/A
Diabetes, n (%)	3 (9.1)	1402 (23.1)
Prior stroke or TIA, n (%)	4 (12.1)	1233 (20.3)
Prior systemic or peripheral arterial embolism, n (%)	2 (6.1)	N/A
Renal disease, n (%)	0 (0)	N/A
Abnormal liver function, n (%)	0 (0)	N/A
Prior intracranial bleeding, n (%)	0 (0)	N/A
Prior other bleeding, n (%)	1 (3.0)	N/A
Labile INR, n (%)	3 (9.1)	N/A
Alcohol abuse, n (%)	3 (9.1)	N/A
CHA$_2$DS$_2$-VASC score		
0-1, n (%)	9 (27.3)	1958 (32.2)
2, n (%)	11 (33.3)	2137 (35.2)
3-6, n (%)	13 (39.4)	1981 (32.6)
HAS BLED score		N/A
0-2, n (%)	29 (87.9)	
3-4, n (%)	4 (12.1)	
Concomitant medications at baseline:		
Other Pgp-inhibitors/inducers, n (%)	1 (3.0)	N/A
Proton pump inhibitors, n (%)	4 (12.1)	847 (13.9)
Antiplatelet agents, n (%)	0 (0)	2352 (38.7)
Non-steroidal anti-inflammatory drugs, n (%)	0 (0)	N/A
Angiotensin converting enzyme inhibitor or angiotensin II antagonists, n (%)	19 (57.6)	4053 (66.7)
Beta-blocking agents, n (%)	28 (84.8)	3872 (63.7)
Statins, n (%)	12 (36.4)	2667 (43.9)
Corticosteroids, n (%)	2 (6.1)	N/A

[*] according to the RELY substudy [18].

The mean HAS BLED score was 1.6 ± 0.9, range 0-4. Three patients had prior bleeding history (ulcer bleeding, $n = 1$; haematochezia, $n = 1$; and haematuria due to INR 6, $n = 1$). One patient was treated with P-gp inhibitor felodipine at a dose 2,5 mg daily. No other P-gp inhibitors or inducers were used concomitantly.

Plasma Concentration of Dabigatran

Trough plasma concentrations of dabigatran were obtained at one week ($n = 29$) and at one month ($n = 29$) after the start of concomitant treatment. Each patient included in the study had at least one plasma concentration sample of dabigatran taken. Median concentration of dabigatran one week and one month after the concomitant treatment start was 102.0 (10th to 90th percentile 48-238, range 8-251) and 84 (10th to 90th percentile 38-255; range 27-302) ng/ml respectively (Fig. 1). The highest plasma concentration of dabigatran in this study was 302 ng/ml due to renal function impairment in a 74-year-old female patient. The treatment with dabigatran was discontinued.

Compliance

Medication compliance was not assessed in this analysis, but can be indirectly estimated out of plasma concentrations. In the RE-LY substudy 10th percentile trough concentration in 110 bid subgroup was 28.2 ng/ml [19]. In the observed cohort, two patients had plasma concentrations of dabigatran <20 ng/ml (8 and 14 ng/ml one week after the concomitant treatment start). The concentrations at one month for these two patients were 64 and 34 ng/ml respectively.

Treatment Length, Kidney Function and Treatment Discontinuation

The median treatment length assessed in May 2014 was 13 (range 1-27) months with a total of 35.5 patient-years. Concomitant treatment was discontinued in 16 (48.5%) cases outlined in Table 2.

Median time to treatment discontinuation was 4.5 (range 1-21) months. The most common reason ($n = 5$) was switching from dronedarone to another antiarrhythmic drug. In two cases the reason was impaired renal function with the risk of dabigatran accumulation, but neither of these two patients experienced any thrombotic or major bleeding events during concomitant treatment. A total of four patients had a drop in eGFR (Table 3) where all patients had initial measurements of plasma dabigatran concentration at one week and one month
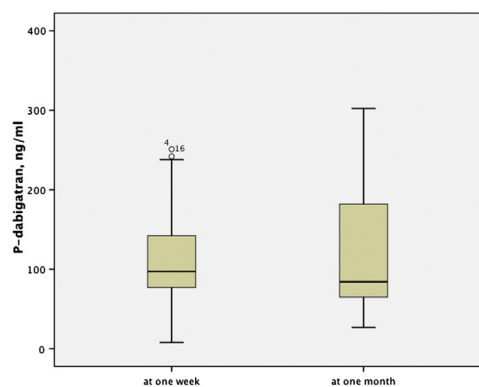

Fig. 1. Plasma dabigatran concentration one week and one month after the start of concomitant treatment.

Table 2
Treatment discontinuation.

Drug	Reason
Dabigatran, n = 6	Switching to warfarin prior to lung vein ablation, n = 2
	Low eGFR, n = 2
	CHA$_2$DS$_2$-VASC score 0 after cardioversion, n = 1
	Switching to apixaban due to smaller pill size, n = 1
Dronedarone, n = 10	Switching to another antiarrhythmic drug,
	n = 5 (flecainide, n = 3; sotalol, n = 1; amiodarone, n = 1)
	Permanent AF, n = 4
	Side effect (skin rash), n = 1

after the treatment start. However, the dabigatran concentrations were not measured at the time of the drop in eGFR apart for one patient whose renal function impairment occurred at one month after the treatment initiation.

Outcomes

No cases of ischemic stroke or systemic embolism occurred during the concomitant treatment of dronedarone and dabigatran in the 33 patients described above. There was one major bleeding event in the cohort (2.8% per patient-year). A 42 year old woman with CHA$_2$DS$_2$-VASC score 5 and HAS-BLED score 3 developed haematochezia with a fall in haemoglobin level from 10.0 to 8.0 g/dL eleven months after the start of concomitant treatment. She had previously had a similar bleeding event during warfarin treatment 2.5 years earlier. Also, the patient´s eGFR was 44 ml/min/1.73 m^2 at baseline and 45 ml/min/1.73 m^2 at the bleeding event with a transient drop to 19 ml/min/1.73 m^2 a month later due to sepsis. The concomitant treatment continued uneventfully during the next twelve months (time of the assessment in May 2014). The majority of the patients observed, had been assigned to intervention by their cardiologists before the concomitant treatment became contraindicated in September 2012. Decision of the cardiologist to assign patients between September 2012 and May 2013 might have been influenced by reports of the initial patients' outcomes (no major bleedings or unacceptably high plasma concentrations).

Discussion

Concomitant treatment with dabigatran and dronedarone can offer potential benefits to AF patients since dronedarone is well tolerated [20] and is associated with a very low risk of pro-arrhythmic events [5]. The current contraindication issued by the EMEA is based on a small study on 16 healthy volunteers at a dose 150 mg bid [6]. We have conducted our study in a real-life clinical setting with a twice as large patient population and using the lower dabigatran dose of 110 mg bid. The median trough plasma concentrations (102 (10th to 90th percentile 48-238) and 84 ng/ml (10th to 90th percentile 38-255) at one week and one month respectively) was observed to be similar to the median trough concentration of 93 (10th to 90th percentile 39.8-215) ng/ml of dabigatran at the 150 mg bid dose without concomitant dronedarone, in RE-LY substudy [21]. Baseline characteristics of patients in the RELY trial are outlined in Table 1. Renal function is a key determinant of plasma concentration of dabigatran. The trough concentration of dabigatran is 30% higher in women compared to men [19]. Our study includes proportionally more women and patients with renal function impairment (eGFR < 80) compared to the RELY substudy. The outcomes of dabigatran treatment at a dose 150 mg are well studied and the rates of major bleeding and thrombosis are low [1,17,22] despite that patients in the RELY study were older and had more cardiovascular comorbidities compared to the present population.

As expected, the median plasma concentration of dabigatran at the dose 110 mg bid in the RE-LY sub-study was 1.3 times lower [19] compared to our study, since only 30% of the RE-LY study population used

Table 3
Cases of eGFR decrease during concomitant treatment.

Gender and age	Time after treatment initiation, months	eGFR drop (ml/min/1.73 m²)	Likely cause	Action taken
Female, 74 years	1	31 to 23	unknown	dabigatran discontinued
Male, 70 years	6	39 to 22	urine retention	dabigatran discontinued
Female, 67 years	2	68 to 32	dehydration	eGFR 42 after rehydration, dabigatran continued
Female, 40 years	12	40 to 19	Sepsis	sepsis treatment, dabigatran continued

concomitant Pgp-inhibitors such as amiodarone, verapamil and quinidine [21]. The trough concentration at the 10th to 90th percentile from 38 to 255 ng/ml at one month in our observed patients indicates 6.7-fold range of variation comparable to the 5.2-5.5-fold variation seen in the RE-LY sub-study [21]. The authors of the RE-LY sub-study assessed the exposure response relationship and came to conclusion that there was no single optimal concentration range fitting all patients.

Although our study population is small, the rate of major bleeding in our study (2.8% per patient-year) is comparable to major bleeding rate of 2.71% for the 110 mg bid dose in RE-LY trial [1] and to the 2.4% major bleeding rate in dabigatran treated patients in our hospital [17]. We did not observe any thrombotic events, probably due to the small size of our study population and the short follow-up.

Two patients in our study with low dabigatran concentrations can be assumed to have compliance problems. Since there are concerns using NOACs in patients with a history of poor compliance (due to lack of regular monitoring), there might be a selection bias towards better compliance in our study compared to the general AF population, where an estimated 75% of INR values are in treatment range [9].

A recent study on Swedish patients treated with dronedarone has shown that patients were younger (median age 65.5) and healthier than other control patients with AF [20]. The mean age of our study population was 7.4-7.5 years lower compared to dabigatran arms of RE-LY trial [1] and 6.4 years lower compared to dabigatran treated patients in our own hospital [17]. This is probably due to selection of AF patients suitable for rhythm control strategy. This could be a challenge in patients older than 80 years, who are recommended a dose of dabigatran 110 mg bid, where no additional dose adjustment during concomitant treatment with dronedarone can be made. A more optimal dose in these patients could perhaps be dabigatran 75 mg bid.

This study has several limitations. We did not perform any other pharmacokinetic measurements such as measurements of cumulative exposure, peak concentration and time to peak concentration since we conducted our study in a real life setting. However, peak concentrations provided no advantages compared with trough concentrations according to RELY sub-study where 30% of patients used concomitant Pgp-inhibitors [19]. As with any study of pharmaceutical agents there is no guarantee that the measured dabigatran concentrations are not an effect of patient non-compliance. On the other hand, being a real-life study, reassuring medication intake with a twice daily regimen was not an option. It is a single centre study with a relatively small number of patients. The patients were already started on treatment and referred to anticoagulation clinic for follow-up. Although a real-life setting, this may introduce some selection bias. However, it offers some important insights on the concomitant treatment with dabigatran and dronedarone, which to our knowledge, never have been published before. We believe that our data do not support the current contraindication but also recognize that larger trials are warranted to assess safety and outcomes of the concomitant treatment.

In conclusion, median trough plasma concentration of dabigatran in our study using the 110 mg bid dose, was observed to be similar to median trough plasma concentration at the dose of 150 mg bid without concomitant dronedarone, seen in earlier studies. Since concomitant treatment offers potential benefits to patients with paroxysmal AF, larger future trials that might refute the current contraindication are warranted.

Potential Conflict of Interest

Acknowledgments

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Paper IV

ORIGINAL ARTICLE

Predictors of Successful Cardioversion with Vernakalant in Patients with Recent-Onset Atrial Fibrillation

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Background: Vernakalant is a novel atrial-selective antiarrhythmic drug able to convert recent-onset atrial fibrillation (AF) with reportedly low proarrhythmic risk. Successful cardioversion predictors are largely unknown. We sought to evaluate clinical and electrocardiographic predictors of cardioversion of recent-onset AF with vernakalant.

Methods: Consecutive patients with AF ≤48 hours admitted for cardioversion with vernakalant (n = 113, median age 62 years, 69 male) were included. Sinus rhythm (SR) within 90 minutes after infusion start was considered to be successful cardioversion. Predictive values of demographics, concomitant therapy, comorbidities, and electrocardiographic parameters were assessed. Atrial fibrillatory rate (AFR), exponential decay, and mean fibrillatory wave amplitude were measured from surface ECG using QRST cancellation and time-frequency analysis.

Results: Cardioversion was achieved in 66% of patients. Conversion rate was higher in women than in men (80% vs 58%, P = 0.02) while none of other clinical characteristics, including index AF episode duration, could predict SR restoration. Female gender was predictive of vernakalant's effect in logistic regression analysis (OR = 2.82 95%CI 1.18–6.76, P = 0.020). There was no difference in AFR (350 ± 60 vs 348 ± 62 fibrillations per minute [fpm], P = 0.893), mean fibrillatory wave amplitude (86 ± 33 vs 88 ± 67 μV, P = 0.852), or exponential decay (1.30 ± 0.42 vs 1.35 ± 0.42, P = 0.376) between responders and nonresponders.

Conclusions: Female gender is associated with a higher rate of SR restoration using intravenous (i.v.) vernakalant for recent-onset AF. ECG-derived indices of AF organization, which previous studies associated with effect of rhythm control interventions, did not predict vernakalant's effect.

Atrial fibrillation (AF) is the most common sustained arrhythmia, accounting for approximately one-third of all hospital admissions for cardiac rhythm disturbances.[1] Lifetime risk for developing AF is one in four, in both men and women older than 40 years of age, according to the Framingham Heart study.[2] The incidence is increasing due to rising prevalence of predisposing conditions in the aging population.[3]

Vernakalant is a novel atrial-selective antiarrhythmic drug (AAD) able to convert recent-onset AF with reportedly low proarrhythmic risk.[4–8] It

acts as sodium- and potassium-channel blocking agent, increasing atrial effective refractory period, reducing reentry and causing AF termination without prolonging ventricular refractoriness.[9,10] The reported conversion rate for new-onset AF with vernakalant is 52%, and median time to conversion is 11 minutes.[4] However, clinical predictors of successful cardioversion are largely unknown. Atrial activity analysis using various signal-processing techniques on surface electrocardiography (ECG) in order to guide AF treatment strategy has received considerable attention in recent years.[11-14] Atrial fibrillatory rate (AFR) measured in fibrillations per minute (fpm) accessed from surface electrocardiography (ECG) is considered a noninvasive index of atrial remodeling,[15-19] and thus may predict the atria's ability to restore and maintain sinus rhythm (SR).[20,21] A baseline fibrillatory rate <360 fpm has predicted successful cardioversion of AF with intravenous (i.v.) ibutilide[16] or oral flecainide.[22] In addition to AFR, alternative ECG-derived indices of atrial signal organization, such as exponential or harmonic decay in the frequency-power spectrum, have been described and an association between greater degree of organization and higher likelihood of SR maintenance following AF cardioversion has been shown.[23] High fibrillatory wave (F-wave) amplitude has also been shown to predict AF termination during catheter ablation of persistent AF,[24] SR maintenance following catheter ablation,[25] and electrical cardioversion.[26] However, no studies have been done on the clinical value of these electrocardiographical markers in acute settings of vernakalant use in patients with recent-onset AF.

We sought to evaluate clinical and electrocardiographic cardioversion predictors in patients with recent-onset AF (lasting for <48 hours) treated with i.v. vernakalant.

METHODS

Inclusion and Exclusion Criteria

We identified and reviewed medical records of all adult patients with recent-onset AF treated with i.v. vernakalant between December 2010 and December 2012 at Skåne University Hospital (a large tertiary care teaching hospital in Sweden).

The study complies with the Declaration of Helsinki, and was approved by the local ethics committee.

Included in the study were patients over 18 years of age, with recent-onset AF with symptom duration <48 hours, who were assessed for pharmacological AF conversion with weight-adjusted i.v. vernakalant by attending cardiologist, and received at least part of the recommended drug dose. Excluded from the study were patients with severe aortic stenosis, systolic blood pressure <100 mmHg, New York Heart Association (NYHA) class III or IV heart failure, QT prolongation at baseline (uncorrected QT interval >440 ms), severe bradycardia, sinus node dysfunction, second- or third-degree atrioventricular block without pacemaker, acute coronary syndrome in the past 30 days, or treatment with class I or III AADs within 4 hours prior to enrolment, as these patients were considered to have contraindications for vernakalant therapy. Patients received a 10-minute infusion of vernakalant (3 mg/kg), followed by a 15-minute observation period, and then a second 10-minute infusion (2 mg/kg) if AF was not terminated by the first infusion as documented in the patients' medical records.

The primary endpoint was the proportion of patients achieving conversion to SR within 90 minutes after the start of the first infusion.

Data Acquisition and Processing

Baseline characteristics, demographics, and electrocardiographic parameters were collected and analyzed for all patients in the study.

When available, left atrial end-diastolic diameter (LADD) and left ventricular ejection fraction (LVEF) from transthoracic echocardiography were assessed. LADD >50 mm and LVEF <50% were used as cutoff values for dichotomization.

AF duration was defined as time elapsed from symptom onset to infusion start.

A standard 12-lead ECG recorded at admission was retrieved from the hospital digital ECG database and processed offline. AFR, exponential decay, and F-wave amplitude were estimated using a 10-second recording of lead V_1 using AFRtracker software (CardioLund Research AB, Lund, Sweden). The method is described in detail elsewhere.[15,17,19,27] In short, ECG signals were preprocessed, including baseline filtering, beat detection, and cross-correlation–based beat classification. Subsequently, spatiotemporal QRST cancellation was used, in which an amplitude- and morphology-adjusted average beat is subtracted

from each beat in the signal. Individual beat averages were used for beats from different beat classes. The resulting residual ECG showing mainly atrial activity was analyzed using sequential atrial signal characterization, which performs time frequency analysis using overlapping windows in order to provide second-by-second AFR trends. Using this method, signal structure of each window is continuously analyzed through its harmonic frequency pattern in order to ensure that the corresponding signal contains an oscillatory atrial signal. Exponential decay was evaluated by estimating the relationship between main peak magnitude and harmonics magnitude. Exponential decay reflects the slope of the line connecting dominant frequency and its first harmonic. More organized rhythms with distinct waveforms have stronger harmonics, resulting in a shallower curve and lower exponential decay.

Statistical Analysis

Descriptive analysis was used to compare demographics and baseline characteristics between responders and nonresponders, including patients who did not receive full treatment due to adverse events (AEs). For patients who received several administrations of vernakalant, only the first treatment outcome was included in the statistical analysis.

Normally distributed data were expressed as mean + standard deviation; otherwise, median and range were used. Statistical significance was assessed using the Student's *t*-test on parametric data, and the Mann-Whitney test on nonparametric data.

Categorical variables are expressed as numbers and percentages, and analyzed using the chi-square test.

All statistical analysis was performed using SPSS (version 21.0, IBM Corp., Armonk, NY, USA).

RESULTS

Study Population and Data Availability

Baseline characteristics and demographics of our study population (n = 113, 69 male, median age 62 years) are outlined in Table 1. Twenty-two patients received vernakalant on several treatment occasions, but only the first treatment outcome was included in our statistical analysis.

Forty-three percent of the study population had lone AF. Seven patients were treated with concomitant class I and III AAD. However, none of the patients in our study received AAD within 4 hours of vernakalant treatment. LADD and LVEF measurements were available for 83 and 84 patients, respectively. Left atrial dilatation was present in 45.3% of converters versus 60% of nonconverters (P = 0.255). Reduced LVEF was observed in seven patients (5.7% converters vs 12.9% nonconverters, P = 0.415).

Median episode duration (time from symptom onset to infusion start) was 8.2 hours, with median time to ECG of 3.1 hours. Twenty-eight percent of patients presented with new-onset AF.

Discontinuation of Vernakalant due to AEs

Vernakalant was administered to 113 patients on 148 treatment occasions. A total of 15 AEs occurred in 14 (1.4%) study patients on 14 vernakalant administration occasions (Table 2). AEs caused discontinuation of the drug administration for seven patients (6.2%). The most common AE that lead to drug discontinuation was hypotension (n = 3) that responded promptly to saline infusion, while other AEs resolved spontaneously shortly after the infusion was discontinued.

Proarrhythmic events were observed in seven (6.2%) patients, with the most common being atrial flutter (n = 4). In three patients, conversion to SR occurred via 2:1 conducted typical counter-clockwise atrial flutter. One patient developed regular small-QRS tachycardia with a ventricular rate of 210 bpm shortly after infusion start, and his arrhythmia was judged as 1:1 conducted atrial flutter by consultant cardiologist. The vernakalant infusion was discontinued and the patient was treated with emergency DC-cardioversion.

Two patients had 5- respective 10-second long asystoles during vernakalant infusion. None of the patients using concomitant class I or III AADs experienced any AEs. There were no cases of ventricular arrhythmia or death following vernakalant administration.

Clinical Predictors of Vernakalant Effect

Cardioversion was successful in 75 patients (66%). Median time to conversion in responders was 10 minutes (range 4–90 minutes, IQR 8–15

Table 1. Demographics, Baseline Characteristics, and Electrocardiographic Parameters

	Study Population (n = 113)	Responders (n = 75)	Nonresponders (n = 38)	P Value
Female/male	44 /69	35/40	9/29	**0.024**
Age (median years) (range)	63 (23–87)	64 (23–87)	62.5 (37–85)	0.932
Height (cm)	176 ± 9	174 ± 10	180 ± 7	**0.014**
Weight (kg)	82 ± 13	81 ± 14	83 ± 12	0.344
BMI	26 ± 3	27 ± 4	26 ± 3	0.323
AF characteristics				
Time to ECG (hours) [IQR]	3.1 [1.4–9.9]	2.8 [1.4–9.5]	5.5 [2.0–12.8]	0.223
Median duration of current AF (hours) [IQR]	8.2 [4.7–16.3]	8 [4.4–16.2]	9.1 [5.7–16.7]	0.400
New-onset AF, n (%)	32 (28.3)	25 (33.3)	7 (18.4)	0.123
AF ablation earlier, n (%)	7 (6.2)	4 (5.3)	3 (7.9)	0.686
Lone AF, n (%)	49 (43.4)	35 (46.7)	14 (36.8)	0.422
Medical history				
Hyperlipidemia	30 (26.5)	17 (22.7)	13 (34.2)	0.259
Hypertension	57 (50.4)	37 (49.3)	20 (52.6)	0.843
Ischemic heart disease	18 (15.9)	9 (12.0)	9 (23.7)	0.172
Diabetes mellitus	8 (7.1)	5 (6.7)	3 (7.9)	1.000
Congestive heart failure	3 (2.7)	1 (1.3)	2 (5.3)	0.261
Concomitant medications				
Beta-blockers, n (%)	88 (77.9)	59 (78.7)	29 (76.3)	0.813
Calcium channel blockers, n (%)	12 (10.6)	7 (9.3)	5 (13.2)	0.534
RAAS-inhibitors, n (%)	35 (31.0)	21 (28.0)	14 (36.8)	0.391
Class I or III AAD, n (%)	7 (6.2)	4 (5.3)	3 (7.9)	0.686
ECG parameters				
AFR (fpm)	350 ± 60	350 ± 60	348 ± 62	0.893
Exponential decay	1.32 ± 0.42	1.30 ± 0.42	1.35 ± 0.42	0.376
F-wave amplitude (μV)	87 ± 47	86 ± 33	88 ± 67	0.852

Bold face values indicate statistical significance (p < 0.05), IQR = Interquartile range.

Table 2. Adverse Events

| Adverse Event	n (%)	Treatment Discontinuation due to AE (n)
Hypotension	3	3
Bradycardia	1	1
Atrial flutter with 1:1 conduction	1	1
Atrial flutter with 2:1 conduction	3	0
QRS-widening	1	1
Sinus arrest	2	0
Transient paresthesia	2	1
Dysgeusia	1	1
Sneezing	1	0

minutes). Conversion rate was higher in women than in men (80% vs 58%, P = 0.024) (Fig. 1), and in patients with shorter rather than taller stature (mean height 174 ± 10 cm in responders vs 180 ± 7 cm in nonresponders, P = 0.014). Body height was strongly linked to gender, being significantly less in women than in men (167 ± 8 vs 181 ± 6 cm, P < 0.00001). No other patient characteristics showed any relationship to treatment outcome.

Female gender was a significant predictor of cardioversion in logistic regression analysis (OR 2.82, 95% CI 1.18–6.76, P = 0.020).
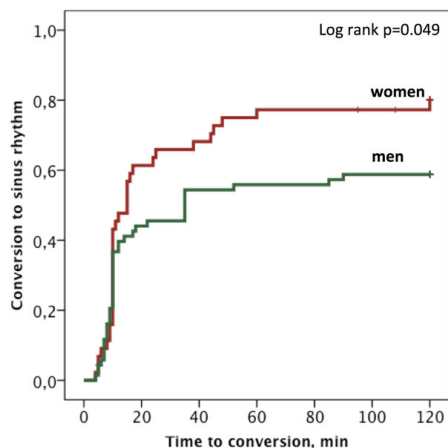
Figure 1. Gender and conversion to SR. Kaplan-Meier curve analysis of time from infusion start to conversion depending on gender.
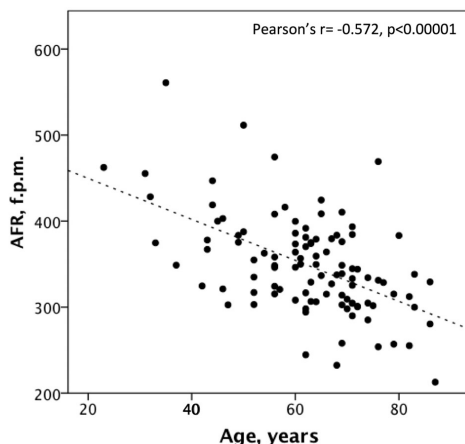
Figure 2. Correlation between AFR and patient age.

ECG-Derived Indices of AF Organization

AFR and exponential decay could not be accessed in five patients due to absence of, or poor quality of, ECG records.

Mean AFR value for the entire group was 350 ± 60 fpm. No statistically significant difference in AFR was found between responders and nonresponders (350 ± 60 vs 348 ± 62 fpm, P = 0.47). As expected, AFR was negatively correlated to patients' age (Fig. 2) and showed weak but significant correlation to AF episode duration (r = 0.221, P = 0.021).

Women had lower mean AFR, exponential decay, and F-wave amplitude compared to men (321 ± 42 vs 367 ± 63, P < 0.001; 1.25 ± 0.35 vs 1.36 ± 0.46, P = 0.184; and 85 ± 30 vs 88 ± 56, P = 0.768). However, there was a large overlap between genders.

None of these electrocardiographic parameters had any value in predicting treatment outcome (Tables 1 and 3).

DISCUSSION

We report an experience of real-life use of vernakalant for converting short-lasting (<48 hours) AF in a tertiary-care hospital. Population size in our observational study (n = 113) is comparable to the number of patients exposed to vernakalant in the ACT I-III and AVRO trials (n = 84–150).[4–8]

The observed conversion rate appears to be higher than previously reported—although those previous studies had included patients with prolonged AF duration,[10–13] which may be the cause of the observed difference in effect.

While ECG-derived atrial remodeling markers failed to predict responders to vernakalant, female gender was identified as an important clinical predictor of conversion.

Table 3. Logistic Regression Analysis of ECG-Derived Indices of AF Organization

	Odds Ratio	95% CI	P Value
AFR	1.00	0.994–1.009	0.652
F-wave amplitude	1.00	0.991–1.008	0.916
Exponential decay	0.72	0.266–1.931	0.510

Gender differences in the age of onset, co-morbidities, treatment patterns, and drug-induced events in patients with AF have been long acknowledged.[28–31] A recent study by our group reported that women are more prone to spontaneous AF termination.[21] Women in our study had lower mean AFR than men. On the other hand, AF incidence has been found to be consistently higher in males of all age categories, both in the Framingham study[2] and in a recent study in the city of Malmö (Sweden), where our study was also conducted.[32] It is unlikely that the difference in treatment outcome between genders can be explained by estrogen effect, since only three women in our study were under the age of 50. Nor can treatment response in women be attributed to extensive drug metabolism, since no gender differences in pharmacokinetics of vernakalant have been found.[33] One possible explanation may be the observed gender-related difference in body height. In previous studies, greater height has been associated with development of AF.[34,35] Taller stature may correspond to larger atrial size, thus providing more anatomical substrate for the development and maintenance of AF. However, only height and gender, but not LA dilatation, were associated with treatment effect in our study. Genetic studies have shown that some genetic variants associated with AF in genome-wide association studies such as PITX2[36] and ZFHX3[37] are also involved in growth pathways.

We have analyzed the electrophysiological parameters, which, in previous studies, were shown to predict therapy response in rhythm control interventions. Notably, the population mean for AFR is in striking agreement with other cohorts analyzed using this methodology.[20,21] Our study has confirmed previous findings, suggesting an inverse association between AFR and age,[38] which can be attributed to slower conduction and longer refractory periods in aging atria.[39] The positive correlation between AFR and AF episode duration is in agreement with previous reports,[11,38] and reflects atrial refractoriness shortening during persistent AF.[40] A recent study using implantable loop recorders has shown that AFR increases during the first 3 hours of spontaneous AF episode, and then becomes stable.[11] Mean time to ECG in our study was 3.1 hours, which allows AFR to reach plateau and be reliably used for analysis.

Lower AFR has been associated with spontaneous conversion,[21] favorable outcome of cardioversion,[16,20,22,41] and intraprocedural termination of AF during catheter ablation.[42,43] Contrary to our expectations and findings from earlier studies, we found no association between lower AFR and better response to vernakalant. The reasons for this are unclear at this time. The size of the population eligible for AFR assessment in our study is comparable with populations' sizes in previous reports, where this marker was studied in different clinical contexts. This suggests that the lack of association with the conversion to SR is probably not due to small population size. Vernakalant pharmacokinetics is influenced by cytochrome p450 2D6 (CYP2D6).[33] Drug effects may be drug-specific and related to individual sensitivity, including the CYP2D6 genotype ("poor vs extensive metabolizers"), and possibly genetically determined ion-channel protein function and its response to pharmacological blockade. Another explanation of the absence of association between lower AFR and positive treatment outcome is that vernakalant's sodium channel inhibitory effect becomes more pronounced at higher rates,[9] thus perhaps making the drug effect more pronounced in patients who are otherwise less likely to restore SR.

The AEs observed in this study were similar to AEs reported by ACT and AVRO trials.[6–8] The incidence of AEs in our retrospective study was generally much lower than in previous prospective trials. One reason may be that minor and transient AEs were not recorded in patient charts, which is a common occurrence in real-life nontrial settings. Percentage of AE leading to vernakalant treatment discontinuation in our study (5.4%) was slightly higher (although in the same range) than that reported in AVRO and ACT studies (3.5–4.5%).[4–8]

Previous reports show that serious AEs related to vernakalant are uncommon. In pooled safety data from vernakalant trials (773 vernakalant patients and 335 patients on placebo), there was one death of a patient with severe aortic stenosis, one case of torsades de pointes related to vernakalant, two cases of complete AV block, and two cases of sinus arrest.[44] In our study, we observed two cases of transient sinus arrest, and one case of 1:1 conducted atrial flutter that was not observed in ACT or AVRO trials, but has been previously reported elsewhere.[45,46] We have not observed any ventricular proarrhythmias associated with vernakalant use.

CONCLUSION

Our results indicate that gender could be a prognostic factor for response to vernakalant, with possible implications for AF conversion therapy choice. On the other hand, ECG-derived markers of atrial signal organization during AF (which, in earlier studies, were associated with effect of rhythm control interventions) failed to predict vernakalant effect.

Study Limitations

The retrospective nature of our study, as well as our reliance on electronic medical charts is a potential limitation of all retrospective analyses. Minor AEs that did not result in treatment discontinuation may not have been recorded, leading to underestimating the true AE rate. However, it is unlikely that severe AEs were not documented.

Despite the limitations inherent to the retrospective nature of our study, we believe that our study provides valuable information on real-life use of vernakalant in nontrial clinical settings.

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