NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	Post-Authorization Safety Study (PASS): Investigating the occurrence of major bleedings in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone.
Protocol number	B0661075
Version identifier of the final study report	1.0
Date of last version of the final study report	09 June 2017
EU Post Authorisation Study (PAS) register number	EUPAS15449
Active substance	B01AA03 - warfarin B01AF02 - apixaban C01BD07 - dronedarone
Medicinal product	Warfarin, Eliquis, Multaq
Product reference	EU/1/11/691/001-015
Procedure number	Not applicable
Marketing Authorisation Holder (MAH)	Bristol-Myers Squibb / Pfizer EEIG
Joint PASS	No
Research question and objectives	*Research question:* What is the occurrence of bleedings and mortality in real life, in patients with AF treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone?

	Primary objective: To compare the occurrence of major bleedings in patients with AF treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone. *Secondary objectives:* To compare the occurrence of intracranial hemorrhage in patients with AF treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone. To compare the occurrence of major gastrointestinal bleedings in patients with AF treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone. To compare the occurrence of all-cause mortality in patients with AF treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone. *Exploratory objective:* To compare the occurrence of bleeding-related mortality in patients with AF treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.
Country(-ies) of study	Sweden
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1. ABSTRACT (STAND-ALONE DOCUMENT)

Title: Post-Authorization Safety Study (PASS): Investigating the occurrence of major bleedings in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone.

Date of Abstract: 09 June 2017

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Keywords: Apixaban, dronedarone, warfarin, atrial fibrillation, major bleeding

Rationale and background: Swedish patients with paroxysmal AF are frequently treated with dronedarone as a way to prevent the occurrence of attacks of AF. Although the interaction with dronedarone has not been tested, from a theoretical point of view there is no contraindication to combine apixaban with dronedarone since dronedarone only inhibits CYP3A4, the main metabolic pathway for apixaban, moderately. The Summary of Product Characteristics (SPC) of apixaban does not give any recommendation against combinatory treatment with dronedarone. Nevertheless, there are some hospitals in Sweden that have decided to continue using warfarin in combination with dronedarone until there are some re-assuring data with apixaban in combination with dronedarone. Therefore, this real-world outcomes data study that aimed to investigate the occurrence of major bleeding among patients treated with dronedarone in combination with warfarin or apixaban, will contribute to an increased knowledge about the appropriate use of apixaban in combination with dronedarone in patients with paroxysmal AF.

Research question and objectives: The research question and primary objective of this study was to investigate the occurrence of bleedings and mortality in real life, in patients with AF treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone. Secondary objectives were to compare the occurrence of subtypes of bleedings (intracranial haemorrhage and major GI bleedings) and all-cause mortality in patients treated with dronedarone/apixaban and patients treated with dronedarone/warfarin.

Study design: The study was a retrospective cohort study using national register linkage data.

Setting: All individuals with a hospital diagnosis of AF were identified through the national Swedish Patient register. For all these patients, information was obtained on dronedarone, apixaban and warfarin prescriptions through the national all-inclusive Prescribed Drug register for the entire study period (from May 29, 2013 to December 31, 2015).

Subjects and study size, including dropouts: Among the 4,530 AF patients that filled a prescription for dronedarone between May 29, 2013 (the day apixaban became available in Sweden) and December 31, 2015, 1,431 had co-treatment with apixaban and 3,099 had co-treatment with warfarin. After exclusion of patients with valvular AF, 1,423 patients on apixaban+dronedarone and 3,010 patients on warfarin+dronedarone remained for the study.

Variables and data sources: Covariates were defined by ICD-10 diagnoses, medication or other conditions observed or documented before or on index date. Covariates included the established risk score for bleeding, the HAS-BLED, and the risk scores for stroke, the CHADS2 and CHA2DS2-VASc. These risk scores were constructed based on information present in the registries. In addition to the variables that is included in the risk scores other covariates known as potential risk factors or confounders were also included, such as other co-morbidities (e.g. dementia, COPD, cancer), co-medications (e.g. acid-suppressive drugs), time since first diagnosis of AF and prior use of oral anticoagulants.

This was a retrospective cohort study where data from different national registers (dispensed drug register, patient register and cause of death register) were linked through civic registration numbers given to all permanent residents in Sweden irrespective of citizenship.

Results: In 2013, more than 92% of dronedarone patients received warfarin rather than apixaban. Two years later, apixaban and warfarin were equally common and since 2016 more dronedarone patients get apixaban than warfarin.

After multivariable adjustment, and analyzed according to the intention-to-treat (ITT) principle, the hazard ratio (HR) for the main bleeding endpoint with apixaban compared to warfarin was 0.99 (95% confidence interval (CI) 0.58-1.78). There were no significant differences between apixaban and warfarin treated patients who suffered a major bleeding event in the analyses made in analogy with the ITT principle. The lack of statistical difference may largely be due to small numbers of patients (19 apixaban and 64 warfarin). Only three apixaban and eight warfarin patients suffered intracranial bleeding corresponding to annual rates of 0.25% and 0.19% in the apixaban and warfarin cohorts respectively (p=0.798). The annual rates for hospitalization for GI-bleeds were 0.42% with apixaban and 0.53% with warfarin (p=0.435). There was a non-significant trend towards lower bleeding risk with apixaban than with warfarin (HR 0.54, CI 0.19-1.50) analyzed on ITT, and on treatment (HR 0.73, CI 0.17-3.15). The absolute numbers of GI bleeds was however small and it is not possible to draw any conclusions in either direction. Eight apixaban treatment and 34 warfarin patients died during follow up representing an annual mortality rate of 0.68% and 0.79% (p=0.931). Of these, only four apixaban and seven warfarin patients were still on combination treatment when death occurred. No statistically significant differences could be seen

Discussion: The incidence of major bleeding events among patients with AF treated with dronedarone in combination with apixaban or in combination with warfarin was low in this study including all individuals in Sweden who had been exposed to these drug combinations between May 29, 2013 and December 31, 2015. No significant difference in favor of either

drug combination was found. Nor were there a consistent, non-significant trend, in favor of either combination. Thus, there is no indication that co-treatment with apixaban and dronedarone should cause more bleeds than co-treatment with warfarin and dronedarone.

The low bleeding rate in this study shows that patients using dronedarone in combination with oral anticoagulants represent a selected low risk population. A consequence of the low event rate in the study is that the study is under-powered for detection of differences in bleeding risk related to treatment regime. There has however been a rapid increase in the use of the apixaban-dronedarone combination in 2016, which has made this combination dominant among dronedarone users. Sufficient statistical power might be found if the study is repeated when data for 2016 and 2017 become available.

Marketing Authorisation Holder(s): Bristol-Myers Squibb / Pfizer EEIG

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AF	Atrial Fibrillation
CABG	Coronary artery bypass graft
CHADS2	**C**ongestive heart failure, **H**ypertension, **A**ge ≥75 years, **D**iabetes mellitus, **S2**: Prior Stroke or TIA or Thromboembolism
CHADS2-VASc	CHADS2- **V**ascular disease, **A**ge 65–74 years, **S**ex category
COPD	Chronic Obstructive Pulmonary Disease
CYP	Cytochrome P
GI	GastroIntestinal
HAS-BLED	**H**ypertension, **A**bnormal renal and liver function, **S**troke, **B**leeding, **L**abile INR, **E**lderly, **D**rugs or alcohol
HR	Hazard Ratio
ICD	International Statistical Classification of Diseases and Related Health Problems
IHD	Ischaemic Heart Disease
ISTH	International Society on Thrombosis and Haemostasis
ITT	Intention To Treat
LMWH	Low Molecular Weight Heparin
NOAC	Non-vitamin k Oral AntiCoagulant
NSAID	Non-Steroidal Anti-Inflammatory Drugs
PASS	Post-Authorization Safety Study
PCI	Percutaneous Coronary Intervention
P-gp	P-glycoprotein
PPI	Proton Pump Inhibitor
SAP	Statistical Analysis Plan
SPC	Summary of Product Characteristics
SSRI	Selective serotonin reuptake inhibitor
TIA	Transient Ischemic Attack
TTR	Time in Therapeutic Range

3. INVESTIGATORS

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5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of Independent Ethics Committee (IEC) approval of protocol	30 April 2016	4 May 2016	n/a
Start of data collection	01 September 2016	30 March 2017	Late due to long waiting time at National Board of Health and Welfare
End of data collection	31 October 2016	4 May 2017	Late due to long waiting time at National Board of Health and Welfare
Registration in the EU PAS register	01 August 2016	31 March 2016	n/a
Draft study report	30 November 2016	4 May 2017	Late due to long waiting time at National Board of Health and Welfare
Final study report	28 February 2017	09 June 2017	

6. RATIONALE AND BACKGROUND

Swedish patients with paroxysmal AF are frequently treated with dronedarone as a way to prevent the occurrence of attacks of AF. Dronedarone is a strong P-glycoprotein (P-gp) inhibitor with a potential to increase the bioavailability of drugs dependent on P-gp for their elimination. Apixaban is a substrate of P-gp, however, apixaban is eliminated from the body by multiple pathways including 25% by renal excretion. The main metabolic pathway for apixaban is through CYP3A4/5, with minor contributions from other CYP isoenzymes. Although the interaction with dronedarone has not been tested, from a theoretical point of view there is no contraindication to combine apixaban with dronedarone since dronedarone only inhibits CYP3A4 moderately. The SPC of apixaban does not give any recommendation against combinatory treatment with dronedarone. Nevertheless, there are hospitals in Sweden using the combination of apixaban and dronedarone in patients while others have decided to continue using warfarin in combination with dronedarone until there are some re-assuring data with apixaban in combination with dronedarone. We aim to investigate the occurrence of major bleeding among patients treated with dronedarone in combination with warfarin or apixaban in a real-life setting.

This is a real-world outcomes data study that will contribute to an increased knowledge about the appropriate use of apixaban in combination with dronedarone in patients with paroxysmal AF. This non-interventional study was designated as a PASS and was conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

Research question:

What is the occurrence of bleedings and mortality in real life, in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone compared against patients on warfarin and dronedarone?

Primary objective:

- To compare the occurrence of major bleedings in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Secondary objectives:

- To compare the occurrence of intracranial hemorrhage in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

- To compare the occurrence of major gastrointestinal bleedings in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

- To compare the occurrence of all-cause mortality in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

Exploratory objective:

- To compare the occurrence of bleeding-related mortality in patients with atrial fibrillation (AF) treated with the combination of apixaban and dronedarone versus the combination of warfarin and dronedarone.

8. AMENDMENTS AND UPDATES

The original study protocol had rules for identification of index dates based on 90 days intervals which in practice excluded the majority of the patients who were on combination treatment with dronedarone and apixaban. Therefore, a change to the protocol was necessary (see Table 1 below).

The rule that caused the problem was found in the point 4 of the steps for identification of the study cohorts (In Study Protocol; Section 8.2 Setting, page 15-16. In statistical analysis plan (SAP); Section 2.1 Study Design, page 5):

"Among patients with a filled prescription of dronedarone, all individuals with a filled prescription of apixaban or warfarin made:

A) within 90 days before the preliminary index date will be identified. The preliminary index date will be renamed index date since that date identifies the date when combination treatment started.

B) within 90 days after the preliminary index date will be identified. The preliminary index date will be replaced by the date of purchase of apixaban or warfarin because this will be the date when combination therapy started."

Instead, each patient's period on dronedarone treatment was identified with a start date and an end date. The end date was estimated from the dispensed quantity of dronedarone tablets and the assumption that 80% of the tablets where taken as prescribed.

For patients who received apixaban or warfarin *after* the preliminary index date (the start date of dronedarone), the preliminary index date was substituted by the start date of the anticoagulant because this was when co-treatment with both dronedarone and either one of the anticoagulants began.

For patients already on anticoagulant treatment when dronedarone was initiated, the preliminary index date was renamed index date because this was when co-treatment began). Ongoing anticoagulant treatment was defined by a filled prescription of apixaban or warfarin within 3 months before the dronedarone starting date.

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	04 May 2017	Substantial	8. RESEARCH METHODS, section 8.2. Setting (page 15-16 of 35)	In the first version of the protocol combination treatment of dronedarone and apixaban/warfarin was defined by first defining patients on dronedarone and then identifying patients that had a filled prescription of either apixaban or warfarin +/- 90 days before the preliminary dronedarone index date. In the second version of the protocol, the 90 days identification rule was omitted since it excluded too many patients on combination therapy.	The original study protocol had rules for identification of index dates based on 90 days intervals which in practice excluded the majortity of the patients who were on combination treatment with dronedarone and apixaban. Therefore, a change to the protocol was necessary.

9. RESEARCH METHODS

The research methods are described in the final protocol in appendix 2. The methodology for the statistical analyses is detailed in the SAP in appendix 4.

9.1. Study design

The study was a retrospective cohort study using national register linkage data. The occurrence of bleeding events between patients with AF treated with the combination of apixaban and dronedarone was compared against patients on the combination of warfarin and dronedarone. All individuals with a hospital diagnosis of AF were identified through the national Swedish Patient register. For all these patients, information was obtained on dronedarone, apixaban and warfarin prescriptions through the national all-inclusive Prescribed Drug register.

Data from the following registers were extracted and linked (for a schematic picture of how data from the different registries were used in the study, see Figure 1):

- Dispensed Drug register (1): Dispensing date and dosing for prescribed drugs. Data was extracted for the time-period from the start of the register July 1, 2005 up to February 28 2017. The information about drug use during 2016 and 2017 could however only be used for descriptive purposes, since the necessary corresponding information from the Patient register needed for the outcome analysis was not yet available.
- Patient register (2): Information on patient demographics, comorbidity and previous and incident events (e.g. major bleedings). Data was extracted from 1997 until the end of 2015. The reason for choosing 1997 as the starting point is that the current version of the International Classification of Diseases (ICD-10) was introduced in Sweden in that year. Diagnoses given earlier than 1997, which has not generated new contacts since then, is not likely to be clinically relevant. Besides starting 1997 makes translation of diagnostic codes between ICD-9 and ICD-10 unnecessary. The reason for terminating harvesting of data at the end of 2015 is due to the current practice at the National Board of Health and Welfare to only make data from the Patient register available on a full calendar year basis. It has been decided that data in the future should be made available continuously but this has not been implemented in time to be of benefit for this study. Use was made of the most recent complete data at the time of data harvest.
- Cause of death register (3): Information on date and cause of death up to the end of 2015.

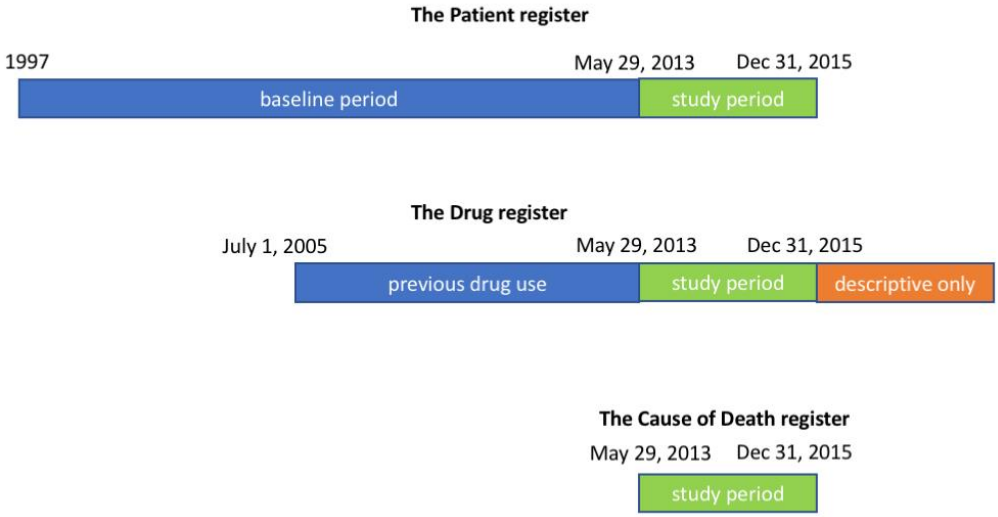

Figure 1. Schematic overview of registry data used in the study.

9.1.1. Time at risk and censoring

Time at risk has been counted from index date. The observation period ended on December 31, 2015.In the analyses made in analogy with the ITT principle, censoring was made at the specified endpoint, death or end of the observation period. In the analyses made in analogy with the on treatment principle, censoring was also made when treatment with dronedarone, apixaban or warfarin had ceased based on exposure estimates or a filled prescription of another oral anticoagulant indicating a therapy switch.

9.2. Setting

1.1.1. Subject Identification

The study population was identified through the following steps:

1) Identification of all individuals with a diagnosis of AF in the Patient Register between July 01, 2005 and December 31, 2015. (See flow chart, Figure 2)
2) Among these, all individuals with at least one filled prescription of dronedarone between May 29, 2013, and December 31, 2015 were identified from the Drug register. All other patients were excluded.
3) The date for the first filled dronedarone prescription was used as preliminary index date.
4) The duration of dronedarone treatment was assessed from the dispensed number of dronedarone tablets and under the assumption that patient's adherence to the dosage instruction was 80%. The date when the drug supply would have been exhausted marked the end date of dronedarone treatment.
5) Patients who filled prescriptions of apixaban or warfarin were identified.
    a. For patients who received apixaban or warfarin *after* the preliminary index date (the start date of dronedarone), the preliminary index date was substituted

by the start date of the anticoagulant because this was when co-treatment with both dronedarone and either one of the anticoagulants began.

b. For patients already on anticoagulant treatment when dronedarone was initiated, the preliminary index date was renamed index date because this was when co-treatment began). Ongoing anticoagulant treatment was defined by a filled prescription of apixaban or warfarin within 3 months before the dronedarone starting date.

6) Patients were allocated to either one of two study cohorts; the dronedarone+apixaban cohort and the dronedarone+warfarin cohort. The first filled prescription decided cohort if both apixaban and warfarin had been dispensed at various times. In case both drugs had been dispensed on the same day, that patient was to be excluded (however there were no such patients).
7) Patients with valvular AF defined as patients with mechanical heart valves (Z952) implanted before index, and patients with a diagnosis of mitral stenosis before index (I342, I050, I052, Q232) were excluded

1.1.2. Inclusion criteria

Patients had to meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Patients that have ≥1 AF diagnosis registered in the Patient register
- Patients ≥18 years
- Patients who had a filled prescription for apixaban or warfarin during the identification period

1.1.3. Exclusion criteria

- Patients with valvular AF (defined as mechanical heart valve or mitral stenosis)

9.3. Subjects

All individuals with a hospital diagnosis of AF were identified through the national Swedish Patient register. For all these patients, information was obtained on dronedarone, apixaban and warfarin prescriptions through the national all-inclusive Prescribed Drug register for the entire study period (from May 29, 2013 to December 31, 2015), Figure 1.

9.4. Variables

A list of covariates with definitions according to the ICD-10 coding system is included in Table 2 and Table 3 below. Covariates are defined by diagnoses, medication or other conditions observed or documented before or on index date.

Covariates include the established risk score for bleeding, the modified HAS-BLED, and the risk scores for stroke, the CHADS2 and CHA2DS2VASc (see Table 4). These risk scores

were constructed based on information present in the registries. In addition to the variables that is included in the above-mentioned risk scores other covariates known as potential risk factors or confounders were also included, such as other co-morbidities (e.g. dementia, chronic obstructive pulmonary disease (COPD), cancer), co-medications (e.g. acid-suppressive drugs), time since first diagnosis of atrial fibrillation and prior use of oral anticoagulants. Endpoint events are events that occurred after index date.

Table 2. Definitions of previous events

Covariate	ICD-10 or procedure code beginning with
Intracerebral bleeding	Hospitalization with I61 as principal or first secondary diagnosis
Intracranial bleeding	Hospitalization with I60-62, S064- 066, I690-962 as principal or first secondary diagnosis
Gastrointestinal bleeding	I850, I983, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922, K926
Urogenital bleeding	N02, N421, N836, N837, N857, N939, N95, R319,
Other bleeding	H113, H313, H356, H431, H450, I312, J942, R04, R58, D629, D683, D698, D699 procedure
Transfusion	procedure codes DR029 and DR033
Any bleeding	Any of intracranial, gastrointestinal, urogenital or other bleeding
Ischaemic stroke	Hospitalization with I63 as principal or first secondary diagnosis
Unspecified stroke	Hospitalization with I64 as principal or first secondary diagnosis
TIA	G45
Systemic embolism	Hospitalization with I74 as principal or first secondary diagnosis
Thromboembolism incl TIA	Hospitalization with I63, I64 or I74 as principal or first secondary diagnosis, and any G45 diagnosis
Thromboemboli no TIA	Hospitalization with I63, I64 or I74 as principal or first secondary diagnosis
Any stroke (HASBLED)	Hospitalization with I61, I63 or I64 as principal or first secondary diagnosis
Myocardial infarction	Hospitalization with I21 or I22 as principal or first secondary diagnosis
PCI	procedure code FNG
CABG	procedure codes FNA, FNB, FNC, FND, FNE, FNF, FNH, FNJ, FNK, FNW
Pulmonary embolism	I26
Deep venous thrombosis	I801-802

Table 3. Definitions of comorbidity

Covariate	ICD-10 or procedure code beginning with
Heart failure	I50,I110,I130,I132,I255,K761,I42-43
Hypertension	I10-15
Diabetes	E10-14 or use of antidiabetic drug (ATC codes beginning with A10)
Ischaemic heart disease without infarction	I20, I240, I248, I249, I25 except I252
Peripheral arterial disease	I70-73
Vascular disease	I21, I22, I252, I70-73 (as in CHA2DS2-VASc)
Mitral stenosis	I342, I050, I052, Q232
Mechanical heart valve	Z952
Other valvular disease	I34-39, I05-08, Q22-23 except valvular AF
Pacemaker or ICD	Z950, Z450, procedure code FPE
Renal failure	N18-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Liver disease	K70-77, procedure codes JJB, JJC
Hypothyroidism	E00-03 , E890
Thyrotoxicosis	E05 within preceding year
COPD	J43-44
Asthma	J45-46
Anaemia	D50-64
Coagulation or platelet defect	D65-69
Cancer	Chapter C except C44 (basalioma) within preceding 3 years
Alcohol abuse ('alcohol index')	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Dementia	F00-03, F051, G300-301, G308-309
Frequent faller	≥2 hospitalizations with diagnosis W00-19 or R296

Table 4. Definition of risk scores

Risk scores composed of diagnoses defined above	
CHADS2,	1 point each for: heart failure, hypertension, age ≥75 years, diabetes. 2 points for thromboembolism
CHA2DS2-VASc	1 point each for : heart failure, hypertension, age 65-74 years, diabetes, vascular disease, female sex 2 points each for 75 years, thromboembolism
HAS-BLED (modified)	1 point each for hypertension, renal failure, liver disease, thromboembolism, any bleeding, age ≥65 years, prescription of antiplatelet agent or Non-Steroidal Anti-Inflammatory Drugs (NSAID), alcohol abuse

1.1.4. Bleeding events

Identification of bleeding events in a retrospective registry study cannot be done in the same way as in a supervised prospective randomized trial where the severity of bleeding events can be assessed individually with access to medical records, lab tests and patient reporting.

Administrative registers have low sensitivity for detection of minor bleeding events not leading to hospitalization, but reported by patients in response to questionnaires in studies. Therefore, only major bleeds were assessed in the present study.

According to the International Society on Thrombosis and Haemostasis (ISTH) a major bleed is a bleed which is fatal, occurs in a critical area or organ, leading to hospitalization and/or prolonged hospital stay and a fall of Hemoglobin count of 20 g/L or transfusion of ≥units of blood (4).

Swedish registry data can identify fatal bleeds from either a diagnosis in the Cause of Death register (underlying cause of death or fist contributory cause of death), or a hospital discharge code of "4" indicating death during hospital stay in conjunction with a bleeding diagnosis as principal or first secondary diagnosis.

The definition of what exactly constitutes a bleeding in a critical organ, apart from intracranial bleeds, is associated with problems of differentiating between trivial and serious bleeds from codes alone.

The placing of a code for bleeding may be seen as an indicator of the severity of the bleed. A bleeding diagnosis placed after 7 or 8 other diagnoses are less likely to be serious than one placed as first diagnosis. In order to detect major bleeds, it therefore seems reasonable to use only diagnoses given as principal or first secondary diagnosis and associated with hospitalization (defined as at least one night in hospital).

Information about drop of hemoglobin count is not available from the Swedish registers, but codes for blood transfusion are. The codes do not tell how many units of blood that were given, but according to Swedish clinical practice transfusion of single units of blood are never given to adult patients.

The main bleeding endpoint is “major bleeding” defined as:

- Any intracranial bleeding, or
- Hospitalization with a bleeding diagnosis
- Fatal bleed defined by a diagnosis in the Cause of Death register (underlying cause of death or fist contributory cause of death), or a hospital discharge code of "4" indicating death during hospital stay in conjunction with a bleeding diagnosis as principal or first secondary diagnosis.

Secondary bleeding endpoints are:

- Any hospitalization with a diagnosis of:
    - Intracranial bleed
    - Gastrointestinal bleed
    - Urogenital bleed
    - Other bleed
- Contacts without overnight stay and a bleeding diagnosis in principal or first secondary diagnosis position.

The above criteria for detection of bleeds have been set up according to the findings in a validation study in which the local medical records of 761 patients with bleedings according to the Patient Register were subjected to manual scrutiny (5).

The bleeding endpoint included the types of bleeding summarized in Table 5 below.

Table 5. Definition of bleeding endpoints

	Code	Meaning
Intracranial bleeds	I60	Subarachnoid haemorrhage
	I61	Intracerebral haemorrhage
	I62	Other non-traumatic intracranial haemorrhage
	S064	Epidural haemorrhage (traumatic)
	S065	Traumatic subdural haemorrhage
	S066	Traumatic subarachnoid haemorrhage
Gastrointestinal bleeds	I850	Esophageal varices with bleeding
	I983	Esophageal varices with bleeding in diseases specified elsewhere
	K228	Haemorrhage of the oesophagus
	K25 K26 K27 K28	with fourth position being 0, 2, 4 or 6 gastric, duodenal, unspecified peptic and gastrojejunal ulcers with bleeding
	K290	Acute haemorrhagic gastritis
	K625	Haemorrhage from anus and rectum
	K661	Haemoperitoneum
	K920	Haematemesis
	K921	Melena
	K922	Unspecified gastrointestinal bleeding
Urogenital bleeds	N02	Recurrent and persistent haematuria
	N421	Congestion and haemorrhage of prostate
	N836	Haematosalpinx
	N837	Haematoma of the broad ligament
	N857	Haematometra
	N939	Abnormal uterine and vaginal bleeding, unspecified
	R319	Unspecified haematuria
Other bleeds	H113	Conjunctival haemorrhage
	H313	Choroidal haemorrhage and rupture
	H356	Retinal haemorrhage
	H431	Vitreous haemorrhage
	H450	Vitreous haemorrhage in diseases classified elsewhere
	I312	Haemopericardium
	J942	Haemothorax
	M250	Haemathrosis
	R04	Haemorrhage from respiratory passages (including nose bleeds and haemoptysis)
	R58	Bleeding, not elsewhere classified
	D629	Acute posthaemorrhagic anaemia
	D683	Haemorrhagic disorder due to circulating anticoagulants
	D698	Other specified haemorrhagic conditions
	D699	Haemorrhagic condition, unspecified
Blood transfusion (Swedish procedure codes)	DR029	Transfusion of allogeneic erythrocytes
	DR033	Transfusion with full blood, allogeneic

9.5. Data sources and measurement

This was a retrospective cohort study using data from national registers where data from the different registers were linked through civic registration numbers given to all permanent residents in Sweden irrespective of citizenship. Similar data, but for earlier time periods, have been used in several studies before (6-10). Data was extracted from national registers and linked through the use of civic registration numbers. The linkage was done by the National Board of Health and Welfare which replaced the civic registration numbers by anonymized numbers before data was made available for the study.

Data from the following registers was extracted and linked (for a schematic summary, see Figure 1):

The dispensed drug register:	The drug register holds detailed information about all filled prescriptions made in all pharmacies all over the country. Reporting is required by law, and information is transferred automatically to the National Board of Health and Welfare whenever a prescription drug is handed over to a patient. The register does not hold information about drugs used during short time hospital stay, or over the counter drugs. For the purpose of this study, information about dispensations between July 1, 2005 and February 28, 2017 was used. For the outcome analyses, however, only information up to the end of 2015 could be used due to a lag behind in the reporting to the Patient register which is necessary for these analyses.
Patient register:	The patient register holds information about all hospital care and about all specialized open care with codes for diagnoses and surgical procedures in the country. It does not hold information from primary care. The patient register was used for identification of previous and concomitant disease and for detection of bleeding events during the study period. Data from 1997 until 31 December 2015 were used.
Cause of death register:	This register holds information about date and underlying and contributory causes of death. Data up to 31 December 2015 was used.

9.6. Bias

In the analyses made in analogy with ITT, patients may have switched from apixaban to warfarin or to another NOAC, or from warfarin to apixaban or another NOAC.

Switches may have been precipitated by a minor bleeding which did not qualify as an endpoint event, in which case this would indicate a patient with a higher future bleeding risk. If the bleeding had qualified as an endpoint event, that patient would have been censored and the bleeding correctly attributed to the first used drug.

The possible effect of this bias could potentially lead to falsely low event rates for the original cohort. However, patients were censored when there were switches in the on treatment-analyses without this giving rise to major alterations. This potential bias is probably of no importance.

9.6.1. Endpoint validity

The study could not use the ISTH definitions of major bleeding events commonly used in clinical trials. The ISTH definition requires information about drop in haemoglobin count, and information whether the number of units of blood that was transfused exceeded two. This information is not available in the registers used. Clinical trials generally use some kind of adjudication of the events to make sure that they are valid. This was not possible in this study which was based on anonymized data.

However, a previous validation study of bleeding events recorded in the Swedish Patient register showed that bleeding diagnoses carried high validity and specificity they were associated with overnight hospital stay (5).

The endpoints "open care bleeds" and "any bleeding with or without hospitalization" are less reliable than bleeds associated with hospitalization. They count a larger number of events and may be of interest for that reason, but it should be recognized that some of them may not represent bleeding event, but rather planned visits for investigation of the causes for anaemia or follow up after previous real or suspected bleeding events.

Information about transfusions is indeed available in the register, but the number of units given is not recorded, and more importantly, given transfusions are not recorded by code at discharge in almost 50% of the cases.

9.6.2. Confounding by indication

Non-randomized cohort studies comparing different treatments are vulnerable to confounding by indication. Doctors may prefer a certain treatment for a certain kind of patient. If something about a patient affects treatment choice and this something is not recorded by diagnosis or as a prescription, it will not be possible to adjust for in the analyses. This will of course distort the results.

Multivariable adjustments can only adjust for observable cofactors. A common approach to this problem, which was used in this study, is to create cohorts that are similar on as many observable cofactors as possible using propensity score matching.

9.7. Study Size

Approximately 9,500 patients with atrial fibrillation filled a prescription of apixaban up to the end of 2014. Considering the accelerating uptake of apixaban in the AF population, another year of data from the registries, is likely to generate a total of 20,000 patients on apixaban available for the study.

A small number of patients could have had apixaban prescribed in primary care without ever having received a hospital diagnosis of atrial fibrillation. Depending on the criteria for selection of the study population (i.e. a diagnosis of atrial fibrillation) these individuals will not be included in the study

From another data set we knew that 310 patients were treated with the combination of dronedarone and apixaban at baseline during 2013 and 2014. The number of patients with the combination dronedarone and warfarin was higher. More patients could have been exposed to the combinations during follow up, although this information was unavailable at the start of

the present study. The proposed study included another full year. The cumulative number of patients with the apixaban-dronedarone combination was estimated to be approximately 1000 patients considering the accelerated uptake of apixaban and a growing acceptance among clinicians for combining dronedarone and apixaban. The number of patients exposed to the combination of warfarin-dronedarone during the same period was estimated to be over 2000.

We hypothesized that the annual rate of major bleeds in the warfarin-dronedarone cohort is 3% and that the apixaban-dronedarone increase bleeds by 33%. Then the needed number of patients needed to test this hypothesis would be approximately 5,512 on each drug combination with a two sided 95% significance level and 80% power. The study was therefore not assumed to have sufficient statistical power to confirm or reject the hypothesis, but it was still deemed to be informative since no systematic studies regarding the outcomes of patients with the apixaban-dronedarone combination have previously been done.

9.8. Data transformation

Detailed methodology for data transformations, particularly complex transformations (e.g., many raw variables used to derive an analytic variable), are documented in the SAP, which is dated, filed and maintained by the sponsor (appendix 4).

Data management and statistical analyses were made with Stata software (Stata MP 14.2, StataCorp, 4905 Lakeway Dr, College Station, TX 77845, USA).The data preparation of the two datasets was done by the National Board of Health and Welfare (Socialstyrelsen) as they are authorized to do so. All data was completely patient de-identified for this study.

Data management and analyses was done exclusively through syntax files which will be saved and will provide a safeguard for traceability of all results, and will also facilitate minor changes of criteria if needed. The investigator Leif Friberg will store data provided by the National Board of Health and Welfare for a period of 10 years after termination of the study, along with syntax files developed for data management and analysis.

9.9. Statistical methods

The methodology for the statistical analyses is detailed in the SAP in appendix 4.

9.9.1. Main summary measures

Means with standard deviations and median values are reported for continuous data. For dichotomous data, crude numbers and proportions are used. Incidence rates are reported as events per 100 years at risk. For multivariable analyses, hazard ratios with 95% confidence intervals are used.

9.9.2. Main statistical methods

Differences in baseline characteristics were tested for with Student´s t-test, Wilcoxon-Mann-Whitney´s rank sum test or Pearson´s Chi2-tests as appropriate.

Event rates were calculated as number of events per 100 years of observation, but expressed as per cents in the text for comprehensibility. Different risk time variables were used for each endpoint.

In order to minimize confounding by indication, due to differences in characteristics of patients who received either treatment propensity score matching was used. First, individual propensity scores were calculated by means of logistic regression for the likelihood of receiving apixaban+dronedarone rather than warfarin+dronedaraone. All variables in Table 6, Table 7 and Table 8 were used as covariates for the regression. Then, pairwise matching of patients with similar propensity scores but different treatments was applied. Matching was made in a 1:1 fashion without replacement with a caliper of 0.01. The propensity matched cohorts thus formed were then tested for any remaining differences (also shown in Table 6, Table 7 and Table 8).

In the multivariable analyses adjustment were done for factors considered relevant as presented in footnotes to the respective tables. In the ITT analyses this included medication in the year before index, while the on treatment analyses included adjustment for antiplatelet drugs and some drugs known to have significant interactions with the study drugs which had been dispensed on index date or within three months after index date. Prescription and dispensing of such drugs may well have been affected of any bleeding events during follow up and interpretation of these on treatment analyses must therefore be made with caution.

Data management and statistical analyses were made with Stata software (Stata MP 14.2, StataCorp, 4905 Lakeway Dr, College Station, TX 77845, USA).

9.9.3. Missing values

According to the nature of administrative registers there could be no missing values. Either there is a diagnosis, a contact, a filled drug prescription, a date of death etcetera, or there is not. For instance, absence of a code for diabetes means that the patient does not have diabetes, not that data is missing.

Registries may be incomplete in the sense that patients with a certain disease have not been given a proper ICD code for that disease. This is however a matter of registry validity, not of missing data.

In rare instances, the data files obtained from the national registries may contain obvious faults. What kind of false information there could be cannot be pre-specified. It may be that some patients are listed with negative age, missing gender, as having had a hospital contact in 1927 or 23044, etc. The files were cleaned from such false information before any analyses were performed. The extent of file cleaning was documented and is summarized shortly below:

- The Drug register was very extensive and had to be divided in separate files in order to be accessible for analysis. Among more than 29 million filled prescriptions for cardiovascular drugs (ATC chapter C) and almost 8 million filled prescriptions for anticoagulant and antithrombotic drugs (ATC codes starting with B01A) all entries had valid identifiers, dates and ATC codes.

- In the Patient register eight contacts out of more than 19 million (19,276,624) lacked identifiers and had to be excluded. Another 4,612 contacts lacked contact dates. Improbable contact dates in the early 1900's or in the future were found for 111 contacts. In all, 0.02 percent of the contacts had to be excluded because of this (data on file).

- In the Cause of Death register 271 out of 78,527 entries (0.3%) lacked a valid date of death and two patients had been entered twice, but with the same death date and the same diagnoses (data on file).

9.9.4. Sensitivity analyses

The main analyses were made in analogy with the *ITT* principle with censoring only at specified events, death or end of observation period. The reason for this is that this method is more robust than on treatment analyses if the only source of information about drug exposure is dispensing data from the pharmacies. Especially for warfarin, which has widely differing dosages, the dispensed quantity is not a reliable source of information regarding discontinuation of treatment.

Nevertheless, two different approaches to *on treatment* analyses are presented as sensitivity analyses.

The first one, here called *the refill method*, assumes that all days between refills of a drug are days on treatment as long as the interval does not exceed 6 months. (This long period was chosen because the only available packet size of warfarin may last up to 6 months in occasional patients). If there was no refill within 6 months, or if there were no more refills, treatment was assumed to have stopped after three months. All days thus considered as treatment days are the added up and used to estimate the date when treatment ended. This method may result in a less exact assessment of the true exposure to apixaban, but has the advantage that both apixaban and warfarin are assessed in the same way.

The second method, here called *the pill count method*, estimates the duration of treatment based on dispensed drug quantities and known dosages. Since the dosage of warfarin is variable and cannot be known from prescription data, the pill count method cannot be used for warfarin. In the analyses made according to the pill count method, exposure is assessed in different ways for the the apixaban+dronedarone cohort and warfarin+dronedarone cohort. The advantage is that the exposure in the apixaban+dronedarone cohort may be more accurately assessed than with the refill method, at the expense of introducing a risk for bias due to use of different methods for assessing exposure.

The potential misclassification of days of exposure in the cohorts is most likely one of diluting effects of treatment rather than one of exaggerating the effects of either combination.

In the analyses made in analogy with the ITT principle, censoring was made at the specified endpoint, death or end of the observation period. In the analyses made in analogy with the on treatment principle, censoring was also made when treatment with dronedarone, apixaban or warfarin had ceased based on exposure estimates or a filled prescription of another oral anticoagulant indicating a therapy switch.

9.9.5. Amendments to the SAP

The SAP was amended according to the description in section 8. SAP section(s) changed; 2 INTRODUCTION, section 2.1, Study Design, (page 5 of 18).

9.10. Quality control

All data was completely patient de-identified for this study. The study used data from national registers where data from the different registers are linked through personal identity numbers. Similar data, but for earlier time periods, have been used in several studies before (6-10). The linkage was done by the National Board of Health and Welfare and unidentified data was provided to the investigator.

9.11. Protection of human subjects

Subject information and consent

Not applicable.

Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by a Institutional Review Board(s) (IRB) and/or Independent Ethics Committee(s) (IEC) for each site participating in the study.

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

The study was approved by the ethical review board in Stockholm (EPN 2016/712-31/1) and confirms to the Declaration of Helsinki.

10. RESULTS

10.1. Participants

The study population was identified through the following steps:

1) Identification of all individuals with a diagnosis of AF in the Patient Register between July 01, 2005 and December 31, 2015. (See flow chart Figure 1)
2) Among these, all individuals with at least one filled prescription of dronedarone between May 29, 2013, and December 31, 2015 were identified from the Drug register. All other patients were excluded.
3) The date for the first filled dronedarone prescription was used as preliminary index date.
4) The duration of dronedarone treatment was assessed from the dispensed number of dronedarone tablets and under the assumption that patient's adherence to the dosage instruction was 80%. The date when the drug supply would have been exhausted marked the end date of dronedarone treatment.
5) Patients who filled prescriptions of apixaban or warfarin were identified.
    a. For patients who received apixaban or warfarin *after* the preliminary index date (the start date of dronedarone), the preliminary index date was substituted by the start date of the anticoagulant because this was when co-treatment with both dronedarone and either one of the anticoagulants began.
    b. For patients already on anticoagulant treatment when dronedarone was initiated, the preliminary index date was renamed index date because this was when co-treatment began). Ongoing anticoagulant treatment was defined by a filled prescription of apixaban or warfarin within 3 months before the dronedarone starting date.
6) Patients were allocated to either one of two study cohorts; the dronedarone+apixaban cohort and the dronedarone+warfarin cohort. The first filled prescription decided cohort if both apixaban and warfarin had been dispensed. No patients had received both warfarin and apixaban on the same day.
7) Patients with valvular AF defined as patients with mechanical heart valves (Z952) implanted before index, and patients with a diagnosis of mitral stenosis before index (I342, I050, I052, Q232) were excluded.

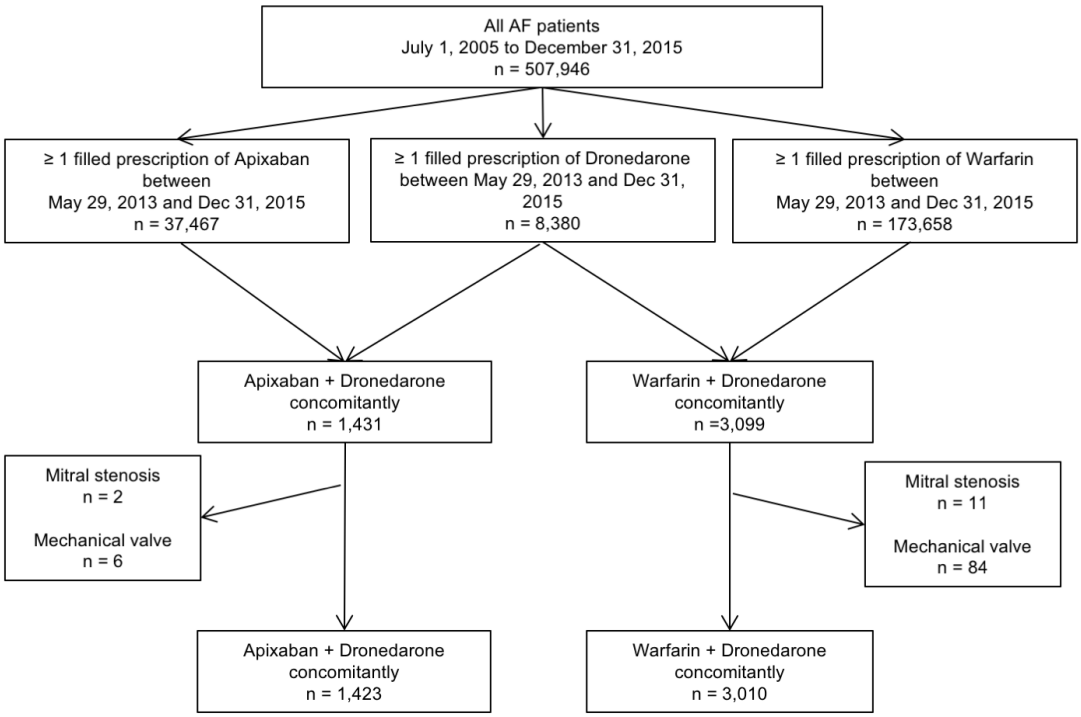

Figure 2. Inclusions/exclusions

10.2. Descriptive data

In all, 507,946 individuals received a hospital diagnosis of atrial fibrillation in Sweden during 2005-2015. Among those, 4,530 filled a prescription for dronedarone between May 29, 2013 (the day apixaban became available in Sweden) and December 31, 2015. During the same period, 37,467 AF patients filled a prescription of apixaban and 173,658 AF patients filled a prescription of warfarin.

Among these dronedarone treated patients, 1,431 had co-treatment with apixaban and 3,099 had co-treatment with warfarin (Figure 2).

Patients with valvular AF, defined as a diagnosis of mitral stenosis or the presence of a mechanical heart valve were excluded from the study, as apixaban is not approved for treatment for use in patients with valvular AF. Nevertheless eight patients with valvular AF received apixaban (0.6% of all with the apixaban-dronedarone combination treatment). None of these suffered a bleeding event and all survived the duration of the observation period. Due to the anonymization of data these patients cannot be contacted or made to change treatment to warfarin. After exclusion of patients with valvular AF, 1,423 patients on apixaban + dronedarone and 3,010 patients on warfarin+dronedarone remained for the study.

In 2013, very few dronedarone-patients got the combination with apixaban. At that time more than 92% of dronedarone patients received warfarin rather than apixaban. Two years later, apixaban and warfarin were equally common and since 2016 more dronedarone patients get apixaban than warfarin (Figure 3). Only 96 of the patients in the apixaban cohort (6.8%) had

been prescribed the lower 2.5 mg apixaban tablet. In the propensity score matched cohort 36 patients (7.1%) had the 2.5 mg tablet.

A small number of patients could have had apixaban prescribed in primary care without ever having received a hospital diagnosis of atrial fibrillation. Depending on the criteria for selection of the study population (i.e. a diagnosis of atrial fibrillation) these individuals were not included in the study

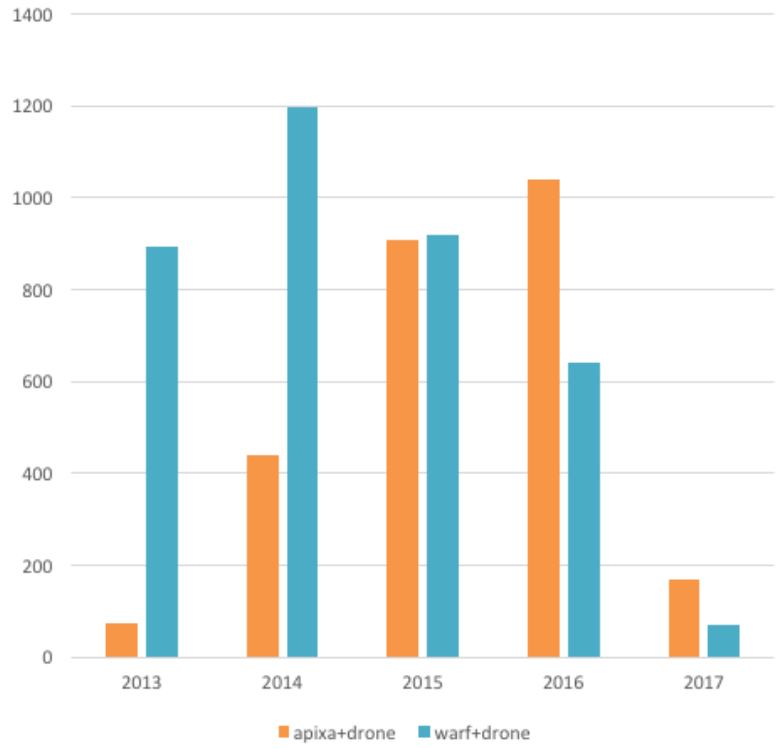

Figure 3. Year of initiation and type of co-treatment

Patients who received the warfarin combination were generally older and with more health problems than patients who received the apixaban combination. Seen in relation to the year of entry to the study, the mean CHA2DS2-VASc score was similar between the cohorts in the first two years, but significantly lower in the apixaban+dronedarone cohort in 2016 (2.26±1.54 vs. 2.75±1.58, $p<0.001$) (Figure 4)

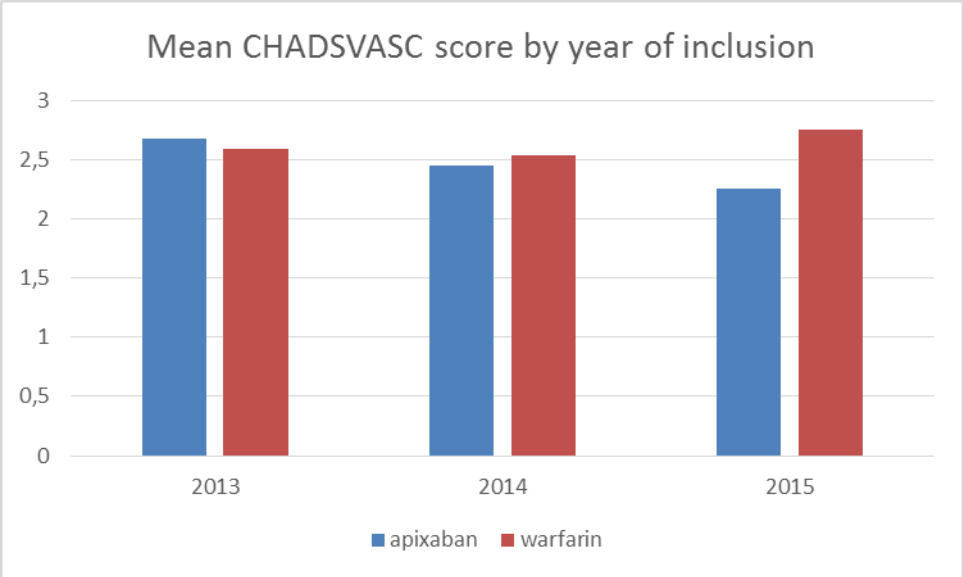

Figure 4. Mean CHA2DS2-VASc score by year of inclusion

10.2.1. Baseline characteristics

The mean age of the warfarin cohort was more than one year higher than in the apixaban cohort (68.1 vs 66.8 years, p<0.001). The prevalence of individual cofactors were mostly similar between the groups, but when added up in risk scores warfarin patients had significantly higher mean scores both on HAS-BLED (1.57 vs 1,45, p<0.001) and CHA_2DS_2-VASc (2.62 vs 2.34, p<0.001) than patients in the apixaban group. A detailed account of similarities and differences between the cohorts at baseline are presented in Table 6, Table 7 and Table 8.

Propensity score matching in order to create two cohorts similar on observable cofactors was succeeded in creating two cohorts of 521 patients in each who did not differ significantly on any of the 66 cofactors assessed. Baseline characteristics of the matched cohorts are shown in the rightmost columns of Table 6, Table 7 and Table 8.

Table 6. Baseline characteristics 1 - Bleeding and thromboembolic history

	All patients			After propensity score matching		
	apixaban+dronedarone n=1,423	warfarin+dronedarone n=3,010	p	apixaban+dronedarone n=521	warfarin+dronedarone n=521	p
Age mean±s.d. (median)	66.8±9.0 (68)	68.1±9.0 (69)	<0.001	66.5±9.8 (68)	66.5±9.8 (68)	0.960
Women	614 (43.2%)	1,319 (43.8%)	0.673	211 (40.5%)	210 (40.3%)	0.950
CHA_2DS_2-VASc score, mean±s.d. (median)	2.34±1.51 (2)	2.62±1.56 (3)	<0.001	2.31±1.60 (2)	2.34±1.73 (2)	0.737
$CHADS_2$ score, mean±s.d. (median)	1.14±1.06 (1)	1.35±1.11 (1)	<0.001	1.16±1.13 (1)	1.18±1.16 (1)	0.746
HASBLED score, mean±s.d. (median)	1.45±0.91 (1)	1.57±0.91 (2)	<0.001	1.45±0.95 (1)	1.48 ±1.02 (2)	0.660
Any bleeding hospitalization	90 (6.3%)	191 (6.4%)	0.979	42 (8.1%)	39 (7.5%)	0.729
Intracerebral	7(0.5%)	6 (0.2%)	0.093	2 (0.4%)	4 (0.8%)	0.413
Other intracranial	13 (0.9%)	19 (0.6%)	0.300	6 (1.2%)	6 (1.2%)	1.000
Gastrointestinal	32 (2.3%)	64 (2.1%)	0.794	13 (2.5%)	12 (2.3%)	0.840
Urogenital	20 (1.4%)	59 (2.0%)	0.193	8 (1.5%)	9 (1.7%)	0.807
Other bleeding	35 (2.5%)	81 (2.7%)	0.652	19 (3.7%)	17 (3.3%)	0.734
Transfusion	39 (2.7%)	85 (2.8%)	0.875	10 (1.9%)	13 (2.5%)	0.527
Anaemia	78 (5.5%)	160 (5.3%)	0.819	25 (4.8%)	25 (4.8%)	1.000
Coagulation or platelet defect	57 (4.0%)	119 (4.0%)	0.934	20 (3.8%)	17 (3.3%)	0.616
Any ischaemic stroke/TIA/systemic embolism	123 (8.6%)	315 (10.5%)	0.058	55 (10.6%)	53 (10.2%)	0.839
Ischaemic stroke	66 (4.6%)	194 (6.5%)	0.017	34 (6.5%)	33 (6.3%)	0.899
Unspecified stroke	7 (0.5%)	37 (1.2%)	0.021	4 (0.8%)	4 (0.8%)	1.000
TIA	56 (3.9%)	122 (4.1%)	0.852	20 (3.8%)	17 (3.3%)	0.616
Systemic embolism	3 (0.2%)	9 (0.3%)	0.598	2 (0.4%)	2 (0.4%)	1.000
Pulmonary embolism	11 (0.8%)	73 (2.4%)	<0.001	4 (0.8%)	9 (1.7%)	0.163
Deep venous thrombosis	14 (1.0%)	65 (2.2%)	0.006	5 (1.0%)	4 (0.8%)	0.738

All variables in table 1 part 1-3 were used as covariates in the logistic regression that generated the propensity scores

Table 7. Baseline characteristics 2 - Other medical history and comorbidity

	All patients			After propensity score matching		
	apixaban+dronedarone n=1,423	warfarin+dronedarone n=3,010	p	apixaban+dronedarone n=521	warfarin+dronedarone n=521	p
Myocardial infarction	122 (8.6%)	292 (9.7%)	0.228	45 (8.6%)	52 (10.0%)	0.455
Ischaemic heart disease without infarction	119 (8.4%)	311 (10.3%)	0.039	57 (10.9%)	48 (9.2%)	0.354
PCI	76 (5.3%)	221 (7.3%)	0.013	35 (6.7%)	37 (7.1%)	0.807
CABG	28 (2.0%)	60 (2.0%)	0.954	12 (2.3%)	12 (2.5%)	0.840
Heart failure	163 (11.5%)	411 (13.7%)	0.042	60 (11.5%)	66 (12.7%)	0.569
Hypertension	836 (58.8%)	1,966 (65.3%)	<0.001	298 (57.2%)	301 (57.8%)	0.851
Diabetes	121 (8.5%)	339 (11.3%)	0.005	36 (6.9%)	49 (9.4%)	0.141
Peripheral arterial disease	55 (3.9%)	125 (4.2%)	0.650	21 (4.0%)	18 (3.5%)	0.624
Valvular disease (other than exclusion criteria)	110 (7.7%)	238 (7.9%)	0.838	39 (7.5%)	38 (7.3%)	0.906
Pacemaker or ICD	101 (7.1%)	241 (8.0%)	0.290	40 (7.7%)	40 (7.7%)	1.000
Renal failure	17 (1.2%)	34 (1.1%)	0.074	8 (1.5%)	12 (2.3%)	0.366
Liver disease	10 (0.7%)	18 (0.6%)	0.681	2 (0.4%)	3 (0.6%)	0.654
Hypothyroidism	114 (8.0%)	255 (8.5%)	0.604	33 (6.3%)	45 (8.6%)	0.158
Thyrotoxicosis within last year	12 (0.8%)	28 (0.9%)	0.775	4 (0.8%)	5 (1.0%)	0.738
COPD	63 (4.4%)	127 (4.2%)	0.750	19 (3.7%)	20 (3.8%)	0.870
Asthma	73 (5.1%)	199 (6.6%)	0.055	34 (6.5%)	28 (5.4%)	0.432
Cancer within last 3 years	109 (7.7%)	209 (6.9%)	0.388	32 (6.1%)	27 (5.2%)	0.503
Alcohol abuse ('alcohol index') *	28 (2.0%)	64 (2.1%)	0.730	12 (2.3%)	13 (2.5%)	0.840
Dementia	1 (0.1%)	6 (0.2%)	0.312	1 (0.2%)	1 (0.2%)	1.000
Frequent faller	19 (1.3%)	43 (1.4%)	0.805	9 (1.7%)	5 (1.0%)	0.282

* Alcohol index is a set of ICD-10 codes used by the Swedish Board of Health and Welfare for annual reporting of alcohol related mortality. The codes used are E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714.

Table 8. Baseline characteristics 3 Filled drug prescriptions within 1 year before index date

		All patients			After propensity score matching		
		apixaban+dronedarone n=1,423	warfarin+dronedarone n=3,010	p	apixaban+dronedarone n=521	warfarin+dronedarone n=521	p
Antithrombotic drugs	Warfarin	210 (14.8%)	2,682 (89.1%)	<0.001	207 (39.7%)	209 (40.1%)	0.899
	Phenprocoumon/Acenocoumarol	1 (0.1%)	-	0.146	-	-	-
	Dabigatran	275 (19.3%)	73 (2.4%)	<0.001	62 (11.9%)	45 (8.6%)	0.083
	Rivaroxaban	124 (8.7%)	59 (2.0%)	<0.001	35 (6.7%)	24 (4.6%)	0.140
	Aspirin	357 (25.1%)	509 (16.9%)	<0.001	131 (25.1%)	130 (25.0%)	0.943
	Dipyridamol	2 (0.1%)	8 (0.3%)	0.412	1 (0.2%)	2(0.4%)	0.563
	Clopidogrel	32 (2.3%)	71 (2.4%)	0.820	16 (3.1%)	18 (3.5%)	0.727
	Prasugrel	-	-	-	-	-	
	Tikagrelor	11 (0.8%)	19 (0.6%)	0.591	5 (1.0%)	6 (1.2%)	0.762
	Low molecular weight heparin(LMWH)	58 (4.1%)	266 (8.8%)	<0.001	26 (5.0%)	27 (5.2%)	0.888
Drugs associated with bleeding	NSAID	233 (16.4%)	289 (9.6%)	<0.001	75 (14.4%)	72 (13.8%)	0.789
	Oral corticosteriod	152 (10.7%)	368 (12.2%)	0.136	56 (10.8%)	57 (10.9%)	0.921
	Proton pump inhibitor	388 (27.3%)	802 (26.6%)	0.663	140 (26.9%)	154 (29.6%)	0.335
Interacting drugs	Antiepileptic drugs	1 (0.1%)	10 (0.3%)	0.102	1 (0.2%)	1 (0.2%)	1.000
	Systemic antimycotic drugs	17 (1.2%)	18 (0.6%)	0.036	5 (1.0%)	4 (0.8%)	0.738
	Rifampicin	1 (0.1%)	1 (0.0%)	0.588	-	1 (0.2%)	0.317
	Ritonavir	-	-	-	-	-	-
	SSRI	93 (6.5%)	209 (6.9%)	0.615	37 (7.1%)	38 (7.3%)	0.905
	Verapamil/diltiazem	43 (3.0%)	109 (3.6%)	0.306	18 (3.5%)	19 (3.7%)	0.867
Cardiovascular drugs	Beta blocker	1,203 (84.5%)	2,645 (87.9%)	0.002	438 (84.1%)	436 (83.7%)	0.866
	Class 1 antiarrhythmic	97 (6.8%)	292 (9.7%)	0.002	56 (10.8%)	55 (10.6%)	0.920
	Amiodarone	33 (2.3%)	129 (4.3%)	0.001	20 (3.8%)	11 (2.1%)	0.101
	Sotalol	89(6.3%)	295 (9.8%)	<0.001	36 (6.91%)	37 (7.1%)	0.903
	Digoxin	115 (8.1%)	372 (12.4%)	<0.001	39 (7.5%)	41 (7.9%)	0.816
	ACE inhibitor/ARB	689 (48.4%)	1,625 (54.0%)	0.001	248 (47.6%)	246 (47.2%)	0.901
	Diuretic	313 (22.0%)	836 (27.8%)	<0.001	125 (24.0%)	116 (22.3%)	0.508
	Statin	477 (33.5%)	1,146 (38.1%)	0.003	188 (36.1%)	178 (34.2%)	0.516

10.2.1. Filled prescriptions at index and up to 3 months after index date

Table 9 shows filled prescriptions during the first 3 month period after index (including index date). Although the information about treatment after index was not fed into the logistic regression for generation of propensity scores, treatment was similar in the cohorts on most of the drugs, except apixaban and warfarin (expected).

Warfarin patients more often received low molecular weight heparin (LMWH) than apixaban treated patients, possibly done during initiation of warfarin treatment due to its slower onset, or in bridging procedures related to surgical procedures. This difference was also statistically significant in the propensity score matched cohorts.

Warfarin patients used diuretics more often after index than apixaban patients (20.4% vs 15.5%, $p<0.001$). A previous diagnosis of heart failure was more common with warfarin than with apixaban (13.7% vs. 11.5%, $p<0.042$) but can hardly be the sole explanation for the difference in the utilization of diuretics. These differences disappeared afterpropensity score matching.

Apixaban patients used non-steroidal anti-inflammatory drugs (NSAID), known to increase bleeding risk, more than twice as often as warfarin patients both before and after index. Propensity score matching made these differences disappear, but introduced another significant difference regarding ulcer-preventive proton pump inhibitors (PPI) which were more common with warfarin treated patients (warfarin cohort 27.3% vs apixaban cohort 18.4%, $p=0.001$).

Table 9. Filled prescriptions at index and up to 3 months after index date

		All patients			After propensity score matching		
		apixaban+dronedarone n=1,423	warfarin+dronedarone n=3,010	p	apixaban+dronedarone n=521	warfarin+dronedarone n=521	
Antithrombotic drugs	Warfarin	38 (2.7%)	2,607 (86.6%)	<0.001	18 (3.5%)	484 (92.9%)	<0.001
	Phenprocoumon/Acenocoumarol	-	-	-	-	-	-
	Apixaban	1,381 (97.1%)	72 (2.4%)	<0.001	497 (95.4%)	10 (1.9%)	<0.001
	Dabigatran	10 (0.7%)	16 (0.5%)	0.486	4 (0.8%)	7 (1.34%)	0.363
	Rivaroxaban	14 (1.0%)	21 (0.7%)	0.315	8 (1.5%)	5 (1.0%)	0.402
	Aspirin	27 (1.9%)	63 (2.1%)	0.666	8 (1.5%)	15 (2.9%)	0.140
	Dipyridamol	-	-	-	-	-	-
	Clopidogrel	10 (0.7%)	30 (1.0%)	0.334	5 (1.0%)	7 (1.3%)	0.561
	Prasugrel	-	-	-	-	-	-
	Tikagrelor	1 (0.1%)	6 (0.2%)	0.312	1 (0.2%)	1 (0.2%)	1.000
	LMWH	13 (0.9%)	112 (3.7%)	<0.001	5 (1.0%)	34 (6.5%)	<0.001
Drugs associated with bleeding	NSAID	52 (3.7%)	54 (1.8%)	<0.001	16 (3.1%)	16 (3.1%)	1.000
	Oral corticosteroid	98 (6.9%)	209 (6.9%)	0.945	36 (6.9%)	36 (6.9%)	1.000
	PPI	274 (19.3%)	627 (20.8%)	0.224	96 (18.4%)	142 (27.3%)	0.001
Interacting drugs	Antiepileptic drugs	1 (0.1%)	9 (0.3%)	0.134	1 (0.2%)	1 (0.2%)	1.000
	Systemic antimycotic drugs	1 (0.1%)	6 (0.2%)	0.312	--	1 (0.2%)	0.317
	Rifampicin	1 (0.1%)	-	0.146	-	-	-
	Ritonavir	-	-	-	-	-	-
	Selective Serotonin Reuptake inhibitor (SSRI)	71 (5.0%)	137 (4.6%)	0.520	29 (5.6%)	30 (5.8%)	0.893
	Verapamil/diltiazem	18 (1.3%)	40 (1.3%)	0.861	10 (1.9%)	6 (1.2%)	0.314
Cardiovascular drugs	Beta blocker	868 (61.0%)	1,865 (62.0%)	0.538	305 (58.5%)	338 (64.9%)	0.035
	Class 1 antiarrhythmic	51 (3.6%)	84 (2.8%)	0.151	14 (2.7%)	22 (4.2%)	0.175
	Amiodarone	52 (3.7%)	114 (3.8%)	0.827	22 (4.2%)	15 (2.9%)	0.241
	Sotalol	17 (1.2%)	46 (1.5%)	0.381	5 (1.0%)	10 (1.9%)	0.193
	Digoxin	44 (3.1%)	107 (3.6%)	0.428	16 (3.1%)	11 (2.1%)	0.330
	ACE inhibitor/ARB	612 (43.0%)	1,401 (46.5%)	0.027	220 (42.2%)	219 (42.0%)	0.950
	Diuretic	220 (15.5%)	614 (20.4%)	<0.001	78 (15.0%)	89 (17.1%)	0.353
	Statin	389 (27.3%)	923 (30.7%)	0.023	155 (29.8%)	145 (27.8%)	0.494

Note that treatment after index was not used in the logistic regression for obtaining propensity score

10.3. Outcome data

10.3.1. The main bleeding endpoint

The mean follow up with the apixaban combination was 304 days (min 1 day, max 931 days) and with the warfarin combination 518 days (min 1 day, max 946 days). This discrepancy was anticipated because warfarin was an established treatment at the start of the study period, whereas treatment with apixaban started from zero and increased gradually.

A short mean follow up confers a disadvantage to the apixaban cohort regarding bleeding event rate since a larger share of the total time at risk will be in the early period when bleedings are more common (there is a continuous selection of anticoagulant tolerant patients the longer treatment goes on).

During this time 19 apixaban- and 64 warfarin-treated patients met the main bleeding endpoint of either intracranial bleeding, hospitalization with bleeding or a fatal bleeding. The bleeding rate was 1.60% in the apixaban cohort and 1.50% in the warfarin cohort (p=0.929) (Figure 5 and Table 10).

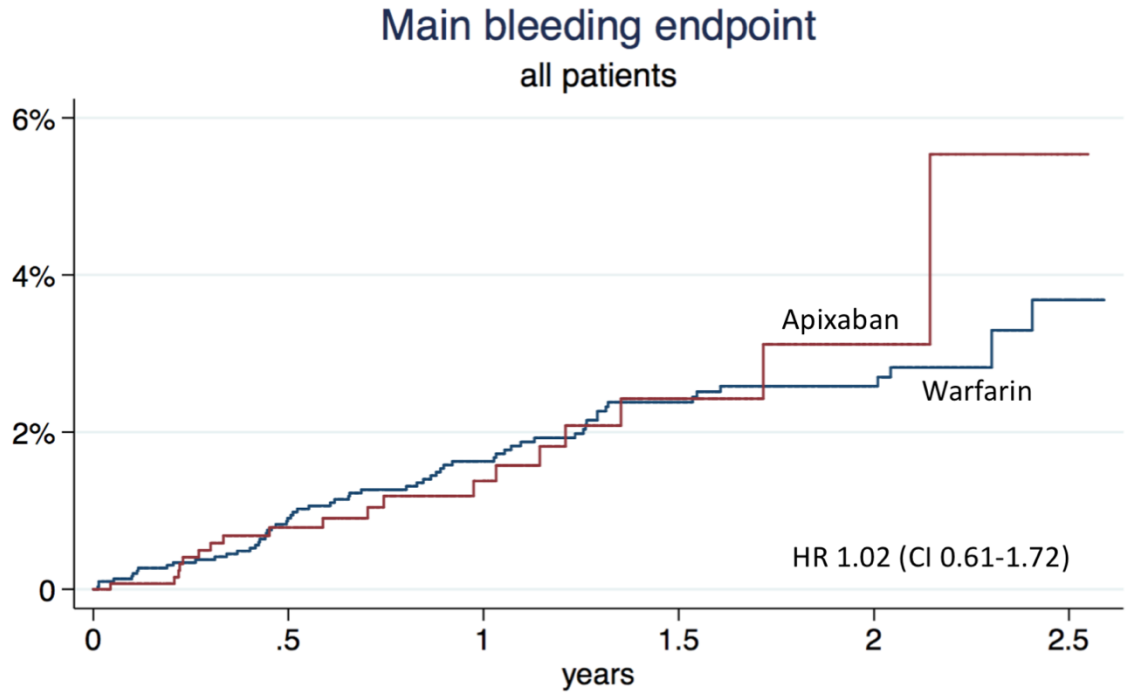

Figure 5. Incidence of the main bleeding endpoint (ITT principle)

Table 10. Outcome events (ITT analysis)

	events		event rate (per 100 yrs at risk)		Hazard ratios for apixa+drone (warfarin+dronedarone as reference)		
All patients	apixa+ drone	warf+ drone	apixa+ drone	warf+ drone	Crude HR (95% CI)	adjusted for age and sex HR (95% CI)	multivariate adjustment* HR (95% CI)
Main bleeding endpoint	19	64	1.60	1.50	1.02 (0.61-1.72)	1.07 (0.64-1.80)	0.99 (0.58-1.70)
Intracranial bleeding	3	8	0.25	0.19	1.19 (0.31-4.52)	1.25 (0.33-4.76)	1.36 (0.33-5.51)
Any bleeding hospitalization	18	63	1.52	1.48	0.98 (0.58-1.67)	1.03 (0.60-1.75)	0.96 (0.56-1.65)
Fatal bleeding	-	2	-	0.05	-	-	
Gastrointestinal bleed hospitalization	5	23	0.42	0.53	0.68 (0.26-1.80)	0.71 (0.27-1.88)	0.54 (0.19-1.50)
Urogenital bleed hospitalization	6	16	0.50	0.37	1.64 (0.63-4.27)	1.74 (0.67-4.55)	1.75 (0.63-4.84)
Other bleed hospitalization	11	335	0.92	0.82	1.17 (0.58-2.34)	1.23 (0.62-2.47)	1.16 (0.57-2.37)
Open care bleed	55	214	4.75	5.18	0.89 (0.66-1.20)	0.90 (0.67-1.22)	0.89 (0.65-1.21)
Any bleeding with or without hospitalization	63	242	5.47	5.89	0.88 (0.66-1.16)	0.90 (0.68-1.19)	0.89 (0.67-1.19)
Death from any cause	8	34	0.68	0.79	0.97 (0.44-2.12)	1.05 (0.48-2.31)	0.83 (0.35-1.92)
After propensity score matching	apixa+ drone	warf+ drone	apixa+ drone	warf+ drone	Crude** HR (95% CI)		
Main bleeding endpoint	6	12	1.26	1.66	0.85 (0.31-2.31)		
Intracranial bleeding	-	2	-	0.27	-		
Any bleeding hospitalization	6	12	1.26	1.66	0.85 (0.31-2.31)		
Fatal bleeding	-	0.1	-	0.14	-		
Gastrointestinal bleed hospitalization	-	2	-	0.27	-		
Urogenital bleed hospitalization	3	6	0.63	0.82	0.87 (0.21-3.57)		
Other bleed hospitalization	6	8	1.26	1.10	1.31 (0.44-3.89)		
Open care bleed	27	42	5.85	6.01	1.00 (0.61-1.64)		
Any bleeding with or without hospitalization	27	48	5.87	6.92	0.85 (0.53-1.38)		
Death from any cause	1	11	0.20	1.50	0.13 (0.02-1.03)		

*Multivariate adjustment for age, sex, any previous bleed, anaemia, previous stroke/TIA or systemic embolism, pulmonary embolism, myocardial infarction, ischaemic heart disease without previous infarction, peripheral arterial disease, heart failure, hypertension, diabetes, hypothyroidism, thyrotoxicosis, valvular defect (other than exclusion criteria), pacemaker/ICD, renal failure, liver disease, chronic obstructive pulmonary disease, asthma, cancer within 3 years, alcohol, dementia, hospitalization for fall accident ≥2, treatment before index with aspirin, dipyridamol, clopidogrel, tikagrelor, LMWH, NSAID, oral corticosteroid, PPI, selective serotonin reuptake inhibitor (SSRI), verapamil/diltiazem, ACE-inhibitor/ARB, diuretic, statin.

** Since propensity score matching caused balance in all covariates, further adjustments are unnecessary and may represent over-adjustment. The main result is therefore the crude estimate.

After multivariable adjustment, and analyzed according to the ITT principle, the hazard ratio (HR) for the main bleeding endpoint with apixaban compared to warfarin was 0.99 (95% confidence interval [CI) 0.58-1.78) (Table 10). In the propensity score cohorts, and without further adjustments, it was HR 0.85 (CI 0.31-2.31)

In the propensity score matched populations, only 6 apixaban- and 12 warfarin-treated patients reached the main bleeding endpoint (p=0.756) (Figure 6 and Table 10).

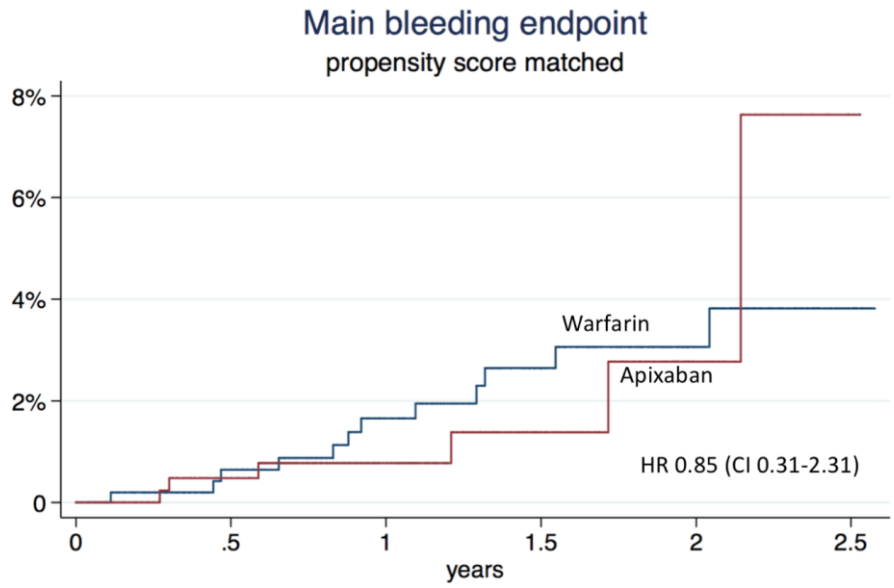

Figure 6. Incidence of the main bleeding endpoint (propensity score matched cohorts).

The two types of on treatment analyses, which included the refill method and the pill count method, produced almost exactly the same results as can be seen from Table 11 and Table 12. Therefore, only results from the refill method are presented in the text from here on.

The on treatment event rate was 1.33% with apixaban compared to 1.43% with warfarin (p=0.686). In the propensity score matched cohorts only two apixaban and seven warfarin treated patients experienced a main bleeding endpoint (HR 0.35, CI 0.08-1.72).

Table 11. Outcome events (on treatment according to refill method)

	events		event rate (per 100 yrs at risk)		Hazard ratios for apixa+drone (warfarin+dronedarone as reference)		
	apixa+ drone	warf+ drone	apixa+ drone	wart+ drone	Crude	adjusted for age and sex	multivariate* adjustment
Major bleeding endpoint	11	35	1.33	1.43	0.87 (0.44-1.72)	0.92 (0.46-1.82)	1.12 (0.55-2.29)
Intracranial bleeding	2	5	0.24	0.20	1.06 (0.21-5.48)	1.17 (0.23-6.06)	1.31 (0.20-8.86)
Any bleeding hospitalization	10	35	1.21	1.43	0.79 (0.39-1.60)	0.83 (0.41-1.69)	1.02 (0.48-2.14)
Fatal bleeding	-	-	-	-	-	-	-
Gastrointestinal bleed hospitalization	3	11	0.36	0.45	0.67 (0.19-2.39)	0.68 (0.19-2.44)	0.73 (0.17-3.15)
Urogenital bleed hospitalization	3	9	0.36	0.37	1.09 (0.29-4.06)	1.13 (0.30-4.23)	1.39 (0.34-5.71)
Other bleed hospitalization	6	19	0.73	0.77	0.90 (0.36-2.29)	0.96 (0.38-2.43)	1.32 (0.49-3.54)
Open care bleed	34	132	4.20	5.56	0.73 (0.50-1.07)	0.75 (0.51-1.10)	0.78 (0.53-1.15)
Any bleeding with or without hospitalization	40	149	4.97	6.29	0.75 (0.52-1.06)	0.77 (0.54-1.10)	0.83 (0.58-1.19)
Death from any cause	4	7	0.48	0.28	1.60 (0.46-5.52)	1.76 (0.51-6.10)	1.60 (0.33-7.76)
After propensity score matching	apixa+ drone	warf+ drone	apixa+ drone	warf+ drone	Crude		
Major bleeding endpoint	2	7	0.60	1.75	0.35 (0.08-1.72)		
Intracranial bleeding	-	-	-	-	-		
Any bleeding hospitalization	2	7	0.60	1.75	0.35 (0.08-1.72)		
Fatal bleeding	-	-	-	-	-		
Gastrointestinal bleed hospitalization	-	-	-	-	-		
Urogenital bleed hospitalization	1	5	0.30	1.25	0.23 (0.03-1.93)		
Other bleed hospitalization	2	6	0.60	1.50	0.41 (0.08-2.06)		
Open care bleed	16	29	4.94	7.48	0.69 (0.37-1.28)		
Any bleeding with or without hospitalization	16	32	4.95	8.27	0.61 (0.33-1.12)		
Death from any cause	-	4	-	0.99	-		

* Multivariate adjustment for age, sex, any previous bleed, anaemia, previous stroke/TIA or systemic embolism, pulmonary embolism, myocardial infarction, ischaemic heart disease without previous infarction, peripheral arterial disease, heart failure, hypertension, diabetes, hypothyroidism, thyrotoxicosis, valvular defect (other than exclusion criteria), pacemaker/ICD, renal failure, liver disease, chronic obstructive pulmonary disease, asthma, cancer within 3 years, alcohol, dementia, hospitalization for fall accident ≥2, treatment at or after index with aspirin, dipyridamol, clopidogrel, tikagrelor, LMWH, NSAID, oral corticosteroid, PPI, antiepileptic drug, systemic antimycotic drug, rifampicin, SSRI or verapamil/diltiazem. Treatment before index with beta-blocker, ACEI/ARB, diuretic, statin.

Table 12. Outcome events (on treatment, with pill count method for apixaban and refill method for warfarin)

	events		event rate (per 100 yrs at risk)		Hazard ratios for apixa+drone (warfarin+dronedarone as reference)		
	apixa+ drone	warf+ drone	apixa+ drone	warf+ drone	Crude	adjusted for age and sex	multivariate* adjustment
Major bleeding endpoint	11	35	1.32	1.43	0.87 (0.44-1.71)	0.91 (0.46-1.81)	1.12 (0.55-2.30)
Intracranial bleeding	2	5	0.24	0.20	1.06 (0.20-5.45)	1.17 (0.23-6.04)	1.31 (0.19-8.83)
Any bleeding hospitalization	10	35	1.21	1.43	0.79 (0.39-1.59)	0.83 (0.41-1.68)	1.02 (0.48-2.14)
Fatal bleeding	-	-	-	-	-	-	-
Gastrointestinal bleed hospitalization	3	11	0.36	0.45	0.67 (0.19-2.39)	0.68 (0.19-2.44)	0.73 (0.17-3.16)
Urogenital bleed hospitalization	3	9	0.36	0.37	1.09 (0.29-4.05)	1.13 (0.30-4.22)	1.38 (0.33-5.70)
Other bleed hospitalization	6	19	0.72	0.77	0.90 (0.36-2.28)	0.95 (0.38-2.41)	1.32 (0.49-3.54)
Open care bleed	34	132	4.19	5.56	0.73 (0.50-1.06)	0.75 (0.51-1.09)	0.77 (0.52-1.14)
Any bleeding with or without hospitalization	40	149	4.95	6.29	0.74 (0.52-1.06)	0.77 (0.54-1.09)	0.83 (0.58-1.19)
Death from any cause	5	7	0.60	0.28	2.05 (0.64-6.56)	2.27 (0.71-7.27)	2.70 (0.67-10.94)
After propensity score matching	apixa+ drone	warf+ drone	apixa+ drone	warf+ drone	Crude		
Major bleeding endpoint	2	7	0.60	1.75	0.35 (0.07-1.70)		
Intracranial bleeding	-	-	-	-	-		
Any bleeding hospitalization	2	7	0.60	1.75	0.35 (0.07-1.70)		
Fatal bleeding	-	-	-	-	-		
Gastrointestinal bleed hospitalization	-	-	-	-	-		
Urogenital bleed hospitalization	1	5	0.30	1.25	0.22 (0.03-1.93)		
Other bleed hospitalization	2	6	0.60	1.50	0.40 (0.08-2.02)		
Any bleeding with or without hospitalization	16	32	4.93	8.27	0.61 (0.33-1.11)		
Open care bleed	16	29	4.91	7.48	0.69 (0.37-1.27)		
Death from any cause	1	4	0.30	0.99	0.28 (0.03-2.50)		

10.4. Main results

There were no significant differences between apixaban and warfarin treated patients who suffered a major bleeding event in the analyses made in analogy with the ITT principle (Table 13, Table 14 and Table 15). The lack of statistical difference may largely be due to small numbers of patients (19 apixaban and 64 warfarin). Among the non-significant differences a higher proportion of apixaban patients than warfarin patients had experienced a previous bleed (26.3% vs 14.1%), was diabetic (26.3% vs 9.4%) or had been using NSAIDs the previous year. Warfarin patients with a major bleeding event on the other hand had non-significantly higher proportion of patients with myocardial infarction (18.8% vs 10.5%), renal failure (4.7% vs zero %) or gastric ulcer protection with a PPI after index (31.3% vs 21.1%).

Table 13. Patients with mainbleeding endpoint. Bleeding and thromboembolic history

	Patients with main bleeding endpoint (ITT)		
	apixaban+dronedarone n=19	warfarin+dronedarone n=64	p
Age mean±s.d. (median)	72.1±7.7 (73)	70.9±8.3 (72)	0.588
Women	6 (31.6%)	23 (35.9%)	0.726
CHA_2DS_2-VASc score, mean±s.d. (median)	3.16±1.26 (3)	2.97±1.70 (3)	0.655
$CHADS_2$ score, mean±s.d. (median)	1.89±1.10 (2)	1.55±1.27 (1)	0.238
HASBLED score, mean±s.d. (median)	2.00±0.67 (2)	1.97±0.93 (2)	0.892
Any bleeding hospitalization	5 (26.3%)	9 (14.1%)	0.210
Intracerebral	-	1 (1.6%)	0.584
Other intracranial	-	1 (1.6%)	0.584
Gastrointestinal	3 (15.8%)	5 (7.8%)	0.301
Urogenital	2 (10.5%)	3 (4.7%)	0.348
Other bleeding	-	5 (7.8%)	0,209
Transfusion	2 (10.5%)	6 (9.4%)	0.881
Anaemia	4 (21.1%)	9 (14.1%)	0.462
Coagulation or platelet defect	2 (10.5%)	7 (10.9%)	0.960
Any ischaemic stroke/TIA/systemic embolism	4 (21.1%)	6 (9.4%)	0.170
Ischaemic stroke	2 (10.5%)	4 (6.3%)	0.527
Unspecified stroke	-	2 (3.1%)	0.435
TIA	2 (10.5%)	1 (1.6%)	0.066
Systemic embolism	-	-	-
Pulmonary embolism	-	1 (1.6%)	0.584
Deep venous thrombosis	-	1 (1.6%)	0.584

Table 14. Patients with main bleeding endpoint. Other medical history and comorbidity

	Patients with main bleeding endpoint (ITT)		
	apixaban+dronedarone n=19	warfarin+dronedarone n=64	p
Myocardial infarction	2 (10.5%)	12 (18.8%)	0.401
Ischaemic heart disease without infarction	3 (15.8%)	9 (14.1%)	0.851
PCI	3 (15.8%)	10 (15.6%)	0.986
CABG	-	2 (3.1%)	0.435
Heart failure	3 (15.8%)	11 (18.2%)	0.886
Hypertension	13 (68.4%)	50 (78.1%)	0.385
Diabetes	5 (26.3%)	6 (9.4%)	0.056
Peripheral arterial disease	-	7 (10.9%)	0.132
Valvular disease (other than exclusion criteria)	2 (10.5%)	9 (14.1%)	0.690
Pacemaker or ICD	2 (10.5%)	9 (14.1%)	0.690
Renal failure	-	3 (4.7%)	0.336
Liver disease	-	1 (1.6%)	0.584
Hypothyroidism	1 (5.3%)	10 (15.6%)	0.242
Thyrotoxicosis within last year	-	-	-
COPD	-	5 (7.8%)	0.209
Asthma	-	6 (9.4%)	0.166
Cancer within last 3 years	5 (26.3%)	16 (25.0%)	0.908
Alcohol abuse ('alcohol index')	-	2 (3.1%)	0.435
Dementia	-	-	-
Frequent faller	-	1 (1.6%)	0.584

Table 15. Patients with main bleeding endpoint. Filled drug prescriptions

		within 1 year **before** index			<3 months **after** index date		
		apixaban+dronedarone n=19	warfarin+dronedarone n=64	p	apixaban+dronedarone n=19	warfarin+dronedarone n=64	p
Antithrombotic drugs	Warfarin	3 (15.8%)	60 (93.8%)	<0.001	-	53 (82.8%)	<0.001
	Apixaban	9 (47.4)			19 (100%)	-	<0.001
	Dabigatran	4 (21.1%)	1 (1.6%)	0.002	-	-	-
	Rivaroxaban	-	-	-	-	2 (3.1%)	0.435
	Aspirin	8 (42.1%)	13 (20.3%)	0.055	2 (10.3%)	1 (1.6%)	0.066
	Dipyridamol	-	1 (1.6%)	0.584	-	-	-
	Clopidogrel	2 (10.5%)	1 (1.6%)	0.066	-	1 (1.6%)	0.584
	Prasugrel	-	-	-	-	-	-
	Tikagrelor	1 (5.3%)	-	0.065	-	-	-
	LMWH	2 (10.3%)	6 (9.4%)	0.881	-	9 (14.1%)	0.083
Drugs associated with bleeding	NSAID	3 (15.8%)	4 (6.3%)	0.189	-	1 (1.6%)	0.584
	Oral corticosteroid	2 (10.5%)	12 (18.8%)	0.401	1 (5.3%)	8 (12.5%)	0.373
	Proton pump inhibitor	5 (26.3%)	28 (43.8%)	0.173	4 (21.1%)	20 (31.3%)	0.389
Interacting drugs	Antiepileptic drugs	-	3 (4.7%)	0.336	-	3 (4.7%)	0.336
	Systemic antimycotic drugs	1 (5.3%)	2 (3.1%)	0.661	-	-	-
	Rifampicin	-	-	-	-	-	-
	Ritonavir	-	-	-	-	-	-
	SSRI	2 (10.5%)	5 (7.8%)	0.709	2 (10.3%)	3 (4.7%)	0.348
	Verapamil/diltiazem	-	4 (6.3%)	0.264	-	1 (1.6%)	0.584
Cardiovascular drugs	Beta blocker	17 (89.5%)	54 (84.4%)	0.579	9 (47.4%)	37 (51.8%)	0.421
	Class 1 antiarrhythmic	1 (5.3%)	5 (7.8%)	0.708	-	2 (3.1%)	0.435
	Amiodarone	-	1 (1.6%)	0.584	1 (5.3%)	3 (4.7%)	0.918
	Sotalol	3 (15.8%)	6 (9.4%)	0.430	-	-	-
	Digoxin	4 (21.1%)	7 (10.9%)	0.254	1 (5.3%)	2 (3.1%)	0.661
	ACE inhibitor/ARB	13 (68.4%)	41 (64.1%)	0.726	10 (52.6%)	35 (54.7%)	0.874
	Diuretic	8 (42.1%)	22 (34.4%)	0.538	7 (36.8%)	17 (26.6%)	0.385
	Statin	10 (52.6%)	36 (56.3%)	0.781	6 (31.6%)	27 (42.2%)	0.407

10.5. Other analyses

10.5.1. Secondary endpoints

For results see Table 10 and Table 11.

10.5.1.1. Intracranial bleeding

Only three apixaban and eight warfarin patients suffered intracranial bleeding corresponding to annual rates of 0.25% and 0.19% in the apixaban and warfarin cohorts respectively (p=0.798). All had terminated combination treatment before the bleeding occurred and hence there were no patients with intracranial bleedings in either cohort for the on treatment analysis (Table 10).

10.5.1.2. Hospitalization for gastrointestinal (GI) bleeding

The annual rates for hospitalization for GI-bleeds were 0.42% with apixaban and 0.53% with warfarin (p=0.435). There was a non-significant trend towards lower bleeding risk with apixaban than with warfarin (HR 0.54, CI 0.19-1.50) analyzed on ITT, and on treatment (HR 0.73, CI 0.17-3.15). The absolute numbers of GI bleeds was however small and it is not possible to draw any conclusions in either direction. In the propensity score matched cohorts there only were two warfarin treated patients, and no apixaban treated patients, who had been hospitalized for a GI bleed (Table 10).

10.5.1.3. Hospitalization for urogenital bleeding

There were few hospitalizations for urogenital bleeds. No differences could be seen between the cohorts (Table 10).

10.5.1.4. Hospitalization for other bleeding events

This category counted hospitalizations for a variety of other bleeds, including nosebleeds, posthaemorrhagic anaemia and bleedings in the eye (see appendix table 1). The crude event rates were 0.92% and 0.82% with apixaban and warfarin respectively (p=0.658). In the crude ITT analysis the HR was 1.15 (CI 0.57-2.37) (Table 10). In the on treatment analysis HR was 1.32 (CI 0.49-3.54). In the propensity score matched cohorts however, the same analysis changed direction and showed HR 0.50 (CI 0.10-2.57) (Table 11). This wide swing of the hazard ratio and the very wide confidence intervals are of course due to the play of chance and to the low number of events. No conclusions should therefore be drawn.

10.5.1.5. Bleeding managed in open care without hospital admission

This endpoint has relatively low positive predictive value of 84.2% since such contacts also could represent follow-up visits after previous bleeds rather than ongoing bleeds , e.g. for gastroscopy after a previous bleed as shown in a previous validation study of bleeding end points in the patient register (5).

All the same, this was an endpoint with much higher incidence which may make the results sufficient statistical power to be of interest. Thus, this endpoint was met by 55 apixaban and 214 warfarin patients corresponding to annual rates of 4.75% and 5.18% (p=0.429). There was however no statistical difference after multivariable adjustment (ITT HR 0.89, CI 0.65-1.21, on treatment HR 0.78, 0.53-1.15). Nor were there any significant differences after propensity score matching (Table 10 and Table 11).

10.5.1.6. Death from any cause

Eight apixaban treatment and 34 warfarin patients died during follow up representing an annual mortality rate of 0.68% and 0.79% (p=0.931). Of these, only four apixaban and seven warfarin patients were still on combination treatment when death occurred. No statistically significant differences could be seen (Table 10). The specific causes of death as recorded in the Cause of Death register and in the patient register in case death had occurred in hospital for patients who appeared to have been on treatment as assessed by the pill count method is presented in Table 16. As can be seen, none of the deaths in either cohort was related to a bleeding event.

Table 16. Diagnoses as given in the Cause of Death- and Patient registries for patients who died while on combination treatment (pill-count method)

				Cause of death register			Patient register if hospital contact at death			
cohort	age	sex	Days at risk	Underlying cause	First contributory cause	Second contributory cause	First diagnosis	Second diagnosis	Third diagnosis	Previous heart failure
apixa	75	M	418	Chronic IHD*	Cardiac arrest	Chronic IHD	Cardiac arrest	Myocardial infarction	Chronic IHD	Yes
apixa	76	M	400	Motor neuron disease	Pulmonary embolism	Motor neuron disease	-	-	-	Yes
apixa	76	F	38	Exposure, unspecified	Complication to hip fracture operation	Myocardial infarction	Hip fracture	Polycytaemia vera	Myocardial infarction	Yes
apixa	74	F	24	Septicaemia	Septicaemia	Chronic IHD	Urinary tract infection	E.coli causative	Septic chock	-
apixa	64	M	429	Myocardial infarction	Unspecified arrhythmia	Heart failure	Prostate cancer	Skeletal metastases	-	Yes
warfarin	76	F	65	Acute myeloic leucemia	Acute myeloic leucemia	-	-	-	-	-
warfarin	73	M	475	COPD** with pneumonia	Pneumonia	COPD	-	-	-	Yes
warfarin	72	F	81	Myocardial infarction	Myocardial infarction	Pulmonary oedema	Cardiac arrest	-	-	-
warfarin	78	M	403	Oesofageal cancer	Oesofageal cancer	Atrial fibrillation	Oesofageal cancer	AF	Aortic insufficiency	-
warfarin	64	M	86	Persist. AF	Heart failure	Diabetes, unspecified	Perm. AF	Other specified care	Parox. AF	Yes
warfarin	71	M	39	Pneumonia	Pneumonia	Myocarditis	-	-	-	-
warfarin	82	F	51	Cardiomyopathy, unspecified	Cardiac arrest	Cardiomyopathy, unspecified	-	-	-	Yes

* IHD= ischaemic heart disease ** COPD= chronic obstructive pulmonary disease

10.6. Adverse events / adverse reactions

This study includes unstructured data (e.g., narrative fields in the database) that was converted to structured (i.e., coded) data solely by a computer using automated/algorithmic methods and/or data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and AEs are not reportable as individual AE reports. The most common AE with anticoagulants is bleeding. However, in this study bleeding is the main outcome event investigated.

11. DISCUSSION

11.1. Key results

The incidence of major bleeding events among patients with AF treated with dronedarone in combination with apixaban or in combination with warfarin was low in this study including all individuals in Sweden who had been exposed to these drug combinations between May 29, 2013 and December 31, 2015. No significant difference in favor of either drug combination was found. Nor were there a consistent, non-significant trend, in favor of either combination. Thus, there is no indication that co-treatment with apixaban and dronedarone should cause more bleeds than co-treatment with warfarin and dronedarone.

11.2. Limitations

Patients receiving dronedarone are generally younger and healthier than AF patients in general and this was reflected by very few endpoint events in both cohorts. Few endpoint events put a limit to how many variables could be introduced with confidence into multivariable analyses. A simple rule of thumb says that one covariate per 10 events could be acceptable. In all, only 83 patients met the composite main bleeding endpoint, which would mean adjustment for 8 cofactors at the most, and far less for the specific endpoints. In the full multivarible analyses as many as 36 covariates were used. The results of these analyses should therefore be interpreted with the greatest caution and are not to seen as the main results of the study.

Propensity score matching for the likelihood of receiving either treatment is a much more reliable way to handle differences between groups when there are few events. The propensity scores are also obtained by multivariable regression, but the big difference is that the outcome is the likelihood of obtaining either treatment. There were 1,423 patients in the smallest cohort. By propensity score matching two cohorts, similar on observable baseline characteristics, was obtained. The direct comparison of the propensity score matched cohorts, without further adjustments, or with adjustment only for residual differences between the groups is therefore produces more reliable results.

11.2.1. Bias

In the analyses made in analogy with ITT, patients may have switched from apixaban to warfarin or to another NOAC, or from warfarin to apixaban or another NOAC.

Switches may have been precipitated by a minor bleeding which did not qualify as an endpoint event, in which case this would indicate a patient with a higher future bleeding risk. If the bleeding had qualified as an endpoint event, that patient would have been censored and the bleeding correctly attributed to the first used drug.

The possible effect of this bias could potentially lead to falsely low event rates for the original cohort. The number of patients who switched away from warfarin was 88 and the number who switched away from apixaban was 42. This would indicate that warfarin, with its larger number of switchers could have come out appearing a little better and apixaban a little worse than it really was like.

However, patients were censored when there were switches in the on treatment-analyses without this giving rise to major alterations. This potential bias is probably of no importance.

In the propensity score matched apixaban cohort, there were 207 patients who previously had used warfarin and had switched, possibly because of some problem with warfarin (22 of them had a previous bleeding hospitalization, but only one also had a bleeding during follow up). In the corresponding warfarin cohort, only three patients had previously been exposed to apixaban of whom none had a previous hospitalization for a bleeding event. This confers more high risk patients to the apixaban than to the warfarin cohort and would therefore tend to bias the results in favor of warfarin. However, since only one of these patients had a bleed during follow up, the effect may have been small on the results.

11.2.2. Endpoint validity

The study could not use the ISTH definitions of major bleeding events commonly used in clinical trials. The ISTH definition requires information about drop in haemoglobin count, and information whether the number of units of blood that was transfused exceeded two. This information is not available in the registers used. Clinical trials generally use some kind of adjudication of the events to make sure that they are valid. This was not possible in this study which was based on anonymized data.

However, a previous validation study of bleeding events recorded in the Swedish Patient register showed that bleeding diagnoses carried high validity and specificity they were associated with overnight hospital stay (5).

The endpoints "open care bleeds" and "any bleeding with or without hospitalization" are less reliable than bleeds associated with hospitalization. They count a larger number of events and may be of interest for that reason, but it should be recognized that some of them may not represent bleeding event, but rather planned visits for investigation of the causes for anaemia or follow up after previous real or suspected bleeding events.

Information about transfusions is indeed available in the register, but the number of units given is not recorded, and more importantly, given transfusions are not recorded by code at discharge in almost 50% of the cases.

The definition used for the main bleeding event in this study, had a positive predictive value of 95.5% and a negative predictive value of 99.4% according to the previous validation study.

11.2.3. Confounding by indication

Non-randomized cohort studies comparing different treatments are vulnerable to confounding by indication. Doctors may prefer a certain treatment for a certain kind of patient. If something about a patient affects treatment choice and this something is not recorded by diagnosis or as a prescription, it will not be possible to adjust for in the analyses. This will of course distort the results.

Multivariable adjustments can only adjust for observable cofactors.

A common approach to this problem is to create cohorts that are similar on as many observable cofactors as possible using propensity score matching. In this study, matching resulted in absence of significant differences on all 66 cofactors tested for in the final regression model. Although it still is possible that there could be a 67th dimension in which there actually is an important difference between the cohorts, the likelihood for this must be assumed to be small as patients who are similar in as many as 66 aspects tend to be very similar in all aspects.

11.2.4. Difference in duration of follow up

The mean follow up was considerably shorter with the apixaban combination than with the warfarin combination (304 vs. 518 days). This may constitute a bias in favour of the warfarin combination, since bleedings tend to come early after initiation of anticoagulant treatment in patients at high risk after initiation, and patients in the apixaban cohort had a higher proportion of the total time at risk in this early high risk phase.

11.2.5. Statistical power

At the conception of the study plan, the hypothesis was that the annual rate of major bleeds in the warfarin-dronedarone cohort would be approximately 3% and that the apixaban-dronedarone combination would increase bleeds by 33%. The number of patients needed to test this hypothesis would be approximately 5,512 on each drug combination with a two sided 95% significance level and 80% power.

It was considered likely that the study would able to identify approximately 1000 patients on the apixaban+dronedarone combination. Thus, from the outset it was known that the study would not have sufficient statistical power to confirm or reject the hypothesis, but it was considered that a study still could be informative since no systematic studies regarding the outcomes of patients with the apixaban-dronedarone combination have been done.

As it turned out the number of patients on the apixaban+dronedarone combination was higher than expected (n=1,431). (Actually, there were data of nearly twice that number if prescriptions during 2016 and the beginning 2017 were used but, unfortunately, this information could not be linked to bleeding outcomes due to a one year lag in the reporting from the Patients- and Cause of Death registries. Therefore the study had to be restricted to the timespan 2013-2015 as originally intended).

Compared to the 3% annual risk of major bleeding with warfarin in the power calculation, the observed event rate was only 1.5%. Recalculation of the power analysis showed that the needed number of patients in each cohort would therefore have to be at least 10,996 to be able to detect a 33% difference in bleeding risk with a two sided 95% significance level and 80% power. Although the number of patients on the apixaban+dronedarone combination was larger than anticipated, the study remains grossly underpowered for the main bleeding endpoint.

The 3% bleeding risk estimate was based on common reports of bleeding risk with oral anticoagulation among patients with atrial fibrillation. In retrospect it would have been better to use a lower estimate of bleeding rates since patients using rhythm control treatment (e.g. dronedarone) by definition have non-permanent AF and thus, due the progressive nature of AF, are younger, have less comorbidity and thus bleeding risk than other AF patients. In this study the mean age was around 67-68 years, whereas most real world studies on AF populations report mean ages around 75-76 years.

The less validated endpoint of bleeds managed in open care without hospitalization was much more frequent (5.18% in the warfarin cohort). The number of patients needed to test the hypothesis against this endpoint would be 3,043 in each cohort. The study was still underpowered for this endpoint, but the number of patients was much closer to what was needed (apixa =1,423, warfarin=3,010). This was also true for the most inclusive of the endpoints, "any bleeding with or without hospitalization". For that endpoint 2,652 would have been needed in each treatment arm. As it turned out, only the warfarin arm reached that number (apixaban =1,423, warfarin =3,010).

11.3. Interpretation

The incidence of major bleeding events among patients with atrial fibrillation treated with dronedarone in combination with apixaban or in combination with warfarin was low in this study including all individuals in Sweden who had been exposed to these drug combinations between May 29, 2013 and December 31, 2015.

In all, 19 apixaban and 64 warfarin treated patients met the main bleeding endpoint of either intracranial bleeding, hospitalization with bleeding or a fatal bleeding. The bleeding rate was 1.60% in the apixaban cohort and 1.50% in the warfarin cohort (p=0.929). The incidence of major bleeding events in both cohorts were lower than the annual bleeding rate of 3% used for the power calculations based on bleeding rates in previous studies on the entire AF population.

No significant difference in favor of either drug combination was found. Nor were there a consistent, non-significant trend, in favor of either combination.

The low bleeding rate in this study shows that patients using dronedarone in combination with oral anticoagulants represent a selected low risk population. Patients using dronedarone have non-permanent forms of AF, and thus have AF in an earlier stage of the disease process. The mean ages in this study were 66.8 and 68.1 in the apixaban and warfarin cohorts respectively, while the mean age in the full AF population is 77.2 years (11). The CHA_2DS_2-VASc score was 2.34 in the apixaban cohort and 2.62 in the warfarin cohort, compared to 3.61 in the full Swedish AF population.

A consequence of the low event rate in the study is that the study is under-powered for detection of differences in bleeding risk related to treatment regime.

11.4. Generalisability

This study includes all individuals in Sweden with atrial fibrillation and combination treatment with either dronedarone and apixaban and dronedarone and warfarin and is therefore by definition representative for Swedish conditions.

Warfarin management in Sweden is generally very good with a mean time in therapeutic range (TTR) well above 70% both in pivotal trials and in clinical practice (12-15).

It is conceivable that the warfarin combination would be associated with higher bleeding rate in countries with less stringent warfarin control and that a benefit therefore could be seen with the apixaban combination.

12. OTHER INFORMATION

Not applicable

13. CONCLUSIONS

The incidence of major bleeding events among patients with atrial fibrillation treated with dronedarone in combination with apixaban or in combination with warfarin was low in this study including all individuals in Sweden who had been exposed to these drug combinations between May 29, 2013 and December 31, 2015.

No significant difference in favor of either drug combination was found. Nor were there a consistent, non-significant trend, in favor of either combination.

Thus, there is no indication that co-treatment with apixaban and dronedarone should cause more bleeds than co-treatment with warfarin and dronedarone.

It must however be recognized that the study did not have sufficient statistical power for detection of differences in bleeding risk related to treatment. There has however been a rapid increase in the use of the apixaban-dronedarone combination in 2016, which has made this combination dominant among dronedarone users. Sufficient statistical power might be found if the study is repeated when data for 2016 and 2017 become available.

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15. LIST OF SOURCE TABLES AND FIGURES

Not Applicable.