Reference Number: RD-SOP-1216
Supplement Version: 3

Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	**R**eal-world **e**vidence for non-valvular **at**rial fibrillation patients **t**reated with oral **a**nticoagulation **i**n the **N**ordics (REATTAIN)
Report version and date	v. 1.0, 26 April 2024
IMPACT study number	20030
Study type / Study phase	Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) <PASS>☒ <Joint PASS: ☐ YES ☒ NO>
EU PAS register number	33167
Active substance (if non-PASS and non-active drug, row may be deleted)	Direct thrombin inhibitor, B01AE07 dabigatran etexilate Direct factor Xa inhibitor, B01AF01 rivaroxaban Direct factor Xa inhibitor, B01AF02 apixaban
Product reference	N/A
Comparator / Reference therapy	Vitamin K antagonist, B01AA03 warfarin
Study Initiator and Funder	Bayer AG 13353 Berlin, Germany
Research question and objectives	To describe the risk of ischemic stroke (IS)/systemic embolism (SE), and intracranial hemorrhage (ICH) in patients with NVAF initiating treatment with reduced doses of individual NOACs (rivaroxaban, apixaban, dabigatran) compared to VKA (warfarin).
Country(-ies) of study	Denmark, Norway, Finland, Sweden
Author	PPD (Quantify Research) PPD (Quantify Research)

	PPD (Bayer) PPD (Bayer)

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG
MAH contact person	PPD Researcher, Integrated Evidence Generation

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1. Abstract

Acronym/Title	REATTAIN
Report version and date	v. 1.0, 26 April 2024
Author	PPD Bayer AG PPD Bayer AG PPD Quantify Research AB PPD Quantify Research AB
IMPACT study number	20030
Keywords	Atrial fibrillation, oral anticoagulants, safety, effectiveness, ischemic stroke, intracranial hemorrhage, real-world evidence
Rationale and background	Oral anticoagulant treatment is essential for the prevention of ischemic stroke or systemic embolism in patients with atrial fibrillation. Evidence from routine clinical practice on the outcomes of reduced doses of non-vitamin K antagonist oral anticoagulants (NOACs) is scarce. This study aimed to assess the effectiveness and safety of these regimens compared to vitamin K antagonists (VKA) for stroke prevention in patients with non-valvular atrial fibrillation.
Research question and objectives	The overall aim of the study is to evaluate the comparative safety and effectiveness of reduced doses of NOACs vs. VKA for stroke prevention in patients with NVAF. **Primary Objective** • To describe the risk of ischemic stroke (IS)/systemic embolism (SE), and intracranial hemorrhage (ICH) in patients with NVAF initiating treatment with reduced doses of individual NOACs (rivaroxaban, apixaban, dabigatran) compared to VKA (warfarin) **Further objectives** Additional objectives are: • To describe the treatment persistence in patients with NVAF initiating treatment with reduced doses of individual NOACs compared to VKA. • To describe the risk of acute kidney injury (AKI) and kidney failure in patients with NVAF initiating

	treatment of reduced doses of individual NOACs compared to VKA. • To describe the risk of severe IS and fatal bleeding in patients with NVAF initiating treatment with reduced doses of an individual NOACs compared to VKA.
Study design	Observational cohort study
Setting	The study was based on data from national registers in four Nordic countries (Denmark, Finland, Norway and Sweden). The study period ran from 1 January 2010 until 31 December 2018. The study was conducted with separate country cohorts, reporting country specific outcomes.
Subjects and study size, including dropouts	Study participants originates from national registers from Denmark, Finland, Norway, and Sweden. The registers have a national coverage and hence, the study population is drawn from the full population within each respective country.
Variables and data sources	Index drug, exposure time and days of supply were used to estimate the individual drug exposure. Outcomes definition included IS/SE, ICH, fatal bleeding, AKI, kidney failure and persistence. Covariates included demographic characteristics, clinical characteristics, comorbidities and comedications. The data was obtained from national administrative registers in Sweden, Denmark, Finland, and Norway, these included the national patient registers, the prescriptions registers and the cause of death registers in each country. Other relevant registries included the national quality of care register on stroke in Sweden.
Results	The study, one of the largest observational investigations to date, involved nearly 135,000 oral anticoagulant-naïve patients, approximately 27,000 of whom received NOACs. The incidence of ischemic stroke and systemic embolism was similar or lower than that of comparable patients who used standard warfarin therapy (rivaroxaban: hazard ratio (HR) 0.93 (95% confidence interval (CI) 0.62-1.40), dabigatran: HR 0.88 (95% CI 0.68-1.14), and apixaban: HR 0.79 (95% CI 0.67-0.94) in meta-analysis across countries.

	The incidences within warfarin groups ranged from 2.16-3.71 per 100 person-years for the four separate countries comparable to those receiving a NOAC. The incidence of intracranial hemorrhage was generally low, with event rates ranging from 0.16 to 1.85 per 100 person-years. In comparison with warfarin patients the meta-analyses across countries yielded HR's; rivaroxaban: HR 1.41 (95% CI 0.78-2.57), dabigatran: 0.35 (95%CI 0.19-0.64), and apixaban: 0.72 (95% CI 0.51-1.04).
Discussion	In this comprehensive nationwide study across Nordic countries, researchers examined AF patients initiated on reduced doses of NOACs, including dabigatran, rivaroxaban, and apixaban. The incidences of ischemic stroke and systemic embolism in patients on reduced NOAC doses were comparable to or even lower than those in patients commencing standard warfarin therapy. The incidence of intracranial hemorrhage events among NOAC-treated patients remained generally low, with rates ranging from 0.16 to 1.85 per 100 person-years. This variability may potentially result from inclusion or non-inclusion of hemorrhagic transformation strokes in the endpoint composite in some of the institutions. HRs for intracranial hemorrhage were generally numerically higher for rivaroxaban compared to the weighted warfarin group, with a pooled HR of 1.41 (95% CI 0.78-2.57). This was primarily influenced by a higher HR observed in Finland among rivaroxaban patients. Finland had a relatively low percentage of new users of reduced dose NOACs, only 7.2%, compared to the other Nordic countries. This resulted in an extremely small sample size and less precise estimates in Finland compared to the other countries, thus the Finish results are more prone to random variability. Conversely, rates among dabigatran and apixaban-treated patients were lower than among comparable warfarin patients, resulting in a pooled HR of 0.35 (95% CI 0.19-0.64) and 0.72 (95% CI 0.51-1.04), respectively. Further differences emerged among Nordic countries, with Finland standing out for offering better protection against ischemic stroke and systemic embolism at the expense of a higher risk of intracranial hemorrhage, particularly with rivaroxaban. Notably, Finland exhibited a relatively low percentage of new users of reduced dose NOACs, suggesting a cautious approach to their use for AF patients.

	The study's findings were consistent with prior research, affirming that reduced dose NOACs in routine clinical use were associated with comparable or lower rates of ischemic stroke and systemic embolism compared to warfarin. The detailed analysis, utilizing comprehensive national registries, highlighted the importance of considering regional variations, timing of NOAC introduction, and differing treatment preferences in understanding outcomes. This research, conducted in a setting with universal healthcare accessibility, similar clinical practices, and high-quality warfarin therapy, contributes insights into the comparative effectiveness and safety of anticoagulants in routine clinical practice, emphasizing the significance of real-world evidence in guiding treatment decisions for AF patients.
Marketing Authorization Holder(s)	Bayer AG

2. List of abbreviations

ACE	Angiotensin-converting enzyme
AE	Adverse event
AF	Atrial fibrillation
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
ATC	Anatomical Therapeutic Chemical
ATT	Among the treated
CCI	Charlson Comorbidity Index
CI	Confidence interval
CKD	Chronic Kidney Disease
HR	Hazard ratio
ICD	International Classification of Diseases
ICH	Intracranial hemorrhage
IPTW	Inverse Probability Treatment Weighting
IQR	Interquartile range
IS	Ischemic stroke
IS1	Ischemic stroke defined from RiksStroke
IS2	Ischemic stroke defined from national registers
ITT	Intention to treat
LAD	Latest available data
MI	Myocardial infarction
NIHSS	National Institute of Health Stroke Scale
NOAC	Non-vitamin K antagonist oral anticoagulants
NVAF	Non-valvular atrial fibrillation
NSAID	Non-steroidal anti-inflammatory drug
OAC	Oral anticoagulant
PAD	Peripheral artery disease
PASS	Post-Authorization Safety Study
REATTAIN	Real-world evidence for non-valvular atrial fibrillation patients treated with oral anticoagulation in the Nordics
RWE	Real-world evidence
SAP	Statistical analysis plan
SE	Systemic embolism
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient ischemic attack
VKA	Vitamin K antagonist

3. Investigators

Study initiator and funder

Role: PPD
Name: PPD
E-mail: PPD

Role: PPD
Name: PPD

Role: PPD
Name: PPD

4. Other responsible parties

Study Team (internal or external)

Role: PPD
Name: PPD
E-mail PPD

Role: PPD
Name: PPD
E-mail: PPD

Contact details of the responsible parties are available upon request.

5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual Date	Comments
Start of data collection	15 December 2017	25 April 2018	
End of data collection	15 September 2018	16 September 2020	
Registration in the EU PAS register	30 January 2020	30 January 2020	
Final report of study results	15 December 2018	30 April 2024	

6. Rationale and background

Atrial Fibrillation (AF) is the most common cardiac arrhythmic disorder, with a prevalence of 1-2% in the general population. It has been estimated that 6-12 million people worldwide will suffer this condition in the US by 2050 and 17.9 million people in Europe by 2060.[1] Evidence regarding the efficacy and safety of direct acting oral anticoagulants (NOACs) for stroke prevention in AF has come from four randomized clinical trials.[2] Subsequently, a large number of observational studies examining real-world usage from Europe and The United States has been presented.[3] Until the presentation of the four randomized landmark studies on stroke prevention in AF (SPAF), warfarin was the mainstay of prevention. Guidelines now advocate NOACs ahead of warfarin as first-line treatment.[4] However, clinical assessment for an appropriate dose remains necessary. Patients with chronic kidney disease in AF carry a heightened risk of stroke and bleeding while on anticoagulant therapy. Poor kidney function necessitates the recommendation of reduced doses of NOACs. Furthermore, consideration of age, body weight or interacting drugs is necessary for proper dose selection.[5] For patients with varying degrees of renal impairment, the dose reduction recommendations in the product information for Rivaroxaban, Apixaban, and Dabigatran differ. For Dabigatran, the suggested dose for patients with creatinine clearance (CrCl) over 30 mL/min is 150 mg, taken orally twice daily; for those with severe renal impairment (CrCl 15-30 mL/min), the recommended dose is reduced to 75 mg twice daily. However, Dabigatran is not recommended for patients with a CrCl less than 15 mL/min or those on dialysis. In the case of Apixaban, a dose of 2.5 mg orally twice daily is recommended for patients who have at least two of the following characteristics: age over 80 years, body weight less than 60 kg, or serum creatinine higher than 5 mg/dL. For Rivaroxaban, a reduced (15 mg) dose is recommended in patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15-29 ml/min) renal impairment. However, no dose adjustment is needed for patients with mild renal impairment (creatinine clearance between 50 and 80 ml/min), the elderly, or those with low body weight. Use of Rivaroxaban it is not recommended for patients with a creatinine clearance less than 15 ml/min. Despite this, studies providing evidence from real-world use of reduced NOAC dosages and related results are currently limited. The objective of this study was to assess the effectiveness and safety of utilizing reduced doses of NOACs and standard warfarin therapy in relation to stroke prevention in a large cohort of non-valvular AF patients from four Nordic countries (Denmark, Finland, Norway, and Sweden).

7. Research question and objectives

The overall aim of the study is to evaluate the comparative safety and effectiveness of reduced doses of NOACs vs. VKA for stroke prevention in patients with NVAF.

All objectives are summarized in Table 2.

Primary Objective

- To describe the risk of ischemic stroke (IS)/systemic embolism (SE), and intracranial hemorrhage (ICH) in patients with NVAF initiating treatment with reduced doses of individual NOACs (rivaroxaban, apixaban, dabigatran) compared to VKA (warfarin)

Further objectives

Additional objectives are:

- To describe the treatment persistence in patients with NVAF initiating treatment with reduced doses of individual NOACs compared to VKA (added as a post-hoc analysis)
- To describe the risk of acute kidney injury (AKI) and kidney failure in patients with NVAF initiating treatment of reduced doses of individual NOACs compared to VKA.
- To describe the risk of severe IS and fatal bleeding in patients with NVAF initiating treatment with reduced doses of an individual NOACs compared to VKA.

Population	Intervention	Comparator	Outcomes	Subgroups	
OAC-naïve NVAF patients	Reduced dose NOAC	VKA	IS/SE, ICH	Elderly (80+)	Primary objectives
				Elderly (85+)	
				Diabetes	
				Diabetes and renal impairment	
				Frail patients	
				Prior IS or SE	
				Prior bleeding	
				Renal impairment (exploratory)	
OAC-naïve NVAF patients	Reduced dose NOAC	VKA	Treatment persistence, AKI, kidney failure, severe IS, fatal bleeding	Elderly (80+)	Further objectives
				Elderly (85+)	
				Diabetes	
				Diabetes and renal impairment	
				Frail patients	
				Prior IS or SE	
				Prior bleeding	
				Renal impairment (exploratory)	

Table 2. PICOS study overview

Key: OAC; Oral Anticoagulants, NVAF; Non-Valvular Atrial Fibrillation, NOAC; Non-Vitamin K Oral Anticoagulants, VKA; Vitamin K Antagonist, IS; Ischemic Stroke, SE; Systemic Embolism, ICH, Intracranial hemorrhage, AKI; Acute Kidney Injury

8. Amendments and updates

Table 3: Amendments

Nr.	*Date*	*Section of study protocol*	*Amendment or Update*	*Reason*
1	*November 2020*	*All*	*Amendment*	*Bayer project leader has been changed.* *Date for the Final Report Milestone has been changed from 15 December 2020 to 15 March 2021.* *Previous secondary objectives were removed due to the following reasons:* *i) The baseline characteristics of the patients taking low dose NOACs and those taking standard dose differ, low doses are indicated for patients with renal impairment (rivaroxaban and dabigatran), concomitant use of verapamil, increased risk of bleeding, and are recommended or can be considered based on age (dabigatran). Thus, patients on standard dose would not be a valid comparison group for patients on low dose.* *ii) The Reattain study planned to classify patients according to renal impairment using the diagnosis by ICD codes. At the time the Reattain study was planned this was the only information available for Bayer and even if it was not highly reliable, it was the best available approach. Since then, laboratory values for glomerular filtration rates (GFR) and serum creatinine have become available for Bayer: the ongoing Sierra UK study included GFR values and the recently initiated FOREWARD study in Denmark includes both markers. Thus, given that that ICD diagnosis codes would not allow an optimal classification of patients by renal impairment status, the Secondary objectives have been removed from the study.* *Secondary objective to compare standard and reduced doses have been removed.* *A method for estimating days of supply for warfarin has been added, based on previous research.*

				We consider it is still important to consider this subgroup even when the classification of renal impairment status is sub-optimal using ICD diagnosis codes as explained above (reasoning for modification of point 8.) because i) dose reduction of rivaroxaban is (only) indicated for patients with renal impairment, thus studying the safety and effectiveness in this population is a patient need and it will not be viewed as promotion of off-label use. ii) Even though ICD codes do not allow a proper optimal classification, clinical recognition via IDC diagnosis is more likely for patients with more advanced renal disease (high CKD stages), thus we can have some insights of the safety and efficacy for these patients. The limitations of using ICD method will be disclosed and discussed. *Further subclassification by stages of CKD or age in combination with renal impairment have been removed to maintain this exploratory subgroup analysis simple instead of adding more complexity due to potential interaction effects.* *Subgroup analysis for renal impairment has been changed from the main subgroup analysis to an exploratory subgroup analysis, given it is based on diagnosis codes which underestimate the true prevalence of renal impairment.* *The Danish QoC register from stroke has been removed from the study due to unavailability. This change was also reflected in the abstract section Data Sources.* *The minimum and maximum values were removed due to reporting reasoning, per Danish regulations, we should not report individual values (usually minimum and maximum represent individual values). Instead we will report p05 and p95th.* *Exclusion criteria has been revised to include:* • *A dispensed prescription of a standard dose NOAC on the index date.* • *A dispensed prescription of an OAC (any dose of rivaroxaban, apixaban, dabigatran, edoxaban, or warfarin) during the lookback period.*
2	*April 2024*	*Exclusion Criteria*	Minor changes and	Exclusion criteria #1 was added to the SAP.

			clarifications to the exclusion criteria in the SAP (working version 2.8 20210121) which was not stated in the final version of the protocol (v2.2. 11.2020).	• New text: [exclusion criteria #1] A dispensed prescription of a standard dose NOAC on the index date. • Rationale: A decision was made by the study team during SAP development to solely focus on a reduced dose NOAC population. This change was noted in the protocol amendment log (Version 2.0 22.09.2020) as "9.3.1 Exposure definition: Text removed: For the comparison between reduced and standard doses of NOACs (secondary objectives), patients will also be censored if they switch from reduced to standard dose or vice versa" Clarification regarding type of diagnosis was made in exclusion criteria #4 in the SAP. • New text: Added a "primary or secondary diagnosis signifying" valvular disease, … • Rationale for change: To clarify that exclusion based on valvular disease, pregnancy, transient cause of AF, or venous thromboembolism, were based on both primary and secondary diagnoses codes in the Swedish National Patient Registry.

9. Research methods

9.1 Study design

REATTAIN was conducted as a non-interventional cohort study based on data from national registers in the Nordics (Denmark, Finland, Norway, and Sweden). The study period ran from 1 January 2010 until 31 December 2018. The different NOACs were introduced at different point of time. For instance, in Sweden, dabigatran and rivaroxaban was introduced in 2008, whereas apixaban in 2012. Given that the different NOACs were not introduced at the same time, this study uses a flexible definition of index date (see 9.2.2) The study was conducted with separate country cohorts, reporting country specific outcomes. Edoxaban was not considered for the study, as it was rarely prescribed in the Nordics prior to 2016.

9.2 Setting

9.2.1 Study population

The source population were patients included in national administrative registers in Denmark, Finland, Norway, and Sweden, based on the inclusion and exclusion criteria (sections 9.2.3.1 and 9.2.3.2). The study population were patients with NVAF who initiated treatment with OACs (VKA or NOAC) in the study period.

9.2.2 Study time frame

The study period began on 1 January 2010 and end on 31 December 2018. The inclusion period ranged from 1 January 2011 to 31 December 2017. The day of the first qualifying OAC dispensing (index drug) constituted the index date (the day of the first qualifying OAC dispensing). The lookback period was defined as the 12 months prior to and including the index date and was used to categorize patients as “new users” of OACs. Patients were followed from the index date until the outcome event of interest, discontinuation of the index drug, death, end of follow-up or the end of the study period, whichever came first. See Figure 1.

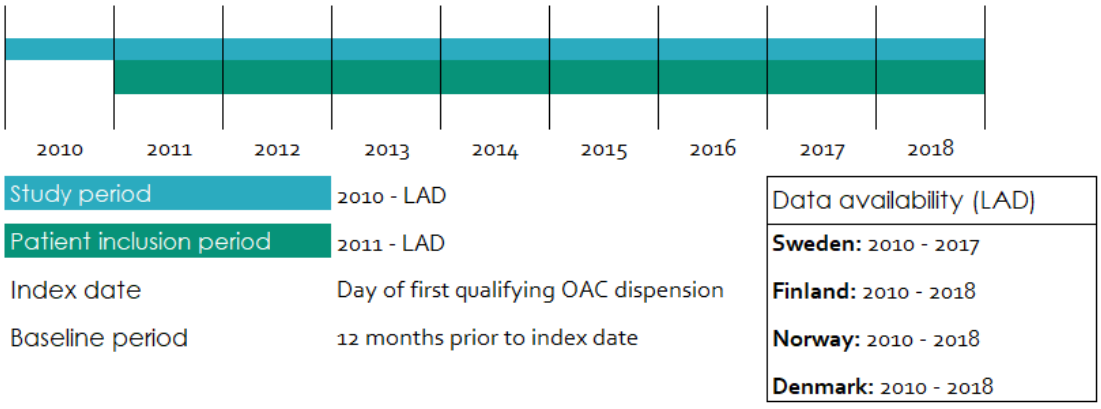

Figure 1. Study time frame

9.2.3 Selection criteria

9.2.3.1 Inclusion criteria

Patients met the following inclusion criteria to be eligible for the study (for detailed definitions see Appendix A: Definitions and operationalizations, ICD-10 and procedure codes):

1. Patients with qualifying OAC (Table 4) dispensed during the inclusion period or on the index date.
2. A primary diagnosis of atrial fibrillation (AF) in the lookback period or on the index date.

Table 4: Qualifying oral anticoagulants for exposure in study

Type of OAC	ATC-code	Active substance	Reduced dose
VKA	B01AA03	warfarin	-
NOAC	B01AE07	dabigatran	110 mg twice daily
NOAC	B01AF01	rivaroxaban	15 mg once daily
NOAC	B01AF02	apixaban	2.5 mg twice daily

9.2.3.2 Exclusion criteria

Patients meeting any of the following exclusion criteria were excluded from the analysis (for detailed definitions see Appendix A: Definitions and operationalizations, ICD-10 and procedure codes, for definitions):

1. A dispensed prescription of a standard dose NOAC on the index date.
2. Age < 18 years at index date
3. Died on index date
4. A primary or secondary diagnosis signifying valvular disease, pregnancy, transient cause of AF (ICD-10 code; I970, I971) or venous thromboembolism in the lookback period or on the index date.
5. A primary diagnosis of active malignant cancer (excl. non-melanoma skin cancer) in the lookback period or on the index date
6. Hip or knee replacement surgery in the 60 days prior to or on the index date.
7. A dispensed prescription of heparin or fondaparinux in the 60 days prior to or on the index date.
8. A primary or secondary diagnosis of end-stage kidney disease or renal replacement therapy in the lookback period or on the index date.
9. More than one OAC (any dose of rivaroxaban, apixaban, dabigatran, edoxaban, or warfarin) prescribed on the index date.
10. A dispensed prescription of an OAC (any dose of rivaroxaban, apixaban, dabigatran, edoxaban, or warfarin) during the lookback period.

9.2.3.3 Sub-group definitions

Analyses were undertaken in nine subgroups. An overview of the subgroups is presented below:

- Elderly (80+)
  - Age ≥80 years at index date

- Elderly (85+)
  - Age ≥85 years at index date
- Diabetes
  - Primary and secondary ICD-10 diagnosis and/or dispensed diabetes drug (ATC) during lookback period
- Frail patients
  - Primary and secondary ICD-10 and procedure codes for Frailty Indicator during lookback period
- Prior IS or SE
  - Primary and secondary ICD-10 diagnosis prior to index date
- Prior bleeding
  - Primary and secondary ICD-10 diagnosis and procedure codes prior to index date
- Diabetes (and in combination with renal impairment) [1]
  - Primary and secondary ICD-10 diagnosis of renal impairment during lookback period in combination with primary and secondary ICD-10 diagnosis of diabetes and/or dispensed diabetes drug (ATC) during lookback period

In addition, given that patients treated with NOAC are usually older, and suffer from renal impairment [2-4] , we added two exploratory subgroup analyses:

- Renal impairment [1]
  - Primary and secondary ICD-10 diagnosis during lookback period. This subgroup is exploratory. Specific analyses were elucidated in the analysis phase of the project and included conducting the main- and sensitivity analyses stratifying by renal impairment plus elderly or prior bleeding.

- Elderly (80+) or Renal impairment
  - Primary and secondary ICD-10 diagnosis during lookback period.
  - Age ≥80 years at index date

9.3 Subjects

Subjects included in the study were defined as patients with NVAF who initiated treatments with OACs (VKA or NOAC). The subjects were selected according to the inclusion and exclusion criteria from the population sourced from the national administrative registers in the four countries of interest for this study.

9.4 Variables

9.4.1 Exposure definitions

- **Exposure time:** Exposure time started on the index date and was calculated as the sum of days of supply:
- **Days of supply:**
  - **rivaroxaban:** The number of tablets in dispensed packages (used once daily)
  - **dabigatran and apixaban:** Half the number of tablets in dispensed packages (used twice daily).

- **warfarin:** Days of supply for warfarin were estimated in two ways, and all results were produced using both methods:
    1. Refill interval method (method 1): Days of supply were based on how long cumulative doses lasted depending on re-calculated dosage for each prescription. To estimate the daily dosage for each warfarin prescription, the following was applied: A standard starting dose (2.5 mg) was assumed for the first prescription. The dosage for subsequent prescriptions was calculated by cumulative doses of previous prescriptions divided by time between first prescription and current prescription. The re-calculated dosage needs to be within a pre-defined interval (1.25 – 10 mg) based on clinical praxis and expertise.
    2. Empirical maintenance dose method (method 2): By applying derived empirical maintenance doses from a previous Swedish study [5]. The study used information from the Swedish anticoagulation and atrial fibrillation register "Auricula" to determine the daily mean doses of warfarin in relation to age and sex. The mean daily dose (mg/day) was calculated with the following equations:
        - 9.344333–0.067688 x Age (years) for men
        - 8.994259–0.068527 x Age (years) for women

9.4.2 Outcomes definition

- **IS and SE** were defined based on primary diagnosis codes.
- **Severe IS** was defined in the following ways:
    - based on severity indicators in quality of care registers, when available
    - based on diagnosis and procedure codes
- **ICH** was defined based on primary diagnoses
- **Fatal bleeding** was defined based on primary diagnosis in combination with subsequent death
- **AKI** was defined based on primary diagnosis codes
- **Kidney failure** (end-stage kidney disease, kidney transplant, or initiation of long-term dialysis) was defined based on diagnosis and procedure codes
- **Persistence** was operationalized as the duration of time from initiation of treatment to discontinuation or switching as described in Section 9.4.1 (i.e., the outcome is discontinuation/switching)

See Table 5 for ICD-10 codes and procedure codes for the outcomes: IS and SE, Severe IS, ICH, Fatal bleeding, AKI and Kidney failure.

Table 5: Outcome definitions – ICD-10 and procedure codes

	Sweden	Norway	Finland	Denmark
Ischemic stroke	**ICD-10 codes:** I63, I64	**ICD-10 codes:** I63, I64	**ICD-10 codes:** I63, I64	**ICD-10 codes:** I63, I64
Systemic embolism	**ICD-10 codes:** I74	**ICD-10 codes:** I74	**ICD-10 codes:** I74	**ICD-10 codes:** I74
Intracranial hemorrhage	**ICD-10 codes:** I60, I61, I62	**ICD-10 codes:** I60, I61, I62	**ICD-10 codes:** I60, I61, I62	**ICD-10 codes:** I60, I61, I62
Kidney failure	**ICD-10 codes:** N185, Z49, Z992, T861, Z940, I120, I132, I1311 **Procedure codes:** DR012, DR013, DR016, DR024, AK050, AK061, AK063, AP019, KAS40, KAS50, KAS00, KAS10, KAS20, KAS60, KAS96, KAS97, TKA20	**ICD-10 codes:** N185, Z49, Z992, T861, Z940, I120, I132, I1311 **Procedure codes:** PCE45B, PCP45B, PCQ45B, SKA0BK, KAS00, KAS01, KAS10, KAS11, KAS20, KAS21, KAS40, KAS41, KAS50, KAS60, KAS61, KAS96, KAS97, RXGD25, RXGD20, A0093, A0094, CHF30, FXP, FXP00, JAGD, JAGD30, JAGD31, JAGD32, JAGD40, JAGD50, JAK10, JAK30, JAX33, JAD10K, JAS10K, JJGD, JJGD00, KAFF00, PHGX00, PHGX05, RAGD, RLGD, RPGD, RXGD, JAK	**ICD-10 codes:** N180, Z49, Z992, T861, Z940, I120, I132, I1311 **Procedure codes:** TK820, FZSP, FXP00, JAK10, TJA33, TJA35, TK823, TK822, TK800, KAXA, KA9AE, KAS40, KAS41, KAS50, KAS00, KAS10, KAS20, KAS60, KAS61, KAS96, KAS97, TKA02, KA2AE, KA2AT	**ICD-10 codes:** N185, Z992, T861, Z940, I120, I132, I1311 **Procedure codes:** BJFD2, KKAS00, KKAS10, KKAS20, KKAS40, KKAS41, KKAS50, KKAS60, KKAS61, KKAS96, KKAS97, KTKA20
Acute kidney injury	**ICD-10 codes:** N17	**ICD-10 codes:** N17	**ICD-10 codes:** N17	**ICD-10 codes:** N17

Fatal bleeding*	**ICD-10 codes:** D50, D62, D649, I60, I61, I62, K64, R58, K22.6., K25, K26, K27, K28, K920, K921, K922	**ICD-10 codes:** D50, D62, D649, I60, I61, I62, K64, R58, K226, K25, K26, K27, K28, K920, K921, K922	**ICD-10 codes:** D50, D62, D649, I60, I62, R58, K226, K25, K26, K27, K28, K920, K921, K922	**ICD-10 codes:** D50, D62, D649, I60, I61, I62, K64, R58, K226, K25, K26, K27, K28, K920, K921, K922
Severe Ischemic stroke*	**ICD-10 codes:** I63, I64	**ICD-10 codes:** I63, I64	**ICD-10 codes:** I63, I64	**ICD-10 codes:** I63, I64

- Note: ICD = International Classification of Diseases. * Death within 30 days

9.4.3 Covariate definition

All information regarding covariates was collected during the lookback period (dichotomous for each of the below listed comorbidities;). The codes used to define the covariates is available in Appendix A: Definitions and operationalizations, ICD-10 and procedure codes. The covariates included in the study are listed below.

Demographic characteristics

- Sex
- Age (at index date)
- Calendar year (at index date)

Prognostic scores based on clinical and demographic characteristics

- CHA2DS2-VASc score
- HAS-BLED score
- Charlson Comorbidity Index (CCI)

Covariates, clinical and life-style characteristics at baseline

- Acute kidney injury
- Alcohol abuse
- Anemia
- Aortic plaque
- Coronary heart disease:
    - Angina pectoris
    - Myocardial infarction
    - Acute ischemic heart diseases
    - Chronic ischemic heart disease
    - Coronary artery bypass graft(s)
    - Percutaneous coronary intervention
- Diabetes mellitus
- Drug abuse
- Gastric or peptic ulcer disease/diseases of gastrointestinal tract
- Heart failure
- Hyperlipidemia
- Hypertension
- Hypothyroidism
- Inflammatory bowel disease
- Liver disease
- Major bleeding
- Malignant cancer
- Obesity
- Other cerebrovascular diseases
- Other metabolic disorders
- Other vascular disease
- Peripherial artery disease

- Psychosis
- Pulmonary disease
- Rheumatoid arthritis/collagen vascular disease
- Renal impairment
- Volume depletion

Comedications

- Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers
- Antiarrhythmics
- Antidepressants
- Antiplatelets
- Antiulcer drugs (except proton-pump inhibitors)
- Beta blockers
- Calcium channel blockers
- Diabetes drugs (incl. insulin)
- Diuretics
- Erythropoietin-simulating agents
- Estrogens
- Lipid modifying agents
- Non-steroidal anti-inflammatory drugs
- Proton-pump inhibitors

Covariates used for propensity score weighting

- Comedication
- ACE/ARB
- Aspirin
- Beta blockers
- Calcium
- Clopidogrel
- NSAID
- Proton-pump inhibitors
- Comorbidities
- Alcohol
- Aortic plaque
- Diabetes
- Hearth failure
- Hyperlipidemia
- Hypertension
- Intracerebral hemorrhage
- IS
- MI
- PAD

- Renal disease (Moderate/severe)
- Renal impairment
- SE
- TIA

Data sources and measurement

This study was conducted on data from registers in Sweden, Denmark, Finland, and Norway. Data was obtained from national administrative registers, including the national patient registers and the prescriptions registers. The cause of death registers were included for Sweden, Norway, and Finland. Other relevant registers included the national quality of care register on stroke in Sweden.

National administrative registers

The national administrative registers in the Nordic countries are summarized in Table 6.

The registers in the four countries provided near-complete coverage of the total population of over 25 million inhabitants – 5.6 million in Denmark, 5.4 million in Finland, 5.1 million in Norway and 9.6 million in Sweden. All included registers have nationwide coverage with linkage made possible using personal identification numbers.

Table 6: Relevant registers in the Nordic countries

Type of register		Specialist care	Prescription/dispensation/ reimbursement	Cause of death
Included variables relevant for this study		Diagnoses (ICD-10), procedures and admission/discharge dates	ATC-codes, strength/size, prescription, date of expedition	Date of death, cause of death
Sweden	**Holder**	*Socialstyrelsen*, the Swedish Board of Health and Welfare		
	Name of register	*Patientregistret*, National Patient Register	*Läkemedelsregistret*, Swedish Prescribed Drug Register	*Dödsorsaksregistret*, Cause of Death Register
Finland	**Holder**	*THL*, National Institute for Health and Welfare	*Kela*, the Social Insurance Institution	*Tilastokeskus*, Statistics Finland
	Name of register	*HILMO* (inpatient), Care Register for Health Care	*Kela*, Finnish Reimbursement Register	Causes of death
Norway	**Holder**	*Helsedirektoratet*, the Norwegian Institute of Health	*Folkhelseinstitutet*, Norwegian Institute of Public Health	

	Name of register	*Norsk pasientregister*, Norwegian Patient Registry	*NorPD*, Norwegian Prescription Database	*Dødsårsaksregisteret*, Norwegian Cause of Death Registry
Denmark	**Holder**	*Sundhedsdatastyrelsen*, Danish Health Data Protection Agency		*CPR-kontoret*, The CPR Office
	Name of register	*Landspatientregisteret* National Patient Register	*Lægemiddelstatistikregisteret* National Prescription Register	*Det Centrale Personregister*, The Central Person Registry

Swedish Quality of Care register for stroke

The Swedish Stroke Register (RiksStroke) is a national quality register on stroke and since 1998 all Swedish hospitals admitting acute stroke patients participate. The register is one of the world's largest stroke registers and includes information on several dimensions of stroke care, including background variables. Information on stroke severity at hospital arrival is registered, as measured by the National Institutes of Health Stroke Scale (NIHSS).

Bias

As a consequence of the observational nature and absence of randomization in this study, various potential biases and mitigation strategies were considered. The overall study design aimed to minimize some of these biases by creating a cohort of new users of OACs diagnosed with NVAF, the indication of interest, and following them over time for the outcomes of interest.

Bias due to missing data

This study relied on register-based data which are known to have a high degree of completeness. Reporting of certain variables used in this study is not voluntary. For example, information on secondary care visits and prescriptions can be expected to be present. If information regarding diagnosis codes or treatment information were partly missing, those records were excluded from analysis.

Outcomes and comorbidities were defined using diagnosis and procedure codes from secondary care in this study. This could lead to a bias when outcomes or comorbidities are undiagnosed or diagnosed in primary care. However, this study included the national health registers covering all diagnoses and procedures recorded in secondary care.

Misclassification bias

Treatment dates were based on the date of filling the prescription at the pharmacy, which may not necessarily match the date of treatment administration. The dispensation of the respective drug does not guarantee that the patient actually took the medication. However, given the relatively long follow-up time, and thus the continuous drug dispensations for each patient, the potential misclassification error was expected to be low.

Access to laboratory values was not available in this study, thus proxies were used instead to identify some patient characteristics, such as level of renal impairment.

Confounding

To avoid confounding the analyses were adjusted using inverse probability of treatment weighting (IPTW). See the statistical analysis plan (SAP) for more details.

Selection bias

By choice of study design this study aimed to minimize selection bias by restricting the study to new users of OACs. While the national registers used in this study have complete coverage of their respective general populations, only prescriptions filled at pharmacies could be captured in the data.

Study size

The actual number of naïve patients (new users of OACs) is presented and summarized in Table 7. The planned scenarios are shown in the study protocol.

Table 7: Number of naïve oral anticoagulant users per drug and country

	Denmark	Norway	Sweden	Finland
Population	5.6 million	5.1 million	9.6 million	5.5 million
Time period	2010 – 2017	2010 – 2018	2010 – 2017	2010 - 2018
Users with AF by oral anticoagulant drug				
VKA				
B01AA03 warfarin	16,141	11,720	42,168	37,985
NOACs (reduced dose)				
B01AE07 dabigatran etexilate	3,498	1,575	1,915	1,194
B01AF01 rivaroxaban	1,912	1,008	1,495	587
B01AF02 apixaban	3,543	2,946	6,055	1,155
Total NOAC	***8,953***	***5,529***	***9,465***	***2,936***

Data transformation

Anonymized analytical datasets comprising all observations and variables required for the planned analyses were created (variables as specified in section 9.4).

All data management and analyses were performed centrally or, if required by national authorities, by local researchers (only applicable for Danish data). A comprehensive statistical analysis plan was developed, which in further detail outlined the definitions and statistical methods used. Data management and statistical analyses were conducted using R, SAS, and STATA.

Statistical methods

All analyses described in this section were performed separately for each country included in the study. The data cleaning and management, as well as the statistical analysis was performed using SAS, STATA 16 or R 4.1.1. All comparison tests were evaluated using a priori significance level of 5%.

9.9.1 Main summary measures

Patients were described at index date in terms of demographic and clinical variables. Continuous variables were reported as number of observations, means, medians, standard deviations, interquartile range (IQR). For categorical variables the numbers and proportions of patients in each category were presented, in line with applicable data protection regulation (i.e., summary measurements are only reported if the number of patients is higher than 5).

9.9.2 Main statistical methods

To determine the risk of outcomes among NOAC users compared with warfarin users, we calculated cause-specific hazard ratios using weighted Cox regression models and weighted cumulative incidence (using an Aalen-Johansen estimator and including death as a competing risk). The weights consisted of inverse probability treatment weights, which were based on propensity scores calculated using boosted regression trees from the twang package. [6] See the stand-alone document "Statistical Analysis Plan (SAP)" for more details regarding the statistical methods used in this study.

9.9.3 Missing values

The national and compulsory health registers included in this study are typically governed by the national authorities in charge of public health and welfare. Reporting of information to the registers is compulsory by all health care providers and pharmacies, thus guaranteeing high completeness rates and nationwide coverage. There is a large number of scientific publications based on the register data sources used in this study. Data was examined for completeness and missing values were anticipated to be minimal based on previous research and the compulsory nature of the data collection. In the very unlikely event that a patient's health care visit or dispensation was not captured at all by the registers, this could not be identified.

If a patient's date of event (date of diagnosis or date of death) was completely missing, the event was excluded, and no imputation was made. If a patient's date of event was partially missing, then:

- If the year was missing, then the date of event was set to missing.
- Missing months were set to July (06).
- Missing days were set to day 15.

Missing data from the quality registers is expected to be higher. However, RiksStroke reports an estimated 94% coverage.

9.9.4 Sensitivity analyses

The following sensitivity analyses were undertaken to explore the impact of key assumptions in the main analysis (more details are provided in the SAP):

Table 8. Performed sensitivity analysis

Type of analysis	**Exclude pat. with events during lookback period**	**ITT population**	**Longer lookback period**	**Follow-up 2 year**	**Follow-up end of data**	**Truncated weights**	**Grace period 60 days**

Incidence	x	x	x	x	x		
Cox regression		x		x	x	x	
Persistence							x

- **Incidence analyses**
  - *Excluded patients with events during the lookback period*: Patients who suffered any outcome belonging to the first set of objectives during lookback period were removed from the study sample.
    - *Rational:* If patients had events during the lookback period it could potentially indicate that the hospital visits (used in the analysis) did not indicate the actual event but instead were follow up visit from a previous event that happened during the lookback period. Removing these patients and evaluating the results could strengthen the main analysis.
  - *Intention to treat (ITT) population*: The analyses were re-performed using an ITT exposure definition, thus, switching dose or to another OAC or discontinuation was not taken into account to censor patients, i.e., patients were followed from the index date until outcome of interest OR; death OR; end of follow-up OR; end of the study period, whichever came first.
    - *Rational:* A sensitivity analysis using the Intention to Treat (ITT) approach was performed to provide a more comprehensive understanding of the treatment's effectiveness and safety in real-world scenarios. The ITT approach, which includes all participants regardless of adherence or treatment modifications, offers insights into the generalizability of the findings, reduces potential selection bias, and presents a conservative estimate of the treatment effect by accounting for non-adherence and dropouts.
  - *Longer lookback period*: The analyses were re-performed assuming a longer lookback period (24 months prior to and including the index date).
    - *Rational:* Including a longer lookback period would affect the time period used for inclusion and exclusion of patients. Major differences in this analysis compared with the main analysis would indicate that the main results are sensitive to the length of the identification period.
  - *Longer follow – up*: The analyses were performed with longer follow ups, 2 years and until end of data availability, respectively.
    - *Rational:* These analyses were performed to evaluate if the main results and findings are sensitive to the choice of follow-up time due to e.g., long-term effects or late-onset outcomes. Extending the follow-up time might also increase the generalizability of the main results given similar findings between analyses.
- **Cox Regression analyses**
  - *Intention to treat (ITT) population*: the rationale for this analysis is described above.
  - *Longer follow – up*: the rationale for this analysis is described above.
  - *Truncated weights:* The weights were truncated to the 99th percentile.
    - *Rational:* Truncating weights to the 99th percentile serves to mitigate the potential disproportionate influence of extreme weights, thereby potentially

enhancing the model's stability and performance. However, given the twang method's ability to optimize the balance of the weights the issue of extreme weights in the main analyses is suspected to be low.

9.9.5 Amendments to the statistical analysis plan

9.9.5.1 Treatment persistence

The analysis of treatment persistence was included as a post-hoc analysis. The probability of treatment persistence was modeled using the Kaplan-Meier where treatment persistence was defined as 1 – the cumulative incidence of non-persistence. The probability of treatment persistence at 365 days was presented together with visualizations of the treatment persistence during the first year. Furthermore, treatment persistence was also modeled using cause-specific Cox regression models. Both an unadjusted and adjusted model controlling for age and sex where fitted. For the main analysis, a 30-day grace period was used to allow for 30 days between end of the current days of supply and a new dispensation. The sensitivity of the results based on the 30-day grace period was explored using a 60-day grace period as a sensitivity analysis (see below). Both method 1 and method 2 for calculating the days of supply for warfarin was evaluated (more details regarding the calculation of days of supply are outlined in the SAP).

Sensitivity analysis of treatment persistence

- **Persistence analyses**
  - *Longer grace period*: A longer grace period of 60 days was explored.
    - *Rational:* A longer grace period might better reflect the real-word adherence patterns of the study population. It might also help to reduce a potential misclassification of non-persistence. Varying the grace period will help to provide an understanding of how different definitions of persistence affect the study outcomes.

9.9.5.2 Meta-analysis of hazard ratios

A meta-analysis of the country-specific weighted hazard ratios for the outcomes in the primary objective IS/SE and ICH was included as a post-hoc analysis to combine findings across countries. A random-effects model was fitted using the R package *metafor* on the estimated HRs for the full population and for the exploratory analysis subgroup elderly (80+) or renal impairment.

Quality control

An extensive and rigorous quality control plan was in place to ensure an efficient and lawful work process with minimal errors and high degree of reproducibility. This included the statistical analysis described in previous sections, but also work done before and after such analyses.

Data was examined for completeness and missing data are anticipated to be minimal based on previous research and the compulsory nature of the data collection.

The analyses were executed as stipulated in the SAP. Designated researchers were responsible for most operational tasks such as data management, analyses, and report writing. When required by national authorities, local researchers performed data extraction, data management and analyses. Such analyses were supervised centrally to guarantee that the same project standards were followed. The team was led by a research leader with experience from similar projects.

The steps involved in data management and analyses were recorded in maintained scripts and logs. This simplified data updates and ensured reproducibility of results, from raw data to end results.

Data analyses were quality controlled according to an in-house protocol that includes a code review. Data cleaning and analytical steps performed were reviewed by a second programmer. Any errors or omissions found during this review were communicated back to the original analyst and updated accordingly.

10. Results

The main results for the REATTAIN study are presented in this section. Please note that complete results for all objectives, cohorts, subgroups, and countries are found in the stand-alone documents referred to in Table 33.

Participants

Sweden

The total number of patients with a dispensation of any AF dose OAC during the period 2010-2017 was 491,508 patients. After excluding those with a standard dose of NOACs and those with an index date outside the period 2011-01-01 to 2017-01-01, the first selection gave a total of 235,131 patients. After applying the rest of the exclusion criteria, the total number of patients was 51,633. Within this final group, there were 42,168 warfarin users. The remaining 9,465 patients were divided among NOACs, with 6,055 using apixaban, 1,915 using dabigatran, and 1,495 using rivaroxaban, as detailed in (

Figure **2**) of the report.

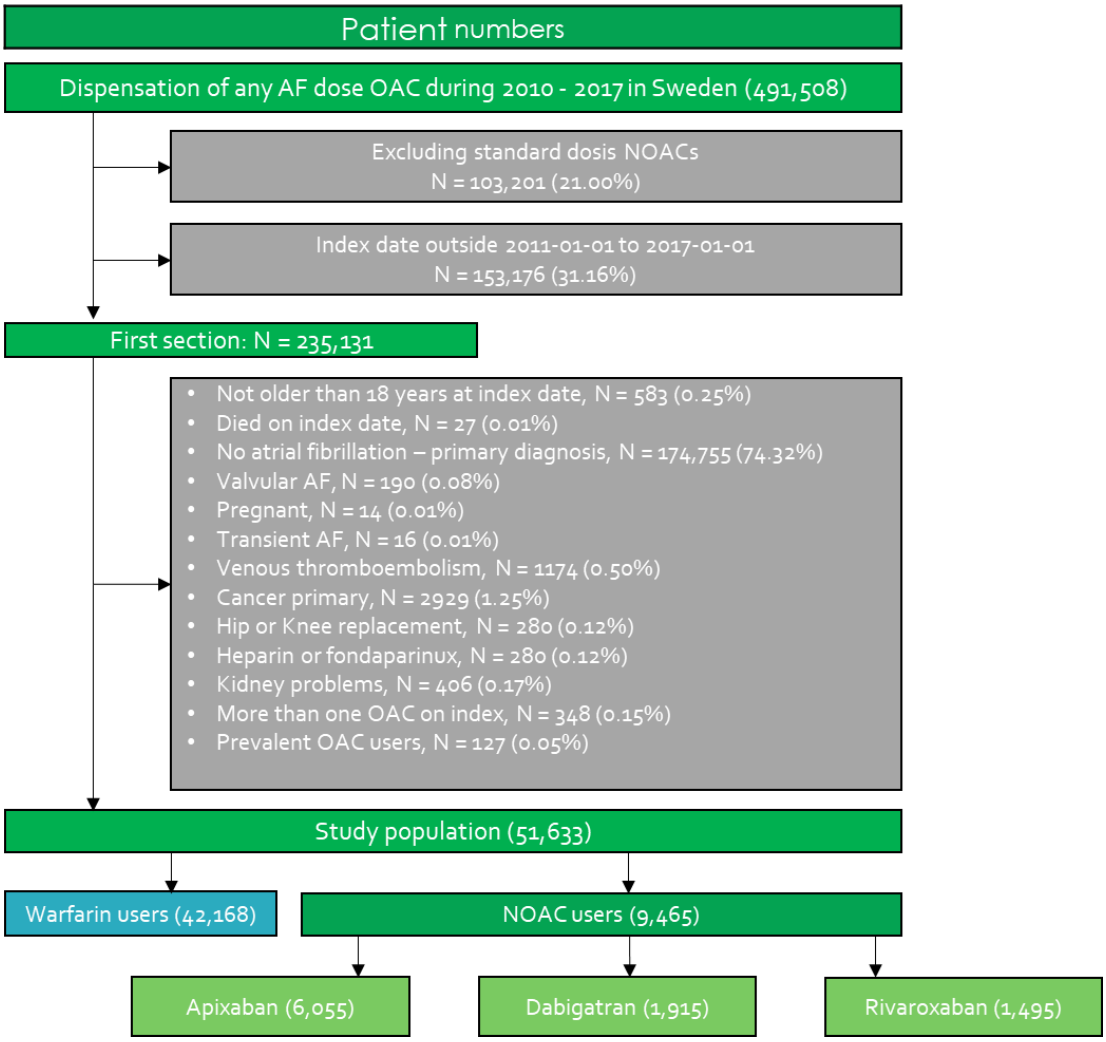

Figure 2 Flowchart of patient selection in Sweden

Norway

The total number of patients with a dispensation of any AF dose OAC during the period 2010-2018 was 160,700 patients. The initial phase of patient selection, which excluded individuals on standard doses of NOACs and those whose index date fell outside of January 1, 2011, to January 1, 2018, resulted in a reduced cohort of 58,157 patients. Further application of additional exclusion criteria led to a refined group of 11,796 patients. Within this final group, 7,604 patients were identified as warfarin users. The remaining 4,192 patients were segmented into three NOAC categories: 2,296 apixaban users, 1,079 dabigatran users, and 817 rivaroxaban users, as illustrated in Figure 3.

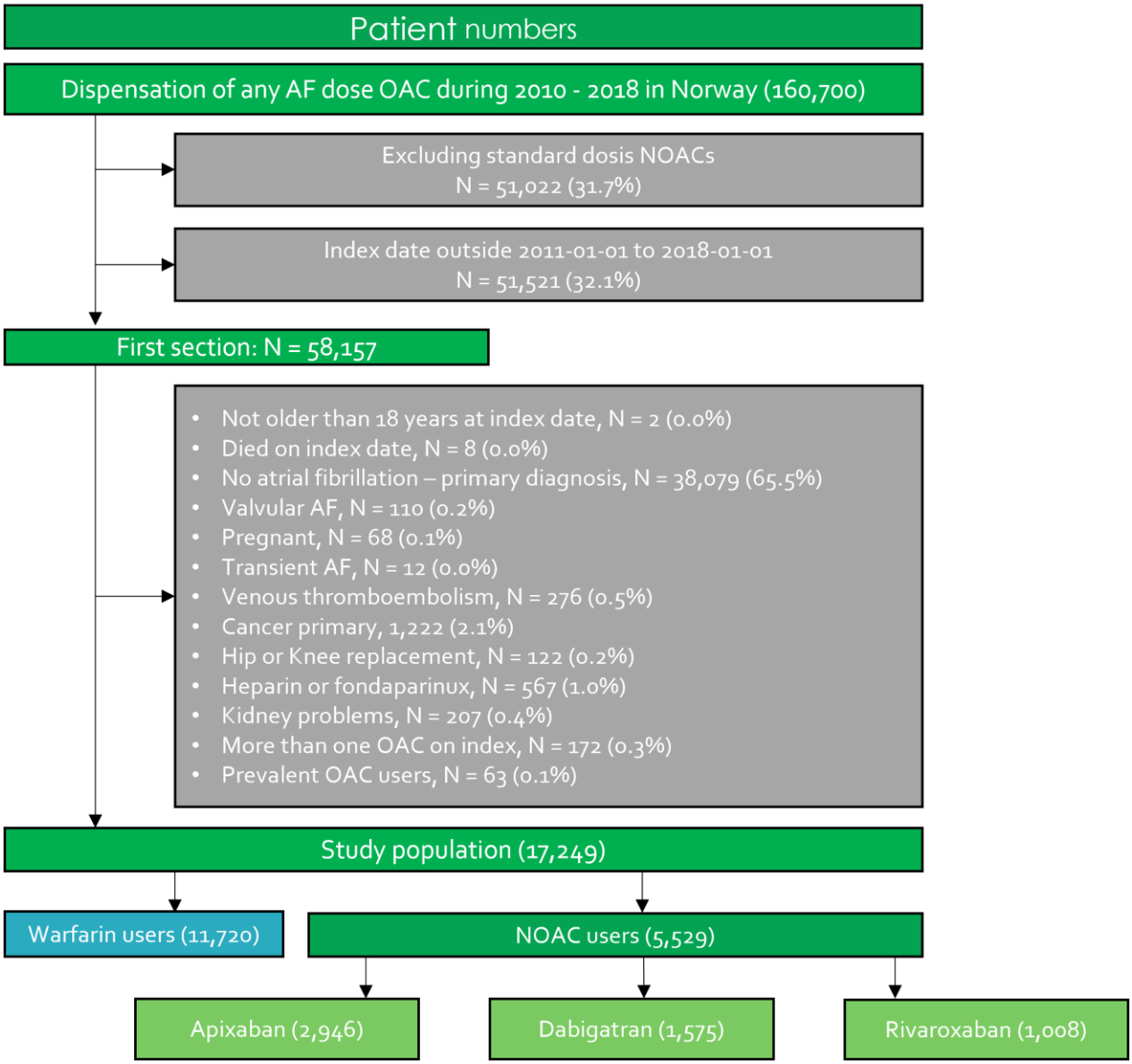

Figure 3. Flowchart of patient selection in Norway

Finland

The initial selection, which filtered out patients on standard doses of NOACs and those with an index date not within January 1, 2011, to January 1, 2018, reduced the cohort to 107,480 patients. Further application of exclusion criteria brought the final count to 40,921 patients. This group comprised 37,985 warfarin users, with the remaining 2,936 patients using NOACs, distributed among apixaban (1,155 users), dabigatran (1,194 users), and rivaroxaban (587 users), as detailed in Figure 4 of the study report.

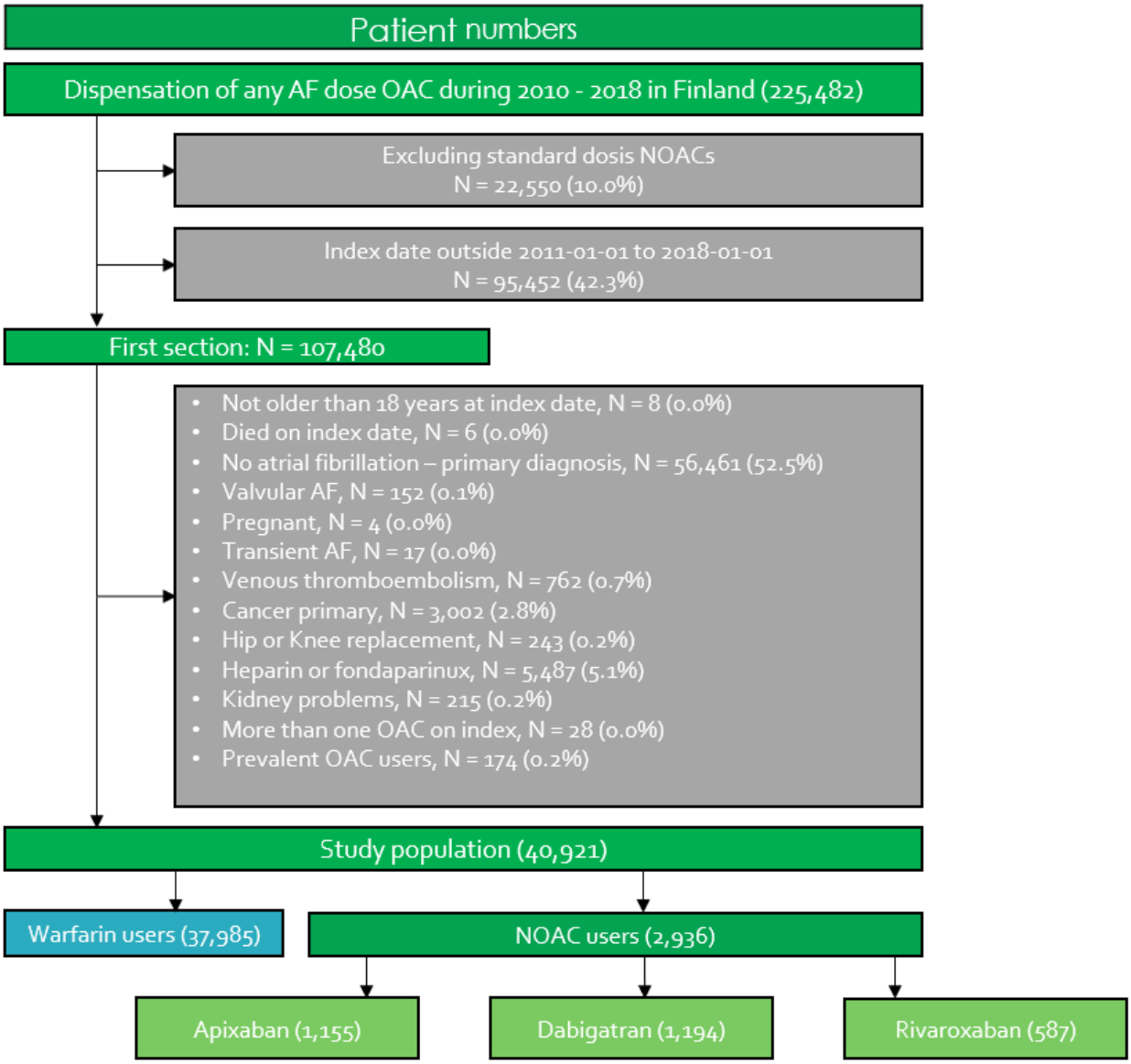

Figure 4. Flowchart of patient selection in Finland

Denmark

The total number of patients with a dispensation of any AF dose OAC during the period 2010-2017 was 224,076 patients. After excluding those with a standard dose of NOACs and those with an index date outside the period 2011-01-01 to 2017-01-01, the first selection gave a total of 128,471 patients. After applying the rest of the exclusion criteria, the total number of patients was 25,094. From those, 16,141 were warfarin users and 8,953 were NOAC users divided into 3 categories: apixaban (3,543 users), dabigatran (3,498 users) and rivaroxaban (1,912 users) respectively (Figure 5).

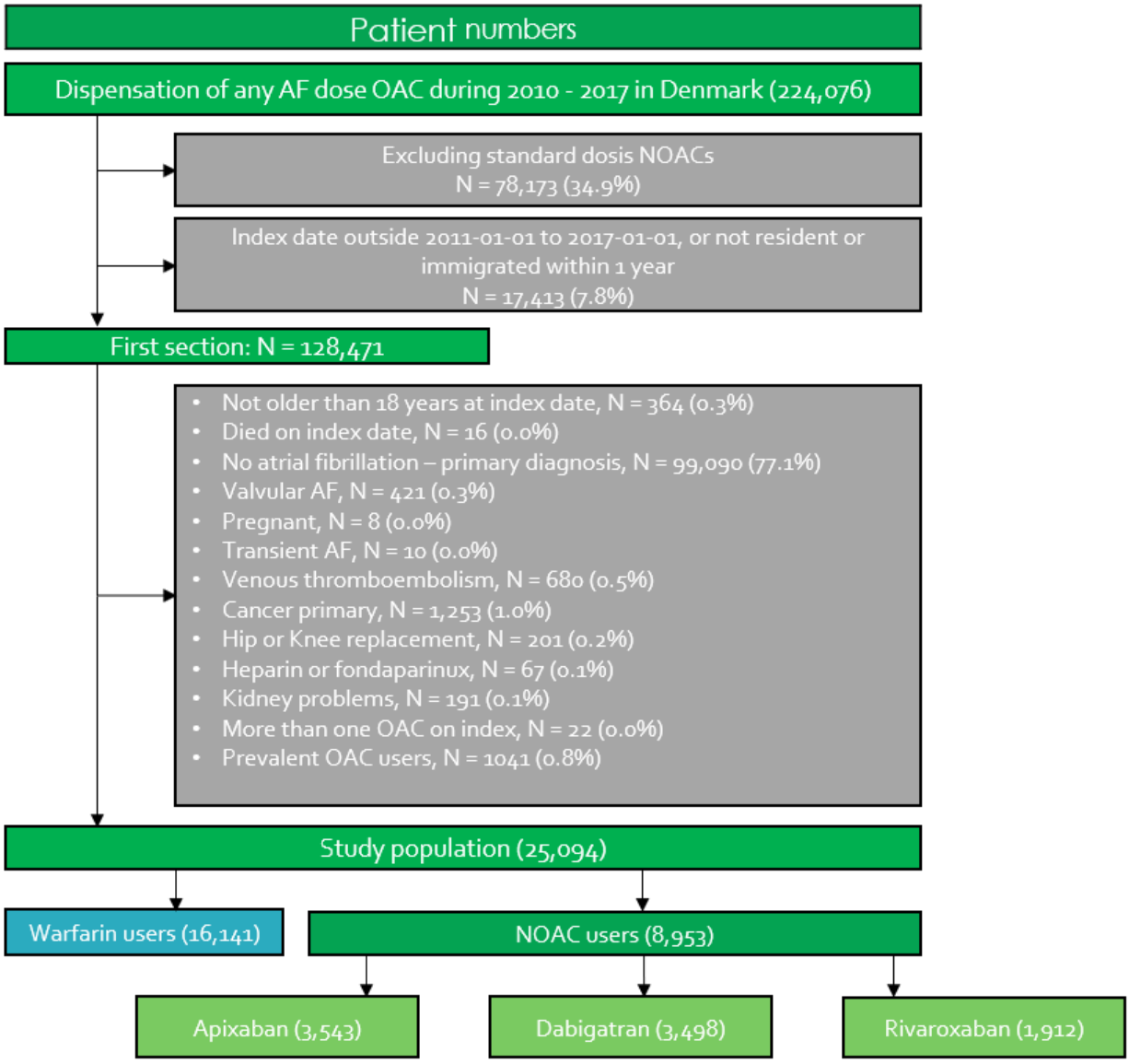

Figure 5. Flowchart of patient selection in Denmark

Descriptive data

The following tables contain results on patient characteristics in the four study populations (Sweden, Norway, Finland and Denmark), including demographic characteristics, clinical characteristics,

comorbidities and comedications. Patient characteristics for the different subgroups in this analysis for the four countries are presented in the stand-alone document "Quantify REATTAIN Patient Characteristics" referred to in Table 33.

Sweden

Table 9 shows patient characteristics for the Swedish cohort group, the mean age was 74.59 years, and 49.37 % were female. The Charlson Comorbidity index mean was higher in patients using apixaban compared to the rest of the cohort. The most frequent comorbidities in this group were hypertension (76.90%) and hearth failure (15.96%).

Norway

Note: Cells with less than 5 patients results cannot be reported due to regulations as described in section 9.9.1.

Table 10 shows patient characteristics for the Norwegian cohort, the mean age was74.45 years, 48.91% were female. The Charlson Comorbidity index mean was higher in patients using apixaban compared to the rest of the cohort. The most frequent comorbidities in this group were hypertension (76.03%) and hearth failure (14.93%), respectively.

Finland

Data on the Finnish cohort is presented in Table 11. The mean age was 74.11 years and 49.91% were female. The Charlson Comorbidity Index mean was higher for patients taking rivaroxaban compared to the rest of the cohort. The most frequent comorbidities for this group were hypertension (68.94%) and diabetes mellitus (13.62%).

Denmark

Note: Cells with less than 5 patients results cannot be reported due to regulations as described in section 9.9.1.

Table 12 shows patient characteristics for the Danish cohort, the mean age was 75 years and 49.91% were female. The Charlson Comorbidity Index mean was higher among patients taking rivaroxaban. The most frequent comorbidities in this group were hypertension (64.94%) and diabetes mellitus (13.62%), respectively.

Table 9. Patient characteristics: Population OAC naïve NVAF patients in Sweden

Patient characteristics at index date	*rivaroxaban 15 mg once/day*		*dabigatran 110 mg twice/day*		*apixaban 2.5 mg twice/day*		*warfarin*		*All patients*	
	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd
Demographic characteristics										
Number of patients, n (%)	1,495	2.90%	1,915	3.71%	6,055	11.73%	42,168	81.67%	51,633	100%
Age, mean, median, sd.	82.06	(84) 8.55	79.53	(81) 8.58	85.04	(86) 7.27	72.6	(73) 10.97	74.59	(76) 11.31
Age group, n (%)										
80+	1,018	68.09%	1,153	60.21%	5,083	83.95%	12,171	28.86%	19,425	37.62%
85+	675	45.15%	549	28.67%	3,567	58.91%	5,700	13.52%	10,491	20.32%
Sex, n (%)										
Females	877	58.66%	1,083	56.55%	4,071	67.23%	19,459	46.15%	25,490	49.37%
Males	618	41.34%	832	43.45%	1,984	32.77%	22,709	53.85%	26,143	50.63%
Clinical characteristics										
CHADS2-VASc score, mean, median, sd.	2.59	(2) 1.04	2.39	(2) 1.03	2.54	(2) 1.03	2.12	(2) 1.10	2.19	(2) 1.10
HAS-BLED score, mean, median, sd.	2.58	(3) 0.83	2.5	(3) 0.85	2.56	(3) 0.88	2.24	(2) 1.00	2.30	(2) 0.98
Charlson Comorbidity Index, mean, median, sd.	1.05	(1) 1.36	0.78	(0) 1.16	1.10	(1) 1.40	0.70	(0) 1.15	0.76	(0) 1.20
Comorbidities, n (%)										
Acute kidney injury	15	1.00%	11	0.57%	63	1.04%	176	0.42%	265	0.51%
Alcohol Abuse	8	0.54%	11	0.57%	31	0.51%	375	0.89%	425	0.82%
Anemia	67	4.48%	79	4.13%	391	6.46%	957	2.27%	1,494	2.89%
Aortic plaque	<5	NA	<5	NA	<5	NA	19	0.05%	24	0.05%
Coronary heart disease:										
Acute ischemic heart diseases	<5	NA	<5	NA	6	0.10%	39	0.09%	48	0.09%
Angina pectoris	124	8.29%	110	5.74%	435	7.18%	2,476	5.87%	3,145	6.09%

Chronic ischemic heart disease	139	9.30%	132	6.89%	571	9.43%	2,985	7.08%	3,827	7.41%
Coronary artery bypass graft(s)	74	4.95%	75	3.92%	237	3.91%	1,611	3.82%	1,997	3.87%
Myocardial infarction	203	13.58%	211	11.02%	826	13.64%	4,087	9.69%	5,327	10.32%
Percutaneous coronary intervention	35	2.34%	37	1.93%	118	1.95%	802	1.90%	992	1.92%
Diabetes mellitus	289	19.33%	255	13.32%	915	15.11%	6,372	15.11%	7,831	15.17%
Drug abuse	<5	NA	<5	NA	<5	NA	56	0.13%	64	0.12%
Gastric or peptic ulcer disease/diseases of gastrointestinal tract	56	3.75%	66	3.45%	212	3.5%	1,152	2.73%	1,486	2.88%
Heart failure	312	20.87%	298	15.56%	1,502	24.81%	6,127	14.53%	8,239	15.96%
Hyperlipidemia	97	6.49%	145	7.57%	351	5.80%	3,272	7.76%	3,865	7.49%
Hypertension	1,246	83.34%	1,540	80.42%	4,789	79.09%	32,129	76.19%	39,704	76.90%
Hypothyroidism	112	7.49%	111	5.80%	422	6.97%	1,976	4.69%	2,621	5.08%
Inflammatory bowel disease	23	1.54%	19	0.99%	80	1.32%	432	1.02%	554	1.07%
Liver disease	<5	NA	13	0.68%	18	0.30%	262	0.62%	NA	0.57%
Major bleeding	91	6.09%	114	5.95%	490	8.09%	1,357	3.22%	2,052	3.97%
Malignant cancer	<5	NA	<5	NA	<5	NA	<5	NA	<5	NA
Obesity	20	1.34%	13	0.68%	46	0.76%	720	1.71%	799	1.55%
Other cerebrovascular disease	31	2.07%	27	1.41%	101	1.67%	369	0.88%	528	1.02%
Other metabolic disorders	40	2.68%	34	1.78%	199	3.29%	564	1.34%	837	1.62%
Other vascular disease	245	16.39%	238	12.43%	787	13.00%	4,678	11.09%	5,948	11.52%
Peripheral artery disease	55	3.68%	67	3.50%	214	3.53%	1,103	2.62%	1,439	2.79%
Psychosis	7	0.47%	17	0.89%	36	0.59%	236	0.56%	296	0.57%
Pulmonary disease	134	8.96%	169	8.83%	601	9.93%	3,261	7.73%	4,165	8.07%
Renal impairment	68	4.55%	23	1.20%	348	5.75%	996	2.36%	1,435	2.78%
Rheumatoid arthritis/collagen vascular disease	110	7.36%	122	6.37%	480	7.93%	2,114	5.01%	2,826	5.47%
Volume depletion	18	1.20%	21	1.10%	121	2.00%	186	0.44%	346	0.67%

Comedications, n (%)										
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	840	56.19%	1,012	52.85%	3,192	52.72%	20,393	48.36%	25,437	49.27%
Antiarrhythmics	23	1.54%	83	4.33%	93	1.54%	2,208	5.24%	2,407	4.66%
Antidepressants	247	16.52%	279	14.57%	1,041	17.19%	4,767	11.30%	6,334	12.27%
Antiplatelets	890	59.53%	1,101	57.49%	3,428	56.61%	21,484	50.95%	26,903	52.10%
Antiulcer drugs (except proton-pump inhibitors)	29	1.94%	31	1.62%	93	1.54%	646	1.53%	799	1.55%
Beta blockers	980	65.55%	1,247	65.12%	3,613	59.67%	25,658	60.85%	31,498	61.00%
Calcium channel blockers	522	34.92%	606	31.64%	2,071	34.2%	12,569	29.81%	15,768	30.54%
Diabetes drugs (incl. insulin)	233	15.59%	223	11.64%	755	12.47%	5,435	12.89%	6,646	12.87%
Diuretics	826	55.25%	840	43.86%	3,094	51.10%	16,749	39.72%	21,509	41.66%
Erythropoietin-simulating agents	5	0.33%	5	0.26%	22	0.36%	109	0.26%	141	0.27%
Estrogens	141	9.43%	232	12.11%	698	11.53%	4,003	9.49%	5,074	9.83%
Lipid modifying agents	586	39.2%	673	35.14%	2,071	34.20%	14,940	35.43%	18,270	35.38%
Non-steroidal anti-inflammatory drugs	210	14.05%	314	16.4%	717	11.84%	8,261	19.59%	9,502	18.40%
Proton-pump inhibitors	451	30.17%	539	28.15%	1,786	29.50%	10,089	23.93%	12,865	24.92%
Covariates used for model, n (%)										
Comedication										
ACE/ARB	840	56.19%	1,012	52.85%	3,192	52.72%	20,393	48.36%	25,437	49.27%
Aspirin	808	54.05%	1,009	52.69%	3,124	51.59%	20,474	48.55%	25,415	49.22%
Beta blockers	980	65.55%	1,247	65.12%	3,613	59.67%	25,658	60.85%	31,498	61.00%
Calcium	522	34.92%	606	31.64%	2,071	34.20%	12,569	29.81%	15,768	30.54%
Clopidogrel	135	9.03%	156	8.15%	486	8.03%	2,250	5.34%	3,027	5.86%
NSAID	210	14.05%	314	16.40%	717	11.84%	8,261	19.59%	9,502	18.40%
Proton-pump inhibitors	451	30.17%	539	28.15%	1,786	29.50%	10,089	23.93%	12,865	24.92%
Comorbidities										
Alcohol	8	0.54%	11	0.57%	31	0.51%	375	0.89%	425	0.82%
Aortic Plaque	<5	NA	<5	NA	<5	NA	19	0.05%	24	0.05%

Diabetes	289	19.33%	255	13.32%	915	15.11%	6,372	15.11%	7,831	15.17%
Heart failure	312	20.87%	298	15.56%	1,502	24.81%	6,127	14.53%	8,239	15.96%
Hyperlipidemia	97	6.49%	145	7.57%	351	5.80%	3,272	7.76%	3,865	7.49%
Hypertension	1,246	83.34%	1,540	80.42%	4,789	79.09%	32,129	76.19%	39,704	76.9%
Intracerebral hemorrhage	<5	NA	8	0.42%	8	0.13%	25	0.06%	43	0.08%
IS	51	3.41%	93	4.86%	243	4.01%	1,213	2.88%	1,600	3.10%
Liver Disease (Moderate/severe)	<5	NA	<5	NA	<5	NA	39	0.09%	49	0.09%
MI	203	13.58%	211	11.02%	826	13.64%	4,087	9.69%	5,327	10.32%
PAD	55	3.68%	67	3.50%	214	3.53%	1,103	2.62%	1,439	2.79%
Renal Disease (Moderate/severe)	90	6.02%	38	1.98%	466	7.70%	1,329	3.15%	1,923	3.72%
Renal impairment	68	4.55%	23	1.20%	348	5.75%	996	2.36%	1,435	2.78%
SE	5	0.33%	<5	NA	25	0.41%	114	0.27%	148	0.29%
TIA	32	2.14%	52	2.72%	134	2.21%	719	1.71%	937	1.81%

Note: Cells with less than 5 patients results cannot be reported due to regulations as described in section 9.9.1.

Table 10. Patient characteristics: Population OAC naïve NVAF patients in Norway

Patient characteristics at index date	*rivaroxaban 15 mg once/day*		*dabigatran 110 mg twice/day*		*apixaban 2.5 mg twice/day*		*warfarin*		*All patients*	
	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd
Demographic characteristics										
Number of patients, n (%)	1008	5.84%	1575	9.13%	2946	17.08%	11720	67.95%	17249	100%
Age, mean, median, sd.	80.3	(81.5) 9.61	79.35	(81) 8.89	83.72	(85) 8.94	70.96	(72) 12.5	74.45	(76) 12.63
Age group, n (%)										
80+	607	60.22%	901	57.21%	2319	78.72%	3261	27.82%	7088	41.09%
85+	369	36.61%	448	28.44%	1607	54.55%	1613	13.76%	4037	23.40%

Sex, n (%)										
Females	565	56.05%	853	54.16%	1938	65.78%	5080	43.34%	8436	48.91%
Males	443	43.95%	722	45.84%	1008	34.22%	6640	56.66%	8813	51.09%
Clinical characteristics										
CHADS2-VASc score, mean, median, sd.	3.7	(4) 1.25	3.58	(4) 1.24	3.94	(4) 1.29	2.89	(3) 1.57	3.18	(3) 1.54
HAS-BLED score, mean, median, sd.	2.66	(3) 0.87	2.54	(3) 0.84	2.64	(3) 0.96	2.27	(2) 1.01	2.38	(3) 0.99
Charlson Comorbidity Index, mean, median, sd.	0.94	(0) 1.34	0.77	(0) 1.13	1.13	(1) 1.42	0.75	(0) 1.19	0.83	(0) 1.24
Comorbidities, n (%)										
Acute kidney injury	27	2.68%	24	1.52%	103	3.5%	155	1.32%	309	1.79%
Alcohol Abuse	9	0.89%	11	0.7%	18	0.61%	54	0.46%	92	0.53%
Anemia	38	3.77%	37	2.35%	163	5.53%	239	2.04%	477	2.77%
Aortic plaque	<5	<5	<5	<5	5	0.17%	8	0.07%	18	0.1%
Coronary heart disease:										
Acute ischemic heart diseases	<5	<5	<5	<5	<5	<5	10	0.09%	12	0.07%
Angina pectoris	52	5.16%	94	5.97%	185	6.28%	822	7.01%	1153	6.68%
Chronic ischemic heart disease	118	11.71%	188	11.94%	372	12.63%	1444	12.32%	2122	12.3%
Coronary artery bypass graft(s)	25	2.48%	34	2.16%	69	2.34%	319	2.72%	447	2.59%
Myocardial infarction	108	10.71%	137	8.7%	295	10.01%	1207	10.3%	1747	10.13%
Percutaneous coronary intervention	16	1.59%	20	1.27%	29	0.98%	295	2.52%	360	2.09%
Diabetes mellitus	122	12.1%	183	11.62%	398	13.51%	1398	11.93%	2101	12.18%
Drug abuse	<5	<5	<5	<5	<5	<5	5	0.04%	6	0.03%
Gastric or peptic ulcer disease/diseases	51	5.06%	55	3.49%	111	3.77%	410	3.5%	627	3.63%

of gastrointestinal tract										
Heart failure	129	12.8%	207	13.14%	531	18.02%	1709	14.58%	2576	14.93%
Hyperlipidemia	23	2.28%	46	2.92%	69	2.34%	422	3.6%	560	3.25%
Hypertension	819	81.25%	1186	75.3%	2206	74.88%	8903	75.96%	13114	76.03%
Hypothyroidism	25	2.48%	42	2.67%	88	2.99%	329	2.81%	484	2.81%
Inflammatory bowel disease	10	0.99%	17	1.08%	29	0.98%	101	0.86%	157	0.91%
Liver disease	<5	<5	5	0.32%	18	0.61%	65	0.55%	91	0.53%
Major bleeding	60	5.95%	60	3.81%	212	7.2%	351	2.99%	683	3.96%
Malignant cancer	<5	<5	<5	<5	<5	<5	<5	<5	<5	<5
Obesity	5	0.5%	9	0.57%	16	0.54%	125	1.07%	155	0.9%
Other cerebrovascular disease	20	1.98%	32	2.03%	48	1.63%	177	1.51%	277	1.61%
Other metabolic disorders	29	2.88%	45	2.86%	129	4.38%	214	1.83%	417	2.42%
Other vascular disease	89	8.83%	115	7.3%	268	9.1%	952	8.12%	1424	8.26%
Peripheral artery disease	66	6.55%	73	4.63%	183	6.21%	504	4.3%	826	4.79%
Psychosis	<5	<5	<5	<5	<5	<5	20	0.17%	28	0.16%
Pulmonary disease	84	8.33%	132	8.38%	301	10.22%	1043	8.9%	1560	9.04%
Renal impairment	67	6.65%	40	2.54%	273	9.27%	415	3.54%	795	4.61%
Rheumatoid arthritis/collagen vascular disease	55	5.46%	90	5.71%	158	5.36%	493	4.21%	796	4.61%
Volume depletion	36	3.57%	38	2.41%	138	4.68%	186	1.59%	398	2.31%
Comedications, n (%)										
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	522	51.79%	775	49.21%	1414	48%	5263	44.91%	7974	46.23%

Antiarrhythmics	40	3.97%	77	4.89%	72	2.44%	1362	11.62%	1551	8.99%
Antidepressants	137	13.59%	182	11.56%	414	14.05%	1157	9.87%	1890	10.96%
Antiplatelets	643	63.79%	994	63.11%	1779	60.39%	6876	58.67%	10292	59.67%
Antiulcer drugs (except proton-pump inhibitors)	27	2.68%	42	2.67%	88	2.99%	317	2.7%	474	2.75%
Beta blockers	572	56.75%	847	53.78%	1570	53.29%	6548	55.87%	9537	55.29%
Calcium channel blockers	328	32.54%	477	30.29%	908	30.82%	3110	26.54%	4823	27.96%
Diabetes drugs (incl. insulin)	105	10.42%	162	10.29%	327	11.1%	1153	9.84%	1747	10.13%
Diuretics	440	43.65%	661	41.97%	1333	45.25%	4409	37.62%	6843	39.67%
Erythropoietin-simulating agents	<5	<5	<5	<5	9	0.31%	17	0.15%	29	0.17%
Estrogens	67	6.65%	102	6.48%	208	7.06%	659	5.62%	1036	6.01%
Lipid modifying agents	459	45.54%	731	46.41%	1261	42.8%	4921	41.99%	7372	42.74%
Non-steroidal anti-inflammatory drugs	226	22.42%	369	23.43%	526	17.85%	2863	24.43%	3984	23.1%
Proton-pump inhibitors	244	24.21%	368	23.37%	854	28.99%	2343	19.99%	3809	22.08%
Covariates used for model, n (%)										
Comedication										
ACE/ARB	522	51.79%	775	49.21%	1414	48%	5263	44.91%	7974	46.23%
Aspirin	600	59.52%	945	60%	1682	57.09%	6625	56.53%	9852	57.12%
Beta blockers	572	56.75%	847	53.78%	1570	53.29%	6548	55.87%	9537	55.29%
Calcium	328	32.54%	477	30.29%	908	30.82%	3110	26.54%	4823	27.96%
Clopidogrel	65	6.45%	76	4.83%	190	6.45%	625	5.33%	956	5.54%
NSAID	226	22.42%	369	23.43%	526	17.85%	2863	24.43%	3984	23.1%
Proton-pump inhibitors	244	24.21%	368	23.37%	854	28.99%	2343	19.99%	3809	22.08%
Comorbidities										
Alcohol	9	0.89%	11	0.7%	18	0.61%	54	0.46%	92	0.53%

Aortic Plaque	<5	<5	<5	<5	5	0.17%	8	0.07%	18	0.1%
Diabetes	122	12.1%	183	11.62%	398	13.51%	1398	11.93%	2101	12.18%
Heart failure	129	12.8%	207	13.14%	531	18.02%	1709	14.58%	2576	14.93%
Hyperlipidemia	23	2.28%	46	2.92%	69	2.34%	422	3.6%	560	3.25%
Hypertension	819	81.25%	1186	75.3%	2206	74.88%	8903	75.96%	13114	76.03%
Intracerebral hemorrhage	<5	<5	<5	<5	9	0.31%	10	0.09%	24	0.14%
IS	33	3.27%	61	3.87%	110	3.73%	380	3.24%	584	3.39%
Liver Disease (Moderate/severe)	<5	<5	<5	<5	8	0.27%	11	0.09%	19	0.11%
MI	108	10.71%	137	8.7%	295	10.01%	1207	10.3%	1747	10.13%
PAD	66	6.55%	73	4.63%	183	6.21%	504	4.3%	826	4.79%
Renal Disease (Moderate/severe)	110	10.91%	80	5.08%	447	15.17%	659	5.62%	1296	7.51%
Renal impairment	67	6.65%	40	2.54%	273	9.27%	415	3.54%	795	4.61%
SE	<5	<5	<5	<5	9	0.31%	26	0.22%	39	0.23%
TIA	22	2.18%	39	2.48%	47	1.6%	210	1.79%	318	1.84%

Note: Cells with less than 5 patients results cannot be reported due to regulations as described in section 9.9.1.

Table 11. Patient characteristics: Population OAC naïve NVAF patients in Finland

Patient characteristics at index date	*rivaroxaban 15 mg once/day*		*dabigatran 110 mg twice/day*		*apixaban 2.5 mg twice/day*		*warfarin*		*All patients*	
	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd	n or mean	% or (median) sd
Demographic characteristics										
Number of patients, n (%)	587	1.43%	1,194	2.92%	1,155	2.82%	37,985	92.83%	40,921	100%
Age, mean, median, sd.	80.24	(81) 9.25	79.58	(81) 8.29	84.78	(85) 7.37	73.52	(74) 11.32	74.11	(75) 11.34
Age group, n (%)										
80+	318	54.17%	635	53.18%	918	79.48%	11,663	30.70%	13,534	33.07%

85+	192	32.71%	273	22.86%	570	49.35%	5,577	14.68%	6,612	16.16%
Sex, n (%)										
Females	353	60.14%	771	64.57%	831	71.95%	20,530	54.05%	22,485	54.95%
Males	234	39.86%	423	35.43%	324	28.05%	17,455	45.95%	18,436	45.05%
Clinical characteristics										
CHADS2-VASc score, mean, median, sd.	2.84	(3) 0.99	2.6	(2) 0.98	2.85	(3) 0.96	2.2	(2) 1.11	2.24	(2) 1.11
HAS-BLED score, mean, median, sd.	2.31	(2) 0.73	2.25	(2) 0.69	2.32	(2) 0.69	1.94	(2) 0.84	1.97	(2) 0.84
Charlson Comorbidity Index, mean, median, sd.	1.07	(1) 1.43	0.67	(0) 1.01	1.06	(1) 1.3	0.65	(0) 1.08	0.67	(0) 1.09
Comorbidities, n (%)										
Acute kidney injury	17	2.90%	<5	NA	10	0.87%	158	0.42%	187	0.46%
Alcohol Abuse	6	1.02%	11	0.92%	7	0.61%	563	1.48%	587	1.43%
Anemia	20	3.41%	35	2.93%	51	4.42%	624	1.64%	730	1.78%
Aortic plaque	<5	NA	<5	NA	<5	NA	10	0.03%	12	0.03%
Coronary heart disease:										
Acute ischemic heart diseases	<5	NA	<5	NA	<5	NA	23	0.06%	26	0.06%
Angina pectoris	23	3.92%	39	3.27%	38	3.29%	1,426	3.75%	1,526	3.73%
Chronic ischemic heart disease	100	17.04%	144	12.06%	188	16.28%	4,031	10.61%	4,463	10.91%
Coronary artery bypass graft(s)	6	1.02%	13	1.09%	12	1.04%	295	0.78%	326	0.80%
Myocardial infarction	43	7.33%	55	4.61%	99	8.57%	1,882	4.95%	2,079	5.08%
Percutaneous coronary intervention	20	3.41%	18	1.51%	37	3.20%	53	0.14%	128	0.31%
Diabetes mellitus	164	27.94%	220	18.43%	228	19.74%	7,620	20.06%	8,232	20.12%
Drug abuse	<5	NA	<5	NA	<5	NA	24	0.06%	25	0.06%
Gastric or peptic ulcer disease/diseases of gastrointestinal tract	9	1.53%	22	1.84%	20	1.73%	655	1.72%	706	1.73%
Heart failure	144	24.53%	202	16.92%	337	29.18%	6,580	17.32%	7,263	17.75%
Hyperlipidemia	41	6.98%	71	5.95%	68	5.89%	1,994	5.25%	2,174	5.31%
Hypertension	553	94.21%	1,091	91.37%	1,069	92.55%	29,358	77.29%	32,071	78.37%

Hypothyroidism	19	3.24%	39	3.27%	30	2.60%	812	2.14%	900	2.20%
Inflammatory bowel disease	5	0.85%	14	1.17%	11	0.95%	271	0.71%	301	0.74%
Liver disease	<5	NA	<5	NA	9	0.78%	185	0.49%	201	0.49%
Major bleeding	29	4.94%	51	4.27%	61	5.28%	840	2.21%	981	2.40%
Malignant cancer	<5	NA	<5	NA	<5	NA	<5	NA	<5	NA
Obesity	8	1.36%	13	1.09%	8	0.69%	533	1.40%	562	1.37%
Other cerebrovascular disease	<5	NA	12	1.01%	7	0.61%	269	0.71%	292	0.71%
Other metabolic disorders	6	1.02%	25	2.09%	33	2.86%	490	1.29%	554	1.35%
Other vascular disease	29	4.94%	49	4.10%	72	6.23%	1,059	2.79%	1,209	2.95%
Peripheral artery disease	24	4.09%	39	3.27%	45	3.90%	1,027	2.70%	1,135	2.77%
Psychosis	<5	NA	<5	NA	7	0.61%	321	0.85%	334	0.82%
Pulmonary disease	42	7.16%	71	5.95%	80	6.93%	2,559	6.74%	2,752	6.73%
Renal impairment	25	4.26%	7	0.59%	64	5.54%	432	1.14%	528	1.29%
Rheumatoid arthritis/collagen vascular disease	21	3.58%	63	5.28%	72	6.23%	1,476	3.89%	1,632	3.99%
Volume depletion	6	1.02%	6	0.50%	12	1.04%	109	0.29%	133	0.33%
Comedications, n (%)										
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	393	66.95%	733	61.39%	766	66.32%	19,835	52.22%	21,727	53.09%
Antiarrhythmics	28	4.77%	68	5.7%	31	2.68%	1,838	4.84%	1,965	4.80%
Antidepressants	87	14.82%	153	12.81%	182	15.76%	4,485	11.81%	4,907	11.99%
Antiplatelets	88	14.99%	142	11.89%	198	17.14%	3,728	9.81%	4,156	10.16%
Antiulcer drugs (except proton-pump inhibitors)	6	1.02%	17	1.42%	8	0.69%	405	1.07%	436	1.07%
Beta blockers	511	87.05%	995	83.33%	976	84.50%	23,583	62.09%	26,065	63.70%
Calcium channel blockers	246	41.91%	440	36.85%	475	41.13%	11,969	31.51%	13,130	32.09%
Diabetes drugs (incl. insulin)	154	26.24%	210	17.59%	217	18.79%	7,196	18.94%	7,777	19.00%
Diuretics	350	59.63%	587	49.16%	668	57.84%	14,804	38.97%	16,409	40.10%
Erythropoietin-simulating agents	<5	NA	<5	NA	<5	NA	58	0.15%	61	0.15%
Estrogens	12	2.04%	56	4.69%	17	1.47%	3,192	8.40%	3,277	8.01%
Lipid modifying agents	291	49.57%	556	46.57%	563	48.74%	15,684	41.29%	17,094	41.77%

Non-steroidal anti-inflammatory drugs	103	17.55%	261	21.86%	162	14.03%	9,976	26.26%	10,502	25.66%
Proton-pump inhibitors	233	39.69%	432	36.18%	458	39.65%	10,484	27.60%	11,607	28.36%
Covariates used for model, n (%)										
Comedication										
ACE/ARB	393	66.95%	733	61.39%	766	66.32%	19,835	52.22%	21,727	53.09%
Aspirin										
Beta blockers	511	87.05%	995	83.33%	976	84.5%	23,583	62.09%	26,065	63.7%
Calcium	246	41.91%	440	36.85%	475	41.13%	11,969	31.51%	13,130	32.09%
Clopidogrel	60	10.22%	91	7.62%	113	9.78%	1,819	4.79%	2,083	5.09%
NSAID	103	17.55%	261	21.86%	162	14.03%	9,976	26.26%	10,502	25.66%
Proton-pump inhibitors	233	39.69%	432	36.18%	458	39.65%	10,484	27.60%	11,607	28.36%
Comorbidities										
Alcohol	6	1.02%	11	0.92%	7	0.61%	563	1.48%	587	1.43%
Aortic Plaque	<5	<5	<5	<5	<5	<5	10	0.03%	12	0.03%
Diabetes	164	27.94%	220	18.43%	228	19.74%	7,620	20.06%	8,232	20.12%
Heart failure	144	24.53%	202	16.92%	337	29.18%	6,580	17.32%	7,263	17.75%
Hyperlipidemia	41	6.98%	71	5.95%	68	5.89%	1,994	5.25%	2,174	5.31%
Hypertension	553	94.21%	1,091	91.37%	1,069	92.55%	29,358	77.29%	32,071	78.37%
Intracerebral hemorrhage	<5	<5	8	0.67%	<5	<5	35	0.09%	47	0.11%
IS	17	2.90%	50	4.19%	54	4.68%	1,396	3.68%	1,517	3.71%
Liver Disease (Moderate/severe)	<5	NA	<5	NA	<5	NA	41	0.11%	44	0.11%
MI	43	7.33%	55	4.61%	99	8.57%	1,882	4.95%	2,079	5.08%
PAD	24	4.09%	39	3.27%	45	3.90%	1,027	2.70%	1,135	2.77%
Renal Disease (Moderate/severe)	45	7.67%	10	0.84%	87	7.53%	720	1.90%	862	2.11%
Renal impairment	25	4.26%	7	0.59%	64	5.54%	432	1.14%	528	1.29%
SE	<5	NA	<5	NA	<5	NA	84	0.22%	89	0.22%
TIA	14	2.39%	40	3.35%	27	2.34%	777	2.05%	858	2.10%

Note: Cells with less than 5 patients results cannot be reported due to regulations as described in section 9.9.1.

Table 12. Patient characteristics: Population OAC naïve NVAF patients in Denmark

Patient characteristics at index date	*rivaroxaban 15 mg once/day*		*dabigatran 110 mg twice/day*		*apixaban 2.5 mg twice/day*		*warfarin*		*All patients*	
	n or mean (sd)	% or median (10%-90%)	n or mean (sd)	% or median (10%-90%)	n or mean (sd)	% or median (10%-90%)	n or mean (sd)	% or median (10%-90%)	n or mean (sd)	% or median (10%-90%)
Demographic characteristics										
Number of patients, n (%)	1,912	7.62%	3,498	13.94%	3,543	14.12%	16,141	64.32%	25,094	
Age, mean (sd) median (10%-90%)	82.1	9.4	80.2	8.2	84	8.3	71	11.8	75	12
Age group, n (%)										
80+	1,279	66.89%	2,169	62.01%	2,787	78.66%	4,003	24.80%	10,238	40.80%
85+	889	46.50%	1,051	30.05%	1,874	52.89%	1,876	11.62%	5,690	22.67%
Sex, n (%)										
Females	1,108	57.95%	1,988	56.83%	2,289	64.61%	7,139	44.23%	12,524	49.91%
Males	804	42.05%	1,510	43.17%	1,254	35.39%	9,002	55.77%	12,570	50.09%
Clinical characteristics										
CHADS2-VASc score, mean (sd) median (10%-90%).	3.24 (1.18)	3 (2-5)	3.07 (1.12)	3 (2-4)	3.23 (1.18)	3 (2-5)	2.41 (1.43)	2 (0-4)	2.68 (1.39)	3 (1-4)
HAS-BLED score, mean (sd) median (10%-90%)	2.49 (.86)	3 (1-3)	2.44 (.84)	3 (1-3)	2.46 (.91)	3 (1-3)	2.16 (1.04)	2 (1-3)	2.27 (.99)	2 (1-3)
Charlson Comorbidity Index, mean (sd) median (10%-90%)	2.14 (2.03)	2 (0-5)	1.69 (1.84)	1 (0-4)	2.09 (1.99)	2 (0-5)	1.50 (1.88)	1 (0-4)	1.66 (1.92)	1 (0-4)
Comorbidities, n (%)										
Acute kidney injury	15	0.78%	11	0.31%	25	0.71%	87	0.54%	138	0.55%

Alcohol Abuse	19	0.99%	40	1.14%	32	0.90%	146	0.90%	237	0.94%
Anemia	72	3.77%	83	2.37%	165	4.66%	266	1.65%	586	2.34%
Aortic plaque	0	0.00%	NA	NA	0	0.00%	NA	NA	NA	NA
Coronary heart disease:										
Acute ischemic heart diseases	NA	NA	6	0.17%	10	0.28%	40	0.25%	NA	NA
Angina pectoris	64	3.35%	134	3.83%	107	3.02%	749	4.64%	1,054	4.20%
Chronic ischemic heart disease	215	11.24%	304	8.69%	303	8.55%	1,403	8.69%	2,225	8.87%
Coronary artery bypass graft(s)	24	1.26%	40	1.14%	37	1.04%	318	1.97%	419	1.67%
Myocardial infarction	127	6.64%	138	3.95%	163	4.60%	725	4.49%	1,153	4.59%
Percutaneous coronary intervention	75	3.92%	63	1.80%	90	2.54%	353	2.19%	581	2.32%
Diabetes mellitus	314	16.42%	416	11.89%	472	13.32%	2,216	13.73%	3,418	13.62%
Drug abuse	0	0.00%	NA	NA	NA	NA	NA	NA	NA	NA
Gastric or peptic ulcer disease/diseases of gastrointestinal tract	43	2.25%	70	2.00%	100	2.82%	360	2.23%	573	2.28%
Heart failure	330	17.26%	420	12.01%	511	14.42%	2,118	13.12%	3,379	13.47%
Hyperlipidemia	72	3.77%	195	5.57%	170	4.80%	1,179	7.30%	1,616	6.44%
Hypertension	1,412	73.85%	2,555	73.04%	2,465	69.57%	10,868	67.33%	17,300	68.94%
Hypothyroidism	35	1.83%	52	1.49%	66	1.86%	161	1.00%	314	1.25%
Inflammatory bowel disease	20	1.05%	35	1.00%	36	1.02%	124	0.77%	215	0.86%
Liver disease	8	0.42%	10	0.29%	13	0.37%	71	0.44%	102	0.41%
Major bleeding	91	4.76%	130	3.72%	233	6.58%	415	2.57%	869	3.46%
Malignant cancer	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Obesity	24	1.26%	50	1.43%	30	0.85%	406	2.52%	510	2.03%

Other cerebrovascular disease	48	2.51%	74	2.12%	92	2.60%	343	2.13%	557	2.22%
Other metabolic disorders	52	2.72%	70	2.00%	124	3.50%	206	1.28%	452	1.80%
Other vascular disease	120	6.28%	208	5.95%	219	6.18%	970	6.01%	1,517	6.05%
Peripheral artery disease	58	3.03%	91	2.60%	114	3.22%	504	3.12%	767	3.06%
Psychosis	NA	NA	10	0.29%	8	0.23%	31	0.19%	NA	NA
Pulmonary disease	201	10.51%	325	9.29%	381	10.75%	1,279	7.92%	2,186	8.71%
Renal impairment	58	3.03%	29	0.83%	118	3.33%	400	2.48%	605	2.41%
Rheumatoid arthritis/collagen vascular disease	45	2.35%	78	2.23%	109	3.08%	374	2.32%	606	2.41%
Volume depletion	71	3.71%	76	2.17%	167	4.71%	181	1.12%	495	1.97%
Comedications, n (%)										
Angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers	1,013	52.98%	1,760	50.31%	1,702	48.04%	7,907	48.99%	12,382	49.34%
Antiarrhythmics	107	5.60%	223	6.38%	215	6.07%	1,334	8.26%	1,879	7.49%
Antidepressants	304	15.90%	497	14.21%	570	16.09%	1,754	10.87%	3,125	12.45%
Antiplatelets	1,056	55.23%	1,793	51.26%	1,806	50.97%	7,670	47.52%	12,325	49.12%
Antiulcer drugs (except proton-pump inhibitors)	13	0.68%	18	0.51%	18	0.51%	64	0.40%	113	0.45%
Beta blockers	1,359	71.08%	2,533	72.41%	2,414	68.13%	11,938	73.96%	18,244	72.70%
Calcium channel blockers	655	34.26%	1,215	34.73%	1,227	34.63%	5,301	32.84%	8,398	33.47%
Diabetes drugs (incl. insulin)	277	14.49%	378	10.81%	418	11.80%	2,048	12.69%	3,121	12.44%
Diuretics	1,334	69.77%	2,114	60.43%	2,213	62.46%	8,457	52.39%	14,118	56.26%

Erythropoietin-simulating agents	0	0.00%	0	0.00%	0	0.00%	2	NA	2	NA
Estrogens	149	7.79%	290	8.29%	338	9.54%	1,065	6.60%	1,842	7.34%
Lipid modifying agents	773	40.43%	1,357	38.79%	1,287	36.33%	6,430	39.84%	9,847	39.24%
Non-steroidal anti-inflammatory drugs	248	12.97%	517	14.78%	406	11.46%	2,806	17.38%	3,977	15.85%
Proton-pump inhibitors	620	32.43%	915	26.16%	1,135	32.03%	3,763	23.31%	6,433	25.64%
Covariates used for model, n (%)										
Comedication										
ACE/ARB	1,013	52.98%	1,760	50.31%	1,702	48.04%	7,907	48.99%	12,382	49.34%
Aspirin	832	43.51%	1,522	43.51%	1,393	39.32%	6,767	41.92%	10,514	41.90%
Beta blockers	1,359	71.08%	2,533	72.41%	2,414	68.13%	11,938	73.96%	18,244	72.70%
Calcium	655	34.26%	1,215	34.73%	1,227	34.63%	5,301	32.84%	8,398	33.47%
Clopidogrel	336	17.57%	387	11.06%	574	16.20%	1,511	9.36%	2,808	11.19%
NSAID	248	12.97%	517	14.78%	406	11.46%	2,806	17.38%	3,977	15.85%
Proton-pump inhibitors	620	32.43%	915	26.16%	1,135	32.03%	3,763	23.31%	6,433	25.64%
Comorbidities										
Alcohol	19	0.99%	40	1.14%	32	0.90%	146	0.90%	237	0.94%
Diabetes	314	16.42%	416	11.89%	472	13.32%	2,216	13.73%	3,418	13.62%
Heart failure	330	17.26%	420	12.01%	511	14.42%	2,118	13.12%	3,379	13.47%
Hyperlipidemia	72	3.77%	195	5.57%	170	4.80%	1,179	7.30%	1,616	6.44%
Hypertension	1,412	73.85%	2,555	73.04%	2,465	69.57%	10,868	67.33%	17,300	68.94%
Intracerebral hemorrhage	NA	NA	8	0.23%	13	0.37%	28	0.17%	NA	NA
IS	89	4.65%	165	4.72%	214	6.04%	651	4.03%	1,119	4.46%
Liver Disease (Moderate/severe)	8	0.42%	10	0.29%	13	0.37%	71	0.44%	102	0.41%
MI	127	6.64%	138	3.95%	163	4.60%	725	4.49%	1,153	4.59%
PAD	58	3.03%	91	2.60%	114	3.22%	504	3.12%	767	3.06%
Renal Disease (Moderate/severe)	91	4.76%	49	1.40%	163	4.60%	530	3.28%	833	3.32%

SE	NA	NA	8	0.23%	14	0.40%	37	0.23%	NA	NA
TIA	27	1.41%	57	1.63%	58	1.64%	277	1.72%	419	1.67%

Note: Cells with less than 5 patients results cannot be reported due to regulations as described in section 9.9.1.

Propensity score weighting

As this study is an observational study, there is no randomization to ensure the absence of systematic differences between treatment populations. To adjust for the potential imbalance, inverse probability of treatment weighting (IPTW) was performed using a nonlinear machine learning model, as described in the SAP. The result of the weighting in terms of standardized mean differences and positivity checks are presented in the stand-alone document ”Quantify REATTAIN Twang – Weighting”.

Main results

This section presents incidence rates, cumulative incidence, cox regression models and persistence analyses. The results presented in this document are for the full study population. For results of subgroup-analyses, please see the stand-alone documents referred to in Table 33: “Quantify REATTAIN Incidence Analysis”, “Quantify REATTAIN Cox Regression Analysis” and “Quantify REATTAIN Persistence Analysis”.

10.4.1 Incidence rates and cumulative incidence

Sweden

Table 13 and Table 14 present the unweighted and weighted incidence rates and cumulative incidence for Sweden. The endpoints include ischemic stroke/systematic embolism, intracranial hemorrhage, fatal bleeding, severe IS1 and IS2, kidney failure and AKI. Severe IS1 is defined using information from RiksStroke, whereas severe IS2 uses the national register. IS1 is only reported for Sweden, given that RiksStroke is exclusive to Sweden.

Incidence rates and cumulative incidence – Unweighted (Sweden)

- **Ischemic Stroke/Systemic Embolism:** rivaroxaban users showed a cumulative incidence of 2.13% and an incidence rate of 2.44 per 100 person-years. Dabigatran and apixaban users had similar incidences of 2.51% and 2.10%, respectively. In contrast, Warfarin users demonstrated a lower incidence of 1.64%.
- **Intracranial Hemorrhage:** rivaroxaban users experienced a higher incidence (0.72%) compared to apixaban (0.58%) and dabigatran (0.15%) users. Warfarin users had an incidence of 0.47%.
- **Fatal Bleeding:** rivaroxaban users had an incidence of 0.44%, while apixaban and dabigatran users had incidences of 0.39% and 0.21%, respectively. Warfarin users showed the lowest incidence at 0.20%.
- **Severe Ischemic Stroke (IS 1):** Incidence of IS 1 was 0.46% for rivaroxaban, 0.37% for dabigatran, and 0.37% for apixaban users. Warfarin users had an incidence of 0.19%.
- **Severe Ischemic Stroke (IS 2):** Incidence of IS 2 was 0.24% for rivaroxaban, 0.37% for dabigatran, and 0.48% for apixaban users. Warfarin users showed the lowest incidence of 0.23%.

- **Kidney Failure:** No cases were reported for dabigatran users. Incidences for rivaroxaban and apixaban users were 0.19% and 0.25%, respectively, comparable to the 0.23% incidence in Warfarin users.
- **Acute Kidney Injury (AKI):** rivaroxaban and apixaban users showed a higher incidence of 0.58%, in contrast to dabigatran users (0.43%) and warfarin users (0.22%).

Table 13. Incidence rates and cumulative incidence – Unweighted (Sweden)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	1,495	25	2.13 (1.43 - 3.15)	2.44 (1.58 - 3.61)
warfarin	42,168	562	1.64 (1.50 - 1.79)	2.01 (1.85 - 2.19)
dabigatran 110 mg twice/day	1,915	36	2.51 (1.80 - 3.49)	2.86 (2.00 - 3.96)
warfarin	42,168	562	1.64 (1.50 - 1.79)	2.01 (1.85 - 2.19)
apixaban 2.5 mg twice/day	6,055	103	2.10 (1.73 - 2.56)	2.50 (2.04 - 3.03)
warfarin	42,168	562	1.64 (1.50 - 1.79)	2.01 (1.85 - 2.19)
Intracranial hemorrhage				
rivaroxaban 15 mg once/day	1,495	8	0.72 (0.36 - 1.45)	0.78 (0.34 - 1.53)
warfarin	42,168	141	0.47 (0.39 - 0.55)	0.50 (0.42 - 0.59)
dabigatran 110 mg twice/day	1,915	<5	0.15 (0.03 - 0.61)	0.16 (0.02 - 0.57)
warfarin	42,168	141	0.47 (0.39 - 0.55)	0.50 (0.42 - 0.59)
apixaban 2.5 mg twice/day	6,055	27	0.58 (0.40 - 0.85)	0.65 (0.43 - 0.95)
warfarin	42,168	141	0.47 (0.39 - 0.55)	0.50 (0.42 - 0.59)
Fatal bleeding				
rivaroxaban 15 mg once/day	1,495	5	0.44 (0.18 - 1.06)	0.48 (0.16 - 1.13)
warfarin	42,168	63	0.20 (0.15 - 0.25)	0.22 (0.17 - 0.29)
dabigatran 110 mg twice/day	1,915	<5	0.21 (0.07 - 0.67)	0.24 (0.05 - 0.69)
warfarin	42,168	63	0.20 (0.15 - 0.25)	0.22 (0.17 - 0.29)
apixaban 2.5 mg twice/day	6,055	19	0.39 (0.25 - 0.62)	0.46 (0.28 - 0.71)
warfarin	42,168	63	0.20 (0.15 - 0.25)	0.22 (0.17 - 0.29)
Severe IS 1				
rivaroxaban 15 mg once/day	1,495	6	0.46 (0.20 - 1.02)	0.58 (0.21 - 1.27)
warfarin	42,168	82	0.23 (0.19 - 0.29)	0.29 (0.23 - 0.36)
dabigatran 110 mg twice/day	1,915	5	0.37 (0.15 - 0.90)	0.39 (0.13 - 0.92)
warfarin	42,168	82	0.23 (0.19 - 0.29)	0.29 (0.23 - 0.36)
apixaban 2.5 mg twice/day	6,055	24	0.48 (0.32 - 0.71)	0.58 (0.37 - 0.86)
warfarin	42,168	82	0.23 (0.19 - 0.29)	0.29 (0.23 - 0.36)
Severe IS 2				
rivaroxaban 15 mg once/day	1,495	<5	0.24 (0.08 - 0.75)	0.29 (0.06 - 0.85)

warfarin	42,168	67	0.19 (0.15 - 0.25)	0.24 (0.18 - 0.30)
dabigatran 110 mg twice/day	1,915	5	0.37 (0.15 - 0.90)	0.39 (0.13 - 0.92)
warfarin	42,168	67	0.19 (0.15 - 0.25)	0.24 (0.18 - 0.30)
apixaban 2.5 mg twice/day	6,055	19	0.37 (0.23 - 0.57)	0.46 (0.28 - 0.71)
warfarin	42,168	67	0.19 (0.15 - 0.25)	0.24 (0.18 - 0.30)
Kidney failure				
rivaroxaban 15 mg once/day	1,495	<5	0.19 (0.05 - 0.79)	0.19 (0.02 - 0.70)
warfarin	42,168	72	0.23 (0.18 - 0.29)	0.26 (0.20 - 0.32)
dabigatran 110 mg twice/day	1,915	0	0.00 (NA - NA)	NA (NA - NA)
warfarin	42,168	72	0.23 (0.18 - 0.29)	0.26 (0.20 - 0.32)
apixaban 2.5 mg twice/day	6,055	12	0.25 (0.14 - 0.45)	0.29 (0.15 - 0.51)
warfarin	42,168	72	0.23 (0.18 - 0.29)	0.26 (0.20 - 0.32)
AKI				
rivaroxaban 15 mg once/day	1,495	7	0.58 (0.27 - 1.23)	0.68 (0.27 - 1.40)
warfarin	42,168	69	0.22 (0.17 - 0.29)	0.25 (0.19 - 0.31)
dabigatran 110 mg twice/day	1,915	6	0.43 (0.19 - 0.98)	0.47 (0.17 - 1.03)
warfarin	42,168	69	0.22 (0.17 - 0.29)	0.25 (0.19 - 0.31)
apixaban 2.5 mg twice/day	6,055	27	0.58 (0.40 - 0.85)	0.65 (0.43 - 0.95)
warfarin	42,168	69	0.22 (0.17 - 0.29)	0.25 (0.19 - 0.31)

Incidence rates and cumulative incidence – Weighted (Sweden)

- **Ischemic Stroke/Systemic Embolism:**
  - Rivaroxaban had a cumulative incidence of 2.13% and an incidence rate of 2.44 per 100 person-years, compared to warfarin (weighted by the rivaroxaban cohort) with 2.24% incidence and 2.80 incidence rate.
  - Dabigatran showed a 2.51% incidence and 2.86 rate, against warfarin (weighted by dabigatran) with 2.15% and 2.68.
  - Apixaban users experienced a 2.10% incidence and 2.50 incidence rate, while warfarin (weighted by apixaban) had a 2.54% incidence and 3.27 incidence rate.
- **Intracranial Hemorrhage:**
  - Rivaroxaban users had 0.72% incidence and 0.78 incidence rate, compared to warfarin (rivaroxaban-weighted) at 0.64% and 0.75.
  - Dabigatran users had 0.15% incidence and 0.16 incidence rate, while warfarin (dabigatran-weighted) showed 0.61% incidence and 0.73 incidence rate.
  - Apixaban users experienced 0.58% incidence and 0.65 incidence rate, versus warfarin (apixaban-weighted) with 0.68% and 0.76.
- **Fatal Bleeding:**
  - Rivaroxaban users had 0.44% incidence and 0.48 incidence rate, similar to warfarin (rivaroxaban-weighted) with 0.44% incidence and 0.64 incidence rate.

- Dabigatran users showed a 0.21% incidence and 0.24 incidence rate, compared to warfarin (dabigatran-weighted) at 0.28% and 0.40 incidence rate.
- Apixaban users had 0.39% incidence and 0.46 incidence rate, while warfarin (apixaban-weighted) showed 0.46% incidence and 0.63 incidence rate.

- **Severe Ischemic Stroke (IS 1):**
  - Rivaroxaban users showed a 0.46% incidence and 0.58 incidence rate while the rivaroxaban-weighted warfarin groups showed a 0.54 incidence and 0.75 incidence rate.
  - Dabigatran users showed a 0.37% incidence and 0.39 incidence rate while the dabigatran-weighted warfarin groups showed a 0.34% incidence and 0.48 incidence rate.
  - Apixaban users showed a 0.48% incidence and 0.58 incidence rate while the apixaban-weighted warfarin groups showed a slighly higher incidence of 0.61% and 0.84 incidence rate.
- **Severe Ischemic Stroke (IS 2):**
  - Rivaroxaban users showed a 0.24% incidence and 0.29 incidence rate while the rivaroxaban-weighted warfarin groups showed a 0.49 incidence and 0.75 incidence rate.
  - Dabigatran users showed a 0.37% incidence and 0.39 incidence rate while the dabigatran-weighted warfarin groups showed a 0.30% incidence and 0.40 incidence rate.
  - Apixaban users showed a 0.37% incidence and 0.46 incidence rate while the apixaban-weighted warfarin groups showed a incidence of 0.56% and 0.76 incidence rate.
- **Kidney Failure**
  - Rivaroxaban users showed a 0.19% incidence and 0.19 incidence rate while the rivaroxaban-weighted warfarin groups showed a 0.36% incidence and 0.43 incidence rate.
  - No kidney failure events was reported for dabigatran users.
  - Apixaban users showed a 0.25% incidence and 0.29 incidence rate while the apixaban-weighted warfarin groups showed a incidence of 0.28% and 0.35 incidence rate.
- **Acute Kidney Injury (AKI):**
  - Rivaroxaban users showed a 0.58% incidence and 0.68 incidence rate while the rivaroxaban-weighted warfarin groups showed a 0.43 incidence and 0.53 incidence rate.
  - Dabigatran users showed a 0.43% incidence and 0.47 incidence rate while the dabigatran-weighted warfarin groups showed a 0.23% incidence and 0.32 incidence rate.
  - Apixaban users showed a 0.58% incidence and 0.65 incidence rate while the apixaban-weighted warfarin groups showed a incidence of 0.46% and 0.49 incidence rate.

Table 14. Incidence rates and cumulative incidence – Weighted (Sweden)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	1,495	25	2.13 (1.43 - 3.15)	2.44 (1.58 - 3.61)
warfarin - weighted by the rivaroxaban cohort	42,168	562	2.24 (1.95 – 2.57)	2.80 (1.83 – 4.10)
dabigatran 110 mg twice/day	1,915	36	2.51 (1.80 – 3.49)	2.86 (2.00 - 3.96)
warfarin - weighted by the dabigatran cohort	42,168	562	2.15 (1.94 - 2.39)	2.68 (1.85 - 3.76)
apixaban 2.5 mg twice/day	6,055	103	2.10 (1.73 - 2.56)	2.50 (2.04 - 3.03)
warfarin - weighted by the apixaban cohort	42,168	562	2.54 (2.18 - 2.96)	3.27 (2.71 - 3.91)
Intracranial hemorrhage				
rivaroxaban 15 mg once/day	1,495	8	0.72 (0.36 - 1.45)	0.78 (0.34 - 1.53)
warfarin - weighted by the rivaroxaban cohort	42,168	141	0.64 (0.51 – 0.81)	0.75 (0.30 – 1.54)
dabigatran 110 mg twice/day	1,915	<5	0.15 (0.03 – 0.61)	0.16 (0.02 – 0.57)
warfarin – weighted by the dabigatran cohort	42,168	141	0.61 (0.49 – 0.77)	0.73 (0.33 – 1.38)
apixaban 2.5 mg twice/day	6,055	27	0.58 (0.40 – 0.85)	0.65 (0.43 – 0.95)
warfarin - weighted by the apixaban cohort	42,168	141	0.68 (0.51 – 0.91)	0.76 (0.51 – 1.10)
Fatal bleeding				
rivaroxaban 15 mg once/day	1,495	5	0.44 (0.18 – 1.06)	0.48 (0.16 – 1.13)
warfarin - weighted by the rivaroxaban cohort	42,168	63	0.44 (0.26 – 0.74)	0.64 (0.24 – 1.40)
dabigatran 110 mg twice/day	1,915	<5	0.21 (0.07 – 0.67)	0.24 (0.05 – 0.69)
warfarin – weighted by the dabigatran cohort	42,168	63	0.28 (0.21 - 0.38)	0.40 (0.13 - 0.94)
apixaban 2.5 mg twice/day	6,055	19	0.39 (0.25 - 0.62)	0.46 (0.28 - 0.71)
warfarin - weighted by the apixaban cohort	42,168	63	0.46 (0.32 – 0.65)	0.63 (0.40 – 0.94)
Severe IS 1				
rivaroxaban 15 mg once/day	1,495	6	0.46 (0.20 – 1.02)	0.58 (0.21 – 1.27)
warfarin - weighted by the rivaroxaban cohort	42,168	82	0.54 (0.36 - 0.79)	0.75 (0.30 - 1.54)
dabigatran 110 mg twice/day	1,915	5	0.37 (0.15 - 0.90)	0.39 (0.13 - 0.92)
warfarin - weighted by the dabigatran cohort	42,168	82	0.34 (0.26 - 0.45)	0.48 (0.18 - 1.05)
apixaban 2.5 mg twice/day	6,055	24	0.48 (0.32 - 0.71)	0.58 (0.37 - 0.86)
warfarin - weighted by the apixaban cohort	42,168	82	0.61 (0.44 – 0.86)	0.84 (0.57 – 1.20)
Severe IS 2				
rivaroxaban 15 mg once/day	1,495	<5	0.24 (0.08 – 0.75)	0.29 (0.06 – 0.85)
warfarin - weighted by the	42,168	67	0.49 (0.32 - 0.75)	0.75 (0.30 - 1.54)

rivaroxaban cohort				
dabigatran 110 mg twice/day	1,915	5	0.37 (0.15 - 0.90)	0.39 (0.13 - 0.92)
warfarin - weighted by the dabigatran cohort	42,168	67	0.30 (0.22 – 0.40)	0.40 (0.13 – 0.94)
apixaban 2.5 mg twice/day	6,055	19	0.37 (0.23 – 0.57)	0.46 (0.28 – 0.71)
warfarin - weighted by the apixaban cohort	42,168	67	0.56 (0.39 - 0.80)	0.76 (0.51 - 1.10)
Kidney failure				
rivaroxaban 15 mg once/day	1,495	<5	0.19 (0.05 - 0.79)	0.19 (0.02 - 0.70)
warfarin - weighted by the rivaroxaban cohort	42,168	72	0.36 (0.25 - 0.51)	0.43 (0.12 - 1.09)
dabigatran 110 mg twice/day	1,915	0	0.00 (NA - NA)	NA (NA - NA)
warfarin - weighted by the dabigatran cohort	42,168	72	0.18 (0.13 - 0.25)	0.24 (0.05 - 0.70)
apixaban 2.5 mg twice/day	6,055	12	0.25 (0.14 - 0.45)	0.29 (0.15 - 0.51)
warfarin - weighted by the apixaban cohort	42,168	72	0.28 (0.20 - 0.39)	0.35 (0.19 - 0.60)
AKI				
rivaroxaban 15 mg once/day	1,495	7	0.58 (0.27 - 1.23)	0.68 (0.27 - 1.40)
warfarin - weighted by the rivaroxaban cohort	42,168	69	0.43 (0.27 - 0.68)	0.53 (0.17 - 1.24)
dabigatran 110 mg twice/day	1,915	6	0.43 (0.19 - 0.98)	0.47 (0.17 - 1.03)
warfarin - weighted by the dabigatran cohort	42,168	69	0.23 (0.16 - 0.31)	0.32 (0.09 - 0.82)
apixaban 2.5 mg twice/day	6,055	27	0.58 (0.40 - 0.85)	0.65 (0.43 - 0.95)
warfarin - weighted by the apixaban cohort	42,168	69	0.46 (0.27 - 0.79)	0.49 (0.29 - 0.77)

Norway

Table 15 and Table 16 present the unweighted and weighted incidence rates and cumulative incidence for Norway. The endpoints include ischemic stroke/systematic embolism, intracranial hemorrhage, fatal bleeding, severe IS2, kidney failure and AKI.

Incidence rates and cumulative incidence – Unweighted (Norway)

- **Ischemic Stroke/Systemic Embolism:** rivaroxaban users had a cumulative incidence of 2.52% and an incidence rate of 2.95 per 100 person-years. In contrast, dabigatran and apixaban users showed slightly lower incidences of 1.41% and 1.96%, respectively. warfarin users demonstrated the lowest incidence at 1.40%.
- **Intracranial Hemorrhage:** rivaroxaban users experienced the highest incidence (1.09%) and incidence rate (1.12). Apixaban users had an incidence of 0.38%, while dabigatran users had the lowest incidence at 0.35%. Warfarin users had an incidence of 0.47%.
- **Fatal Bleeding:** rivaroxaban users had a cumulative incidence of 0.28%, while apixaban users experienced a higher incidence at 0.58%. No fatal bleeding events were reported for dabigatran users. Warfarin users showed the lowest incidence at 0.21%.

- **Severe Ischemic Stroke (IS 2):** No severe ischemic stroke events were reported for rivaroxaban users. Apixaban users had an incidence of 0.40%. Both dabigatran and warfarin users showed lower and comparable incidences of 0.15% and 0.13%, respectively.
- **Kidney Failure:** No kidney failure events were reported for Rivaroxaban users. Apixaban users showed a cumulative incidence of 0.45%, slightly lower than the 0.53% incidence in warfarin users. Dabigatran users had an incidence of 0.11%.
- **Acute Kidney Injury (AKI):** Rivaroxaban users showed a higher incidence of AKI at 1.49%, followed by apixaban users at 1.05%. Dabigatran users had a lower incidence of 0.25%, and warfarin users showed an incidence of 0.38%.

Table 15. Incidence rates and cumulative incidence – Unweighted (Norway)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	1,008	21	2.52 (1.64 - 3.86)	2.95 (1.83 - 4.51)
warfarin	11,720	129	1.40 (1.17 - 1.68)	1.78 (1.48 - 2.11)
dabigatran 110 mg twice/day	1,575	18	1.41 (0.89 - 2.26)	1.67 (0.99 - 2.65)
warfarin	11,720	129	1.40 (1.17 - 1.68)	1.78 (1.48 - 2.11)
apixaban 2.5 mg twice/day	2,946	44	1.96 (1.46 - 2.65)	2.27 (1.65 - 3.05)
warfarin	11,720	129	1.40 (1.17 - 1.68)	1.78 (1.48 - 2.11)
Intracranial haemorrhage				
rivaroxaban 15 mg once/day	1,008	8	1.09 (0.54 - 2.17)	1.12 (0.48 - 2.20)
warfarin	11,720	33	0.47 (0.32 - 0.67)	0.45 (0.31 - 0.63)
dabigatran 110 mg twice/day	1,575	<5	0.35 (0.13 - 0.95)	0.37 (0.10 - 0.95)
warfarin	11,720	33	0.47 (0.32 - 0.67)	0.45 (0.31 - 0.63)
apixaban 2.5 mg twice/day	2,946	8	0.38 (0.19 - 0.78)	0.41 (0.18 - 0.81)
warfarin	11,720	33	0.47 (0.32 - 0.67)	0.45 (0.31 - 0.63)
Fatal bleeding				
rivaroxaban 15 mg once/day	1,008	<5	0.28 (0.07 - 1.12)	0.28 (0.03 - 1.01)
warfarin	11,720	14	0.21 (0.12 - 0.37)	0.19 (0.10 - 0.32)
dabigatran 110 mg twice/day	1,575	0	0.00 (NA - NA)	NA (NA - NA)
warfarin	11,720	14	0.21 (0.12 - 0.37)	0.19 (0.10 - 0.32)
apixaban 2.5 mg twice/day	2,946	12	0.58 (0.33 - 1.04)	0.62 (0.32 - 1.07)
warfarin	11,720	14	0.21 (0.12 - 0.37)	0.19 (0.10 - 0.32)
Severe IS 2				
rivaroxaban 15 mg once/day	1,008	0	0.00 (NA - NA)	NA (NA - NA)
warfarin	11,720	11	0.13 (0.07 - 0.25)	0.15 (0.08 - 0.27)
dabigatran 110 mg twice/day	1,575	<5	0.15 (0.04 - 0.61)	0.19 (0.02 - 0.67)
warfarin	11,720	11	0.13 (0.07 - 0.25)	0.15 (0.08 - 0.27)

apixaban 2.5 mg twice/day	2,946	9	0.40 (0.21 - 0.77)	0.46 (0.21 - 0.88)
warfarin	11,720	11	0.13 (0.07 - 0.25)	0.15 (0.08 - 0.27)
Kidney failure				
rivaroxaban 15 mg once/day	1,008	0	0.00 (NA - NA)	NA (NA - NA)
warfarin	11,720	40	0.53 (0.38 - 0.73)	0.55 (0.39 - 0.75)
dabigatran 110 mg twice/day	1,575	<5	0.11 (0.02 - 0.80)	0.09 (0.00 - 0.52)
warfarin	11,720	40	0.53 (0.38 - 0.73)	0.55 (0.39 - 0.75)
apixaban 2.5 mg twice/day	2,946	9	0.45 (0.23 - 0.87)	0.46 (0.21 - 0.88)
warfarin	11,720	40	0.53 (0.38 - 0.73)	0.55 (0.39 - 0.75)
AKI				
rivaroxaban 15 mg once/day	1,008	10	1.49 (0.80 - 2.76)	1.40 (0.67 - 2.57)
warfarin	11,720	29	0.38 (0.25 - 0.56)	0.40 (0.27 - 0.57)
dabigatran 110 mg twice/day	1,575	<5	0.25 (0.08 - 0.78)	0.28 (0.06 - 0.81)
warfarin	11,720	29	0.38 (0.25 - 0.56)	0.40 (0.27 - 0.57)
apixaban 2.5 mg twice/day	2,946	23	1.05 (0.70 - 1.59)	1.18 (0.75 - 1.78)
warfarin	11,720	29	0.38 (0.25 - 0.56)	0.40 (0.27 - 0.57)

Incidence rates and cumulative incidence – Weighted (Norway)

- **Ischemic Stroke/Systemic Embolism:**
  - Rivaroxaban showed a cumulative incidence of 2.52% and an incidence rate of 2.95 per 100 person-years. In comparison, warfarin (weighted by the rivaroxaban cohort) had a lower incidence of 1.71% and a incidence rate of 2.16.
  - Dabigatran had a 1.41% incidence and 1.67 incidence rate, against warfarin (weighted by dabigatran) with a higher incidence of 1.92% and a incidence rate of 2.39.
  - Apixaban users experienced a 1.96% incidence and 2.27 incidence rate, similar to warfarin (weighted by apixaban) at 1.99% incidence and 2.50 incidence rate.
- **Intracranial Hemorrhage:**
  - Rivaroxaban users had a 1.09% incidence and 1.12 incidence rate, comparable to warfarin (rivaroxaban-weighted) at 1.08% and 1.00 incidence rate.
  - Dabigatran users had an incidence of 0.35% and an incidece rate of 0.37, while warfarin (dabigatran-weighted) showed a higher incidence of 0.83% and a incidence rate of 0.83.
  - Apixaban users experienced a 0.38% incidence and 0.41 incidence rate, compared to a higher incidence of 1.15% and a incidence rate of 0.95 in warfarin users (apixaban-weighted).
- **Fatal Bleeding:**
  - Rivaroxaban users had a 0.28% incidence and 0.28 incidence rate, similiar to warfarin (rivaroxaban-weighted) at 0.30% incidence and 0.33 incidence rate.

- Dabigatran users showed no fatal bleeding events, compared to warfarin (Dabigatran-weighted) with a 0.36% incidence and 0.41 incidence rate.
- Apixaban users had a 0.58% incidence and 0.62 incidence rate, while warfarin (apixaban-weighted) showed a lower incidence of 0.37% and a incidence rate of 0.35.

- **Severe Ischemic Stroke (IS 2):**
  - No events were reported for rivaroxaban users, while Warfarin (rivaroxaban-weighted) had an incidence of 0.22% and a incidence rate of 0.33.
  - Dabigatran users had a lower incidence of 0.15% and rate of 0.19, compared to warfarin (dabigatran-weighted) at 0.26% and an incidence rate of 0.31.
  - Apixaban users showed an incidence of 0.40% and incidence rate of 0.46, against warfarin (apixaban-weighted) with a lower incidence of 0.23% and rate of 0.29.
- **Kidney Failure:**
  - No kidney failure events were reported for rivaroxaban users, while warfarin (rivaroxaban-weighted) had a incidence of 0.64% and an incidence rate of 0.83.
  - Dabigatran users had a lower incidence of 0.11% and incidence rate of 0.09, compared to warfarin (dabigatran-weighted) at 0.41% and an incidece rate of 0.52.
  - Apixaban users showed an incidence of 0.45% and rate of 0.46, while warfarin (apixaban-weighted) had a higher incidence of 0.65% and incidence rate of 0.71.
- **Acute Kidney Injury (AKI):**
  - Rivaroxaban users had a incidence of 1.49% and incidence rate of 1.40, compared to warfarin (rivaroxaban-weighted) with a lower incidence of 0.61% and rate of 0.82.
  - Dabigatran users showed a lower incidence of 0.25% and rate of 0.28, similar to warfarin (dabigatran-weighted) users at 0.45% and incidence rate of 0.51.
  - Apixaban users showed a 1.05% incidence and 1.18 incidence rate, compared to a lower incidence of 0.53% and rate of 0.70 in warfarin users (apixaban-weighted).

Table 16. Incidence rates and cumulative incidence – Weighted (Norway)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	1,008	21	2.52 (1.64 - 3.86)	2.95 (1.83 - 4.51)
warfarin - weighted by the rivaroxaban cohort	11,720	129	1.71 (1.34 - 2.17)	2.16 (1.15 - 3.70)
dabigatran 110 mg twice/day	1,575	18	1.41 (0.89 - 2.26)	1.67 (0.99 - 2.65)
warfarin - weighted by the dabigatran cohort	11,720	129	1.92 (1.52 - 2.42)	2.39 (1.52 - 3.59)
apixaban 2.5 mg twice/day	2,946	44	1.96 (1.46 - 2.65)	2.27 (1.65 - 3.05)
warfarin - weighted by the apixaban cohort	11,720	129	1.99 (1.41 – 2.82)	2.50 (1.80 – 3.38)
Intracranial hemorrhage				
rivaroxaban 15 mg once/day	1,008	8	1.09 (0.54 – 2.17)	1.12 (0.48 – 2.20)
warfarin - weighted by the rivaroxaban cohort	11,720	33	1.08 (0.55 – 2.12)	1.00 (0.37 – 2.17)
dabigatran 110 mg twice/day	1,575	<5	0.35 (0.13 – 0.95)	0.37 (0.10 – 0.95)
warfarin - weighted by the dabigatran cohort	11,720	33	0.83 (0.55 - 1.27)	0.83 (0.36 - 1.63)
apixaban 2.5 mg twice/day	2,946	8	0.38 (0.19 - 0.78)	0.41 (0.18 - 0.81)
warfarin - weighted by the apixaban cohort	11,720	33	1.15 (0.59 – 2.24)	0.95 (0.54 – 1.54)
Fatal bleeding				
rivaroxaban 15 mg once/day	1,008	<5	0.28 (0.07 – 1.12)	0.28 (0.03 – 1.01)
warfarin - weighted by the rivaroxaban cohort	11,720	14	0.30 (0.16 - 0.55)	0.33 (0.04 - 1.20)
dabigatran 110 mg twice/day	1,575	0	0.00 (NA - NA)	NA (NA - NA)
warfarin - weighted by the dabigatran cohort	11,720	14	0.36 (0.19 - 0.68)	0.41 (0.11 - 1.06)
apixaban 2.5 mg twice/day	2,946	12	0.58 (0.33 - 1.04)	0.62 (0.32 - 1.07)
warfarin - weighted by the apixaban cohort	11,720	14	0.37 (0.18 - 0.74)	0.35 (0.13 - 0.77)
Severe IS 2				
rivaroxaban 15 mg once/day	1,008	0	0.00 (NA - NA)	NA (NA - NA)
warfarin - weighted by the rivaroxaban cohort	11,720	11	0.22 (0.11 - 0.43)	0.33 (0.04 - 1.19)
dabigatran 110 mg twice/day	1,575	<5	0.15 (0.04 - 0.61)	0.19 (0.02 - 0.67)
warfarin - weighted by the dabigatran cohort	11,720	11	0.26 (0.13 - 0.52)	0.31 (0.06 - 0.90)
apixaban 2.5 mg twice/day	2,946	9	0.40 (0.21 - 0.77)	0.46 (0.21 - 0.88)
warfarin - weighted by the apixaban cohort	11,720	11	0.23 (0.11 - 0.46)	0.29 (0.10 - 0.69)
Kidney failure				
rivaroxaban 15 mg once/day	1,008	0	0.00 (NA - NA)	NA (NA - NA)
warfarin - weighted by the	11,720	40	0.64 (0.41 - 0.99)	0.83 (0.27 - 1.93)

rivaroxaban cohort				
dabigatran 110 mg twice/day	1,575	<5	0.11 (0.02 - 0.80)	0.09 (0.00 - 0.52)
warfarin - weighted by the dabigatran cohort	11,720	40	0.41 (0.28 - 0.61)	0.52 (0.17 - 1.20)
apixaban 2.5 mg twice/day	2,946	9	0.45 (0.23 - 0.87)	0.46 (0.21 - 0.88)
warfarin - weighted by the apixaban cohort	11,720	40	0.65 (0.39 - 1.10)	0.71 (0.36 - 1.23)
AKI				
rivaroxaban 15 mg once/day	1,008	10	1.49 (0.80 - 2.76)	1.40 (0.67 - 2.57)
warfarin - weighted by the rivaroxaban cohort	11,720	29	0.61 (0.34 - 1.09)	0.82 (0.27 - 1.92)
dabigatran 110 mg twice/day	1,575	<5	0.25 (0.08 - 0.78)	0.28 (0.06 - 0.81)
warfarin - weighted by the dabigatran cohort	11,720	29	0.45 (0.26 - 0.75)	0.51 (0.17 - 1.20)
apixaban 2.5 mg twice/day	2,946	23	1.05 (0.70 - 1.59)	1.18 (0.75 - 1.78)
warfarin - weighted by the apixaban cohort	11,720	29	0.53 (0.32 - 0.90)	0.70 (0.36 - 1.23)

Finland

Table 17 and Table 18 present the unweighted and weighted incidence rates and cumulative incidence for Finland. The endpoints include ischemic stroke/systematic embolism, intracranial hemorrhage, fatal bleeding, severe IS2, kidney failure and AKI.

Incidence rates and cumulative incidence – Unweighted (Finland)

- **Ischemic Stroke/Systemic Embolism:** rivaroxaban users had a lower cumulative incidence of 1.26%, compared to warfarin users who showed a higher incidence of 2.20%. Dabigatran users had a cumulative incidence of 1.57%, while apixaban users had a slightly higher incidence of 2.17%.
- **Intracranial Hemorrhage:** rivaroxaban users experienced a higher incidence of 1.81% compared to apixaban (0.29%) and dabigatran (0.24%) users. Warfarin users had an incidence of 0.47%.
- **Fatal Bleeding:** rivaroxaban users had a cumulative incidence of 0.17%. In contrast, apixaban users showed a higher incidence of 0.54%, and dabigatran users had an incidence of 0.32%. Warfarin users demonstrated the lowest incidence at 0.09%.
    - Note: The ICD-10 code I61 was not include in the Finnish definitions of fatal bleeding.
- **Severe Ischemic Stroke (IS 2):** rivaroxaban users showed an incidence of 0.62%, while dabigatran users had a slightly lower incidence of 0.23%. Apixaban users had the lowest incidence of 0.12%, with warfarin users showing an incidence of 0.18%.
- **Kidney Failure:** rivaroxaban users had an incidence of 0.47%, no kidney failure events were reported for dabigatran users. Apixaban users showed a higher incidence of 0.74%, compared to a lower incidence of 0.20% in warfarin users.
- **Acute Kidney Injury (AKI):** rivaroxaban and apixaban users showed higher incidences of 0.65% and 0.72%, respectively, in contrast to dabigatran users (0.15%) and warfarin users (0.30%).

Table 17. Incidence rates and cumulative incidence – Unweighted (Finland)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	587	6	1.26 (0.57 - 2.80)	1.39 (0.51 - 3.02)
warfarin	37,985	732	2.20 (2.04 - 2.37)	2.60 (2.42 - 2.80)
dabigatran 110 mg twice/day	1,194	14	1.57 (0.92 - 2.68)	1.74 (0.95 - 2.92)
warfarin	37,985	732	2.20 (2.04 - 2.37)	2.60 (2.42 - 2.80)
apixaban 2.5 mg twice/day	1,155	21	2.17 (1.42 - 3.33)	2.35 (1.46 - 3.60)
warfarin	37,985	732	2.20 (2.04 - 2.37)	2.60 (2.42 - 2.80)
Intracranial hemorrhage				
rivaroxaban 15 mg once/day	587	8	1.81 (0.91 - 3.62)	1.85 (0.80 - 3.64)
warfarin	37,985	138	0.47 (0.39 - 0.55)	0.48 (0.41 - 0.57)
dabigatran 110 mg twice/day	1,194	<5	0.24 (0.06 - 0.97)	0.25 (0.03 - 0.89)
warfarin	37,985	138	0.47 (0.39 - 0.55)	0.48 (0.41 - 0.57)
apixaban 2.5 mg twice/day	1,155	<5	0.29 (0.09 - 0.92)	0.33 (0.07 - 0.98)
warfarin	37,985	138	0.47 (0.39 - 0.55)	0.48 (0.41 - 0.57)
Fatal bleeding				
rivaroxaban 15 mg once/day	587	<5	0.17 (0.02 - 1.21)	0.23 (0.01 - 1.28)
warfarin	37,985	28	0.09 (0.06 - 0.13)	0.10 (0.07 - 0.14)
dabigatran 110 mg twice/day	1,194	<5	0.32 (0.10 - 1.02)	0.37 (0.08 - 1.09)
warfarin	37,985	28	0.09 (0.06 - 0.13)	0.10 (0.07 - 0.14)
apixaban 2.5 mg twice/day	1,155	5	0.54 (0.22 - 1.29)	0.56 (0.18 - 1.30)
warfarin	37,985	28	0.09 (0.06 - 0.13)	0.10 (0.07 - 0.14)
Severe IS 2				
rivaroxaban 15 mg once/day	587	<5	0.62 (0.20 - 1.92)	0.69 (0.14 - 2.02)
warfarin	37,985	58	0.18 (0.14 - 0.23)	0.20 (0.15 - 0.26)
dabigatran 110 mg twice/day	1,194	<5	0.23 (0.05 - 0.96)	0.25 (0.03 - 0.89)
warfarin	37,985	58	0.18 (0.14 - 0.23)	0.20 (0.15 - 0.26)
apixaban 2.5 mg twice/day	1,155	<5	0.12 (0.02 - 0.88)	0.11 (0.00 - 0.62)
warfarin	37,985	58	0.18 (0.14 - 0.23)	0.20 (0.15 - 0.26)
Kidney failure				
rivaroxaban 15 mg once/day	587	<5	0.47 (0.12 - 1.87)	0.46 (0.06 - 1.66)
warfarin	37,985	65	0.20 (0.16 - 0.26)	0.23 (0.18 - 0.29)
dabigatran 110 mg twice/day	1,194	0	0.00 (NA - NA)	NA (NA - NA)
warfarin	37,985	65	0.20 (0.16 - 0.26)	0.23 (0.18 - 0.29)
apixaban 2.5 mg twice/day	1,155	7	0.74 (0.35 - 1.56)	0.78 (0.31 - 1.61)
warfarin	37,985	65	0.20 (0.16 - 0.26)	0.23 (0.18 - 0.29)
AKI				
rivaroxaban 15 mg once/day	587	<5	0.65 (0.21 - 2.05)	0.69 (0.14 - 2.02)

warfarin	37,985	98	0.30 (0.24 - 0.37)	0.34 (0.28 - 0.42)
dabigatran 110 mg twice/day	1,194	<5	0.15 (0.02 - 1.08)	0.12 (0.00 - 0.69)
warfarin	37,985	98	0.30 (0.24 - 0.37)	0.34 (0.28 - 0.42)
apixaban 2.5 mg twice/day	1,155	7	0.72 (0.34 - 1.52)	0.78 (0.31 - 1.61)
warfarin	37,985	98	0.30 (0.24 - 0.37)	0.34 (0.28 - 0.42)

Note: The ICD-10 code I61 was not include in the Finnish definitions of fatal bleeding.

Incidence rates and cumulative incidence – Weighted (Finland)

- **Ischemic Stroke/Systemic Embolism:**
  - Rivaroxaban had a cumulative incidence of 1.26% and an incidence rate of 1.39 per 100 person-years, compared to warfarin (weighted by the rivaroxaban cohort) with a higher incidence of 2.53% and an incidence rate of 3.14.
  - Dabigatran showed a 1.57% incidence and an incidence rate of 1.74 per 100 person-years, against warfarin (weighted by dabigatran) with a higher incidence of 2.50% and an incidence rate of 2.99.
  - Apixaban users experienced a 2.17% incidence and an incidence rate of 2.35 per 100 person-years, while warfarin (weighted by apixaban) had a higher incidence of 2.95% and an incidence rate of 3.71.
- **Intracranial Hemorrhage:**
  - Rivaroxaban users had a incidence of 1.81% and an incidence rate of 1.85 per 100 person-years, compared to warfarin (rivaroxaban-weighted) at a lower 0.54% incidence and an incidence rate of 0.72.
  - Dabigatran users had lower incidences (0.24%) and incidence rates (0.25 per 100 person-years), while warfarin (dabigatran-weighted) showed a higher incidence of 0.62% and an incidence rate of 0.68.
  - Apixaban users experienced a lower incidence of 0.29% and an incidence rate of 0.33 per 100 person-years, versus warfarin (apixaban-weighted) with a incidence of 0.74% and an incidence rate of 0.89.
- **Fatal Bleeding:**
  - Rivaroxaban users had a incidence of 0.17% and an incidence rate of 0.23 per 100 person-years, similar to warfarin (rivaroxaban-weighted) with an incidence of 0.16% and an incidence rate of 0.24.
  - Dabigatran users showed a incidence of 0.32% and an incidence rate of 0.37 per 100 person-years, compared to warfarin (dabigatran-weighted) at a lower 0.13% incidence and an incidence rate of 0.23.
  - Apixaban users had a higher incidence of 0.54% and an incidence rate of 0.56 per 100 person-years, while warfarin (apixaban-weighted) showed a lower incidence of 0.24% and an incidence rate of 0.38.
  - Note: The ICD-10 code I61 was not include in the Finnish definitions of fatal bleeding.

- **Severe Ischemic Stroke (IS 2):**
    - Rivaroxaban users showed an incidence of 0.62% and an incidence rate of 0.69 per 100 person-years, compared to warfarin (rivaroxaban-weighted) with a lower incidence of 0.27% and an incidence rate of 0.48.
    - Dabigatran users had a similiar incidence of 0.23% and an incidence rate of 0.25 per 100 person-years, against warfarin (dabigatran-weighted) with an incidence of 0.24% and an incidence rate of 0.34.
    - Apixaban users experienced a incidence of 0.12% and an incidence rate of 0.11 per 100 person-years, while warfarin (apixaban-weighted) showed a higher incidence of 0.43% and an incidence rate of 0.63.
- **Kidney Failure**
    - Rivaroxaban users had an incidence of 0.47% and an incidence rate of 0.46, compared to warfarin (rivaroxaban-weighted) with a slightly lower incidence of 0.24 and an incidence rate of 0.47.
    - Dabigatran users had no events, while warafin users (dabigatran-weighted) showed an incidence of 0.24% and an incidence rate of 0.34.
    - Apixaban users experienced a higher incidence (0.74%) and incidence rate (0.78) than warfarin users (weighted by the apixaban cohort) with incidence of 0.23% and an incidence rate of 0.37.
- **Acute Kidney Injury (AKI):**
    - Rivaroxaban users had an incidence of 0.65% and an incidence rate of 0.69, compared to warfarin (rivaroxaban-weighted) with an incidence of 0.42 and an incidence rate of 0.71.
    - Dabigatran users had a incidence of 0.15% and an incidence rate of 0.12 per 100 person-years, against warfarin (dabigatran-weighted) with an incidence of 0.36% and an incidence rate of 0.45.
    - Apixaban users experienced a higher incidence (0.72%) and incidence rate (0.78) than warfarin users (weighted by the apixaban cohort) with incidence of 0.45% and an incidence rate of 0.62.

Table 18. Incidence rates and cumulative incidence – Weighted (Finland)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	587	6	1.26 (0.57 - 2.80)	1.39 (0.51 - 3.02)
warfarin- weighted by the rivaroxaban cohort	37,985	732	2.53 (2.21 - 2.88)	3.14 (1.67 - 5.37)
dabigatran 110 mg twice/day	1,194	14	1.57 (0.92 - 2.68)	1.74 (0.95 - 2.92)
warfarin - weighted by the dabigatran cohort	37,985	732	2.50 (2.26 - 2.76)	2.99 (1.95 - 4.37)
apixaban 2.5 mg twice/day	1,155	21	2.17 (1.42 - 3.33)	2.35 (1.46 - 3.60)
warfarin - weighted by the apixaban cohort	37,985	732	2.95 (2.57 - 3.37)	3.71 (2.48 - 5.33)
Intracranial hemorrhage				
rivaroxaban 15 mg once/day	587	8	1.81 (0.91 - 3.62)	1.85 (0.80 - 3.64)
warfarin - weighted by the rivaroxaban cohort	37,985	138	0.54 (0.42 – 0.70)	0.72 (0.15 – 2.10)
dabigatran 110 mg twice/day	1,194	<5	0.24 (0.06 – 0.97)	0.25 (0.03 – 0.89)
warfarin - weighted by the dabigatran cohort	37,985	138	0.62 (0.46 – 0.83)	0.68 (0.25 – 1.48)
apixaban 2.5 mg twice/day	1,155	<5	0.29 (0.09 – 0.92)	0.33 (0.07 – 0.98)
warfarin - weighted by the apixaban cohort	37,985	138	0.74 (0.53 - 1.03)	0.89 (0.36 - 1.83)
Fatal bleeding				
rivaroxaban 15 mg once/day	587	<5	0.17 (0.02 - 1.21)	0.23 (0.01 - 1.28)
warfarin - weighted by the rivaroxaban cohort	37,985	28	0.16 (0.10 - 0.28)	0.24 (0.01 - 1.33)
dabigatran 110 mg twice/day	1,194	<5	0.32 (0.10 - 1.02)	0.37 (0.08 - 1.09)
warfarin - weighted by the dabigatran cohort	37,985	28	0.13 (0.08 - 0.21)	0.23 (0.03 - 0.82)
apixaban 2.5 mg twice/day	1,155	5	0.54 (0.22 - 1.29)	0.56 (0.18 - 1.30)
warfarin - weighted by the apixaban cohort	37,985	28	0.24 (0.14 - 0.40)	0.38 (0.08 - 1.11)
Severe IS 2				
rivaroxaban 15 mg once/day	587	<5	0.62 (0.20 - 1.92)	0.69 (0.14 - 2.02)
warfarin- weighted by the rivaroxaban cohort	37,985	58	0.27 (0.17 - 0.41)	0.48 (0.06 - 1.72)
dabigatran 110 mg twice/day	1,194	<5	0.23 (0.05 - 0.96)	0.25 (0.03 - 0.89)
warfarin - weighted by the dabigatran cohort	37,985	58	0.24 (0.17 - 0.33)	0.34 (0.07 - 1.00)
apixaban 2.5 mg twice/day	1,155	<5	0.12 (0.02 - 0.88)	0.11 (0.00 - 0.62)
warfarin - weighted by the apixaban cohort	37,985	58	0.43 (0.30 - 0.63)	0.63 (0.20 - 1.47)
Kidney failure				
rivaroxaban 15 mg once/day	587	<5	0.47 (0.12 - 1.87)	0.46 (0.06 - 1.66)

warfarin - weighted by the rivaroxaban cohort	37,985	65	0.24 (0.18 - 0.33)	0.47 (0.06 - 1.70)
dabigatran 110 mg twice/day	1,194	0	0.00 (NA - NA)	NA (NA - NA)
warfarin - weighted by the dabigatran cohort	37,985	65	0.22 (0.16 - 0.31)	0.34 (0.07 - 1.00)
apixaban 2.5 mg twice/day	1,155	7	0.74 (0.35 - 1.56)	0.78 (0.31 - 1.61)
warfarin - weighted by the apixaban cohort	37,985	65	0.23 (0.15 - 0.36)	0.37 (0.08 - 1.09)
AKI				
rivaroxaban 15 mg once/day	587	<5	0.65 (0.21 - 2.05)	0.69 (0.14 - 2.02)
warfarin- weighted by the rivaroxaban cohort	37,985	98	0.42 (0.32 - 0.55)	0.71 (0.15 - 2.07)
dabigatran 110 mg twice/day	1,194	<5	0.15 (0.02 - 1.08)	0.12 (0.00 - 0.69)
warfarin - weighted by the dabigatran cohort	37,985	98	0.36 (0.28 - 0.45)	0.45 (0.12 - 1.16)
apixaban 2.5 mg twice/day	1,155	7	0.72 (0.34 - 1.52)	0.78 (0.31 - 1.61)
warfarin - weighted by the apixaban cohort	37,985	98	0.45 (0.33 - 0.61)	0.62 (0.20 - 1.46)

Note: The ICD-10 code I61 was not include in the Finnish definitions of fatal bleeding.

Denmark

Table 19 and Table 20 present the unweighted and weighted incidence rates and cumulative incidence for Denmark. The endpoints include ischemic stroke/systematic embolism, intracranial hemorrhage, fatal bleeding, severe IS2, kidney failure and AKI.

Incidence rates and cumulative incidence – Unweighted (Denmark)

- **Ischemic Stroke/Systemic Embolism:** rivaroxaban users had a cumulative incidence of 1.47% and an incidence rate of 1.83 per 100 person-years, similar to warfarin users who showed a 1.51% incidence and 1.85 incidence rate. Dabigatran users had a higher cumulative incidence of 2.03% and incidence rate of 2.33, while apixaban users matched warfarin and rivaroxaban users with a 1.51% incidence and 1.85 incidence rate.
- **Intracranial Hemorrhage:** rivaroxaban users experienced a lower incidence of 0.36% compared to warfarin users (0.42%). Dabigatran users had the lowest incidence of 0.18%, while apixaban users experienced the highest incidence of 0.56%.
- **Fatal Bleeding:** rivaroxaban users had the highest cumulative incidence of 1.16% and incidence rate of 1.44 per 100 person-years, compared to warfarin users who demonstrated a lower incidence of 0.33%. Dabigatran users showed a cumulative incidence of 0.48%, and apixaban users had a higher incidence of 0.89%.
- **Severe Ischemic Stroke (IS 2):** rivaroxaban users showed an incidence of 0.28%, higher than warfarin users who had an incidence of 0.13%. Dabigatran users had a slightly higher incidence of 0.32%, while apixaban users had an incidence of 0.19%.

- **Kidney Failure:** Rivaroxaban users had a similar incidence of 0.21% compared to warfarin users (0.19%). Dabigatran users reported the lowest incidence of 0.06%, while apixaban users had a incidence of 0.09%.
- **Acute Kidney Injury (AKI):** rivaroxaban users experienced a incidence of 0.45%, warfarin users had an incidence of 0.25%, while dabigatran users had a incidence of 0.31%, and apixaban users showed a incidence of 0.42%.

Table 19. Incidence rates and cumulative incidence – Unweighted (Denmark)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	1,912	24	1.47 (0.96 - 2.16)	1.83 (1.24 - 2.81)
warfarin	16,141	198	1.51 (1.31 - 1.74)	1.85 (1.62 - 2.14)
dabigatran 110 mg twice/day	3,498	60	2.03 (1.56 - 2.60)	2.33 (1.82 - 3.03)
warfarin	16,141	198	1.51 (1.31 - 1.74)	1.85 (1.62 - 2.14)
apixaban 2.5 mg twice/day	3,543	47	1.51 (1.12 - 1.99)	1.85 (1.40 - 2.50)
warfarin	16,141	198	1.51 (1.31 - 1.74)	1.85 (1.62 - 2.14)
Intracranial hemorrhage				
rivaroxaban 15 mg once/day	1,912	6	0.36 (0.15 - 0.76)	0.45 (0.21 - 1.20)
warfarin	16,141	47	0.42 (0.31 - 0.57)	0.44 (0.33 - 0.59)
dabigatran 110 mg twice/day	3,498	5	0.18 (0.07 - 0.40)	0.19 (0.08 - 0.57)
warfarin	16,141	47	0.42 (0.31 - 0.57)	0.44 (0.33 - 0.59)
apixaban 2.5 mg twice/day	3,543	16	0.56 (0.33 - 0.90)	0.62 (0.39 - 1.07)
warfarin	16,141	47	0.42 (0.31 - 0.57)	0.44 (0.33 - 0.59)
Fatal bleeding				
rivaroxaban 15 mg once/day	1,912	19	1.16 (0.72 - 1.78)	1.44 (0.93 - 2.35)
warfarin	16,141	36	0.33 (0.23 - 0.46)	0.33 (0.24 - 0.47)
dabigatran 110 mg twice/day	3,498	13	0.48 (0.27 - 0.81)	0.50 (0.30 - 0.92)
warfarin	16,141	36	0.33 (0.23 - 0.46)	0.33 (0.24 - 0.47)
apixaban 2.5 mg twice/day	3,543	27	0.89 (0.60 - 1.28)	1.05 (0.73 - 1.58)
warfarin	16,141	36	0.33 (0.23 - 0.46)	0.33 (0.24 - 0.47)
Severe IS 2				
rivaroxaban 15 mg once/day	1,912	5	0.28 (0.11 - 0.62)	0.38 (0.16 - 1.13)
warfarin	16,141	18	0.13 (0.08 - 0.21)	0.17 (0.11 - 0.28)
dabigatran 110 mg twice/day	3,498	9	0.32 (0.16 - 0.59)	0.35 (0.18 - 0.74)
warfarin	16,141	18	0.13 (0.08 - 0.21)	0.17 (0.11 - 0.28)
apixaban 2.5 mg twice/day	3,543	6	0.19 (0.08 - 0.41)	0.23 (0.11 - 0.62)
warfarin	16,141	18	0.13 (0.08 - 0.21)	0.17 (0.11 - 0.28)
Kidney failure				

rivaroxaban 15 mg once/day	1,912	<5	0.21 (0.06 - 0.60)	0.23 (0.07 - 1.12)
warfarin	16,141	22	0.19 (0.12 - 0.29)	0.20 (0.14 - 0.32)
dabigatran 110 mg twice/day	3,498	<5	0.06 (0.01 - 0.23)	0.08 (0.02 - 0.77)
warfarin	16,141	22	0.19 (0.12 - 0.29)	0.20 (0.14 - 0.32)
apixaban 2.5 mg twice/day	3,543	<5	0.09 (0.03 - 0.24)	0.12 (0.04 - 0.58)
warfarin	16,141	22	0.19 (0.12 - 0.29)	0.20 (0.14 - 0.32)
AKI				
rivaroxaban 15 mg once/day	1,912	8	0.45 (0.21 - 0.87)	0.61 (0.31 - 1.36)
warfarin	16,141	30	0.25 (0.17 - 0.36)	0.28 (0.20 - 0.41)
dabigatran 110 mg twice/day	3,498	9	0.31 (0.15 - 0.57)	0.35 (0.18 - 0.74)
warfarin	16,141	30	0.25 (0.17 - 0.36)	0.28 (0.20 - 0.41)
apixaban 2.5 mg twice/day	3,543	14	0.42 (0.24 - 0.69)	0.55 (0.33 - 0.98)
warfarin	16,141	30	0.25 (0.17 - 0.36)	0.28 (0.20 - 0.41)

Incidence rates and cumulative incidence – Weighted (Denmark)

- **Ischemic Stroke/Systemic Embolism:**
  - Rivaroxaban users had a cumulative incidence of 1.47% and an incidence rate of 1.83 per 100 person-years, lower than warfarin users (weighted by the rivaroxaban cohort) with a 1.88% incidence and 2.46 incidence rate.
  - Dabigatran users showed a 2.03% incidence and 2.33 incidence rate, against warfarin (weighted by dabigatran) with a 2.10% incidence and 2.64 incidence rate.
  - Apixaban users experienced a 1.51% incidence and 1.85 incidence rate, against warfarin (weighted by apixaban) at 2.25% incidence and 3.00 incidence rate.
- **Intracranial Hemorrhage:**
  - Rivaroxaban users had a 0.36% incidence and 0.45 incidence rate, compared to warfarin (rivaroxaban-weighted) at 0.55% and an incidence rate of 0.63.
  - Dabigatran users had a incidence of 0.18% and incidence rate of 0.19, while warfarin (dabigatran-weighted) showed a higher incidence of 0.54% and an 0.60 incidence rate.
  - Apixaban users experienced a 0.56% incidence and 0.62 incidence rate, compared to warfarin (apixaban-weighted) with a 0.70% incidence and 0.83 incidence rate.
- **Fatal Bleeding:**
  - Rivaroxaban users had a 1.16% incidence and 1.44 incidence rate, higher than warfarin (rivaroxaban-weighted) at 0.64% incidence and 0.68 incidence rate.
  - Dabigatran users showed a 0.48% incidence and 0.50 incidence rate, similiar to warfarin (dabigatran-weighted) at 0.46% incidence and 0.49 incidence rate.
  - Apixaban users had a slightly higher incidence of 0.89% and 1.05 incidence rate, while warfarin (apixaban-weighted) showed a 0.79% incidence and 0.82 incidence rate.

- **Severe Ischemic Stroke (IS 2):**
  - Rivaroxaban users showed a 0.28% incidence and 0.38 incidence rate, similar to warfarin (rivaroxaban-weighted) at 0.28% incidence and 0.39 incidence rate.
  - Dabigatran users had a 0.32% incidence and 0.35 incidence rate, compared to warfarin (dabigatran-weighted) at 0.26% incidence and 0.33 incidence rate.
  - Apixaban users experienced a 0.19% incidence and 0.23 rate, against warfarin (apixaban-weighted) with a 0.32% incidence and 0.47 incidence rate.
- **Kidney Failure:**
  - Rivaroxaban users showed a incidence of 0.21% and incidence rate of 0.23, while warfarin (rivaroxaban-weighted) had a incidence of 0.19% and incidence rate of 0.22.
  - Dabigatran users showed a incidence of 0.06% and an incidence rate of 0.08, while warfarin (dabigatran-weighted) users experienced a 0.14% incidence and 0.16 incidence rate.
  - Apixaaban users showed a incidence of 0.09% and an incidence rate of 0.12, while warfarin (apixaban-weighted) had a higher incidence of 0.19% and an incidence rate of 0.21.
- **Acute Kidney Injury (AKI):**
  - Rivaroxaban users had a incidence of 0.45% and rate of 0.61, compared to warfarin (rivaroxaban-weighted) at 0.43% incidence and an 0.47 incidence rate.
  - Dabigatran users showed a incidence of 0.31% and rate of 0.35, similar to warfarin (dabigatran-weighted) at 0.30% incidence and 0.34 incidence rate.
  - Apixaban users had a 0.42% incidence and 0.55 rate, compared to warfarin (apixaban-weighted) at 0.44% incidence and 0.50 incidence rate.

Table 20. Incidence rates and cumulative incidence – Weighted (Denmark)

Endpoint	1 year follow-up			
	Number of patients	Events	Cumulative incidence (%) (95% CI)	Incidence rate 100 person-years (95% CI)
Ischemic stroke/Systemic embolism				
rivaroxaban 15 mg once/day	1,912	24	1.47 (0.96 - 2.16)	1.83 (1.24 - 2.81)
warfarin	16,141	198	1.88 (1.24 - 2.73)	2.46 (1.99 - 3.08)
dabigatran 110 mg twice/day	3,498	60	2.03 (1.56 - 2.60)	2.33 (1.82 - 3.03)
warfarin	16,141	198	2.10 (1.59 - 2.71)	2.64 (2.20 - 3.20)
apixaban 2.5 mg twice/day	3,543	47	1.51 (1.12 - 1.99)	1.85 (1.40 - 2.50)
warfarin	16,141	198	2.25 (1.70 - 2.91)	3.00 (2.34 - 3.90)
Intracranial hemorrhage				
rivaroxaban 15 mg once/day	1,912	6	0.36 (0.15 - 0.76)	0.45 (0.21 - 1.20)
warfarin	16,141	47	0.55 (0.23 - 1.16)	0.63 (0.43 - 0.97)
dabigatran 110 mg twice/day	3,498	5	0.18 (0.07 - 0.40)	0.19 (0.08 - 0.57)
warfarin	16,141	47	0.54 (0.29 - 0.93)	0.60 (0.39 - 0.98)
apixaban 2.5 mg twice/day	3,543	16	0.56 (0.33 - 0.90)	0.62 (0.39 - 1.07)
warfarin	16,141	47	0.70 (0.40 - 1.16)	0.83 (0.43 - 1.77)
Fatal bleeding				
rivaroxaban 15 mg once/day	1,912	19	1.16 (0.72 - 1.78)	1.44 (0.93 - 2.35)
warfarin	16,141	36	0.64 (0.28 - 1.32)	0.68 (0.43 - 1.14)
dabigatran 110 mg twice/day	3,498	13	0.48 (0.27 - 0.81)	0.50 (0.30 - 0.92)
warfarin	16,141	36	0.46 (0.23 - 0.83)	0.49 (0.33 - 0.77)
apixaban 2.5 mg twice/day	3,543	27	0.89 (0.60 - 1.28)	1.05 (0.73 - 1.58)
warfarin	16,141	36	0.79 (0.45 - 1.31)	0.82 (0.50 - 1.45)
Severe IS 2				
rivaroxaban 15 mg once/day	1,912	5	0.28 (0.11 - 0.62)	0.38 (0.16 - 1.13)
warfarin	16,141	18	0.28 (0.10 - 0.69)	0.39 (0.19 - 0.94)
dabigatran 110 mg twice/day	3,498	9	0.32 (0.16 - 0.59)	0.35 (0.18 - 0.74)
warfarin	16,141	18	0.26 (0.12 - 0.52)	0.33 (0.19 - 0.62)
apixaban 2.5 mg twice/day	3,543	6	0.19 (0.08 - 0.41)	0.23 (0.11 - 0.62)
warfarin	16,141	18	0.32 (0.16 - 0.60)	0.47 (0.20 - 1.33)
Kidney failure				
rivaroxaban 15 mg once/day	1,912	<5	0.21 (0.06 - 0.60)	0.23 (0.07 - 1.12)
warfarin	16,141	22	0.19 (0.04 - 0.62)	0.22 (0.13 - 0.38)
dabigatran 110 mg twice/day	3,498	<5	0.06 (0.01 - 0.23)	0.08 (0.02 - 0.77)
warfarin	16,141	22	0.14 (0.04 - 0.37)	0.16 (0.09 - 0.30)
apixaban 2.5 mg twice/day	3,543	<5	0.09 (0.03 - 0.24)	0.12 (0.04 - 0.58)
warfarin	16,141	22	0.19 (0.06 - 0.47)	0.21 (0.12 - 0.40)
AKI				
rivaroxaban 15 mg once/day	1,912	8	0.45 (0.21 - 0.87)	0.61 (0.31 - 1.36)

warfarin	16,141	30	0.43 (0.16 - 0.96)	0.47 (0.29 - 0.82)
dabigatran 110 mg twice/day	3,498	9	0.31 (0.15 - 0.57)	0.35 (0.18 - 0.74)
warfarin	16,141	30	0.30 (0.14 - 0.60)	0.34 (0.22 - 0.57)
apixaban 2.5 mg twice/day	3,543	14	0.42 (0.24 - 0.69)	0.55 (0.33 - 0.98)
warfarin	16,141	30	0.44 (0.22 - 0.80)	0.50 (0.30 - 0.93)

The following figures illustrate the cumulative incidence curves for the unweighted (Figure 6 and Figure 7) and the weighted (Figure 8 and

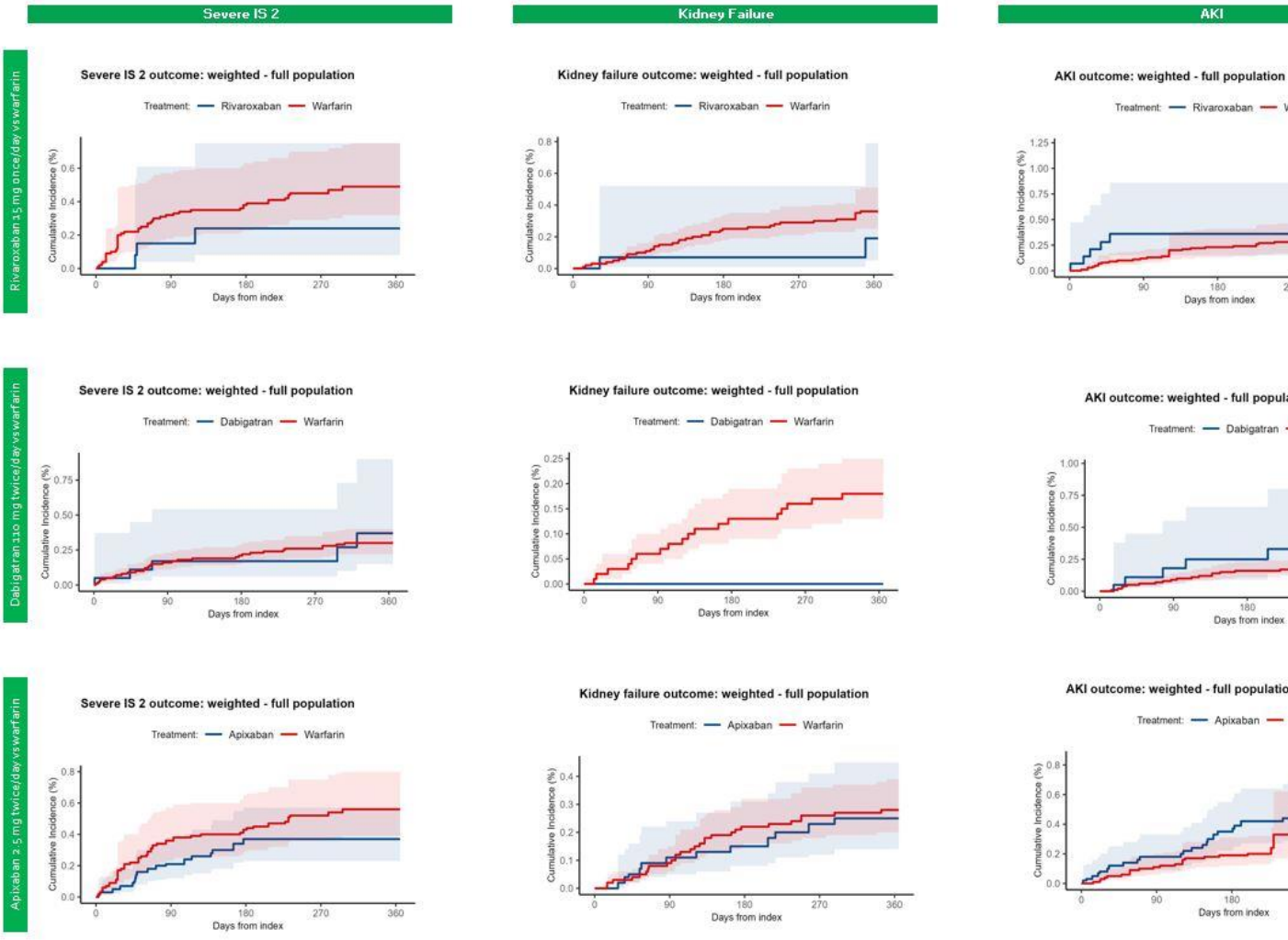

Figure **9**) endpoints in Sweden. The endpoints included ischemic stroke/systemic embolism, intracranial hemorrhage, fatal bleeding, severe IS2, kidney failure and AKI. For the figure illustrating the cumulative incidence for the unweighted and weighted endpoint severe IS1 for Sweden please see stand-alone document referred to in Table 33: "Quantify REATTAIN Incidence Analysis"

For Norway, Figure 10 and

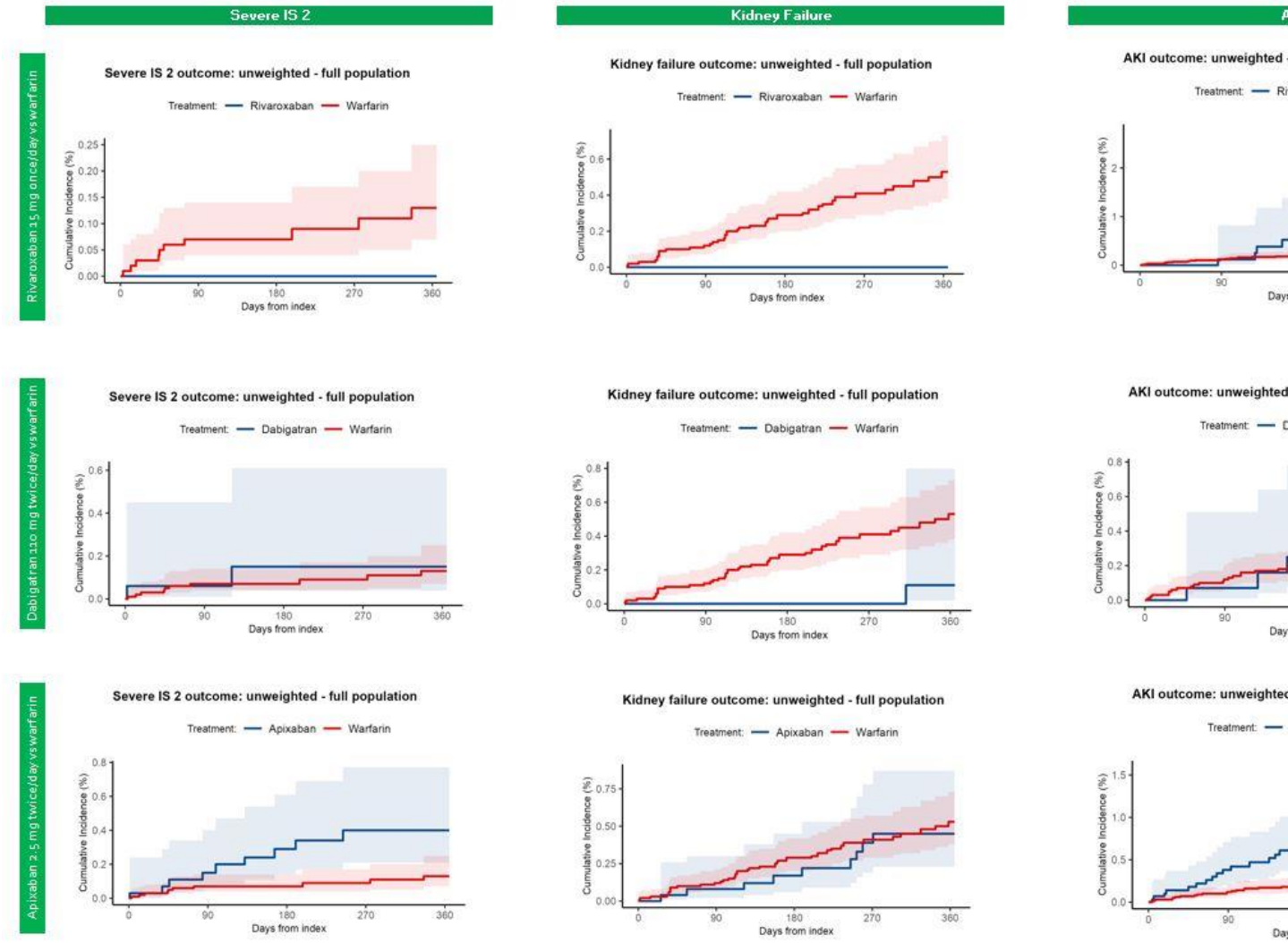

Figure **11**, illustrate the cumulative incidence curves for the unweighted endpoints. Figure 12 and Figure **13** represent the cumulative incidence curves for the weighted endpoints. The endpoints included ischemic stroke/systemic embolism, intracranial hemorrhage, fatal bleeding, severe IS2, kidney failure and AKI.

For Finland, Figure 14 and Figure 15 illustrate the cumulative incidence curves for the unweighted endpoints. Figure 16 and Figure 17 present the cumulative incidence curves for the weighted endpoints. The endpoints included ischemic stroke/systemic embolism, intracranial hemorrhage, fatal bleeding, severe IS2, kidney failure and AKI.

For Denmark, Figure 18 illustrates the cumulative incidence curves for the unweighted endpoints and Figure 19 presents the cumulative incidence curves for the weighted endpoints. The endpoints included ischemic stroke/systemic embolism and intracranial hemorrhage.

Reference Number: RD-SOP-1216
Supplement Version: 3

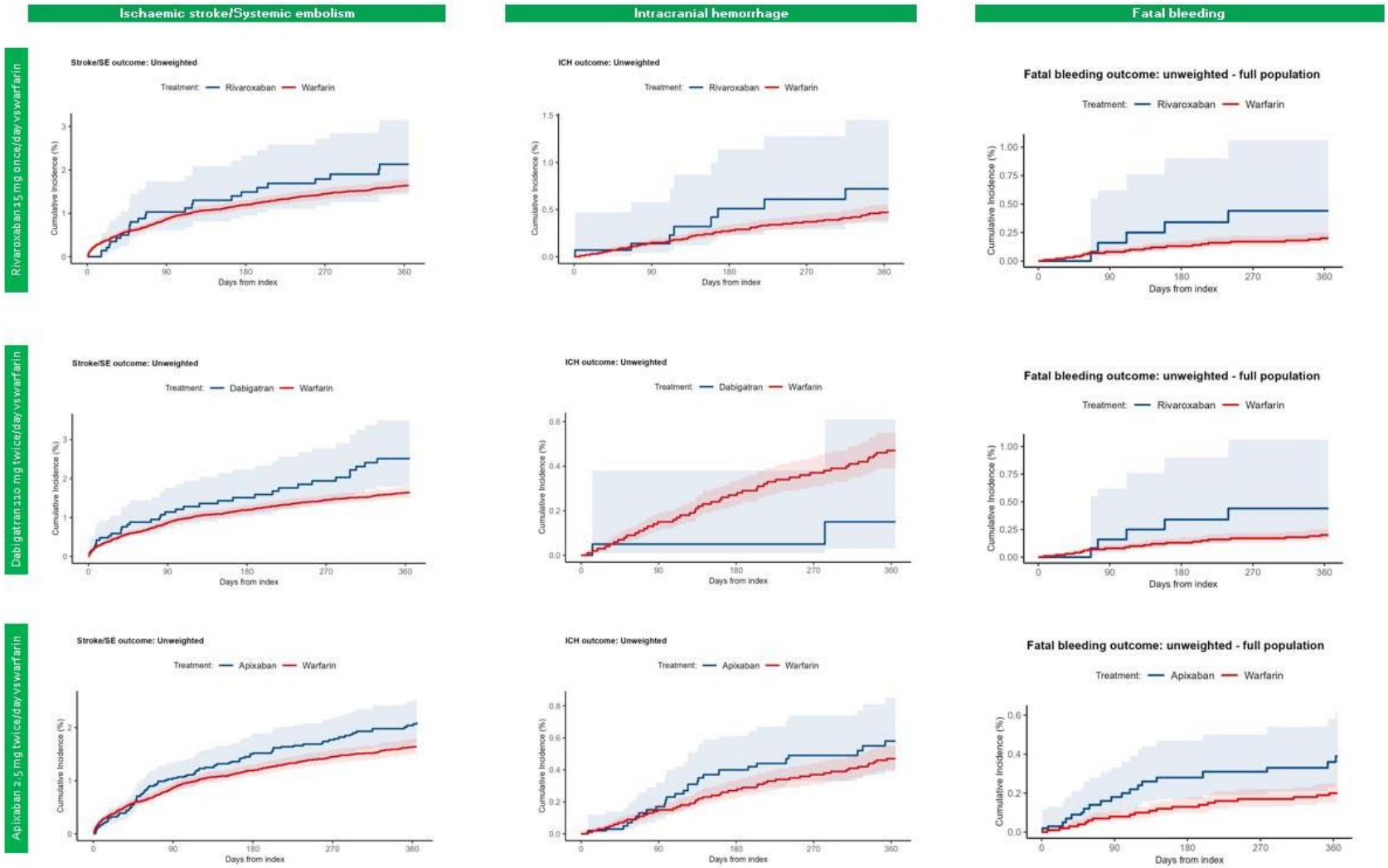

Figure 6 Cumulative incidence curves for the unweighted endpoints (Sweden)

Reference Number: RD-SOP-1216
Supplement Version: 3

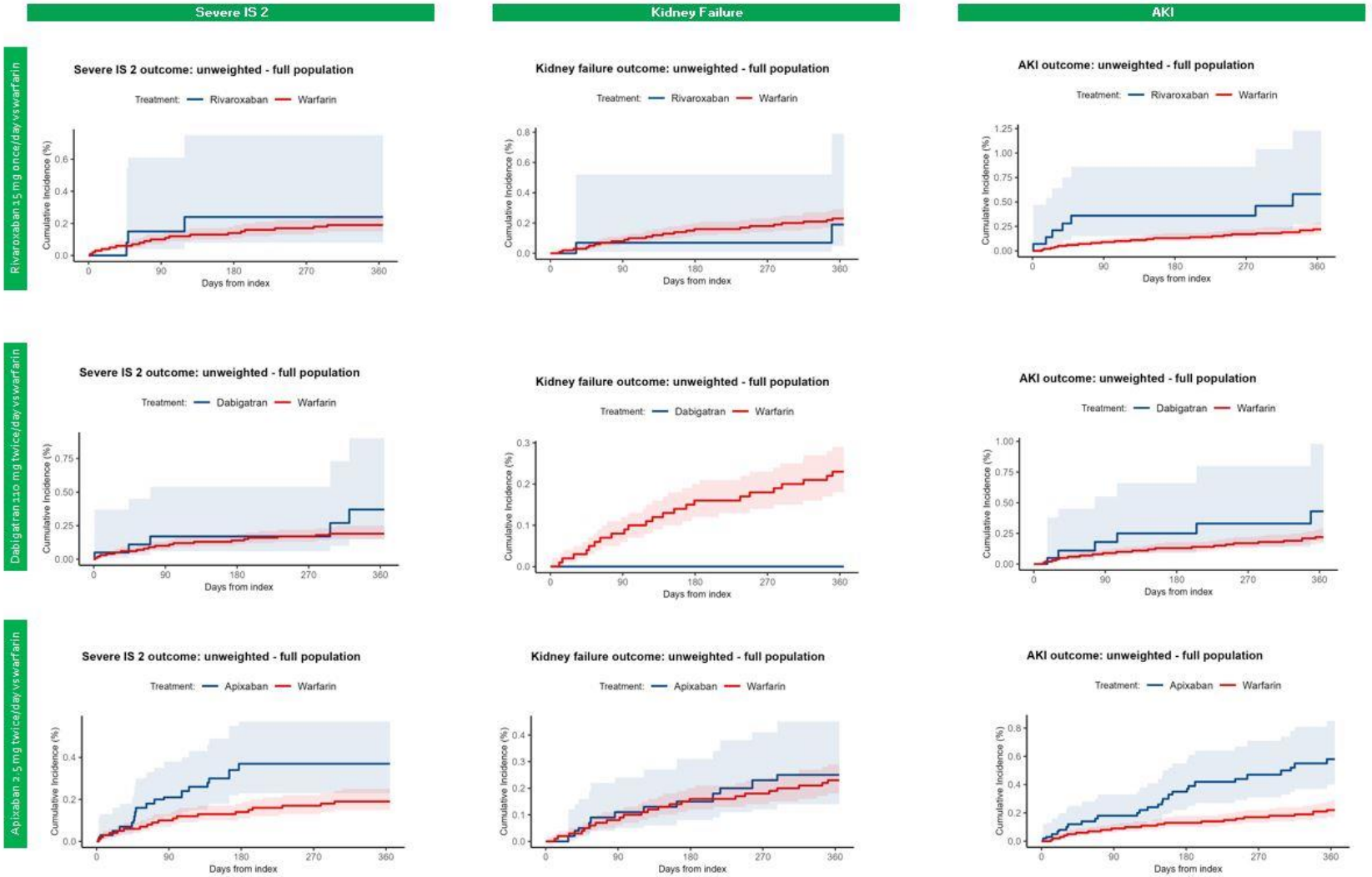

Figure 7 Cumulative incidence curves for the unweighted endpoints (Sweden) cont.

Reference Number: RD-SOP-1216
Supplement Version: 3

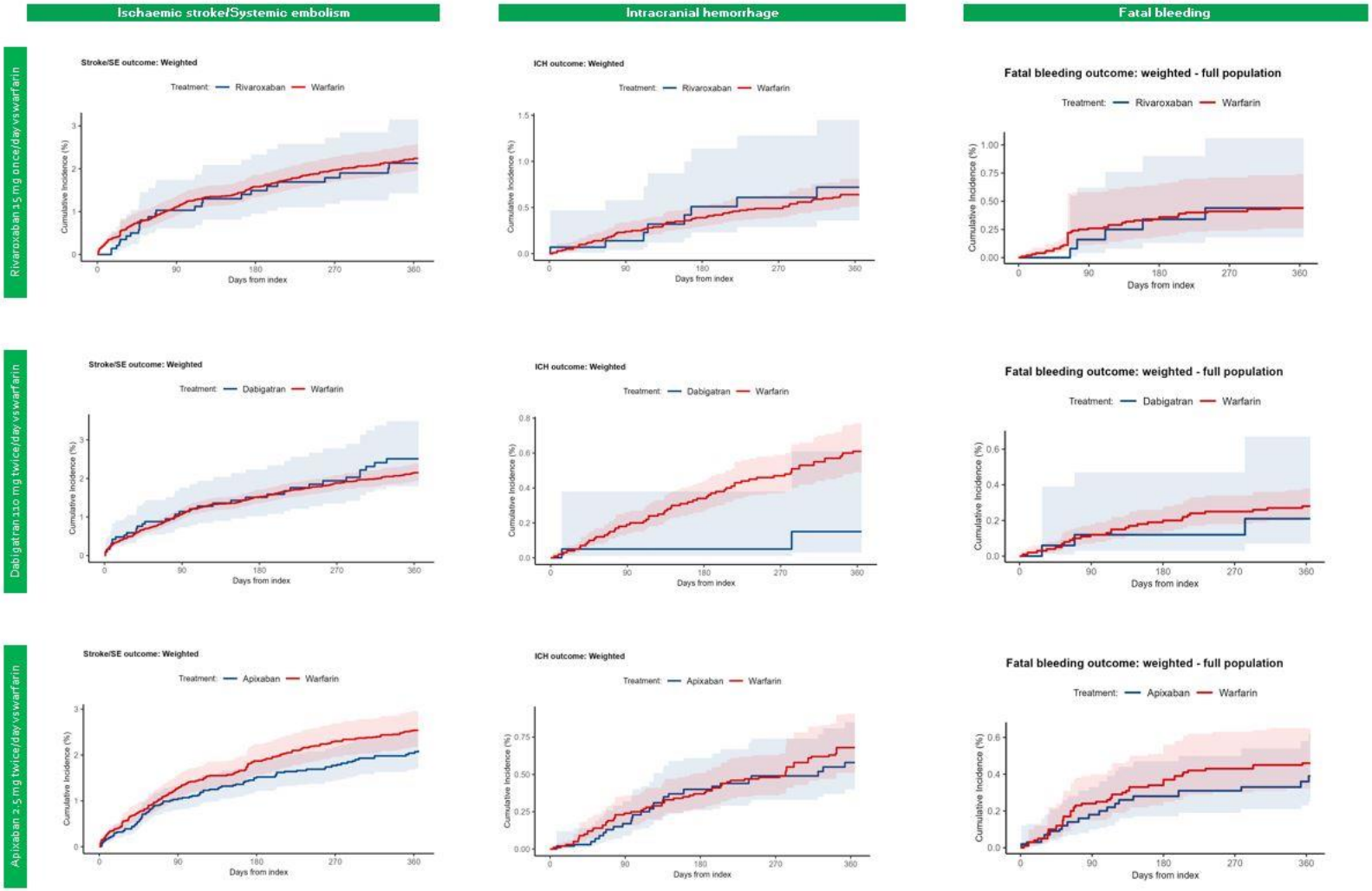

Figure 8 Cumulative incidence curves for the weigthed endpoints (Sweden)

Reference Number: RD-SOP-1216
Supplement Version: 3

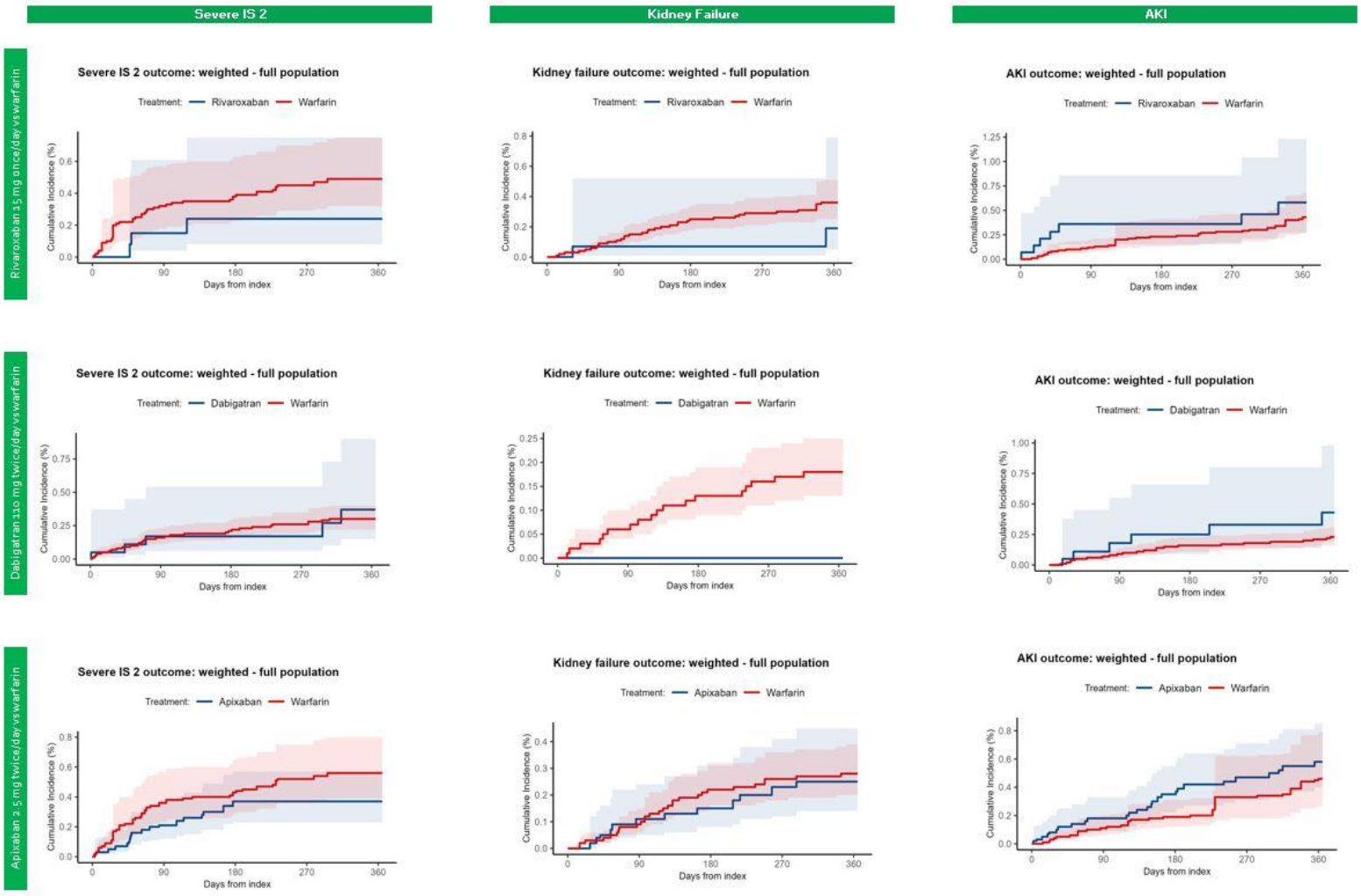

Figure 9 Cumulative incidence curves for the weigthed endpoints (Sweden) cont.

Reference Number: RD-SOP-1216
Supplement Version: 3

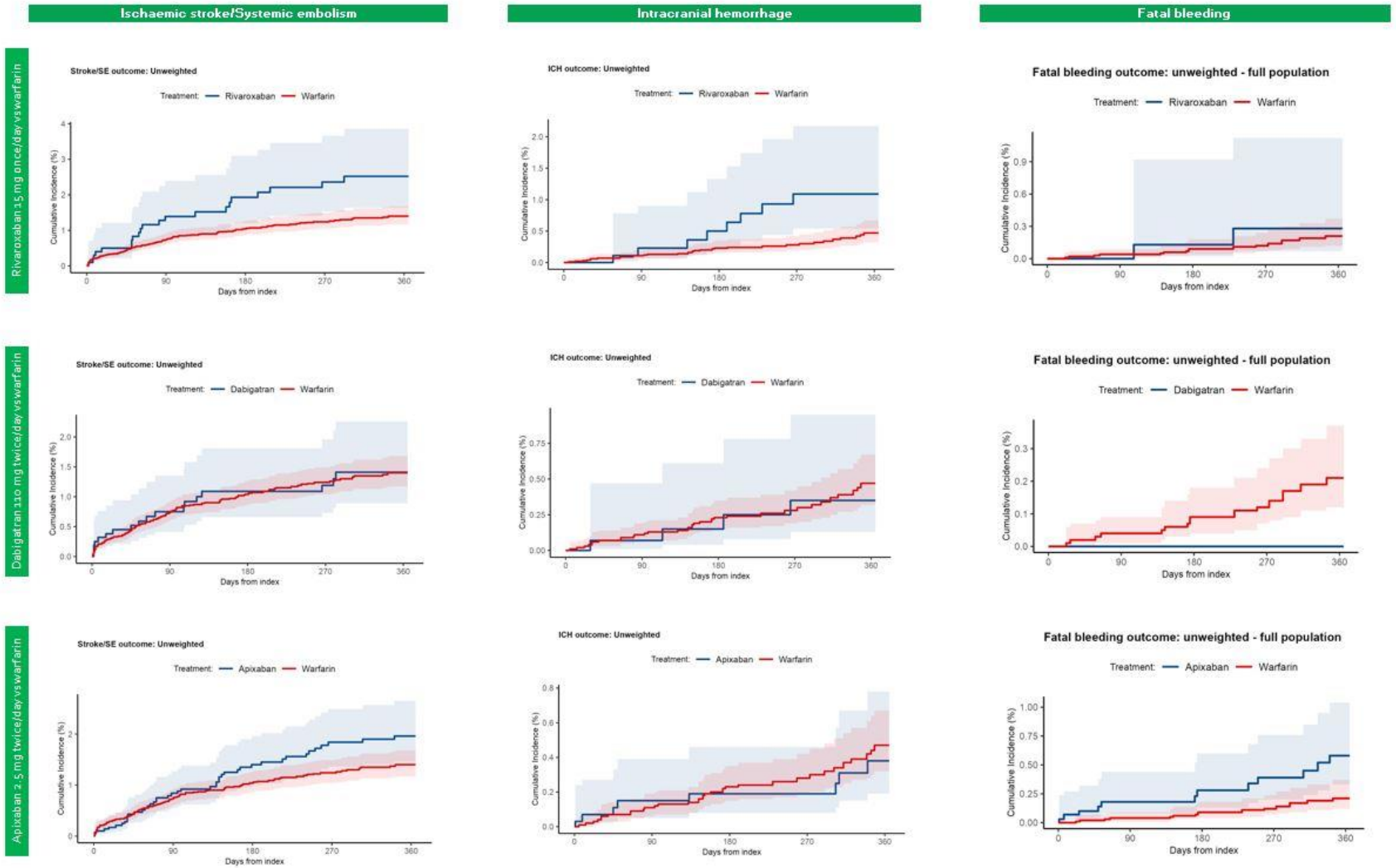

Figure 10. Cumulative incidence for the unweighted endpoints (Norway)

Reference Number: RD-SOP-1216
Supplement Version: 3

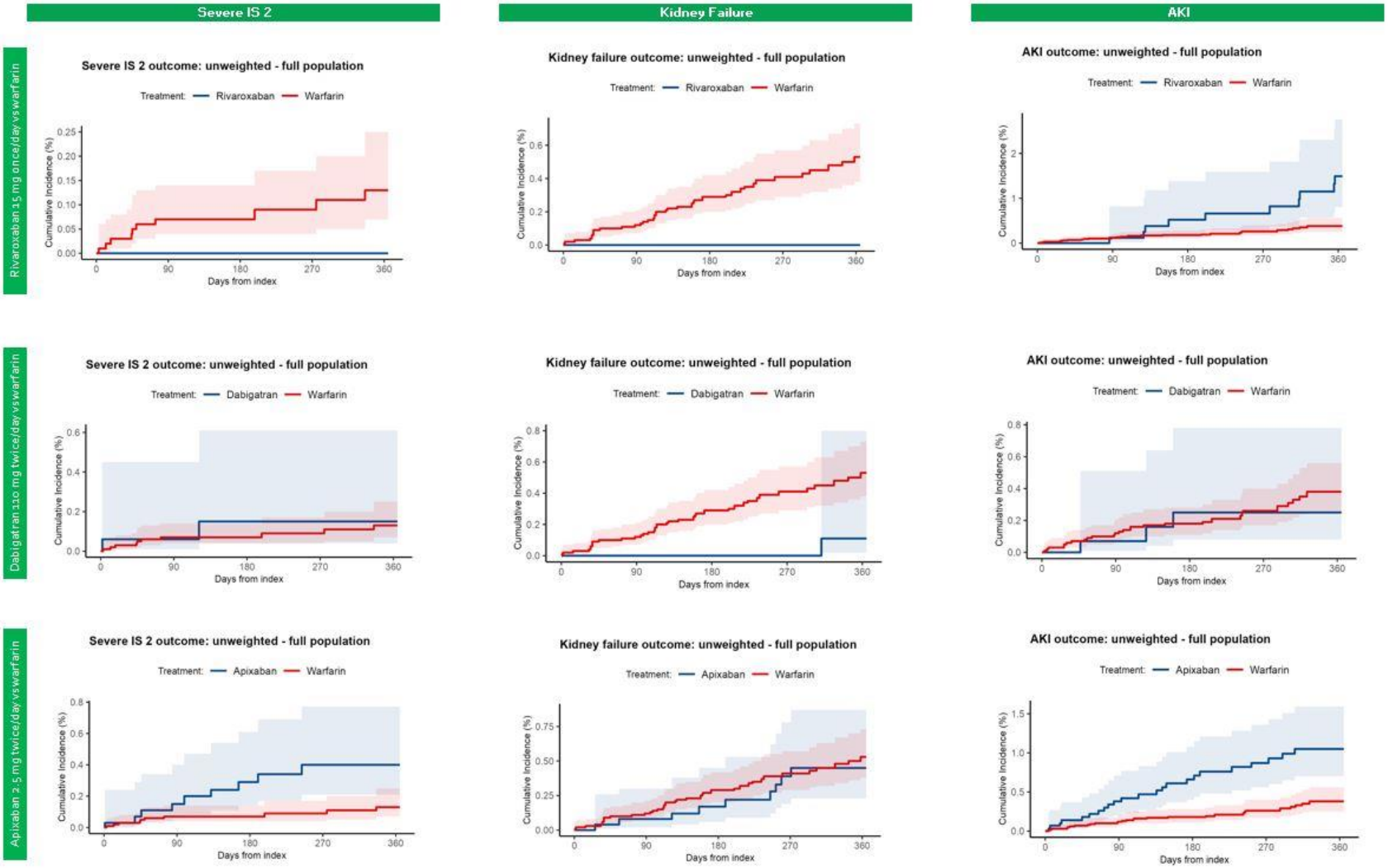

Figure 11. Cumulative incidence for the unweighted endpoints (Norway) cont.

Reference Number: RD-SOP-1216
Supplement Version: 3

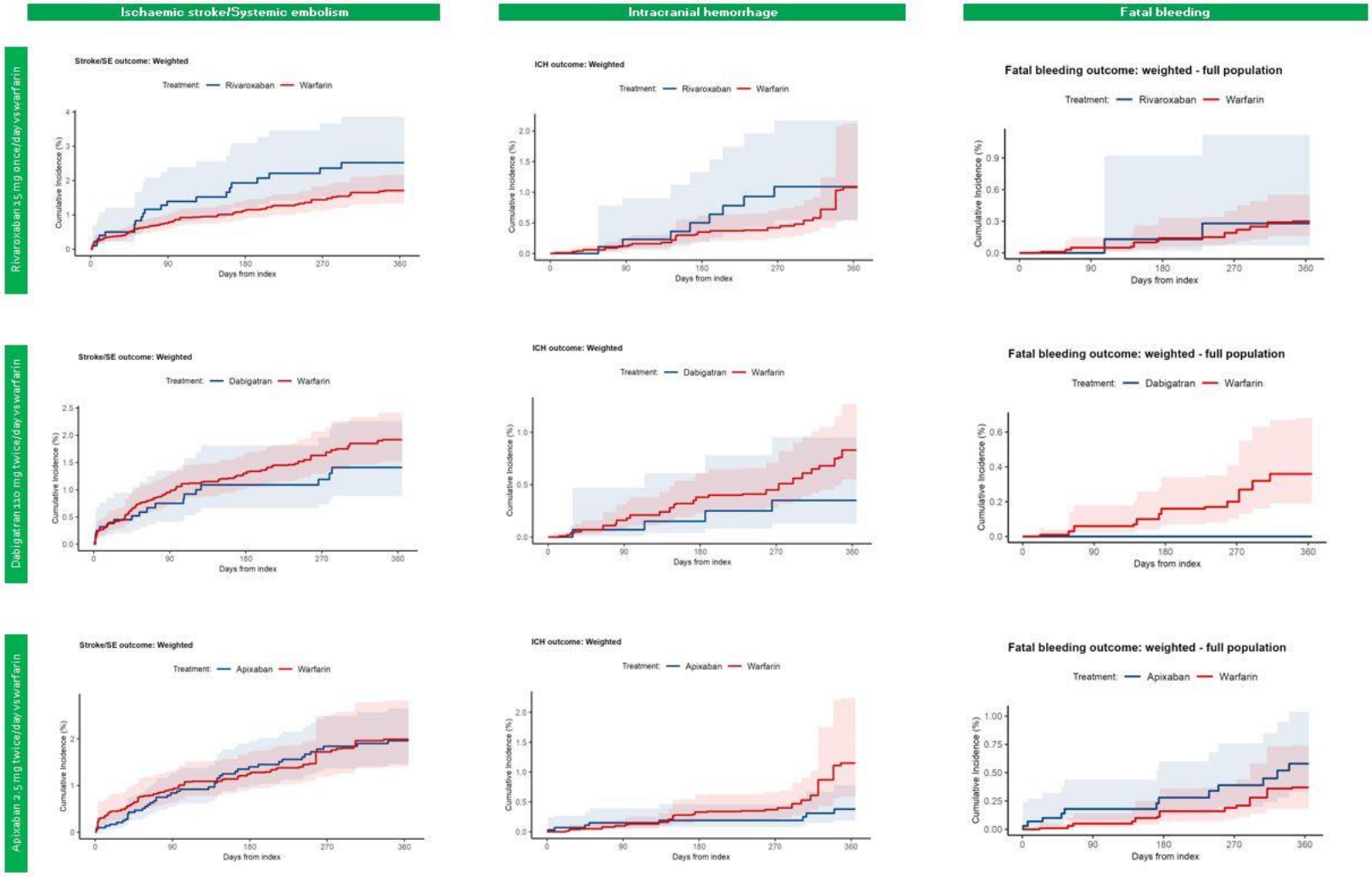

Figure 12. Cumulative incidence for the weighted endpoints (Norway)

Reference Number: RD-SOP-1216
Supplement Version: 3

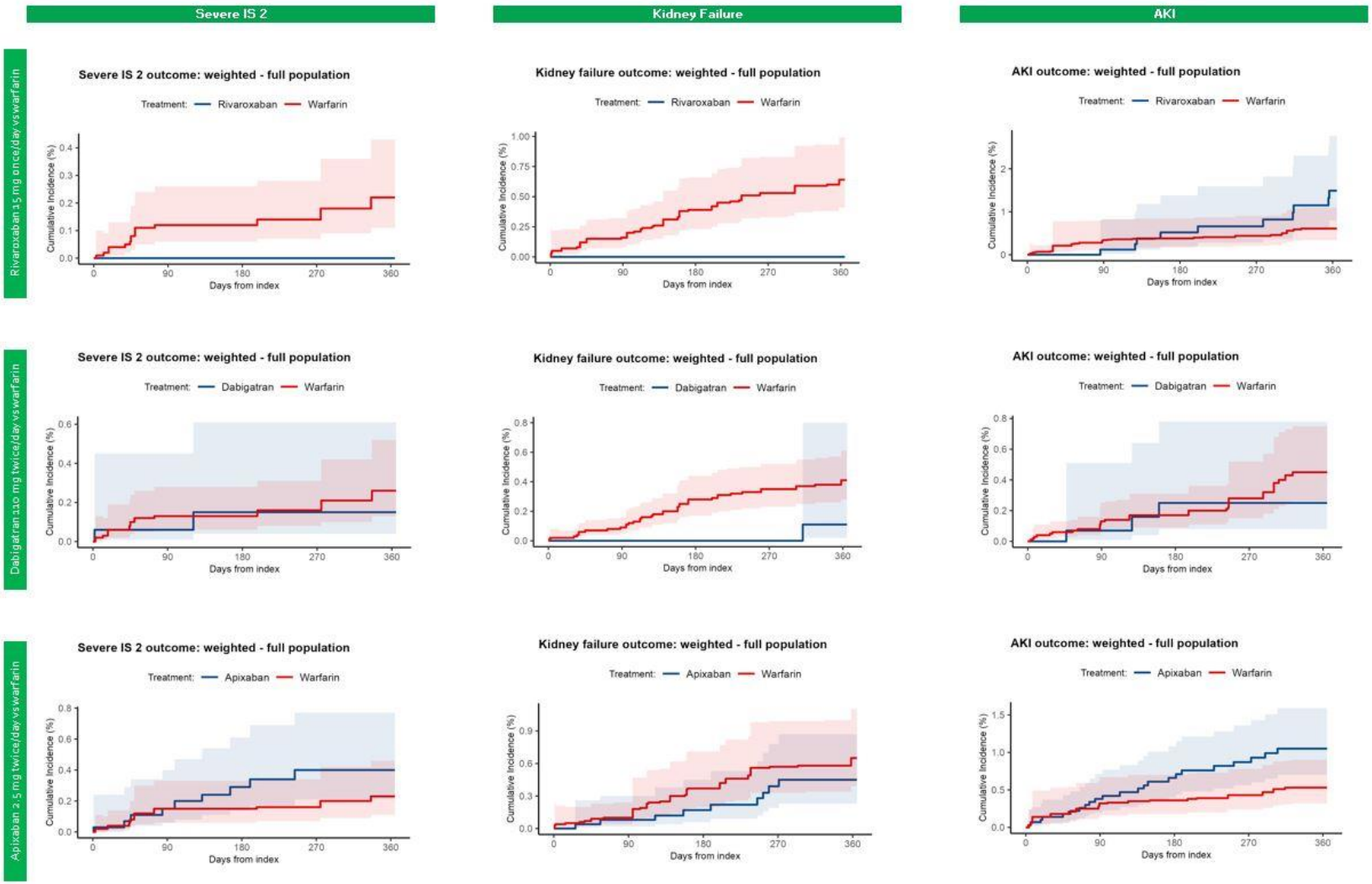

Figure 13. Cumulative incidence for the weighted endpoints (Norway) cont.

Reference Number: RD-SOP-1216
Supplement Version: 3

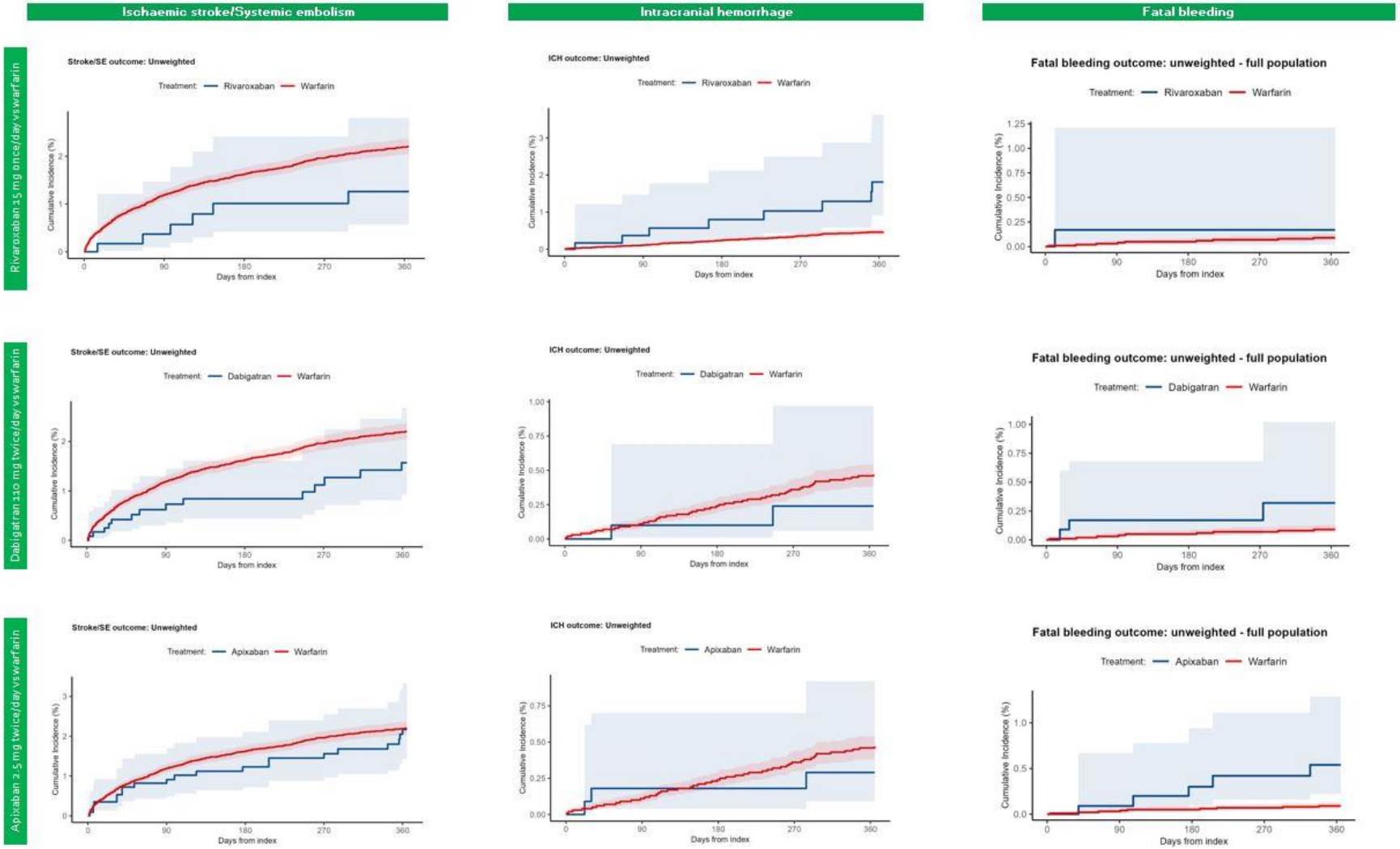

Figure 14. Cumulative incidence for the unweighted endpoints (Finland)

Reference Number: RD-SOP-1216
Supplement Version: 3

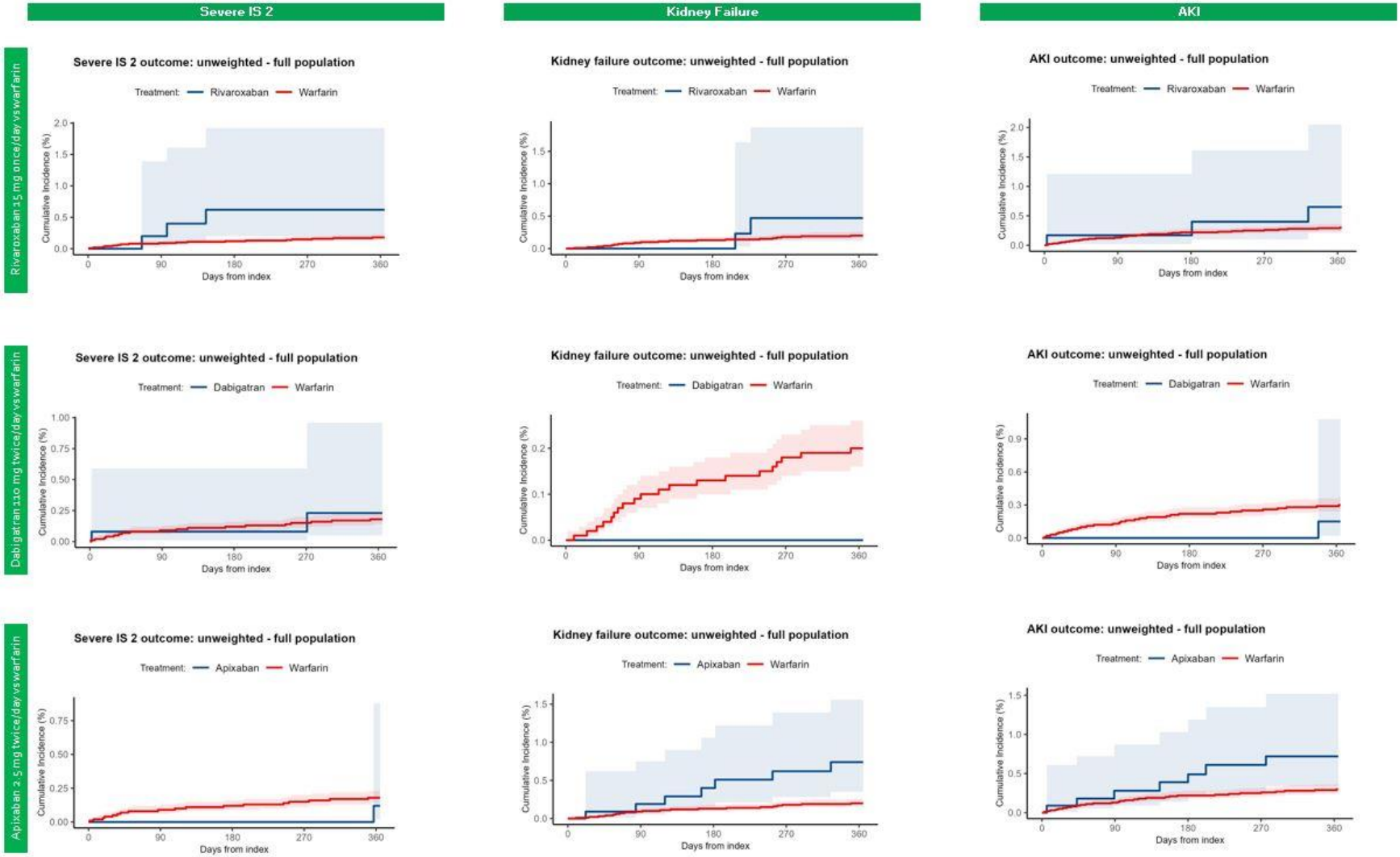

Figure 15. Cumulative incidence for the unweighted endpoints (Finland) cont.

Reference Number: RD-SOP-1216
Supplement Version: 3

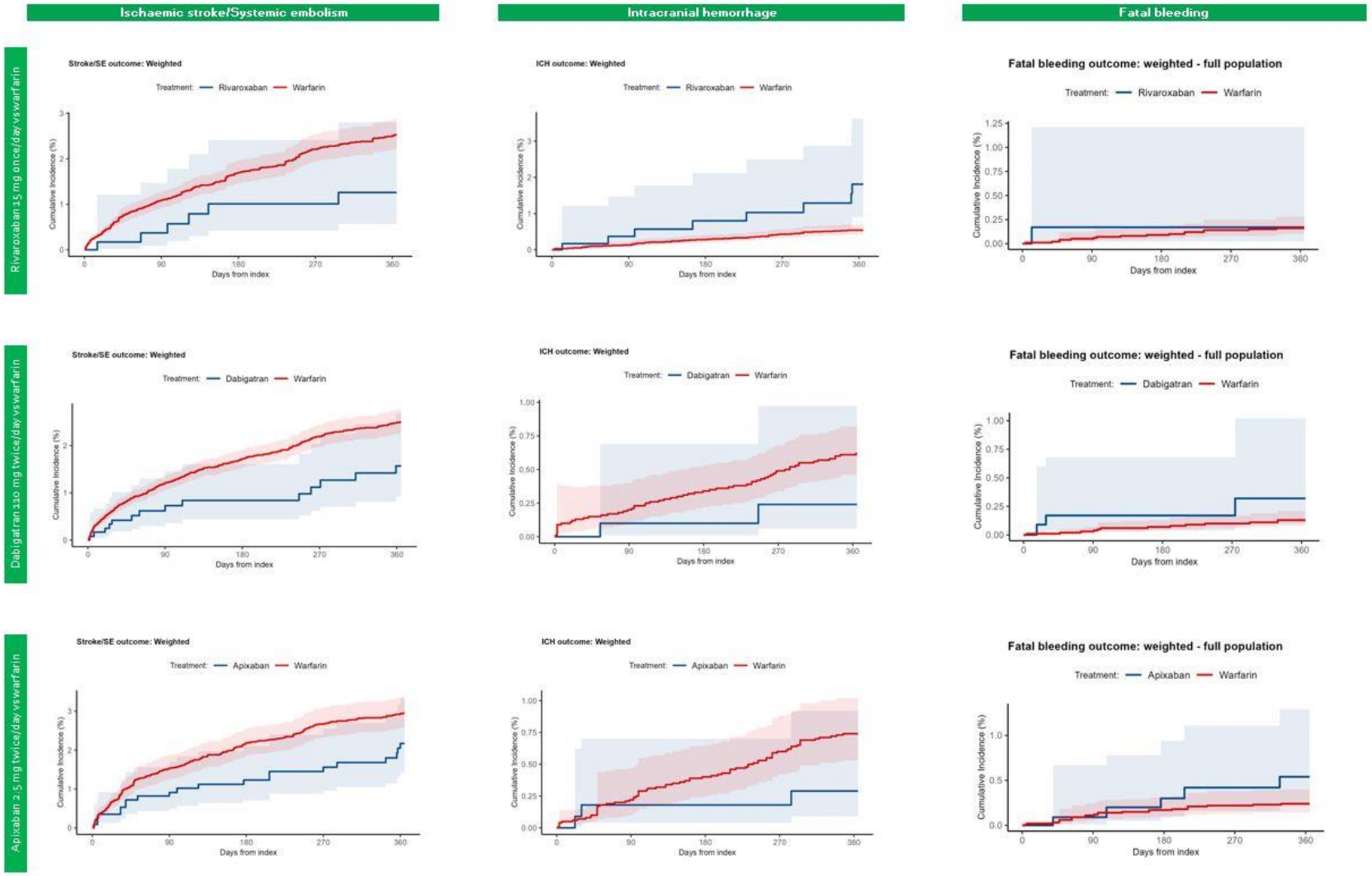

Figure 16. Cumulative incidence for the weighted endpoints (Finland)

Reference Number: RD-SOP-1216
Supplement Version: 3

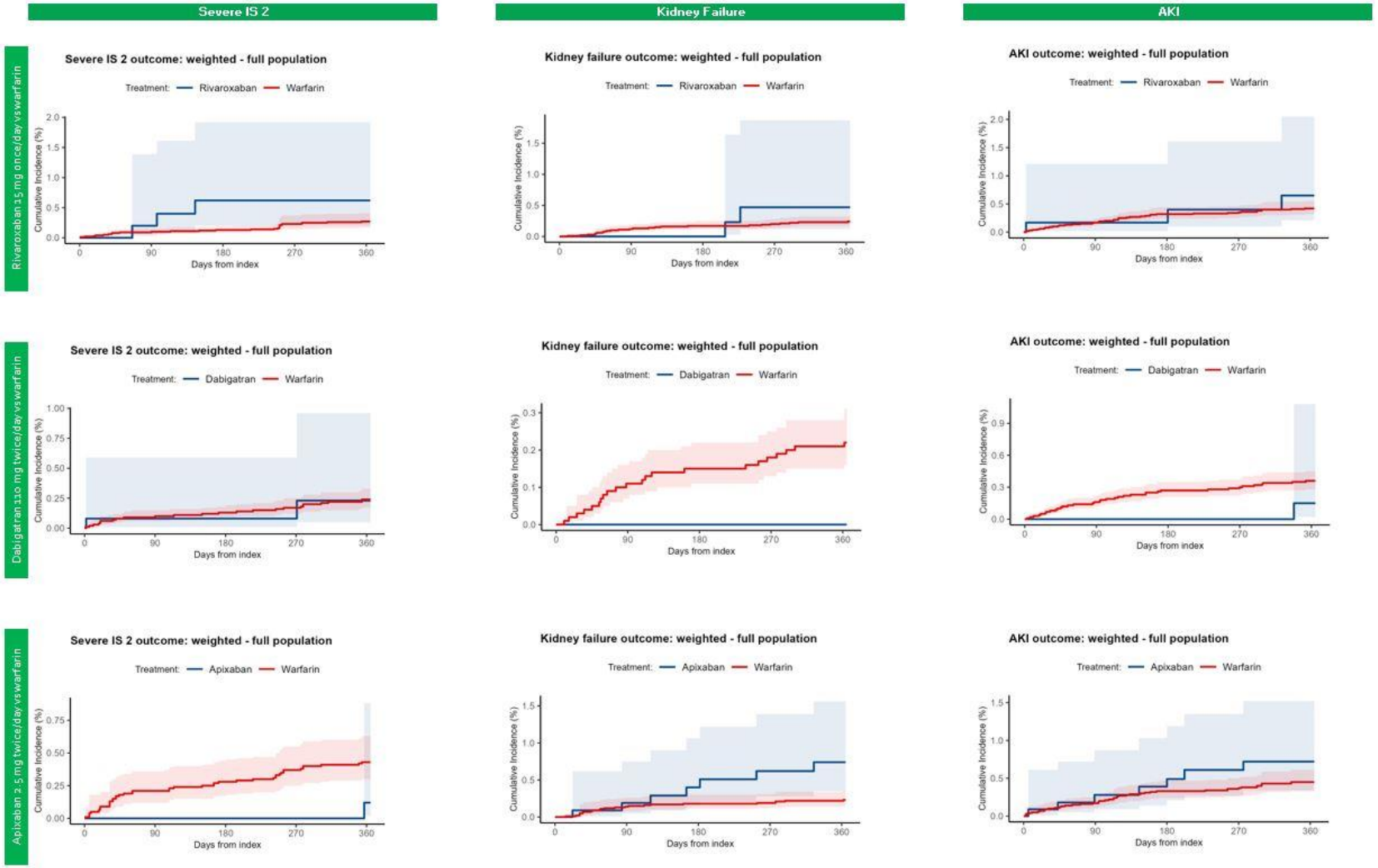

Figure 17. Cumulative incidence for the weighted endpoints (Finland) cont.

Reference Number: RD-SOP-1216
Supplement Version: 3

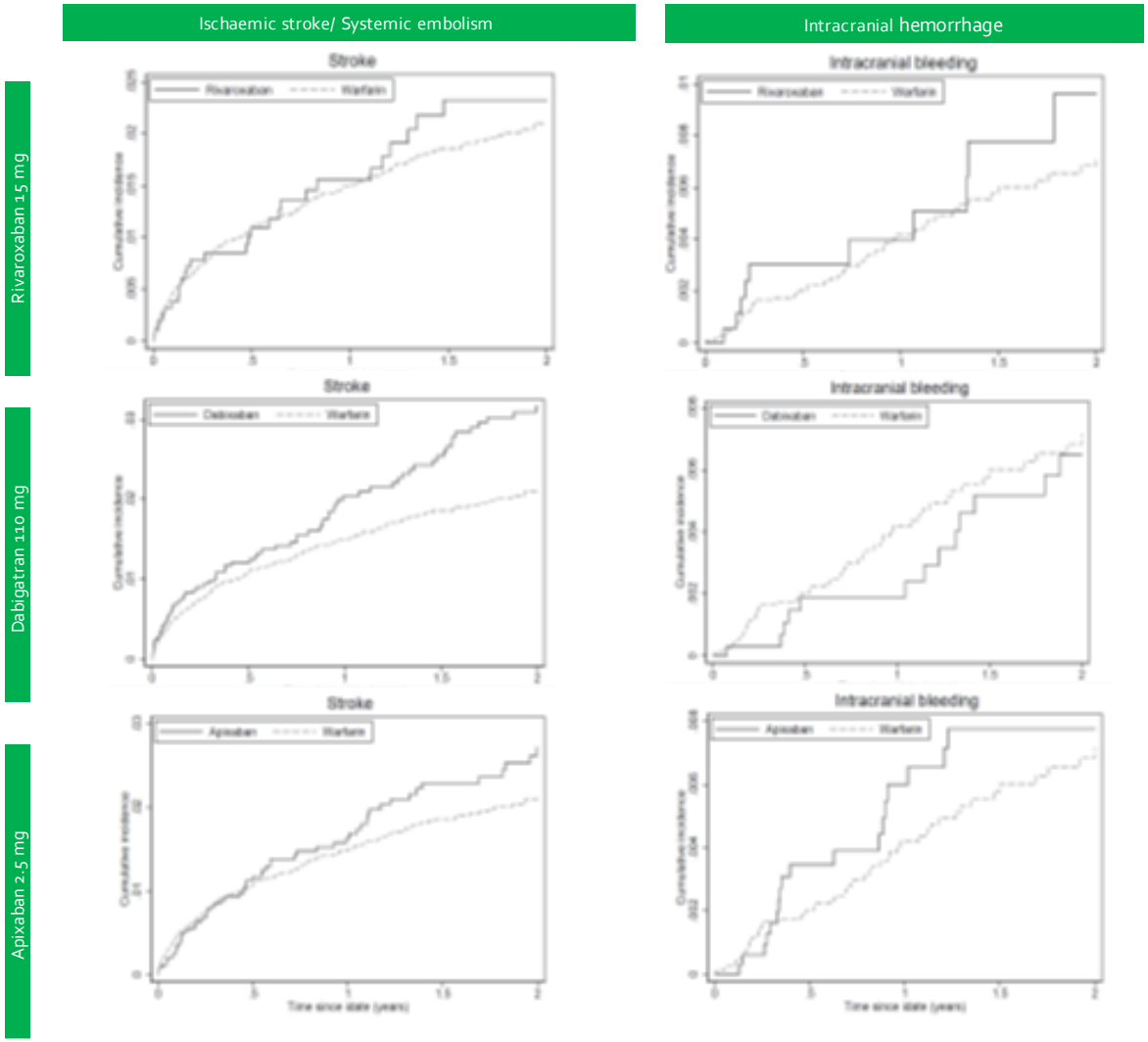

Figure 18. Cumulative incidence for the unweighted endpoints (Denmark)

Reference Number: RD-SOP-1216
Supplement Version: 3

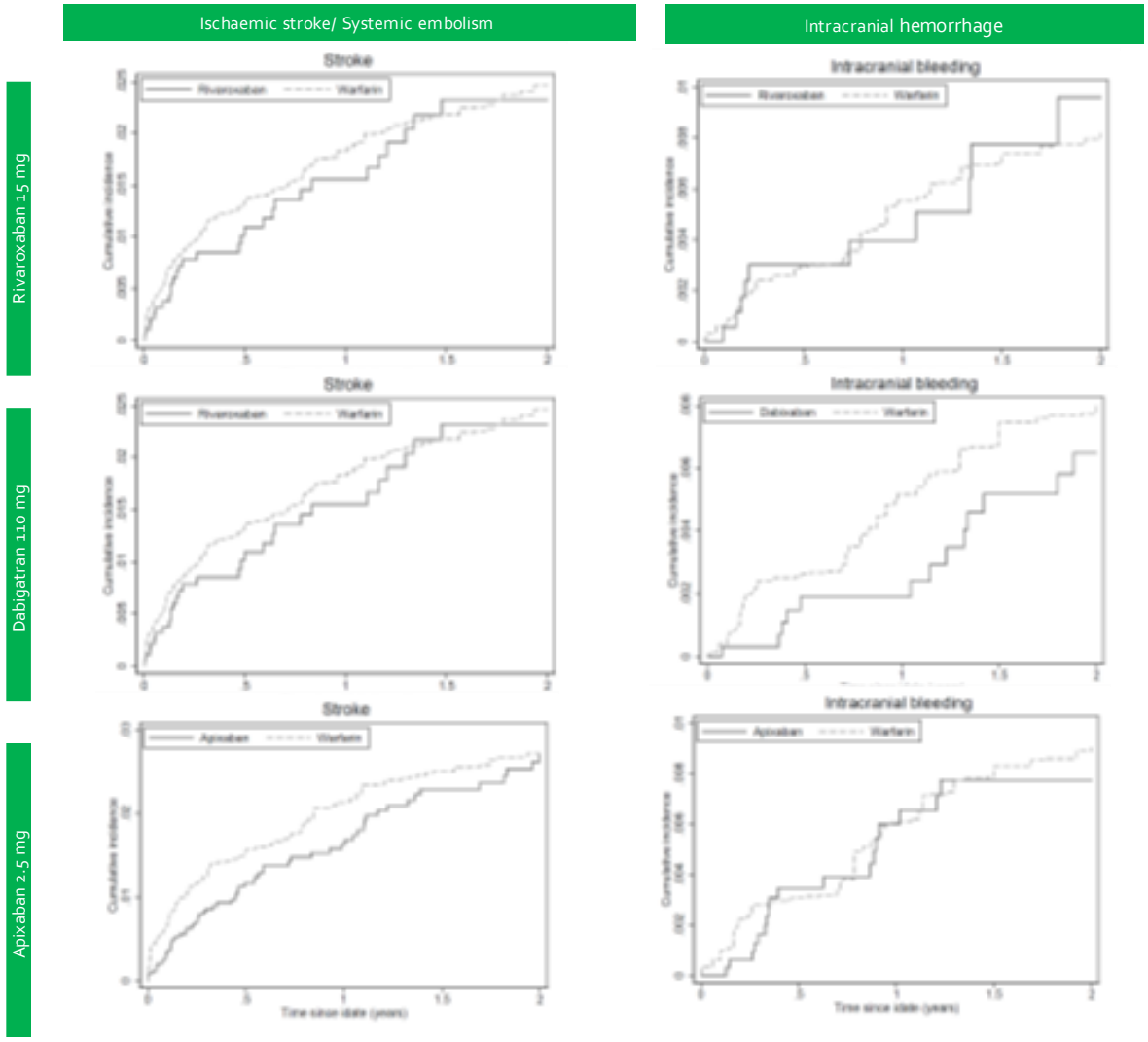

Figure 19. Cumulative incidence for the weighted endpoints (Denmark) cont.

10.4.2 Cox regression model results

The following section presents the results of the Cox regression models for Sweden, Norway, Finland and Denmark.

For specific results on the subgroups of the Cox regression analyses see the stand-alone document "Quantify REATTAIN Cox Regression Analysis" referred to in Table 33.

Sweden

Table 21 presents the cause-specific hazard ratios for the study outcomes at one year in patients with NVAF according to the initiated NOAC treatment compared with warfarin in Sweden.

Ischemic Stroke/Systemic Embolism:

- **Rivaroxaban vs Warfarin:** The unweighted model showed a lower risk in the warfarin group (HR = 0.78, CIs = 0.52 – 1.17, p-value = 0.23), although not statistically significant. The weighted model suggested a higher risk in the warfarin group (HR = 1.06, CIs = 0.70 - 1.62, p-value = 0.77), but this was also not significant.
- **Dabigatran vs Warfarin:** In the unweighted model, warfarin showed a lower risk (HR = 0.68, CIs = 0.48 - 0.95, p-value = 0.02), which was statistically significant. However, the weighted model indicated a higher risk with warfarin (HR = 0.89, CIs = 0.63 - 1.25, p-value = 0.51), but this was not significant.
- **Apixaban vs Warfarin:** The unweighted model warfarin showed a lower risk (HR = 0.77, CIs = 0.62 - 0.95, p-value = 0.02),, which was significant. The weighted model indicated a higher risk with warfarin (HR = 1.21, CIs = 0.95 - 1.55, p-value = 0.13), though not significant.

Intracranial Hemorrhage:

- **Rivaroxaban vs Warfarin:** The unweighted model suggested a lower risk in the warfarin group (HR = 0.63, CIs = 0.31 – 1.28, p-value = 0.20), not statistically significant. The weighted model indicated a comparable risk (HR = 0.91, CIs = 0.44 - 1.88, p-value = 0.79).
- **Dabigatran vs Warfarin:** The unweighted model indicated a higher risk in the warfarin group (HR = 3.13, CIs = 0.77 - 12.62, p-value = 0.11), but not significant. The weighted model showed a significantly higher risk in the warfarin group (HR = 4.19, CIs = 1.05 - 16.73, p-value = 0.04).
- **Apixaban vs Warfarin:** The unweighted model suggested a lower risk in the warfarin group (HR = 0.75, CIs = 0.50 - 1.14, p-value = 0.17), not significant. The weighted model showed a slightly higher risk in the warfarin group (HR = 1.11, CIs = 0.70 - 1.77, p-value = 0.66), also not significant.

Fatal Bleeding:

- **Rivaroxaban vs Warfarin:** The unweighted model indicated a lower risk in the warfarin group (HR = 0.44, CIs = 0.18 - 1.09, p-value = 0.08), not significant. The weighted model showed similar risks between groups (HR = 1.07, CIs = 0.38 - 3.02, p-value = 0.89), not significant.
- **Dabigatran vs Warfarin:** The unweighted model showed a comparable risk (HR = 0.91, CIs = 0.29 - 2.91, p-value = 0.88). The weighted model indicated a higher risk in the warfarin group (HR = 1.35, CIs = 0.42 - 4.33, p-value = 0.61), but not significant.

- **Apixaban vs Warfarin:** The unweighted model suggested a significantly lower risk in the warfarin group (HR = 0.47, CIs = 0.28 - 0.79, p-value < 0.01). The weighted model indicated a higher risk in the warfarin group (HR = 1.20, CIs = 0.68 - 2.15, p-value = 0.53), but not significant.

Severe Ischemic Stroke (IS 1)

- **Rivaroxaban vs Warfarin:** The unweighted analysis for rivaroxaban vs warfarin presented a HR of 0.47 (CIs = 0.21 - 1.08), not statistically significant (p-value = 0.07). The weighted model indicated no difference to warfarin (HR = 1.08, CIs =0.43 - 2.70, p-value = 0.88).
- **Dabigatran vs Warfarin:** The unweighted analysis for dabigatran vs warfarin presented a HR of 0.71 (CIs = 0.29 - 1.76), that wasn't statistically significant (p-value = 0.46). The weighted model showed no difference to warfarin (HR = 1.08, CIs =0.44 - 2.66, p-value = 0.87).
- **Apixaban vs Warfarin:** In the unweighted model, apixaban showed a significantly higher risk compared to warfarin (HR = 0.48, CIs = 0.30 - 0.76, p-value < 0.01). However, the weighted model showed a higher risk with warfarin (HR = 1.30, CIs = 0.77 - 2.20), but this difference was not statistically significant (p-value = 0.33).

Severe Ischemic Stroke (IS 2)

- **Rivaroxaban vs Warfarin:** The unweighted analysis for rivaroxaban vs warfarin presented a HR of 0.77 (CIs = 0.24 - 2.44), this was not statistically significant (p-value = 0.65). The weighted model indicated a higher risk with warfarin (HR = 1.99, CIs = 0.57 - 6.88), but this was not statistically significant (p-value = 0.28).
- **Dabigatran vs Warfarin:** The unweighted analysis for dabigatran vs warfarin presented a HR of 0.58 (CIs =0.23 - 1.44), no statistically significant difference (p-value = 0.24). The weighted model showed a comparable risk with warfarin (HR = 0.91, CIs = 0.37 - 2.28, p-value = 0.86).
- **Apixaban vs Warfarin:** In the unweighted model, apixaban showed a significantly higher risk compared to warfarin (HR = 0.49, CIs = 0.29 - 0.82, p-value = 0.01). However, the weighted model showed a higher risk with warfarin (HR = 1.48, CIs = 0.83 - 2.66), but this difference was not statistically significant (p-value = 0.19).

Kidney Failure:

- **Rivaroxaban vs Warfarin:** Unweighted model indicated a numerically increased risk with warfarin (HR = 1.27, CIs = 0.31 - 5.18, p-value = 0.74); however not significant. Weighted model showed a higher risk with warfarin (HR = 2.09, CIs = 0.52 - 8.40, p-value = 0.30); not significant.
- **Dabigatran vs Warfarin:** There were too few events or too small sample size for the models to converge.
- **Apixaban vs Warfarin:** Unweighted model showed lower risk for warfarin (HR = 0.85, CIs = 0.46 - 1.57; p-value = 0.61); not significant. Weighted model showed a slightly higher risk with warfarin compared to apixaban (HR = 1.12, CIs = 0.59 - 2.13, p-value = 0.73); not significant.

Acute Kidney Injury (AKI):

- **Rivaroxaban vs Warfarin:** Unweighted model showed a lower risk with warfarin (HR = 0.35, CIs = 0.16 - 0.77, p-value = 0.01), statistically significant. Weighted model also indicated a lower risk with warfarin compared to rivaroxaban, but not statistically significant (HR = 0.64, CIs = 0.27 - 1.52, p-value = 0.30).

- **Dabigatran vs Warfarin:** Unweighted model showed a lower risk with warfarin (HR = 0.51, CIs = 0.22 - 1.18, p-value = 0.12); not significant. The weighted model showed also lower risk with warfarin (HR = 0.53, CIs = 0.23 - 1.26, p-value = 0.15); however not significant.
- **Apixaban vs Warfarin:** Unweighted model indicated a lower risk with warfarin (HR = 0.37, CIs = 0.24 - 0.58, p-value < 0.01); significant. Weighted model also showed a lower risk with warfarin (HR = 0.71, CIs = 0.39 - 1.31; p-value = 0.0.28); not significant.

Norway

Table 22 presents the cause-specific hazard ratios for the study outcomes at one year in patients with NVAF according to the initiated NOAC treatment compared with warfarin in Norway.

Ischemic Stroke/Systemic Embolism:

- **Rivaroxaban vs Warfarin:** The unweighted model's HR of 0.55 (CIs = 0.35 - 0.87, p=0.01) and weighted model's HR of 0.65 (CIs = 0.40 - 1.05, p=0.08) suggested a lower risk of ischemic stroke/systemic embolism in the warfarin group compared to rivaroxaban. However, the results were not significant in the weighted model in comparison to the unweighted model.
- **Dabigatran vs Warfarin:** The unweighted HR of 0.97 (CIs = 0.59 - 1.59, p=0.91) and weighted HR of 1.31 (CIs = 0.78 - 2.20, p=0.30) indicated a lower risk in the warfarin group in the unweighted model but a higher risk for warfarin in the weighted model, however neither result was statistically significant.
- **Apixaban vs Warfarin:** The unweighted HR of 0.73 (CIs = 0.52 - 1.03, p=0.07) suggested a lower risk in the warfarin group, but this was not statistically significant. The weighted HR of 1.01 (CIs = 0.66 - 1.55, p=0.95) showed no difference in risk between warfarin and apixaban.

Intracranial Hemorrhage:

- **Rivaroxaban vs Warfarin:** The unweighted HR of 0.41 (CIs = 0.19 - 0.89, p=0.02) indicated a lower risk in the warfarin group compared to rivaroxaban, which was statistically significant. The weighted HR of 0.84 (CIs = 0.34 - 2.10, p=0.71) however showed no significant difference.
- **Dabigatran vs Warfarin:** Neither the unweighted HR of 1.24 (CIs = 0.44 - 3.52, p=0.68) nor the weighted HR of 2.16 (CIs = 0.74 - 6.27, p=0.16) showed a statistically significant difference.
- **Apixaban vs Warfarin:** Both models, unweighted (HR=1.13, CIs = 0.52 - 2.44, p=0.76), and weighted (HR 2.43, CIs = 0.95 - 6.18, p=0.06) indicated no significant difference.

Fatal Bleeding:

- **Rivaroxaban vs Warfarin:** Neither model showed a significant difference (unweighted HR 0.73, CIs = 0.17 – 3.22, p=0.68; weighted HR 1.02, CIs = 0.22 - 4.73, p=0.98).
- **Dabigatran vs Warfarin:** There were too few events or too small sample size for the models to converge.
- **Apixaban vs Warfarin:** The unweighted model (HR 0.33, CIs = 0.15 - 0.71, p<0.01) indicated a significantly lower risk in the warfarin group, but this significance was not seen in the weighted model (HR 0.55, CIs = 0.23 – 1.31, p=0.18).

Severe Ischemic Stroke (IS 2)

- **Rivaroxaban vs Warfarin:** There were too few events or too small sample size for the models to converge.
- **Dabigatran vs Warfarin:** Neither model showed a significant difference (unweighted HR 0.77, CIs =0.17 - 3.47, p=0.73; weighted HR 1.50, CIs = 0.32 - 7.02, p=0.61).
- **Apixaban vs Warfarin:** The unweighted model (HR 0.31, CIs = 0.13 - 0.74, p=0.01) indicated a significantly lower risk in the warfarin group, but the weighted model (HR 0.58, CIs = 0.22 - 1.51, p=0.27) did not show this significance.

Kidney Failure:

- **Rivaroxaban vs Warfarin:** There were too few events or too small sample size for the models to converge.
- **Dabigatran vs Warfarin:** Neither model showed a significant difference (unweighted HR 5.90, CIs = 0.81 - 42.97, p=0.08; weighted HR 4.97, CIs = 0.74 - 33.27, p=0.10).
- **Apixaban vs Warfarin:** No significant difference was observed in either model (unweighted HR 1.18, CIs = 0.57 - 2.44, p=0.65; weighted HR 1.54, CIs = 0.68 - 3.49, p=0.30).

Acute Kidney Injury (AKI):

- **Rivaroxaban vs Warfarin:** The unweighted model showed a significantly lower risk in the warfarin group (HR 0.29, CIs = 0.14 - 0.60, p<0.01), but this was not showed in the weighted model (HR 0.56, CIs =0.24 - 1.35, p=0.20).
- **Dabigatran vs Warfarin:** Neither model showed a significant difference (unweighted HR 1.40, CIs = 0.43 - 4.61, p=0.58; weighted HR 1.54, CIs = 0.43 - 5.46, p=0.51).
- **Apixaban vs Warfarin:** The unweighted model showed a significant lower risk in the warfarin group (HR 0.33, CIs = 0.19 - 0.57, p<0.01), but the weighted model (HR 0.55, CIs = 0.27 - 1.10, p=0.09) did not show this significance.

Finland

Table 23 presents the cause-specific hazard ratios for the study outcomes at one year in patients with NVAF according to the initiated NOAC treatment compared with warfarin in Finland.

Ischemic Stroke/Systemic Embolism:

- **Rivaroxaban vs Warfarin:** The unweighted model suggested a higher risk with warfarin compared to rivaroxaban (HR = 1.82, CIs = 0.81 - 4.06, p-value = 0.15), although not statistically significant. The weighted model showed a similar trend (HR = 2.03, CIs = 0.90 - 4.59, p-value = 0.09); however also not significant.
- **Dabigatran vs Warfarin:** The unweighted model suggested a higher risk with warfarin (HR = 1.50, CIs = 0.88 – 2.54, p-value = 0.13), not statistically significant. The weighted model indicated a similar pattern (HR = 1.69, CIs = 1.00 - 2.87, p-value = 0.05), not reaching significance.

- **Apixaban vs Warfarin:** The unweighted model indicated no significant difference (HR = 1.05, CIs = 0.68 - 1.63, p-value = 0.81). The weighted model indicated a slightly higher risk with warfarin, but not significant (HR = 1.48, CIs = 0.95 - 2.31, p-value = 0.08).

Intracranial Hemorrhage:

- **Rivaroxaban vs Warfarin:** The unweighted model indicated a significantly lower risk with warfarin (HR = 0.26, CIs = 0.13 - 0.54, p-value < 0.001), the same was shown in the weighted model (HR = 0.32, CIs = 0.15 - 0.68, p-value < 0.001).
- **Dabigatran vs Warfarin:** The unweighted model suggested a higher risk with warfarin compared to dabigatran, not significant (HR = 1.95, CIs = 0.48 – 7.89, p-value = 0.35). The weighted model also indicated a non-significant higher risk with warfarin (HR = 2.71, CIs = 0.65 – 11.35, p-value = 0.17).
- **Apixaban vs Warfarin:** The unweighted model showed no significant difference (HR = 1.45, CIs = 0.46 – 4.54, p-value = 0.53), and the weighted model indicated a higher risk with warfarin, but not significant (HR = 2.40, CIs = 0.74 - 7.84, p-value = 0.15).

Fatal Bleeding:

- **Rivaroxaban vs Warfarin:** Both models indicated no significant differences (unweighted HR = 0.42, CIs =0.06 - 3.06, p-value = 0.39; weighted HR = 0.76, CIs = 0.10 - 5.75, p-value = 0.79).
- **Dabigatran vs Warfarin:** The unweighted model suggested a significant lower risk with warfarin compared to dabigatran (HR = 0.26, CIs = 0.08 - 0.87, p-value = 0.03), while the weighted model showed no significant difference (HR = 0.39, CIs = 0.12 - 1.30, p-value = 0.13).
- **Apixaban vs Warfarin:** The unweighted model indicated a significantly lower risk with warfarin (HR = 0.17, CIs = 0.07 - 0.44, p-value < 0.001). The weighted model showed no significant difference (HR = 0.51, CIs = 0.18 - 1.39, p-value = 0.19).
- Note: The ICD-10 code I61 was not include in the Finnish definitions of fatal bleeding.

Severe Ischemic Stroke (IS 2):

- **Rivaroxaban vs Warfarin:** The unweighted model showed a significantly lower risk with warfarin (HR = 0.29, CIs = 0.09 - 0.92, p-value = 0.04). However, the weighted model did not find a significant difference (HR = 0.38, CIs = 0.11 - 1.29, p-value = 0.12).
- **Dabigatran vs Warfarin:** Both models showed no significant difference (unweighted HR = 0.84, CIs = 0.20 - 3.44, p-value = 0.81; weighted HR = 1.08, CIs = 0.27 - 4.41, p-value = 0.91).
- **Apixaban vs Warfarin:** Unweighted model indicated a higher risk with warfarin (HR = 1.79, CIs = 0.25 - 12.92, p-value = 0.56), however no significant difference. And the weighted model showed a higher risk with warfarin, but also not significant (HR = 4.73, CIs = 0.73 - 30.79, p-value = 0.10).

Kidney Failure:

- **Rivaroxaban vs Warfarin:** No significant difference was observed in either model (unweighted HR = 0.48, CIs = 0.12 - 1.96, p-value = 0.30; weighted HR = 0.63, CIs =0.16 - 2.49, p-value = 0.51).

- **Dabigatran vs Warfarin:** There were too few events or too small sample size for the models to converge.
- **Apixaban vs Warfarin:** The unweighted model indicated a significantly lower risk with warfarin (HR = 0.28, CIs = 0.13 - 0.61, p-value < 0.001), and the weighted model also showed a significantly lower risk with warfarin (HR = 0.36, CIs = 0.15 - 0.84, p-value = 0.02).

Acute Kidney Injury (AKI):

- **Rivaroxaban vs Warfarin:** The unweighted model showed a lower risk with warfarin (HR = 0.48, CIs = 0.15 - 1.52, p-value = 0.21), not significant. The weighted model indicated a similar finding (HR = 0.72, CIs = 0.23 - 2.23, p-value = 0.57), but also not significant.
- **Dabigatran vs Warfarin:** Unweighted model showed a higher risk with warfarin (HR = 2.77, CIs = 0.39 - 19.87, p-value = 0.31), not significant. The weighted model showed a higher risk with warfarin (HR = 3.42, CIs = 0.50 - 23.25, p-value = 0.21), also not significant.
- **Apixaban vs Warfarin:** Unweighted model indicated a significantly lower risk with warfarin (HR = 0.42, CIs = 0.20 - 0.91, p-value = 0.03), but the weighted model showed no significant difference (HR = 0.65, CIs = 0.30 - 1.45, p-value = 0.30).

Denmark

Table 24 presents the cause-specific hazard ratios for the study outcomes at one year in patients with NVAF according to the initiated NOAC treatment compared with warfarin in Denmark. Due to differences in data processors for Denmark and the rest of the included countries, Cox regression models for the Danish population was fitted using warfarin as the reference group, i.e., a hazard ratio below 1 favors the NOAC group and a hazard ratio above 1 favors the warfarin group.

Ischemic Stroke/Systemic Embolism:

- **Rivaroxaban vs Warfarin:** The unweighted model showed a similar risk (HR = 1.02, CIs = 0.67 - 1.56, p-value = 0.92). The weighted model indicated a lower risk with rivaroxaban (HR = 0.80, CIs =0.46 - 1.38, p-value = 0.42), but also not significant.
- **Dabigatran vs Warfarin:** The unweighted model indicated a higher risk with dabigatran (HR = 1.33, CIs = 0.99 - 1.77, p-value = 0.06), not significant. The weighted model showed no significant difference (HR = 0.94, CIs = 0.65 - 1.35, p-value = 0.73).
- **Apixaban vs Warfarin:** In the unweighted model, apixaban showed a similar risk (HR = 1.05, CIs = 0.76 - 1.44, p-value = 0.77). The weighted model suggested a lower risk with apixaban (HR = 0.68, CIs =0.46 - 0.99, p-value = 0.05), however, not enough to be significant.

Intracranial Hemorrhage:

- **Rivaroxaban vs Warfarin:** The unweighted model indicated a comparable risk (HR = 1.05, CIs = 0.45 - 2.45, p-value = 0.91). The weighted model suggested a lower risk with rivaroxaban (HR = 0.78, CIs = 0.26 - 2.33, p-value = 0.66), not significant.
- **Dabigatran vs Warfarin:** The unweighted model suggested a lower risk with dabigatran (HR = 0.44, CIs = 0.18 - 1.12, p-value = 0.08), not significant. The weighted model showed

however a significantly lower risk for dabigatran users (HR = 0.33, CIs = 0.12 - 0.93, p-value = 0.04).

- **Apixaban vs Warfarin:** The unweighted model showed a higher risk with apixaban (HR = 1.44, CIs =0.82 - 2.54, p-value = 0.21), not significant. On the contrary, the weighted model indicated a lower risk with apixaban (HR = 0.78, CIs = 0.39 - 1.56, p-value = 0.49), however also not significant.

Fatal Bleeding:

- **Rivaroxaban vs Warfarin:** The unweighted model showed a significantly higher risk with rivaroxaban (HR = 4.38, CIs = 2.51 - 7.64, p-value = <0.01). The weighted model also indicated a higher risk with rivaroxaban compared to warfarin, (HR = 2.30, CIs = 0.99 - 5.36, p-value = 0.05); however, this was not significant.
- **Dabigatran vs Warfarin:** No significant difference was observed in either model (unweighted HR = 1.49, CIs = 0.79 - 2.81, p-value = 0.22; weighted HR = 1.04, CIs =0.46 - 2.33, p-value = 0.93).
- **Apixaban vs Warfarin**: The unweighted model indicated a significantly higher risk with apixaban (HR = 3.20, CIs = 1.94 - 5.27, p-value = 0.00). The weighted model showed no significant difference (HR = 1.33, CIs = 0.72 - 2.47, p-value = 0.36).
- The ICD-10 code I61 was not include in the Finnish definitions of fatal bleeding.

Severe Ischemic Stroke (IS 2):

- **Rivaroxaban vs Warfarin:** The unweighted model suggested a higher risk with rivaroxaban (HR = 2.40, CIs = 0.89 - 6.47, p-value = 0.08), not significant. The weighted model showed no significant difference (HR = 1.11, CIs = 0.31 - 4.00, p-value = 0.87).
- **Dabigatran vs Warfarin:** The unweighted model indicated a higher risk with dabigatran (HR = 2.21, CIs = 0.99 - 4.93, p-value = 0.05), not significant. The weighted model showed no significant difference (HR = 1.13, CIs = 0.43 - 3.02, p-value = 0.80).
- **Apixaban vs Warfarin:** The unweighted model suggested a higher risk with apixaban (HR = 1.48, CIs = 0.59 - 3.73, p-value = 0.41), not significant. The weighted model indicated a lower risk with apixaban (HR = 0.56, CIs =0.20 - 1.57, p-value = 0.27), also not significant.

Kidney Failure:

- **Rivaroxaban vs Warfarin:** No significant difference was observed in either model (unweighted HR = 1.11, CIs = 0.33 - 3.71, p-value = 0.87; weighted HR = 1.04, CIs = 0.19 - 5.62, p-value = 0.97).
- **Dabigatran vs Warfarin:** The unweighted model suggested a lower risk with dabigatran (HR = 0.39, CIs = 0.09 - 1.64, p-value = 0.20), not significant. The weighted model showed a similar trend (HR = 0.53, CIs = 0.09 - 3.01, p-value = 0.47), also not significant.
- **Apixaban vs Warfarin:** The unweighted model indicated a lower risk with apixaban (HR = 0.59, CIs = 0.18 - 1.97, p-value = 0.39), not significant. The weighted model also showed no significant difference (HR = 0.61, CIs = 0.14 - 2.66, p-value = 0.51).

Acute Kidney Injury (AKI):

- **Rivaroxaban vs Warfarin:** The unweighted model indicated a significantly higher risk with rivaroxaban (HR = 2.23, CIs = 1.02 - 4.86, p-value = 0.04). The weighted model showed no significant difference (HR = 1.40, CIs = 0.47 - 4.17, p-value = 0.55).
- **Dabigatran vs Warfarin:** No significant difference was observed in either model (unweighted HR = 1.30, CIs = 0.62 - 2.75, p-value = 0.49; weighted HR = 1.12, CIs = 0.43 - 2.94, p-value = 0.82).
- **Apixaban vs Warfarin:** The unweighted model suggested a significantly higher risk with apixaban (HR = 2.04, CIs = 1.08 - 3.84, p-value = 0.03), significant. The weighted model showed no significant difference (HR = 1.20, CIs = 0.54 - 2.69, p-value = 0.65).

Table 21. Cause-specific hazard ratios compared with warfarin - entire cohort (Sweden)

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Ischemic stroke/ Systemic embolism**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.78	0.23	0.52 - 1.17	1.06	0.77	0.70 - 1.62
Warfarin vs dabigatran (reference)	0.68	0.02	0.48 - 0.95	0.89	0.51	0.63 - 1.25
Warfarin vs apixaban (reference)	0.77	0.02	0.62 - 0.95	1.21	0.13	0.95 - 1.55
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Intracranial hemorrhage**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.63	0.20	0.31 - 1.28	0.91	0.79	0.44 - 1.88
Warfarin vs dabigatran (reference)	3.13	0.11	0.77 - 12.62	4.19	0.04	1.05 - 16.73
Warfarin vs apixaban (reference)	0.75	0.17	0.50 - 1.14	1.11	0.66	0.70 - 1.77
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Fatal bleeding**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.44	0.08	0.18 - 1.09	1.07	0.89	0.38 - 3.02
Warfarin vs dabigatran (reference)	0.91	0.88	0.29 - 2.91	1.35	0.61	0.42 - 4.33
Warfarin vs apixaban (reference)	0.47	0.00	0.28 - 0.79	1.20	0.53	0.68 - 2.15
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Severe IS 1**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.47	0.07	0.21 - 1.08	1.08	0.88	0.43 - 2.70

Warfarin vs dabigatran (reference)	0.71	0.46	0.29 - 1.76	1.08	0.87	0.44 - 2.66
Warfarin vs apixaban (reference)	0.48	0.00	0.30 - 0.76	1.30	0.33	0.77 - 2.20
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Severe IS 2**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.77	0.65	0.24 - 2.44	1.99	0.28	0.57 - 6.88
Warfarin vs dabigatran (reference)	0.58	0.24	0.23 - 1.44	0.92	0.86	0.37 - 2.28
Warfarin vs apixaban (reference)	0.49	0.01	0.29 - 0.82	1.48	0.19	0.83 - 2.66
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Kidney failure**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	1.27	0.74	0.31 - 5.18	2.09	0.30	0.52 - 8.40
Warfarin vs dabigatran (reference)	NA	NA	NA - NA	NA	NA	NA - NA
Warfarin vs apixaban (reference)	0.85	0.61	0.46 - 1.57	1.12	0.73	0.59 - 2.13
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**AKI**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.35	0.01	0.16 - 0.77	0.64	0.31	0.27 - 1.52
Warfarin vs dabigatran (reference)	0.51	0.12	0.22 - 1.18	0.53	0.15	0.23 - 1.26
Warfarin vs apixaban (reference)	0.37	0.00	0.24 - 0.58	0.71	0.28	0.39 - 1.31

Note: Results from the Cox regressions should not be compared between NOAC treatments due to different weights applied to each warfarin cohort. NOAC group is the reference category, therefore a hazard ratio below 1 favors warfarin and a hazard ratio above 1 favors the NOAC group.

Table 22. Cause-specific hazard ratios compared with warfarin - entire cohort (Norway)

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Ischemic stroke/ Systemic embolism**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.55	0.01	0.35 - 0.87	0.65	0.08	0.40 - 1.05
Warfarin vs dabigatran (reference)	0.97	0.91	0.59 - 1.59	1.31	0.30	0.78 - 2.20
Warfarin vs apixaban (reference)	0.73	0.07	0.52 - 1.03	1.01	0.95	0.66 - 1.55
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Intracranial hemorrhage**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.41	0.02	0.19 - 0.89	0.84	0.71	0.34 - 2.10
Warfarin vs dabigatran (reference)	1.24	0.68	0.44 - 3.52	2.16	0.16	0.74 - 6.27
Warfarin vs apixaban (reference)	1.13	0.76	0.52 - 2.44	2.43	0.06	0.95 - 6.18
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Fatal bleeding**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.73	0.68	0.17 - 3.22	1.02	0.98	0.22 - 4.73
Warfarin vs dabigatran (reference)	NA	NA	NA - NA	NA	NA	NA - NA
Warfarin vs apixaban (reference)	0.33	0.00	0.15 - 0.71	0.55	0.18	0.23 - 1.31
	Severe IS 2					

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Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	NA	NA	NA - NA	NA	NA	NA - NA
Warfarin vs dabigatran (reference)	0.77	0.73	0.17 - 3.47	1.50	0.61	0.32 - 7.02
Warfarin vs apixaban (reference)	0.31	0.01	0.13 - 0.74	0.58	0.27	0.22 - 1.51

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Kidney failure**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	NA	NA	NA - NA	NA	NA	NA - NA
Warfarin vs dabigatran (reference)	5.90	0.08	0.81 - 42.97	4.97	0.10	0.74 - 33.27
Warfarin vs apixaban (reference)	1.18	0.65	0.57 - 2.44	1.54	0.30	0.68 - 3.49

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**AKI**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.29	0.00	0.14 - 0.60	0.56	0.20	0.24 - 1.35
Warfarin vs dabigatran (reference)	1.40	0.58	0.43 - 4.61	1.54	0.51	0.43 - 5.46
Warfarin vs apixaban (reference)	0.33	0.00	0.19 - 0.57	0.55	0.09	0.27 - 1.10

Note: Results from the Cox regressions should not be compared between NOAC treatments due to different weights applied to each warfarin cohort. NOAC group is the reference category, therefore a hazard ratio below 1 favors warfarin and a hazard ratio above 1 favors the NOAC group.

Table 23. Cause-specific hazard ratios compared with warfarin - entire cohort (Finland)

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Ischemic stroke/ Systemic embolism**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	1.82	0.15	0.81 - 4.06	2.03	0.09	0.90 - 4.59
Warfarin vs dabigatran (reference)	1.50	0.13	0.88 - 2.54	1.69	0.05	1.00 - 2.87
Warfarin vs apixaban (reference)	1.05	0.81	0.68 - 1.63	1.48	0.08	0.95 - 2.31
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Intracranial hemorrhage**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.26	0.00	0.13 - 0.54	0.32	0.00	0.15 - 0.68
Warfarin vs dabigatran (reference)	1.95	0.35	0.48 - 7.89	2.71	0.17	0.65 - 11.35
Warfarin vs apixaban (reference)	1.45	0.53	0.46 - 4.54	2.40	0.15	0.74 - 7.84
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Fatal bleeding**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.42	0.39	0.06 - 3.06	0.76	0.79	0.10 - 5.75
Warfarin vs dabigatran (reference)	0.26	0.03	0.08 - 0.87	0.39	0.13	0.12 - 1.30
Warfarin vs apixaban (reference)	0.17	0.00	0.07 - 0.44	0.51	0.19	0.18 - 1.39
	Severe IS 2					
	Unweighted model			Weighted model		

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.29	0.04	0.09 - 0.92	0.38	0.12	0.11 - 1.29
Warfarin vs dabigatran (reference)	0.84	0.81	0.20 - 3.44	1.08	0.91	0.27 - 4.41
Warfarin vs apixaban (reference)	1.79	0.56	0.25 - 12.92	4.73	0.10	0.73 - 30.79

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Kidney failure**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.48	0.30	0.12 - 1.96	0.63	0.51	0.16 - 2.49
Warfarin vs dabigatran (reference)	NA	NA	NA - NA	NA	NA	NA - NA
Warfarin vs apixaban (reference)	0.28	0.00	0.13 - 0.61	0.36	0.02	0.15 - 0.84

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**AKI**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Warfarin vs rivaroxaban (reference)	0.48	0.21	0.15 - 1.52	0.72	0.57	0.23 - 2.23
Warfarin vs dabigatran (reference)	2.77	0.31	0.39 - 19.87	3.42	0.21	0.50 - 23.25
Warfarin vs apixaban (reference)	0.42	0.03	0.20 - 0.91	0.65	0.30	0.30 - 1.45

Note: Results from the Cox regressions should not be compared between NOAC treatments due to different weights applied to each warfarin cohort. NOAC group is the reference category, therefore a hazard ratio below 1 favors warfarin and a hazard ratio above 1 favors the NOAC group. The ICD-10 code I61 was not include in the Finnish definitions of fatal bleeding.

Table 24. Cause-specific hazard ratios compared with warfarin - entire cohort (Denmark)

Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Ischemic stroke/ Systemic embolism**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Rivaroxaban vs warfarin (reference)	1.02	0.92	0.67 - 1.56	0.8	0.42	0.46 - 1.38
Dabigatran vs warfarin (reference)	1.33	0.06	0.99 - 1.77	0.94	0.73	0.65 - 1.35
Apixaban vs warfarin (reference)	1.05	0.77	0.76 - 1.44	0.68	0.05	0.46 - 0.99
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Intracranial hemorrhage**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Rivaroxaban vs warfarin (reference)	1.05	0.91	0.45 - 2.45	0.78	0.66	0.26 - 2.33
Dabigatran vs warfarin (reference)	0.44	0.08	0.18 - 1.12	0.33	0.04	0.12 - 0.93
Apixaban vs warfarin (reference)	1.44	0.21	0.82 - 2.54	0.78	0.49	0.39 - 1.56
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Fatal bleeding**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Rivaroxaban vs warfarin (reference)	4.38	0	2.51 - 7.64	2.3	0.05	0.99 - 5.36
Dabigatran vs warfarin (reference)	1.49	0.22	0.79 - 2.81	1.04	0.93	0.46 - 2.33
Apixaban vs warfarin (reference)	3.2	0	1.94 - 5.27	1.33	0.36	0.72 - 2.47
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Severe IS 2**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI

Rivaroxaban vs warfarin (reference)	2.4	0.08	0.89 - 6.47	1.11	0.87	0.31 - 4.00
Dabigatran vs warfarin (reference)	2.21	0.05	0.99 - 4.93	1.13	0.8	0.43 - 3.02
Apixaban vs warfarin (reference)	1.48	0.41	0.59 - 3.73	0.56	0.27	0.20 - 1.57
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**Kidney failure**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Rivaroxaban vs warfarin (reference)	1.11	0.87	0.33 - 3.71	1.04	0.97	0.19 - 5.62
Dabigatran vs warfarin (reference)	0.39	0.2	0.09 - 1.64	0.53	0.47	0.09 - 3.01
Apixaban vs warfarin (reference)	0.59	0.39	0.18 - 1.97	0.61	0.51	0.14 - 2.66
Hazard ratio for effectiveness and safety outcomes for individual NOAC vs warfarin, ATT effects with unweighted population and warfarin weighted toward NOAC population.	**AKI**					
	Unweighted model			Weighted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
Rivaroxaban vs warfarin (reference)	2.23	0.04	1.02 - 4.86	1.4	0.55	0.47 - 4.17
Dabigatran vs warfarin (reference)	1.3	0.49	0.62 - 2.75	1.12	0.82	0.43 - 2.94
Apixaban vs warfarin (reference)	2.04	0.03	1.08 - 3.84	1.2	0.65	0.54 - 2.69

Note: Results from the Cox regressions should not be compared between NOAC treatments due to different weights applied to each warfarin cohort. For Denmark, the warfarin group is the reference category, therefore a hazard ratio below 1 favors the NOAC group and a hazard ratio above 1 favors the warfarin group.

10.4.3 Treatment persistence

The following section presents the results of the treatment persistence analyses for Sweden, Norway, Finland, and Denmark. These results are representative for the entire cohorts for method 1, and 30 days grace period.

For the results of method 2, and 60 days grace period, see stand-alone document referred to in Table 33: “Quantify REATTAIN Persistence Analysis”.

Sweden

Table 25 presents the treatment persistence at one year in patients with NVAF according to initiated treatment in Sweden. The highest persistence at 365 days was observed in apixaban patients (75.84%), while the lowest was among patients using warfarin (39.37%).

Figure 20 illustrates the plot over the treatment persistence for the four relevant treatment groups in this study.

The results of the cox regression on treatment persistence are presented in Table 26. These results indicated that apixaban had the lowest hazard ratio in reference to warfarin in both the unadjusted and the adjusted models.

Table 25. Treatment persistence at one year (Sweden)

Treatment persistence during one year in patients with NVAF according to initiated treatment	Number of patients	Persistence at 365 days (%)
rivaroxaban	1,495	66.96
dabigatran	1,915	59.22
apixaban	6,055	75.84
warfarin	42,168	39.37

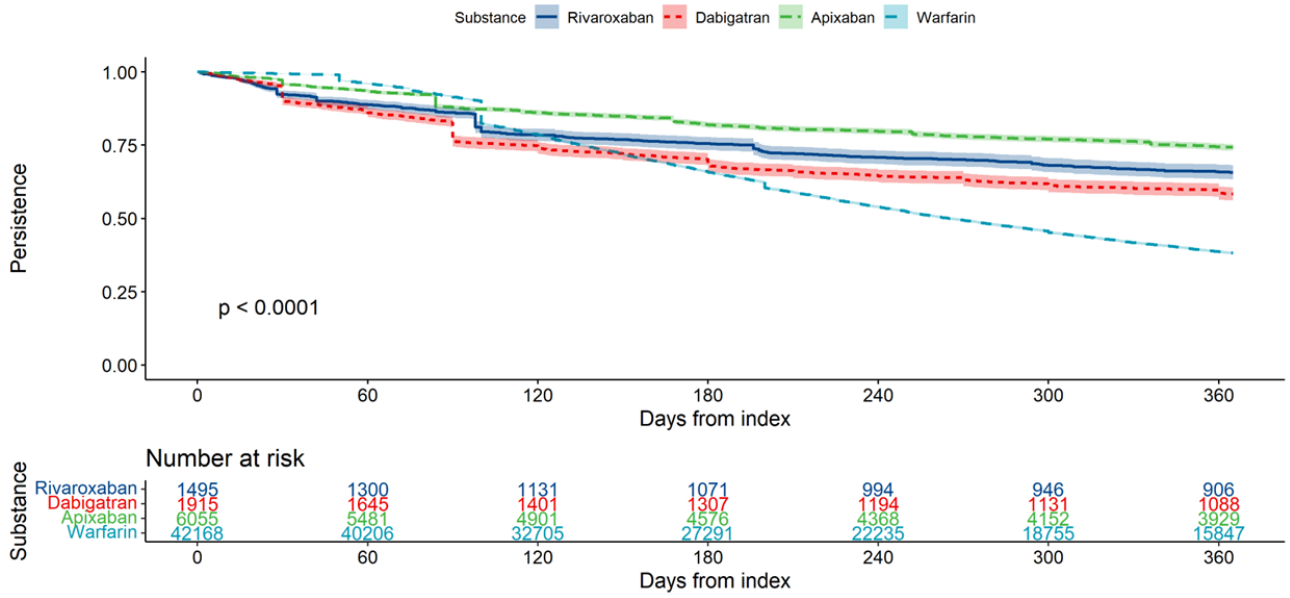

Figure 20. Treatment persistence using method 1 and 30 day grace period (Sweden)

Table 26. Cox regression - Treatment persistence (Sweden)

Treatment persistence during one year in patients with NVAF according to initiated treatment	**Treatment persistence**					
	Unadjusted model			Adjusted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
rivaroxaban (Ref: warfarin)	0.49	0.00	0.45 - 0.54	0.50	0.00	0.46 - 0.55
dabigatran (Ref: warfarin)	0.64	0.00	0.59 - 0.68	0.65	0.00	0.60 - 0.69
apixaban (Ref: warfarin)	0.34	0.00	0.32 - 0.35	0.34	0.00	0.32 - 0.36
Age at index (years)				1.05	0.00	1.02 - 1.07
Male (Ref: female)				1.00	0.00	1.00 - 1.00

The adjusted model was controlled for age and sex.

Norway

Table 27 presents treatment persistence at year in patients with NVAF according to initiated treatment in Norway. The highest persistence was observed in rivaroxaban patients (57.74%), while the lowest was among patients using warfarin (32.92%). Figure 21 illustrates the plot over the treatment persistence for the four relevant groups.

The results of the Cox regression on treatment persistence are presented in Table 28. These results show that rivaroxaban users had the lowest hazard ratio, indicating the lowest risk of non-persistence compared to warfarin users.

Table 27. Treatment persistence at one year (Norway)

Treatment persistence during one year in patients with NVAF according to initiated treatment	Number of patients	Persistence at 365 days (%)
rivaroxaban	1,008	57.74
dabigatran	1,575	52.70
apixaban	2,946	55.23
warfarin	11,720	32.92

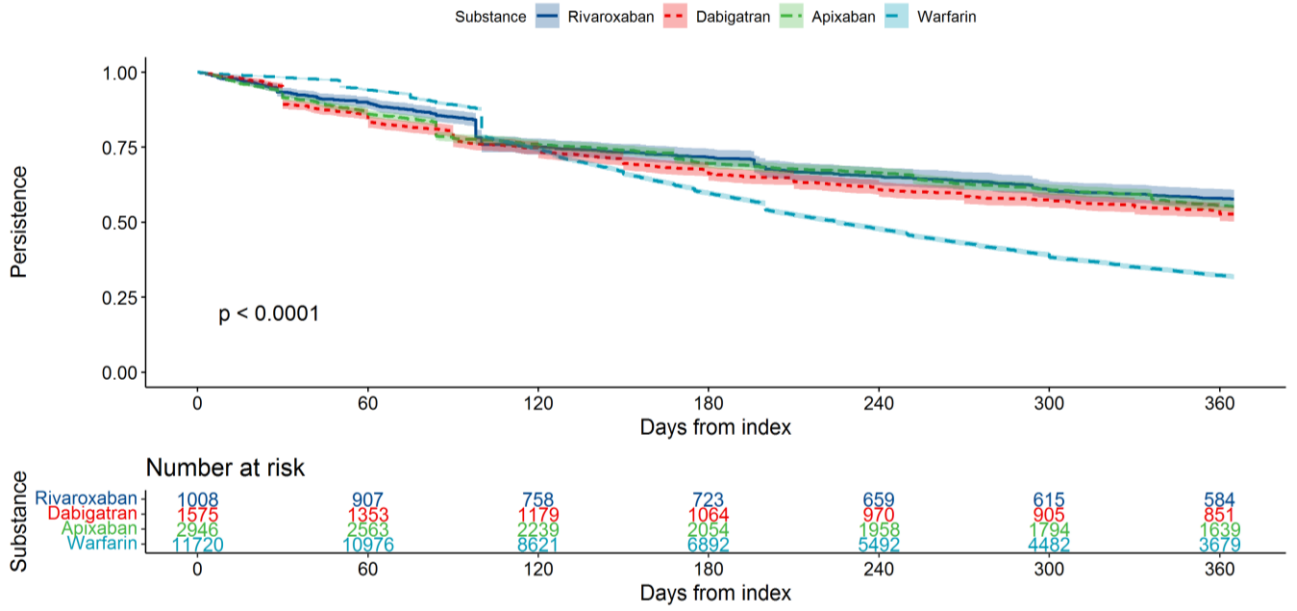

Figure 21. Treatment persistence using method 1 and 30 day grace period (Norway)

Table 28. Cox regression - Treatment persistence (Norway)

Treatment persistence during one year in patients with NVAF according to initiated treatment	Treatment persistence					
	Unadjusted model			Adjusted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
rivaroxaban (Ref: warfarin)	0.53	0.00	0.49 - 0.59	0.56	0.00	0.51 - 0.62
dabigatran (Ref: warfarin)	0.63	0.00	0.58 - 0.68	0.66	0.00	0.61 - 0.71
apixaban (Ref: warfarin)	0.57	0.00	0.54 - 0.61	0.62	0.00	0.58 - 0.66
Age at index (years)				1.00	0.91	0.96 - 1.04
Male (Ref: female)				0.99	0.00	0.99 - 1.00

The adjusted model was controlled for age and sex.

Finland

Table 29 presents the treatments persistence at one year in patients with NVAF according to initiated treatment in Finland. The highest persistence was observed in apixaban patients (64.24%), while the lowest was among patients using warfarin (51.24%) and dabigatran (51.68%). Figure 22 illustrates the plot over the treatment persistence for the four relevant groups.

The results of the Cox regression on treatment persistence is presented in Table 30. These results show that the apixaban cohort had the lowest hazard ratio, indicating the lowest risk of non-persistence compared to warfarin users.

Table 29. Treatment persistence at 365 days (Finland)

Treatment persistence during one year in patients with NVAF according to initiated treatment	Number of patients	Persistence at 365 days (%)

rivaroxaban	587	59.97
dabigatran	1,194	51.68
apixaban	1,155	64.24
warfarin	37,985	51.24

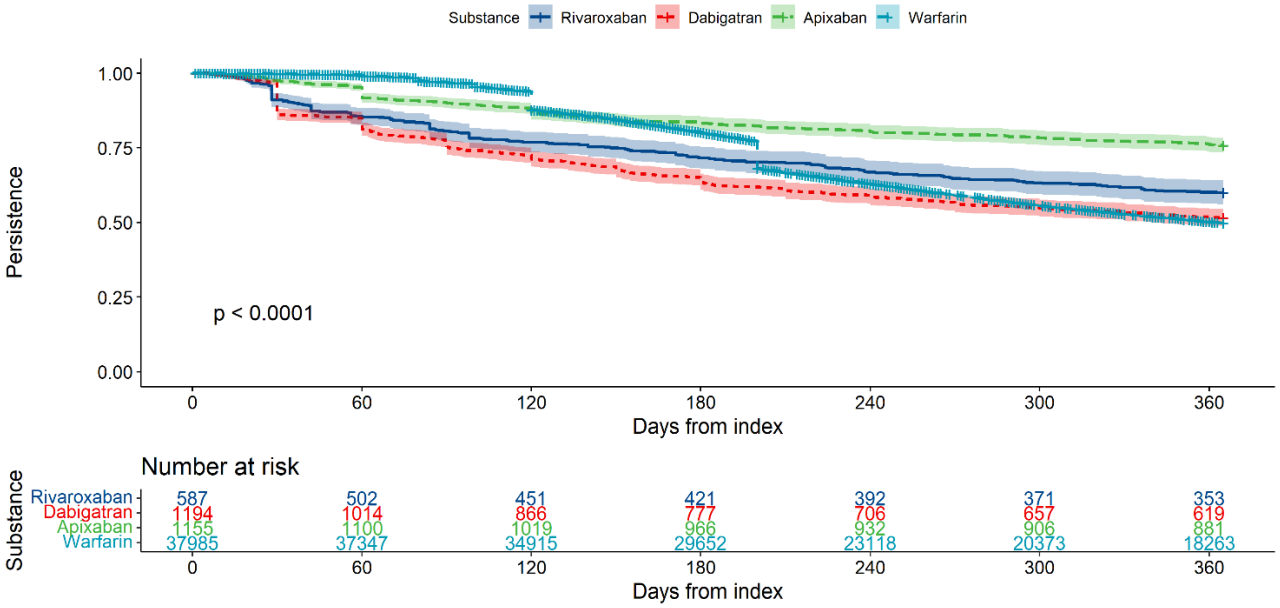

Figure 22. Treatment persistence using method 1 and 30 day grace period (Finland)

Table 30. Cox regression - Treatment persistence (Finland)

Treatment persistence during one year in patients with NVAF according to initiated treatment	**Treatment persistence**					
	Unadjusted model			Adjusted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
rivaroxaban (Ref: warfarin)	0.82	0.00	0.72 - 0.94	0.82	0.00	0.72 - 0.93
dabigatran (Ref: warfarin)	1.11	0.01	1.02 - 1.20	1.11	0.02	1.02 - 1.20
apixaban (Ref: warfarin)	0.69	0.00	0.63 - 0.76	0.69	0.00	0.62 - 0.76
Age at index (years)				1.01	0.36	0.98 - 1.04
Male (Ref: female)				1.00	0.97	1.00 - 1.00

The adjusted model was controlled for age and sex.

Denmark

Table 31 presents the treatment persistence at one year in patients with NVAF according to initiated treatment in Denmark. The highest persistence at 365 days was observed in apixaban patients (73.6%), while the lowest was among patients using warfarin (40.7%). Figure 23 illustrates the plot over the treatment persistence for the treatment groups.

The results of the Cox regression on treatment persistence is presented in Table 32. These results show that apixaban users had the lowest hazard ratio, indicating the lowest risk of non-persistence compared to warfarin users.

Table 31. Treatment persistence at 365 days (Denmark)

Treatment persistence during one year in patients with NVAF according to initiated treatment	Number of patients	Persistence at 365 days (%)
rivaroxaban	1,710	68.5
dabigatran	3,474	62.9
apixaban	3,168	73.6
warfarin	16,012	40.7

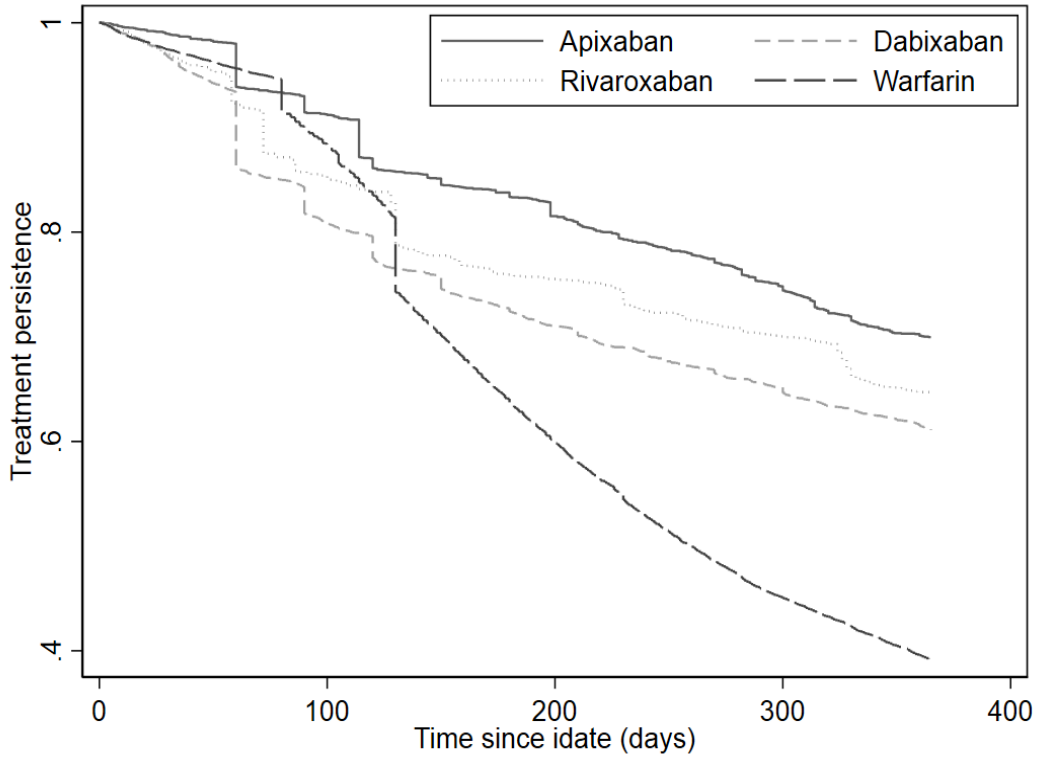

Figure 23. Treatment persistence using method 1 and 30 day grace period (Denmark)

Table 32. Cox regression - Treatment persistence (Denmark)

Treatment persistence during one year in patients with NVAF according to initiated treatment	**Treatment persistence**					
	Unadjusted model			Adjusted model		
	Hazard ratio	p-value	(95% CI)	Hazard ratio	p-value	95% CI
rivaroxaban (Ref: warfarin)	0.50	0.00	0.45 - 0.54	0.48	0.00	0.44 - 0.53
dabigatran (Ref: warfarin)	0.57	0.00	0.54 - 0.61	0.57	0.00	0.54 - 0.61
apixaban (Ref: warfarin)	0.39	0.00	0.36 - 0.42	0.38	0.00	0.35 - 0.41
Age at index (years)						

Male (Ref: female)						

The adjusted model was controlled for age and sex. Coefficients not shown for Denmark.

10.4.4 Meta-analysis

The following section presents the results of the post-hoc meta-analysis of hazard ratios for the full population across Sweden, Norway, Finland and Denmark.

For results on the subgroup Elderly (80+) or Renal Impairment see the stand-alone document "Quantify REATTAIN Cox Regression Analysis" referred to in Table 33.

- **Rivaroxaban vs Warfarin:** There was no significant difference for ischemic stroke/systemic embolism (meta-analysis HR: 0.93; 95% CI: 0.62-1.40) or for intracranial hemorrhage (meta-analysis HR: 1.41; 95% CI: 0.78-2.57).
- **Dabigatran vs Warfarin:** There was no significant difference for ischemic stroke/systemic embolism (meta-analysis HR: 0.88; 95% CI: 0.68-1.14), but there was a significant reduction in the risk of intracranial hemorrhage with dabigatran (meta-analysis HR: 0.35; 95% CI: 0.19-0.64).
- **Apixaban vs Warfarin:** There was a significant reduction in the risk of ischemic stroke/systemic embolism with apixaban (meta-analysis HR: 0.79; 95% CI: 0.67-0.94), but no significant difference of intracranial hemorrhage (meta-analysis HR: 0.72; 95% CI: 0.51-1.04).

10.5 Other analyses

This section presents the sensitivity analyses on incidence rates, cumulative incidence and Cox regression models. Detailed information for the sensitivity analyses conducted for the subgroups, as well as other variations can be found in the stand-alone documents referred to in Table 33.

10.5.1 Sensitivity analyses on incidence rates and cumulative incidence

The results of these analyses can be consulted in the stand-alone document "Quantify REATTAIN Incidence Analysis".

The following section summarizes the main findings from the sensitivity analyses, exploring the robustness of the IS/SE and ICH outcomes, compared to the main analysis:

Sweden

- **Exclude Patients with Events During Baseline:**
  - Showed generally similar trends to the main analysis with minor differences in incidences.
- **ITT Population:**
  - Revealed increased incidences for Stroke/SE and ICH outcomes for NOACs compared to warfarin, indicating potentially different outcomes in a real-world setting.
- **Longer Baseline Period (2-Years):**

- Displayed similar patterns to the main analysis, suggesting consistent findings over extended baseline periods.

- **Follow-up: 2 Years:**
  - Indicated increased cumulative incidences for both events across NOACs and warfarin as expected, no large differences between groups.
- **Follow-up: End of Data:**
  - Indicated increased cumulative incidences for both events across NOACs and warfarin as expected, slightly more pronounced increase in NOAC groups.

Norway

- **Exclude Patients with Events During Baseline:**
  - Results were similar to the main analysis.
- **ITT Population:**
  - Revealed a slight increase in incidences for all NOACs compared to Warfarin.
- **Longer Baseline Period (2-Years):**
  - Indicated a slight increase in incidences of IS/SE for rivaroxaban and ICH for apixaban compared to warfarin, while dabigatran's results were consistent with the main analysis.
- **Follow-up: 2 Years:**
  - Indicated increased cumulative incidences for both events across NOACs and warfarin as expected, no large differences between groups.
- **Follow-up: End of Data:**
  - Revealed a more pronounced increase in cumulative incidences for warfarin compared to NOACs.

Finland

- **Exclude Patients with Events During Baseline:**
  - Similar trends as main analysis.
- **ITT Population:**
  - Rivaroxaban and dabigatran showed increased incidences compared to warfarin, while apixaban's rates were similar.
- **Longer Baseline Period (2-Years):**
  - Consistent with main analysis.
- **Follow-up: 2 Years:**
  - Cumulative incidence of IS/SE was similar across groups, while incidence of ICH increased more for the warfarin population compared to NOACs.
- **Follow-up: End of Data:**

- Higher increase in the cumulative incidences for rivaroxaban compared to warfarin.

Denmark

- **Exclude Patients with Events During Baseline:**
  - Similar trends as the main analysis, with the exception that dabigatran showed a higher cumulative incidence than warfarin compared to the main analysis.
- **ITT Population:**
  - Most NOACs showed an increased incidence in IS/SE and/or ICH compared to warfarin.
- **Longer Baseline Period (2-Years):**
  - Similar to the main analysis.
- **Follow-up: 2 Years:**
  - The incidence of IS/SE for dabigatran was higher than warfarin, compared to the opposite relation found in the main analysis. The incidence of events for the other NOACs increased in a similar way compared to the corresponding warfarin group.
- **Follow-up: End of Data:**

All NOACs showed an increased incidence of both events compared to warfarin, with dabigatran showing the most significant increase in IS/SE.

10.5.2 Sensitivity analyses for the Cox regression model

The following section summarizes the main findings from the sensitivity analyses compared to the main analysis. The results of these analyses can be consulted in the stand-alone document "Quantify REATTAIN Cox Regression Analysis":

Sweden

- **ITT Population:**
  - Similar to the main analysis, there were no significant differences in IS/SE for rivaroxaban and apixaban, compared to warfarin. Dabigatran had a significantly lower risk of ICH in the main analysis, but this was not the case in the ITT analysis.
- **2-Year Follow-Up:**
  - The findings were similar to the main analysis with dabigatran indicating a significantly lower risk of ICH across both scenarios.
- **End of Data Follow-Up:**
  - The pattern remained consistent with the main analysis for both outcomes.
- **Truncated weights: 99th percentile**
  - The results were very similar to the main analysis.

Norway

- **ITT Population:**
  - No significant differences were shown in the main analysis and this pattern was sustained in the ITT analysis.
- **2-Year Follow-Up:**
  - The findings were consistent with the main analysis.
- **End of Data Follow-Up:**
  - The pattern remained consistent with the main analysis for both outcomes.
- **Truncated weights: 99th percentile**
  - The results were very similar to the main analysis.

Finland

- **ITT Population:**
  - There was a general decrease in the relative risk of both events in the warfarin group compared to the NOAC groups. However, significance was consistent with the main analysis.
- **2-Year Follow-Up:**
  - Rivaroxaban had a significantly lower risk of IS/SE compared to warfarin, which was not true in the main analysis. All other findings stayed consistent compared to the main analysis.
- **End of Data Follow-Up:**
  - The pattern remained consistent with the main analysis for both outcomes.
- **Truncated weights: 99th percentile**
  - The results were very similar to the main analysis.

Denmark

- **ITT Population:**
  - The findings were consistent with the main analysis.
- **2-Year Follow-Up:**
  - There was no longer a significantly lower risk of ICH in the dabigatran group compared to warfarin. The other findings were consistent with the main analysis.
- **End of Data Follow-Up:**
  - Similar to the 2-year follow-up analysis, there was no longer a significantly lower risk of ICH in the dabigatran group compared to warfarin, while other result stayed similar.

- **Truncated weights: 99th percentile**
    - There was no longer a significantly lower risk of ICH in the dabigatran group compared to warfarin. The other findings were consistent with the main analysis.

10.5.3 Sensitivity analyses for the treatment persistence

The performed sensitivity analyses consisted of a longer grace period of 60 days. The results of these analyses can be consulted in the stand-alone document "Quantify REATTAIN Persistence Analysis".

Safety data (Adverse events/adverse reactions)

No adverse events/adverse reactions were found or studied in addition to the events evaluated as part of the study objectives.

11. Discussion

Key results

In this study involving AF patients in selected Nordic countries who were initiated on reduced doses of NOACs, namely dabigatran, rivaroxaban, and apixaban, the incidences of ischemic stroke and systemic embolism were comparable or even lower than those of similar patients who commenced standard warfarin therapy. NOAC patients had higher CHA_2DS_2-VASc and HAS-BLED scores, were older and had higher proportion of renal disease compared to the patients in the warfarin group.

Weighted warfarin rates of ischemic stroke generally exceeded those of equivalent NOAC-treated patients. Notably, Norway (rivaroxaban) and Sweden (dabigatran) exhibited higher stroke rates within NOACs compared to warfarin. Meta-analyses within each NOAC category indicated significantly lower HRs for apixaban initiators versus warfarin initiators (0.79, 95% CI 0.67-0.94). HRs approached unity for dabigatran (0.88, 95% CI 0.68-1.14) and rivaroxaban (0.93, 95% CI 0.62-1.40).

The incidence of intracranial hemorrhage events among NOAC-treated patients remained generally low, with rates ranging from 0.16 to 1.85 per 100 person-years. This variability may potentially result from inclusion or non-inclusion of hemorrhagic transformation strokes in the endpoint composite in some of the institutions. HRs for intracranial hemorrhage were generally numerically higher for rivaroxaban compared to the weighted warfarin group, with a pooled HR of 1.41 (95% CI 0.78-2.57). This was primarily influenced by a higher HR observed in Finland among rivaroxaban patients. Finland had a relatively low percentage of new users of reduced dose NOACs, only 7.2%, compared to the other Nordic countries. This resulted in an extremely small sample size and less precise estimates in Finland compared to the other countries, thus the Finish results are more prone to random variability. Conversely, rates among dabigatran and apixaban-treated patients were lower than among comparable warfarin patients, resulting in a pooled HR of 0.35 (95% CI 0.19-0.64) and 0.72 (95% CI 0.51-1.04), respectively.

The NOAC groups differed in terms of proportions with apparent indications for reduced dose prescription, with nearly 40% of dabigatran users potentially having other reasons for reduced dosages, such as body weight, interacting medications, or renal impairment, which were not documented in a hospital setting. It is unknown how much the different labels regarding dose reduction contributed to the results, for example for rivaroxaban no dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min), elderly or with low body weight.

The other outcomes, including fatal bleeding, severe ischemic stroke, kidney failure, acute kidney injury, generally occurred less frequently than ischemic stroke/systemic embolism, and intracranial hemorrhage. This was especially the case for kidney failure, were less than five events were reported across most countries, the low number of events limit the conclusion that can be drawn.

For fatal bleeding, the study's findings from the Cox regression suggest that the risks of fatal bleeding associated with rivaroxaban, dabigatran, and apixaban are not significantly different from those associated with warfarin in any of the countries. Similarly, there were no HRs for severe ischemic stroke (IS 2) that was found to be significantly different between the NOAC groups and warfarin. Severe ischemic stroke using RiksStroke data (IS 1) was only available for Sweden and showed no significant difference in the weighted HR between any the NOAC groups and warfarin. The HR for acute kidney injury during the study period was found to be significantly lower in rivaroxaban users compared to warfarin users in the weighted model. The other NOAC groups showed no significant difference of acute kidney injury compared to the warfarin group. The risk of kidney failure was found to be significantly higher in the apixaban group compared to warfarin users, however no significant differences were observed for the other NOACs.

The differences observed between the Nordic countries can likely be attributed to various factors, including differences in the timing of NOAC introduction, variations in criteria for dose reduction, and differing treatment preferences for specific patient groups.

Limitations

Reliance on administrative and observational data carries potential limitations: Whilst the national records are efficacious in providing exhaustive and detailed information on diagnoses and treatments, it should be noted that they are limited in supply of essential lifestyle, socioeconomic, prescription pattern and other unperceivable personal factors.

The study participants were considered at risk if they were on treatment, which essentially would require direct information from the patient or the general practitioner if treatment has been discontinued. Estimating this using register data involve assumptions and decisions that cannot be ascertained; meanwhile for fixed-dose treatments such as the NOACs, the automated calculation of treatment persistence/endurance is more reliable than for variable doses such as warfarin. This dilemma is additionally complicated by the absence of international normalized ratio (INR) measurements directing the warfarin dosage . Our sensitivity analyses did, however, show that the results were robust towards alterations on how treatment durations were calculated.

A bias of choice of therapy and dose adjustment cannot be excluded, for example dose reduction may well have been provided more or less often to patients who had an increased or decreased risk of the studied outcomes. In addition, presence of other conditions may well affect the choice to adjust the dose in ways that could not be reliably quantified with the available data. Also, the different label recommendations with regard to individual conditions that warrant dose adjustment may have

introduced selection bias if indirect comparisons between the NOACs are attempted, let alone for comparison with warfarin which dose is determined based solely on INR results rather than comorbidities.

While inverse probability weighting has been shown to mitigate the effect of confounding bias, there is still a risk of uncontrolled residual confounding.[20] We acknowledge that the lack of lifestyle, socioeconomic status, prescription pattern and preferences and information from patient journals could be reasons for the presence of such bias. Evidently the differences in baseline characteristics between warfarin and the individual NOAC populations, and potential different characteristics between the NOACs, country difference indicate differential prescribing. As expected, reduced dose of NOACs is targeting a narrower population compared to warfarin. After weighting, we saw that the warfarin populations resembled their NOAC counterpart, with standardized mean differences below 0.1 across a large range of characteristics. The findings from the weighted analyses were also in line with the sensitivity analysis on a patient population resembling that of patients eligible for reduced dose NOAC treatment but indication bias cannot be completely ruled out.

As NOAC-naive patients were studied, this per se may have introduced a bias as initiation of therapy is linked to higher risk in the initiation period especially higher bleeding risk.

Interpretation

It's important to note that our study did not aim to directly compare the various NOACs with each other. Therefore, readers should exercise caution when interpreting the results, as HRs cannot be directly compared between the different NOAC treatments. This caution is warranted because different weights were applied to each warfarin cohort, depending on the specific NOAC being considered. The baseline characteristics of the subpopulations varied significantly, leading to substantial variation in rates among the weighted warfarin populations for different NOACs.

Our study reveals that, despite seemingly similar economic, political, and social structures across four countries, significant differences do exist, which can complicate the interpretation of the results. Variations in patients' comorbidity profiles may be genuine and, to some extent, attributable to disparities in disease recognition and documentation. Additionally, our data highlights unequal treatment preferences among countries, with only 7% of patients in Finland receiving NOACs, compared to 32-36% in Norway and Denmark within this cohort. The contrast between the higher levels of comorbidity in Finnish NOAC-patients and the resulting increased incidence of bleeding events in Finnish rivaroxaban patients may indicate different risks of the populations.

Generalizability

This study is likely one of the largest observational studies to date on the use of reduced dose NOACs and warfarin among AF patients, involving almost 135,000 patients who had not received oral anticoagulants (OAC-naïve) from the Nordic Countries, including approximately 27,000 NOAC patients. The Nordic countries provided an excellent setting for studying the comparative effectiveness and safety of NOACs compared to warfarin in routine clinical practice, thanks to their comprehensive national registries covering the entire populations, prospectively collected administrative data, person-

level linkage between registries, and complete follow-up. Other advantages included universal healthcare accessibility, similar clinical practice, comparable record-keeping practices, and consistent patterns of hospitalization, specialist care referrals, and high-quality warfarin therapy.

The findings of our study are generally consistent with previous observational studies and meta-analyses, demonstrating that in routine clinical use, reduced-dose NOACs is associated with comparable or even lower rates of ischemic stroke and systemic embolism compared with warfarin, along with similar or lower rates of major bleeding and reduced rates of intracranial bleeding.[2,15–18].

In a combined analysis utilizing Scandinavian population-based registries, Halvorsen and colleagues evaluated the risk of stroke, systemic embolism, and bleeding associated with NOACs at both standard and reduced doses when compared to warfarin in anticoagulation-naïve patients with AF.[19] In this study by Halvorsen et al., the results for patients on reduced doses indicated that all three NOACs demonstrated similar efficacy as warfarin in terms of stroke prevention. However, there was a reduced risk of major bleeding with apixaban at a reduced dose compared to warfarin, along with an increased risk of major bleeding with rivaroxaban at a reduced dose compared to warfarin, as observed in propensity score matched groups.

It is conceivable that variations between Scandinavian countries and the outcomes of this study, along with similar investigations, can be attributed to multiple factors, including disparities in data sources, patient characteristics, and medical practices.

Other information

This study was fund by Bayer AG

Conclusion

In this Nordic observational cohort study of patients with AF commencing reduced doses of NOACs, the risk of ischemic stroke and systemic embolism was comparable to patient initiating standard warfarin therapy. Rates of intracranial hemorrhage were comparable to or lower for patients on NOACs compared to warfarin. Furthermore, the risk of acute kidney injury was found to be lower in patient's taking rivaroxaban while the risk of kidney failure was found to be higher in patients with apixaban, relative to that of warfarin. The risk of fatal bleeding and severe ischemic stroke was not found to be significantly different in patients commencing reduced doses of NOACs compared to patients with warfarin.

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Appendices

Annex 1: List of stand-alone documents

Table 33: List of stand-alone documents

Document Name	Final version and date (if available)*
Appendix A: Definitions and operationalizations, ICD-10 and procedure codes	v.4.0 2023-11-24
Post Authorization Safety Study (PASS) Information (Study Protocol)	v.2.2 2021-01-18
Statistical Analysis Plan (SAP)	v.3.2 2021-05-18
Quantify REATTAIN Cox Regression Analysis	v.3.0 2024-04-26
Quantify REATTAIN Incidence Analysis	v.3.0 2024-04-26
Quantify REATTAIN Patient Characteristics	v.2.0 2023-11-23
Quantify REATTAIN Persistence Analysis	v.2.0 2023-11-23
Quantify REATTAIN Attrition	v.2.0 2023-11-23
Quantify REATTAIN Twang - Weighting	v.3.0 2024-04-26