Post Authorization Safety Study (PASS) Report - Study Information

Acronym/Title	Treatment and outcomes among patients with atrial fibrillation and acute coronary syndromes in Sweden
Report version and date	Version 1.0; 1 June 2018
Study type / Study phase	Observational, Phase IV PASS Joint PASS: ☒ YES ☐ NO
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Study Initiator and Funder	Bayer AG, 51368 Leverkusen, Germany
Research question and objectives	This population-based study will describe prescription patterns of antithrombotic drugs in real life among patients with atrial fibrillation and acute coronary syndrome in Sweden, and will study safety and effectiveness endpoints related to the most commonly administered treatment regimens. The primary objectives are: • To describe the variety of antithrombotic treatment regimens administered in patients with atrial fibrillation and acute coronary syndrome and to estimate the treatment duration of the most common regimens. • To assess the incidence of bleeding events associated with hospitalization and effectiveness outcomes, including death, in patients with acute coronary syndrome and atrial fibrillation: overall and among subgroups.

Country(-ies) of study	Sweden
Author	[redacted]

Marketing authorization holder

Marketing authorization holder(s)	Bayer AG, 51368 Leverkusen, Germany
MAH contact person	[redacted]

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1. Abstract

Acronym/Title	Treatment and outcomes among patients with atrial fibrillation and acute coronary syndromes in Sweden
Report version and date **Author**	v.1.0; 1 June 2018 [redacted]
Keywords	ACS, AF, PCI, NOAC, antiplatelet, antithrombotic therapy
Rationale and background	Patients with a history of acute coronary syndrome (ACS) and atrial fibrillation (AF) are at high risk for major adverse cardiovascular events, therefore they are prescribed combination therapy consisting of an anticoagulant and one or more antiplatelet agents, particularly if a percutaneous coronary intervention (PCI) has been conducted. Such drug combinations are associated with increased risk of bleeding complications. In recent years several new non-vitamin K anticoagulants (NOACs) and antiplatelet drugs have been introduced; however, although they have been extensively studied individually, the safety and efficacy of most of the combined regimens have not been evaluated in randomized controlled trials. The recently completed PIONEER AF-PCI trial demonstrated a good safety profile of a regimen containing rivaroxaban [1]; however, the study was not designed to assess the regimen's efficacy. It is important to understand how patients with AF and ACS (including those undergoing PCI) are treated in real-life settings and to determine the outcomes associated with these treatment regimens.
Research question and objectives	This population-based study will describe the real life prescription patterns of antithrombotic drugs in patients with AF and ACS in Sweden, and will evaluate safety and effectiveness endpoints for the most commonly administered treatment regimens. The primary objectives are: • To describe the variety of antithrombotic treatment regimens administered in patients with AF and ACS and to estimate the treatment duration of the most common regimens. • To assess the incidence of bleeding events associated with hospitalization and effectiveness outcomes,

	including death, in patients with ACS and AF: overall and among subgroups.
Study design	This is a retrospective cohort study which utilized non-randomized unselected data from nationwide mandatory health registers in Sweden.
Setting	In Sweden all registered oral anticoagulants (OACs; warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) are used in clinical practice. Phenprocoumon can be prescribed under a special license in case of intolerance to other oral anticoagulants. Oral antiplatelet drugs used are acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel and dipyridamol. Ticlopidine was deregistered in 2006, but may still be used under a special license.
Subjects and study size, including dropouts	The inclusion period started on 1st December 2011 and included patients up to 1st October 2016. Cohorts were followed up for a minimum of 3 months, thus the inclusion period ended 3 months before the end of the observation period. During the inclusion period, a total of 111,197 individuals were hospitalized with a diagnosis of ACS. Of these individuals, 23,180 also had a diagnosis of AF. After exclusions, 13,275 patients remained in the study cohort, of whom 9,375 did not undergo PCI, 320 had PCI without a stent and 3,580 had PCI with stent implantation during hospitalization.
Variables and data sources	Detailed descriptive variables including baseline characteristics were captured for the population, including co-medications and comorbidities. CHA_2DS_2Vasc scores were calculated. Antithrombotic drug combinations, drug strength, treatment duration and most commonly prescribed regimens were identified. Exposure of a certain drug or a drug combination during follow-up was estimated as the number of days the dispensed drug supply would be expected to last if drug adherence was 90%, thus allowing for occasional dropped doses. The assumed dosages were the standard dose for the particular strength of the drug. Patients on non-standard dosing were classified as receiving “other treatment”. For warfarin, where a standard dosing does not exist, an approach based on assessment of refill intervals was employed. To measure safety and effectiveness outcomes the variables indicating the following events were analysed: hospitalization or death with a diagnosis of bleeding; hospitalization for recurrent ACS; revascularization procedure; ischaemic stroke

	or systemic embolism; death from any cause.Data sources included The Patient register, The Dispensed Drug register, The Cause of Death register and the LISA (longitudinal integration database for health insurance and labour market studies).
Results	There was a great diversity in treatments given to AF patients who experienced ACS-episodes. The most common regimens did not include an oral anticoagulant, in contrast to current national and international guideline recommendations. Dual antiplatlet therapy, the standard treatment for ACS patients without AF, is frequently used for AF patients as well. Elderly and frail patients, at high risk for both bleeds and thromboses, generally received less aggressive antithrombotic drug regimens than younger and healthier patients. This complicated the interpretation of outcome data. Differences in bleeding rates between high risk and low risk patients were attenuated by the choice of antithrombotic regimen, while differences regarding ischaemic stroke and reinfarction may have been exaggerated for the same reason. The diversity of regimens made most of the groups including a NOAC too small for valid comparisons of the benefits or risks associated with individual regimens.
Discussion	This study shows that there is no single standard therapy for patients with AF who also have an episode of ACS. There is little or no scientific evidence regarding the benefit or harm for the majority of these regimens. There were clear differences between patients given different regimens; more potent antithrombotic regimens generally were given to younger and healthier patients with lower perceived bleeding risks. Elderly patients with higher perceived bleeding risk were more often given regimens consisting of only antiplatelet drugs and no oral anticoagulation. It was not possible to determine which treatment regimen was better or worse because of selection biases and undocumented reasons why doctors preferred one treatment over the other. The most common treatment among patients with ACS and AF was dual antiplatelet therapy, the standard treatment for ACS patients without AF, indicating that the awareness of the need for oral anticoagulation in this patient population was not adequately recognized by prescribing doctors.
Marketing Authorization Holder(s)	Bayer AG, 51368 Leverkusen, Germany

Names and affiliations of principal investigators	[redacted]

2. List of abbreviations

ACE	Angiotensin-converting-enzyme
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AP	Antiplatelet
ARB	Angiotensin II receptor blocker
CABG	Coronary artery bypass graft
CHA_2DS_2-VASc	Congestive Heart Failure, Hypertension, Age ≥ 75 years, Diabetes Mellitus, Stroke or Transient Ischaemic Attack Symptoms Previously, Vascular disease, Age 65–74 years, Sex category (i.e. female sex)
CI	Confidence interval
CKD	Chronic kidney disease
GI	Gastrointestinal
HASBLED	Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INRs, Elderly, Drugs or alcohol
HR	Hazard ratio
ICD	Implantable cardioverter defibrillator
ICD-10	International Classification of Diseases, Tenth Revision
NOAC	Non-vitamin K antagonist oral anticoagulant
NSAID	Nonsteroidal anti-inflammatory drug
OR	Odds ratio
PCI	Percutaneous coronary intervention
PPI	Proton pump inhibitor
TIA	Transient ischaemic attack

3. Investigators

Principal investigator: [redacted]

4. Other responsible parties

Marketing authorization holder: Bayer AG, 51368 Leverkusen, Germany

MAH contact person and study epidemiologist: [redacted]

Study medical expert: [redacted]

Study safety lead: [redacted]

Study statistician: [redacted]

Real life evidence strategy and outcomes data generation: [redacted]

5. Milestones

This study was conducted between January 2017 and April 2018.

Milestone	**Project timeline**
Protocol development and submission for review and comment	May– June 2017
Ethics Submission & Approval	July–August 2017
Data Extraction	October 2017
Data Analysis and reporting	January–March 2018

6. Rationale and background

Patients with a history of acute coronary syndrome (ACS; i.e. acute myocardial infarction [AMI]) or unstable angina pectoris) and atrial fibrillation (AF) are at high risk for major adverse cardiovascular events [2-4]. These patients require an anticoagulant and one or more antiplatelet agents [5], particularly if a percutaneous coronary intervention (PCI) was conducted. Such drug combinations are associated with increased risk of bleeding complications. Aggressive combinations with higher bleeding risk are generally used in the first few months following PCI when the risk of stent thrombosis and reinfarction is high, with less intense treatment used in subsequent months, according to the perceived thrombotic and haemorrhagic risk to the patient. During recent years, several new non-vitamin K anticoagulants (NOACs) and antiplatelet drugs have been introduced; however, although they have been extensively studied individually in randomized controlled trials (RCTs), the safety and efficacy of most of the combined regimens have not been evaluated in RCTs.

The recently completed PIONEER AF-PCI trial demonstrated a good safety profile of a regimen containing rivaroxaban [1]; however, the study was not designed to assess its efficacy. It is important to understand how patients with AF and ACS (including those undergoing PCI) are treated in real-life settings and to determine the outcomes associated with each treatment regimen.

In Sweden, extensive health registers capture life-long data on the entire population and are linked via a unique personal identification number. These provide an excellent opportunity to study routine clinical practice and associated outcomes.

7. Research question and objective

This population-based study will describe prescription patterns of antithrombotic drugs in patients with AF and ACS in Sweden, and will study safety and effectiveness endpoints related to the most commonly administered treatment regimens.

7.1 Primary objectives

The primary objectives of the study were:

- To describe the variety of antithrombotic treatment regimens administered in patients with AF and ACS and to estimate the treatment duration of the most common regimens.
- To assess the incidence of bleeding events associated with hospitalization and effectiveness outcomes, including death, in patients with ACS and AF: overall and among subgroups.

7.2 Secondary objectives

Not applicable

8. Amendments and updates

9. Research methods

9.1 Study design

This is a retrospective cohort study which utilized non-randomized unselected data from nationwide mandatory health registers in Sweden. Patients with AF and ACS were grouped according to anticoagulant treatment regimen at baseline. The baseline period was defined by a prescription of a NOAC or antiplatelet agent within 90 days before and up to 7 days after the index date (defined as a hospital discharge after an ACS event). Due to the wide variation in dose requirements for warfarin and in order to capture all individuals with ongoing treatment, the baseline period for warfarin was defined as 183 days before and up to 7 days after the index date. It was assumed that most patients would collect their prescription within the 7-day period after hospital discharge.

Patients on anticoagulant treatment were followed from the index date to the date of a specified outcome, death or end of follow-up. Incidence of the events was calculated for the total follow-up period and additionally for the 7-day overlap period after the index date (to allow patients time to collect their medicines from a pharmacy before the start of calculating exposure time) to identify any events that might have occurred (although this number was expected be very small). Treatment history data was defined by a filled prescription before (excluding) the index date.

During follow up, censoring occurred:

- when there was a switch to another oral anticoagulant;
- when available drug supply was assumed to be exhausted indicating treatment cessation (estimated according to the refill method described)
- at the first occurrence of a specified endpoint event;
- at emigration;
- at death;
- at end of follow-up on December 31, 2016.

Linkage of data was achieved using personal identification numbers given to all permanent residents in Sweden irrespective of citizenship. These numbers are permanent and are used in all contacts with authorities and health services thus permitting individual patients to be followed over their lifetime, with the exception of emigration. It is not possible for residents to opt out of these registers. For data protection reasons, data is anonymized before being made available for research purposes and access to data is strictly regulated. The Patient Register, Dispensed Drug- and the Cause of Death register are maintained by the National Board of Health and Welfare, while the LISA register is maintained by Statistics Sweden.

9.1.1 Primary end-points

- Composition and frequency of treatment regimens (that include combinations of a vitamin K antagonist, antiplatelet therapy, a P2Y12 inhibitor without or with rivaroxaban) in patients with both AF and ACS, including those who underwent PCI with or without a stent.
- Prescribed strength and treatment duration of the most common treatment regimens.
- Safety outcomes: hospitalization or death with a diagnosis of bleeding ("clinically relevant bleedings").
- Effectiveness outcomes: hospitalization for recurrent ACS, revascularization procedure (PCI or coronary artery bypass grafting [CABG]), ischaemic stroke or systemic embolism; death from any cause.

9.1.2 Secondary end-points

Not applicable

9.2 Setting

In Sweden all registered oral anticoagulants (OACs; warfarin, dabigatran, rivaroxaban, apixaban, edoxaban) are used in clinical practice. Phenprocoumon can be prescribed under a special license in case of intolerance to other oral anticoagulants, but it was used by only 310 patients in Sweden for any indication in 2015. Oral antiplatelet drugs used are acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel and dipyridamol. Ticlopidine was deregistered in 2006, but was still used under a special license by 41 patients in 2015.

9.3 Subjects

All individuals who received an anticoagulant or antithrombotic drug from any pharmacy in Sweden between 9 December 2011 (the date of rivaroxaban introduction in Sweden) and 31 December 2016 were identified in the national Dispensed Drug registry. For these individuals, information was obtained about drug use since the start of the Drug register in 2005, from the national Patient register since 1997 and from the national Cause of Death register. Individuals hospitalized for an episode of ACS, defined as unstable angina pectoris or myocardial infarction, between 9 December 2011 and 30 September 2016 were identified from the Patient register. Within the ACS cohort, individuals with a concurrent or previous diagnosis of AF were identified. The index date and start of follow up was defined as seven days after the

hospital discharge date. These additional seven days were required in order to record dispensing of newly initiated drugs; therefore, patients had to survive at least a week after hospital discharge to be included in the study.

Patients who were discharged to other hospitals or clinics were excluded from the study because drugs administered to patients in hospital are not dispensed by pharmacies and therefore not included in the Drug registry. Patients undergoing CABG surgery were excluded for the same reason since they are discharged from thoracic surgery clinics to cardiology-, internal medicine or rehabilitation clinics before being discharged to home. Furthermore, CABG surgery rarely is performed directly during the acute coronary episode; the aim is to stabilize patients, either pharmacologically or with PCI, before proceeding with revascularization. Patients without a dispensation for an antithrombotic drug were excluded because of heterogeneity of circumstances; this is explained in more detail in Section 10.2.1 Patients using non-standard dosages of non-vitamin K oral anticoagulants (NOACs) for the AF indication (e.g. rivaroxaban, 2.5 mg and 10 mg; dabigatran, 75 mg) were also excluded.

Separate cohorts were formed for patients based on the intervention that was conducted during the index hospitalization: PCI with stent implantation, PCI without stent implantation or no PCI. Cohorts were followed up for a minimum of 3 months, thus the inclusion period ended 3 months before the end of the observation period.

9.4 Variables

9.4.1 Baseline characteristics

The following variables were collected:

- demographic (age, sex, marital status, immigrant status) and socioeconomic status (educational level, disposable income after taxes and transfers);
- medical history and concomitant disease (the definitions of medical conditions by International Classification of Diseases [ICD-10] codes specified in the protocol had to be changed in a few instances; these changes are highlighted in Table 54);
- CHA_2DS_2VASc scores calculated based on the presence/history of congestive heart failure, hypertension, age, diabetes mellitus, vascular disease, female sex and prior thromboembolic event;
- medical treatment history (not including anticoagulants and antithrombotic drugs) prior to the diagnosis of ACS (dispensed 4 months before the index date and within 7 days from the index date): beta blockers, angiotensin-converting-enzyme inhibitors, angiotensin II receptor blocker, statins, verapamil, diltiazem, digoxin, diuretics, dihydropyridine calcium blockers, class 1 and class 3 antiarrhythmic drugs, nonsteroidal anti-inflammatory drugs, proton pump inhibitors;
- composition and frequency of every anticoagulant and antithrombotic treatment regimen at baseline (purchased 4 months before and within 7 days after the index date): this information was obtained from the national Dispensed Drug register. In case of dispensations for more than one antithrombotic drug at baseline the following rules were applied:

- in case of recorded dispensation of more than one NOAC or NOAC plus warfarin (at index date), the latest drug defined a treatment group as combinations of different OACs should not be possible;
- in case of recorded dispensation of more than one NOAC or NOAC plus warfarin at the index date, such patients were excluded from the outcome analysis;
- other combinations of antithrombotic drugs were analyzed as separate groups in subgroups of sufficient size to make analyses meaningful.

9.4.2 Drug exposure

Time at risk was counted from the index date plus seven days to allow time for patients to collect prescribed drugs. Duration of the most commonly prescribed regimens was calculated in the following way:

Exposure of a certain drug or a drug combination during follow up was estimated as the number of days the dispensed drug supply would be expected to last if drug adherence was 90%, thus allowing for occasional dropped doses.

The assumed dosages were the standard dose for the particular strength of the drug, namely:

- Rivaroxaban 2.5 mg twice daily, 15 and 20 mg once daily
- Dabigatran 110 and 150 mg twice daily
- Apixaban 2.5 and 5 mg twice daily

Patients on non-standard dosing (e.g. rivaroxaban, 10 mg; dabigatran, 75 mg) were classified as receiving “other treatment”; in these cases drug exposure during follow up was not estimated.

Once daily dosing was assumed for acetylsalicylic acid, clopidogrel and prasugrel and twice daily for ticagrelor and dipyridamol. For warfarin, where a standard dosing does not exist, an approach based on assessment of refill intervals was employed. All days between subsequent refills were considered to be days on treatment as long as the refill interval did not exceed 6 months, in which case treatment was assumed to have stopped 3 months after the preceding dispensation. The last dispensation was assumed to have lasted 3 months. This is a modification of a method which previously been evaluated in a study of 25,000 patients with known dosages, and International Normalized Ratio values [6]. The method aims to estimate the total exposure time rather than warfarin dose.

9.4.3 Outcomes of interest

- Antithrombotic treatment regimens in patients with AF and ACS including those who underwent PCI with or without a stent placing.
- Safety outcomes: hospitalization or death with a diagnosis of bleeding (“clinically relevant bleedings”).
- Effectiveness outcomes:
  - hospitalization for recurrent ACS;
  - revascularization procedure (PCI or CABG);
  - ischaemic stroke or systemic embolism;

- death from any cause.

9.5 Data sources and measurements

The Patient register

The Patient register started 1964 as a register of hospitalizations in Sweden and reached national coverage in 1987. In 2001, specialized open care and day surgery was added to the register. It does not carry information from primary care or nursing homes. The register holds information about dates of admission and discharge, primary and secondary diagnoses, surgical procedures and additional information. The register has frequently been used for research purposes and the data quality is generally of very high standard.

The Dispensed Drug register

This register started on July 1, 2005 in its present form. Details about all dispensed prescription drugs are registered automatically in all pharmacies all over the country. All pharmacies are required to participate by law thus there are practically no missing data regarding prescription drugs. However, over the counter drugs are not available in the register, nor are medication given during acute hospitalization. Drugs used in homes for the elderly and nursery homes are included.

The Cause of Death register

The Cause of Death register lists dates, underlying and up to 48 contributory causes of death as well as information about accidental and violent death since 1961.

The LISA register

The LISA (longitudinal integration database for health insurance and labour market studies) register holds detailed information about each individual´s education, income, line of work, family and hundreds of other socioeconomic variables. The LISA register is maintained by Statistics Sweden and is updated every year. For the purpose of this study we obtained information about emigration, immigration, immigrant status (Swedish origin, yes/no), marital status, cohabitation (yes/no), educational level and disposable income after taxes and transfers.

9.6 Bias

This study was based on data providing complete coverage of all age groups. Since all data recording was independent of a patient's memory or agreement to participate, patient non-response or recall bias are non-existent.

Potential for misclassification of indication exists where the assignment of indication of use depends on the proper and accurate recording of the condition in the database.

9.7 Study size

This is a population-based study. The entire source population of Sweden is about 10 million inhabitants. Annually there are approximately 50,000 ACS hospitalizations in Sweden, and about half of them have an myocardial infarction; among those 10–15% have AF. This interim report is based on all data available during time of study (09 Dec 2011–31 Dec 2016).

9.8 Data transformation

Stata software was used for data management and preparation of files for the statistical analyses which also were performed in Stata.

The National Board of Health and Welfare maintains the registers and provided excerpts in accordance with our demands after approval by the local ethics committee and by the legal department at the National Board of Health and Welfare.

After linking was done, personal identifiers were removed and substituted by anonymized numbers. The files were delivered as encrypted csv-files. The delivered data volume was over 70 Gigabyte, and therefore had to be divided into smaller files for technical reasons. From these files, a working file was prepared for statistical analyses.

Data is protected by encryption on computers with limited access and under PIN code protection as requested by the Board of Health and Welfare.

This study is based on routinely collected clinical data (secondary data) and does not involve any primary data collection.

9.9 Statistical methods

9.9.1 Main summary measures

The first part of the study (Section 10.2) characterizes the study population at baseline, i.e. at hospital discharge after an episode of ACS. Only descriptive measures are used, including crude numbers, means with standard deviations, medians, interquartile ranges and proportions. No significance testing is performed in this section.

9.9.2 Main statistical methods

The second part of the study (Section 10.3) evaluates outcomes. Crude unadjusted incidences are presented graphically as Kaplan–Meier plots. Event rates are presented as number of events per 100 years of exposure of the respective antithrombotic drug combination. Multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) are estimated with Cox regressions according to the pre-specified protocol. The covariates are presented under each table. The choice of covariates was based on generally recognized associations between the factor and the specific outcome. Not more than one covariate per ten outcome events was allowed. As many of the subgroups consisted of small numbers of patients with few or no events, adjustment with all covariates was not always possible. Adjustments with a limited set of covariates are presented in italics. HRs were not calculated when there were fewer than ten events or when there were no events in the comparator category.

The Kaplan–Meier curves for the ACS outcome and, to a lesser extent, the all-cause mortality endpoint demonstrated higher incidences in the first few months than later on during follow

up. This constitutes a violation of the proportional hazards assumption on which Cox regression is based; therefore, Parametric Weibull regressions, which are tolerant to changes in risk over time, have been added as sensitivity analyses, where appropriate. This is further explained in conjunction with Table 22B.

In the final part of the study (Section 10.5), outcomes are compared in patients receiving rivaroxaban and warfarin, respectively, using propensity score matching. This was done as an additional sensititivity analysis because of important differences on observed baseline charcteristics during the work process. These propensity scores were obtained by logistic regression using all covariates in baseline Table 3 as covariates. Matching was then made pairwise 1:1 of patients with similar scores and either warfarin or rivaroxaban treatment with a caliper of 0.01, without replacement and within the common support. Differences in baseline characteristics before and after matching were tested with Chi2-tests and Wilcoxon signed rank tests as appropriate (Table 46).

9.9.3 Missing values

Owing to the nature of the Swedish registers, missing data is not possible. However, in very rare instances data may appear to be miscoded or incomprehensible, e.g. patients with impossible high age, patients without gender, missing date for a contact. If the correction of such erroneous data cannot be made, then the patient was excluded.

As a general strategy, no data imputation strategies were applied to supplement missing data. The requirement for inclusion is complete data for critical variables; otherwise this individual is not eligible to be a member of the study population.

9.9.4 Sensitivity analyses

9.9.5 Amendments to the statistical analysis plan

9.10 Quality control

The Swedish Board of Health and Welfare, which maintains the national health registries, continually control quality and integrity of data. More than 99% of non-psychiatric hospitalizations have technically correct entries in the Patient Register. Several studies have assessed the validity of diagnoses in the Swedish patient register, regarding both sensitivity and specificity [7-9]. The review by Ludvigsson *et al*, 2011 [8] provides an excellent overview of several validation studies, confirming that validity of diagnoses differs in the registers. Diagnoses signifying discrete events are mostly correct (e.g. stroke, myocardial infarction), whereas diagnoses related to long-term conditions may sometimes be omitted in patients with several other competing diagnoses of higher importance. Regarding missing diagnoses in the Patient Register, some degree of validation can be obtained by cross-linking data with quality registers for diseases that have such specific registers (e.g. stroke, heart failure, ischaemic heart disease, diabetes). In previous studies where the investigators performed such cross-linking, more patients were generally found in the Patient Register than in the quality registers, indicating good sensitivity to identify such events.

A quality assurance procedure was employed to ensure that all data management steps and the statistical analyses were conducted appropriately. Data management and all data analyses were performed through syntax files which were recorded and made available for scrutiny by Bayer.

Plausibility checks confirmed that the data extraction and record linkage from the various national registers was accurately performed by the data provider (Swedish National Board of Health and Welfare). Various internal plausibility checks were conducted, e.g. to identify variable values out of expected range. File preparation and statistical analytical procedures were recorded in syntax files which allow all figures to be traced back to the original source files obtained from the data provider. This also allows tracing and correcting any subsequent errors in derived variables. Syntax files also facilitate independent external scrutiny of data quality. Back-ups of data files were performed daily and kept in a secure location. The originals and the final analysis file were archived.

10. Results

10.1 Participants

During the 4 year and 10 month inclusion period, a total of 111,197 individuals were hospitalized with a diagnosis of ACS, defined by a hospital discharge ICD-10 code I200 for unstable angina pectoris or I21 for acute myocardial infarction. Of these individuals, 23,180 (20.8%) also had a diagnosis of AF. AF was first diagnosed during the index hospitalization in 1,423 patients (6.1%) and 5,776 patients (24.9%) received their first AF diagnosis 1–31 days before index. The majority (74.7%) did not receive revascularization during the index hospitalization for ACS. Of those who did undergo revascularization, the most common procedure was PCI with stent implantation (Figure 1).

In total, 2,026 patients (8.7%) died during the index hospitalization (Figure 2); these patients were excluded from further analyses. A further 6,756 patients were discharged to another clinic or hospital and continued to receive their medication as inpatients. It was not possible to determine which treatment they received from the Dispensed Drug register, therefore these patients were also excluded (immortal time bias would have followed if data from later dispensing had been used for allocation of treatment group).

Few patients had a CABG during the acute ACS episode. CABG is most often performed some weeks or months later when the patient's condition has been stabilized. Most of the these patients (77.4%) were discharged to another clinic or hospital where their medication use could not be assessed using the Dispensed Drug register. Since the design of the study was ill suited for CABG patients, these patients were excluded from the study.

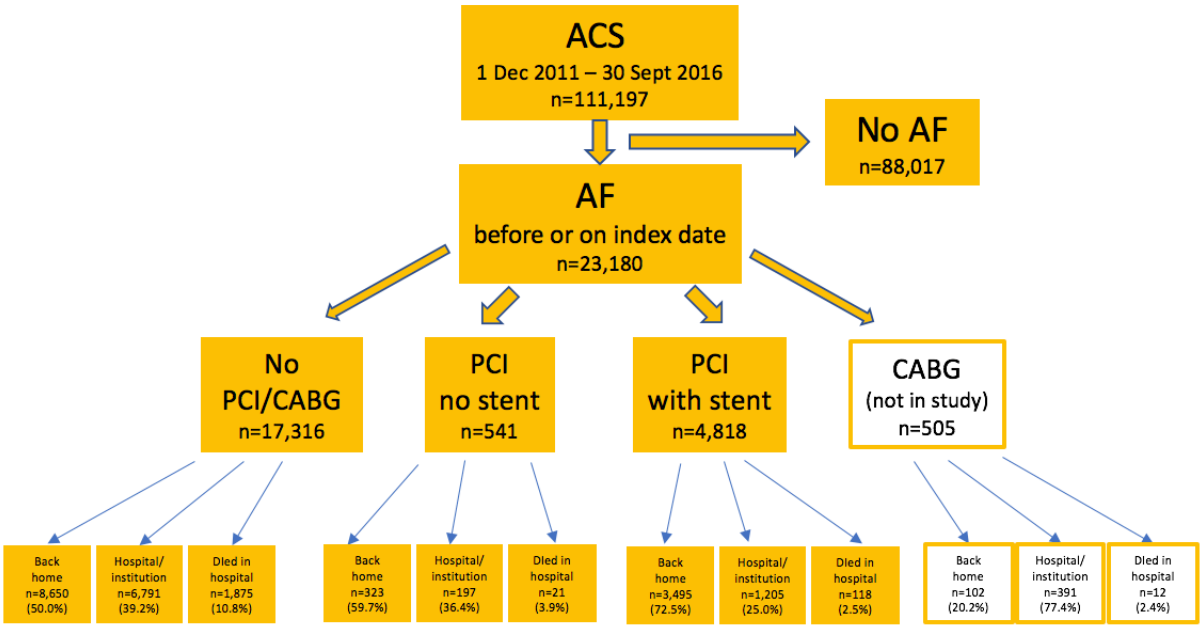


Figure 1. Identification of study patients and mode of hospital discharge

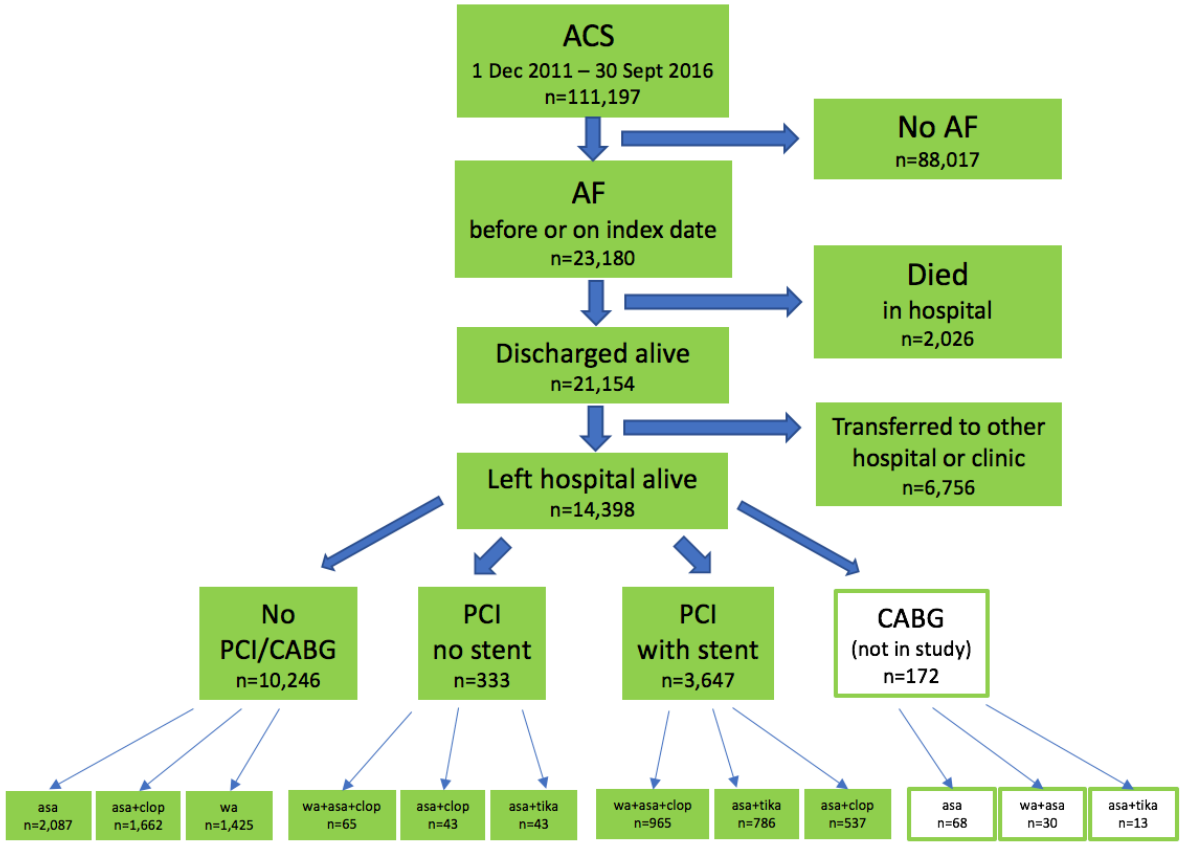


Figure 2. Exclusions and the most common drug combinations for each cohort

10.2 Descriptive data

10.2.1 Antithrombotic drugs used

Among the 14,226 patients who had been discharged home or to a home for the elderly or disabled, 94 different combinations of antithrombotic drugs were used, not counting different drug strengths or dosages (Table 1). The drugs considered were warfarin (wa), phenprocoumon (phen), dabigatran (dabi), rivaroxaban (riva), apixaban (apixa), acetylsalicylic acid (asa), dipyridamol (dip), clopidogrel (clop), tikagrelor (tika), prasugrel (prasu), low molecular weight heparin (lmwh), unfractionated heparin, cilostazol (cilo) and fondaparinux (fonda). These abbreviations are used in tables and graphs for practical reasons, but are avoided in the text. Unfractionated heparin was originally included in the analyses but was subsequently withdrawn when it was determined that it had only been used by four patients at 100 IU/mL, which is the dose used for the maintenance of indwelling catheters.

Table 1. Combinations of antithrombotic drugs. Drugs dispensed between 122 days before up to 7 days after discharge for ACS, with sufficient supply to last into the observation period.

	All	No PCI/CABG	PCI without stent	PCI with stent
apixa	243	235	4	4
apixa+asa	216	204	9	3
apixa+asa+cilo	1	1	0	0
apixa+asa+clop	167	54	6	107
apixa+asa+clop+lmwh	2	1	0	1
apixa+asa+clop+tika	6	3	0	3
apixa+asa+dip	2	2	0	0
apixa+asa+lmwh	2	2	0	0
apixa+asa+tika	25	8	2	15
apixa+clop	100	61	3	36
apixa+clop+lmwh	1	1	0	0
apixa+clop+tika	1	0	0	1
apixa+clop+tika+lmwh	2	0	0	2
apixa+dip	1	1	0	0
apixa+dip+clop	2	2	0	0
apixa+lmwh	5	5	0	0
apixa+tika	47	14	2	31
asa	2,162	2,087	17	58
asa+clop	2,242	1,662	43	537
asa+clop+cilo	1	1	0	0
asa+clop+lmwh	42	28	7	7
asa+clop+prasu	3	2	0	1
asa+clop+tika	53	30	2	21
asa+dip	42	39	0	3
asa+dip+clop	51	46	0	5
asa+dip+tika	15	5	0	10
asa+fonda	1	1	0	0
asa+lmwh	96	93	1	2
asa+prasu	18	3	3	12
asa+tika	1,355	526	43	786
asa+tika+lmwh	11	5	0	6
asa+tika+prasu	1	0	0	1
asa+tika+prasu+lmwh	1	0	0	1

clop	430	336	2	92
clop+lmwh	24	22	0	2
clop+prasu	2	1	0	1
clop+tika	8	6	0	2
dabi	64	63	1	0
dabi+asa	34	34	0	0
dabi+asa+clop	49	14	1	34
dabi+asa+clop+lmwh	1	1	0	0
dabi+asa+lmwh	1	1	0	0
dabi+asa+prasu	1	0	0	1
dabi+asa+tika	9	3	2	4
dabi+clop	21	7	1	13
dabi+clop+tika	2	0	0	2
dabi+dip+clop	1	1	0	0
dabi+tika	19	4	1	14
dabi+tika+lmwh	1	0	0	1
dip	15	14	0	1
dip+clop	14	14	0	0
dip+clop+lmwh	1	1	0	0
dip+tika	2	0	0	2
fonda	1	1	0	0
No dispensing ≤ 7 days	916	846	13	57
lmwh	63	60	1	2
phen	1	1	0	0
phen+asa+clop	2	0	0	2
prasu	6	1	0	5
riva	94	94	0	0
riva+asa	58	54	1	3
riva+asa+clop	83	21	2	60
riva+asa+lmwh	3	3	0	0
riva+asa+tika	12	4	0	8
riva+clop	38	22	3	13
riva+clop+lmwh	2	1	0	1
riva+lmwh	3	3	0	0
riva+tika	19	9	2	8
tika	93	42	1	50
tika+lmwh	1	0	0	1
wa	1,464	1,425	14	25
wa+asa	971	912	34	25
wa+asa+clop	1,446	416	65	965
wa+asa+clop+lmwh	57	17	3	37
wa+asa+clop+prasu	4	0	0	4
wa+asa+clop+tika	13	5	0	8
wa+asa+clop+tika+lmwh	2	1	0	1
wa+asa+dip	8	8	0	0
wa+asa+dip+clop	12	6	0	6
wa+asa+fonda	1	1	0	0
wa+asa+lmwh	49	47	2	0
wa+asa+prasu	5	2	0	3
wa+asa+tika	154	61	4	89
wa+asa+tika+lmwh	11	5	0	6
wa+clop	706	369	30	307
wa+clop+lmwh	37	19	1	17
wa+clop+prasu	1	1	0	0
wa+clop+tika	6	2	0	4
wa+dip	2	2	0	0

wa+dip+clop	1	1	0	0
wa+lmwh	83	80	2	1
wa+prasu	1	0	0	1
wa+tika	176	59	5	112
wa+tika+lmwh	5	1	0	4
Total	14,226	10,246	333	3,647

For 6.4% of the patients (916/14,226), no dispensation of an antithrombotic drug had been recorded within the first week after hospital discharge. Of those, 244 patients had been discharged to homes for the elderly or disabled. Although patients living in such institutions obtain their medication by prescription from pharmacies and thus are included in the Drug register, it is likely that many of them are registered within the first week after hospital discharge. Patients living in homes for the elderly usually get their medication in individualized blister packs called APO-dose which takes some time to set up. According to the national Swedish pharmacy "Apoteket" which is responsible for APO-dose, delivery should be made within 5 working days, which means that some patients will not receive their new medication within the 7 day period. Patients using APO-dose commonly receive a limited supply of tablets when they leave hospital for use until they receive their APO dose blisters. Extending the window of detection from 7 to 14 days demonstrated that 110 of the 244 patients were dispensed an antithrombotic drug.

Of the 672 who were discharged apparently without antithrombotic treatment, 257 made a delayed fill of the prescription in the 7 to 14 day post-discharge period. Of the remaining 415 patients, 399 had anaemia, previous hospitalization for bleeding, dementia or had been hospitalized for a fall on more than one occasion. Due to the diversity of individual circumstances regarding patients without a antithrombotic drug dispensation within the first 7 days, these patients were excluded.

Four patients were excluded for use of the incorrect dose of rivaroxaban; three patients who were using the 10 mg rivaroxaban tablet, which is not an approved dose for stroke prevention in AF nor for coronary protection, and one patient using the 2.5 mg rivaroxaban tablet. Although the 2.5 mg tablet is approved for ACS prevention, it is not a relevant or approved dose for stroke prevention in AF. Table 2 shows the dose strengths of NOACs that were prescribed.

Table 2. Dose strength on index prescription of NOACs

	Strength	All	Without antiplatelet	With 1 antiplatelet	With 2 antiplatelets	With ≥3 antiplatelets
Dabigatran	150 mg	61	20	19	22	-
	110 mg	142	44	55	42	1
	75 mg	-	-	-	-	-
Rivaroxaban	20 mg	158	51	62	45	-
	15 mg	150	41	55	54	
	10 mg	3	2	1	-	-
	2.5 mg	1	-	-	1	-
Apixaban	5 mg	359	111	151	94	3
	2.5 mg	462	132	218	107	5

The higher standard dose was used by 29.7% of patients receiving dabigatran, 50.6% of patients receiving rivaroxaban and 43.7% of patients receiving apixaban. Surprisingly, no relationship between the choice of NOAC dose strength and the number of concomitant antiplatelet drugs used could be observed.

After exclusions, 13,306 patients remained in the study cohort, of whom 9,398 did not undergo PCI, 320 had PCI without stent implantation and 3,588 had PCI with stent implantation during hospitalization. Characteristics of the patients who were excluded from the study are presented in Table 3.

10.2.2 Excluded patients

Patients who were excluded from the study are characterized according to exclusion criteria and compared with patients who were included in the study cohort in Table 3. Patients excluded because of CABG were younger, had lower CHA_2DS_2-VASc score and fewer comorbidities than other patients. Otherwise, the excluded and included patient groups did not differ much; all had median ages around 80 years and high CHA_2DS_2-VASc scores of around 5, as can be seen in Table 3.

Table 3. Baseline characteristics of excluded patients

		Excluded				Included
		To other clinic or hospital (n=6,756)	**CABG (n=172)**	**No dispensation within 7 days (n=916)**	**Irregular dose of rivaroxaban (n=4)**	**All studied patients (n=13,306)**
Procedure	No PCI	5,195	n/a	846	2	9,398
	PCI without stent	187		13	-	320
	PCI with stent	1,053		57	2	3,588
Duration of AF,[A] years	mean	3.5±4.6	1.0±2-6	4.5±4.7	3.2±2.9	4.3±4.7
	median	1.0	0.3	3.3	3.1	2.8
Demography						
Female sex		37.2	36.1%	44.3%	2	41.3%
Age, years	mean	77.1±9.6	71.5±7.3	80.6±10.1	80.8±5.3	79.5±9.8
	median	78	72	83	82	81
Living alone		51.8%	36.1%	61.7%	1	56.3%
University level studies		15.1%	18.6%	14.6%	-	14.4%
Disposable income (1000 SEK), median		172	196	158	285	163
Immigrant[B]		13.4%	15.7%	13.3%	-	13.4%
Medical history						
CHA_2DS_2-VASc	mean	4.9±1.8	3.6±1.8	5.2±1.7	5.3±1.5	5.1±1.7
	median	5	3	5	6	5
HASBLED	mean	2.9±1.1	2.7±0.9	2.5±1.1	2.8±0.5	3.1±1.0
	median	3	3	2	3	3
Hospitalized with bleeding		18.7%	8.1%	26.2%	-	17.4%
Intracranial		4.0%	0.6%	5.8%	-	3.3%
Gastrointestinal		9.8%	4.7%	16.1%	-	10.1%
Urogenital		10.2%	5.8%	12.9%	-	10.1%
Other		7.0%	2.9%	9.2%	-	6.1%
Thromboembolic event		25.7%	18.0%	28.3%	-	27.7%
Ischaemic stroke		17.9%	14.5%	18.7%	-	19.0%
Unspecified stroke		6.1%	2.3%	7.4%	-	6.6%
Systemic embolism		2.4%	1.7%	3.4%	-	2.2%
TIA		9.1%	3.5%	11.2%	-	10.5%
Myocardial infarction >30 days before index		28.6%	22.7%	32.8%	1	34.5%
Peripheral artery disease		17.2%	11.1%	16.8%	2	15.0%
Heart failure		47.0%	26.7%	55.2%	3	47.3%
Mechanical heart valve		2.3%	-	2.3%	-	2.1%
Pacemaker/ICD		10.9%	9.9%	14.6%	1	12.9%
Hypertension		79.5%	69.8%	76.4%	4	78.4%
Diabetes		31.5%	34.9%	27.7%	2	30.9%
Cancer within 3 years		12.5%	5.8%	15.4%	-	11.4%
Anaemia		20.4%	10.5%	29.0%	-	20.5%
Chronic kidney disease		13.1%	3.5%	17.8%	-	12.3%
Liver disease		1.6%	1.7%	2.4%	-	1.5%
Dementia		3.3%	-	8.1%	-	5.5%
Frequent falls		10.5%	1.2%	15.1%	-	8.6%
Drugs dispensed within 4 months before up to one week after hospital discharge						
Beta blocker		72.1%	85.5%	61.9%	4	85.3%
Digoxin		9.2%	6.4%	9.8%	1	14.3%
Class 1 anti-arrhythmic		0.6%	-	0.4%	-	0.7%
Class 3 anti-arrhythmic		3.9%	16.3%	2.4%	-	4.1%
ACE-inhibitor		39.7%	40.1%	27.7%	2	47.6%
ARB		25.6%	29.1%	20.4%	1	27.0%
Diuretic		45.5%	43.0%	49.9%	4	57.6%
Statin		56.5%	80.2%	31.6%	3	67.0%
NSAID		6.1%	5.2%	4.9%	-	5.2%
Proton pump inhibitor		32.8%	34.9%	36.5%	1	42.2%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

10.2.3 Duration of treatment

The median duration of treatment with triple therapy (one oral anticoagulant and 2 or more antiplatelet agents) was approximately 3 months, irrespective of the choice of oral anticoagulant (Tables 4 and 5). The median duration of dual therapy (one oral anticoagulant and one antiplatelet agent) was also around 3 months for patients without PCI, but was around 6 months for patients who had undergone a PCI procedure and slightly longer if a stent was applied.

The over-representation of 110 days treatment duration in Tables 4 and 5 is due to the assessment method used. According to the protocol, "Exposure of a certain drug or a drug combination during follow up will be estimated as the number of days the dispensed drug supply would be expected to last if drug adherence was 90%, thus allowing for occasional dropped doses" (Study protocol, Section 9.3.2). A common packet size contains 100 tablets; with once daily dosing, one packet would last 100 days with perfect adherence. Therefore, allowing for 10% missed doses, a pack containing 100 tablets would last for 110 days. For drugs with twice daily dosing, a prescription for two 100 tablet packs would fulfil the same need. Due to Swedish prescription regulations, most prescriptions are made for drug use over 3 month periods, for which packet sizes of 100 tablets are well suited.

The diversity of treatment durations is largely due to random chance and the very low number of patients in some of the sub-groups. For example, the duration of 505 days for apixaban monotherapy among patients with PCI without stents is based on only 4 patients.

Table 4. Duration of treatment with the most frequently used antithrombotic drug combinations

Most common combinations over all		**asa+clop n=2,242**	**asa n=2,162**	**wa n=1,464**	**wa+asa+clop n=1,446**	**asa+tika n=1,355**	**wa+asa n=971**
Duration of treatment, days	mean	273±285	597±539	557±449	150±115	294±187	275±306
	median	150	399	405	110	311	156
	Q1-Q3	110-419	185-883	182-832	110-191	112-429	110-332
Most common combinations with warfarin		**warfarin n=1,464**	**wa+asa+clop n=1,446**	**wa+asa n=971**	**wa+clop n=706**	**wa+tika n=176**	**wa+asa+tika n=154**
Duration of treatment, days	mean	557±449	150±115	275±306	241±205	177±115	109±87
	median	405	110	156	182	119	96
	Q1-Q3	182-832	110-191	110-332	110-337	110-222	53-128
Most common combinations with dabigatran		**dabigatran n=64**	**dabi+asa+clop n=49**	**dabi+asa n=34**	**dabi+clop n=21**	**dabi+tika n=19**	**dabi+asa+tika n=9**
Duration of treatment, days	mean	572±444	149±119	238±280	231±145	207±202	90±85
	median	410	110	110	221	187	55
	Q1-Q3	220-847	100-142	58-305	110-332	98-221	38-111
Most common combinations with rivaroxaban		**rivaroxaban n=92**	**riva+asa+clop n=82**	**riva+asa n=58**	**riva+clop n=38**	**riva+tika n=18**	**riva+asa+tika n=12**
Duration of treatment, days	mean	446±349	139±91	157±168	266±154	173±78	156±126
	median	329	110	110	221	187	110
	Q1-Q3	156-653	108-189	70-198	111-340	110-225	91-196
Most common combinations with apixaban		**apixaban n=243**	**apixa+asa n=216**	**apixa+asa+clop n=167**	**apixa+clop n=100**	**apixa+tika n=47**	**apixa+asa+tika n=25**
Duration of treatment, days	mean	445±285	169±154	129±93	234±173	211±117	113±78
	median	395	111	110	186	217	110
	Q1-Q3	217-633	60-221	85-135	110-332	146-242	73-124

Table 5. Median duration of anticoagulant treatment regimens

	No PCI			PCI without stent			PCI with stent		
	OAC alone	OAC+ 1AP	OAC+ ≥2AP	OAC alone	OAC+ 1AP	OAC+ ≥2AP	OAC alone	OAC+ 1AP	OAC+ ≥2AP
Warfarin	402	118	110	597	149	110	403	221	110
Dabigatran	420	110	103	156	249	43	-	203	110
Rivaroxaban	329	111	110	-	190	69	-	228	110
Apixaban	395	113	109	505	191	114	408	221	110

10.2.4 Baseline characteristics

The most frequently used antithrombotic drug regimens after hospitalization for ACS were dual antiplatelet therapy with aspirin and clopidogrel and aspirin monotherapy (Table 6; Figure 2). Among ACS patients without PCI and a stent, these two regimens accounted for more than 52% of the drugs used. Among patients with PCI and stent implantation, only 54% (1,976/3,647) had a drug regimen that included an oral anticoagulant as recommended by both Swedish and International guidelines for patients with concomitant AF and ACS. This observation has been made repeatedly in the annual reports from the national SWEDEHEART registry. The use of oral anticoagulants in this patient group has increased over the years, but it remains low.

The combination of aspirin and clopidogrel has been standard treatment for ACS patients without AF for many years in Sweden. In the past it has been common in clinical practice to switch patients with AF from oral anticoagulation to antiplatelet therapy when they have an ACS episode, particularly if they had PCI and a stent. Concern regarding increased bleeding risk made doctors feel that they had to choose between stroke prevention and protection of the heart. Previously, many doctors prioritized the risk of recurrent myocardial infarction over stroke prevention. Today, knowledge about the relative magnitudes of risk for stent thrombosis and stroke has increased, together with increased realization that oral anticoagulants also are useful for prevention of myocardial infarctions.

The group who received aspirin monotherapy were the oldest (median, 86 years), rarely had a PCI procedure (96.5%) and had a very high stroke risk score according to CHA_2DS_2-VASc (mean score, 5.5). One in five of these patients had previously been hospitalized with a bleeding diagnosis (22.7%) and a similar proportion had a history of ischaemic stroke (20.8%). Many had experienced a myocardial infarction prior to the index ACS episode (38.0%) or had a prior diagnosis of heart failure (54.2%). Among the diagnoses that could constitute potential barriers to oral anticoagulant (OAC) use were dementia (11.7%) and repeated hospitalizations for falls (16.0%). Although elderly and with high comorbidity, the aspirin monotherapy group did not differ as much from other major treatment groups than would be expected; the mean CHA_2DS_2-VASc score was just as high (or higher) in patients receiving warfarin monotherapy and in the warfarin plus aspirin groups, as were the proportions of patients with a history of myocardial infarction or ischaemic stroke (Table 6).

Patients using a single antithrombotic drug, whether that was warfarin, a NOAC or an antiplatelet, were older than patients using combination therapies. Patients using three drugs were younger than those who used two drugs (Tables 7–12).

Monotherapies were mainly used in patients without PCI (warfarin, 97.4%; dabigatran, 98.4%; rivaroxaban, 100%; apixaban, 96,7%; antiplatelet monotherapy, 97.7%), while the most aggressive combinations consisting of an oral anticoagulant plus two or more

antiplatelet agents were predominantly used in PCI patients who received stent implantation (warfarin 63.1%, dabigatran 64.6%, rivaroxaban 68.7%, apixaban 60.8%). Patients who had undergone PCI were generally younger (74.2 vs. 81.8 years) than patients who had not undergone PCI. Subsequently, PCI patients had fewer comorbidities and also received more potent antithrombotic drug combinations with associated higher bleeding risks.

It should be noted that drug dispensing data does not allow for exact distinction between concomitant and sequential drug regimens when follow up is short and there are few dispensings. Some patients may therefore appear to be on combination treatment while they in reality may have discontinued one of the drugs. A patient who received a drug that would last three months may have stopped early. A patient who used a drug before the ACS episode may have stopped and switched to another drug at discharge. The only thing that can be known is whether he or she had a supply left of that drug at the beginning of the observation period. When that supply would have been exhausted (assuming 90% compliance) and there had not been a refill, that patient was censored from follow-up. However, that patient would be analysed as having been discharged with that particular drug combination. This is a methodological limitation inherent in studies using registry information without possibilities to directly ask patients about their medication.

A small number of patients discharged with NOAC therapy had previously received mechanical heart valves (dabigatran, 3; rivaroxaban, 1; apixaban, 7). Two events occurred among these patients during follow up. A 76 year old woman with very frequent hospitalizations died from ischaemic heart disease and heart failure while receiving apixaban monotherapy and an 85 year old man receiving apixaban plus aspirin was readmitted to hospital for ACS two weeks after discharge. No other complications were noted among these patients who had received NOACs despite current recommendations.

The Patiens register does not hold useful information about type of AF (paroxysmal, persistent or permanent). However, the time from the first recorded AF diagnosis in the patient register indicates that most patients using warfarin (median duration, 3.1 years) and antiplatelet regimens without OAC (median duration, 3.0 years) had permanent AF considering the progressive nature of the disease. In comparison, patients using a NOAC had a shorter history of AF (dabigatran, 11 months; rivaroxaban, 6 months; apixaban, 2 months) and a larger proportion of patients could be assumed to have paroxysmal AF.

A previous diagnosis of chronic kidney disease (CKD) was more common in patients treated with warfarin based therapies (11.8%) and antiplatelet based regimens (13.8%). The proportion with a CKD diagnosis among NOAC treated patients was 2.5% with dabigatran, 5.8% with rivaroxaban and 9.3% with apixaban.

Table 6. Baseline characteristics - the most frequently used regimens

		asa+clop n=2,242	asa n=2,162	wa n=1,464	wa+asa+clop n=1,446	asa+tika n=1,355	wa+asa n=971
Procedure	No PCI	74.1%	96.5%	97.3%	28.8%	38.8%	93.9%
	PCI without stent	1.9%	0.8%	1.0%	4.5%	3.2%	3.5%
	PCI with stent	24.0%	2.7%	1.7%	66.7%	58.0%	2.6%
Duration of AF,[A] years	mean	4.3±4.4	4.1±4.5	5.4±4.8	4.1±4.7	4.7±4.9	4.3±4.7
	median	3.0	2.6	4.2	2.5	3.2	2.6
Demography							
Female sex		43.9%	51.3%	47.8%	27.2%	32.0%	46.9%
Age, years	mean	81.5±9.5	84.0±9.4	81.4±8.2	75.4±8.2	74.3±11.0	80.4±8.8
	median	84	86	83	76	75	82
Living alone		62.3%	65.8%	58.3%	45.0%	50.8%	54.9%
University level studies		11.6%	10.6%	12.2%	17.7%	18.9%	11.8%
Disposable income (1000 SEK), median		155	151	159	183	179	160
Immigrant[B]		13.5%	12.9%	11.8%	12.9%	14.5%	13.3%
Medical history							
CHA_2DS_2-VASc	mean	5.2±1.7	5.5±1.6	5.6±1.6	4.7±1.6	4.1±1.8	5.5±1.6
	median	5	5	6	5	4	5
HASBLED	mean	3.3±1.0	3.4±1.0	2.5±0.9	3.1±0.9	2.9±1.0	3.3±0.9
	median	3	3	2	3	3	3
Hospitalized with bleeding		17.6%	22.8%	20.0%	11.7%	11.1%	15.9%
Intracranial		3.7%	5.0%	2.9%	1.6%	3.0%	2.1%
Gastrointestinal		10.1%	12.2%	10.9%	7.7%	5.7%	8.4%
Urogenital		9.2%	10.9%	11.9%	9.8%	8.6%	10.5%
Other		6.2%	7.3%	7.7%	4.1%	4.1%	6.4%
Thromboembolic event		25.9%	30.2%	34.2%	22.6%	13.4%	33.2%
Ischaemic stroke		17.4%	20.8%	25.3%	14.5%	7.5%	22.0%
Unspecified stroke		6.0%	8.7%	8.2%	4.6%	3.3%	7.3%
Systemic embolism		2.3%	2.4%	3.2%	1.8%	1.0%	2.7%
TIA		10.0%	10.1%	11.7%	9.3%	6.3%	13.4%
Myocardial infarction >30 days before index		40.1%	38.1%	35.7%	30.6%	27.4%	39.1%
Peripheral artery disease		16.0%	16.4%	16.3%	13.4%	10.3%	17.2%
Heart failure		46.8%	54.1%	60.9%	42.8%	28.0%	50.4%
Mechanical heart valve		1.6%	0.7%	3.4%	2.1%	0.7%	3.6%
Pacemaker/ICD		10.9%	12.0%	17.2%	13.2%	9.1%	16.6%
Hypertension		78.4%	77.2%	80.9%	79.3%	71.0%	83.2%
Diabetes		30.3%	29.0%	34.4%	32.5%	26.5%	32.4%
Cancer within 3 years		11.2%	12.8%	11.1%	8.6%	9.5%	10.7%
Anaemia		20.6%	30.2%	25.0%	10.7%	12.1%	18.5%
Chronic kidney disease		13.1%	15.8%	15.2%	7.8%	7.4%	12.9%
Liver disease		1.9%	1.9%	1.3%	1.0%	1.2%	1.2%
Dementia		8.0%	11.7%	4.3%	1.0%	3.3%	3.2%
Frequent falls		10.5%	16.0%	7.2%	2.8%	5.0%	6.8%
Drugs dispensed within 4 months before up to one week after hospital discharge							
Beta blocker		85.0%	77.4%	82.7%	90.7%	86.7%	89.5%
Digoxin		12.0%	12.9%	21.1%	16.2%	7.1%	18.5%
Class 1 anti-arrhythmic		0.5%	0.3%	0.8%	1.0%	1.0%	0.6%
Class 3 anti-arrhythmic		3.1%	2.6%	3.9%	6.0%	4.0%	4.8%
ACE-inhibitor		48.0%	37.8%	43.2%	56.7%	56.0%	48.3%
ARB		25.4%	19.8%	28.0%	34.4%	26.4%	30.4%
Diuretic		58.8%	64.3%	69.3%	51.2%	39.1%	64.8%
Statin		67.4%	41.1%	52.2%	89.8%	84.9%	67.0%
NSAID		6.5%	5.0%	1.6%	4.8%	8.9%	4.0%
Proton pump inhibitor		41.2%	43.7%	34.2%	48.7%	36.9%	43.3%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

Table 7. Baseline characteristics - combinations including warfarin

		Warfarin monotherapy (n=1,464)	Warfarin+ 1 antiplatelet (n=1.939)	Warfarin+ ≥2 antiplatelets (n=1,812)
Procedure	No PCI	97.3%	73.3%	32.7%
	PCI without stent	1.0%	3.7%	4.1%
	PCI with stent	1.7%	23.0%	63.1%
Duration of AF,[A] years	mean	5.4±4.8	4.6±4.8	4.2±4.7
	median	4.2	3.0	2.4
Demography				
Female sex		47.8%	40.1%	27.3%
Age, years	mean	81.4±8.2	79.0±8.9	75.4±8.4
	median	83	80	76
	Q1-Q3	77-87	73-86	70-82
Living alone		58.3%	52.2%	45.1%
University level studies		12.2%	14.8%	17.4%
Income (1000 SEK), median		159	168	181
Immigrant[B]		11.8%	13.2%	13.3%
Medical history				
CHA_2DS_2-VASc score	mean	5.6±1.6	5.2±1.6	4.7±1.7
	median	6	5	5
	Q1-Q3	5-7	4-6	4-6
HASBLED score	mean	2.5±0.9	3.2±0.9	3.1±0.9
	median	2	3	3
	Q1-Q3	2-3	3-4	3-4
Hospitalized with bleeding		20.0%	16.4%	12.3%
Intracranial		2.9%	2.3%	1.7%
Gastrointestinal		10.9%	9.3%	8.2%
Urogenital		11.9%	10.0%	9.8%
Other		7.7%	6.1%	4.5%
Thromboembolic event		34.2%	30.1%	23.8%
Ischaemic stroke		25.3%	20.0%	15.3%
Unspecified stroke		8.2%	6.1%	4.6%
Systemic embolism		3.2%	2.3%	1.9%
TIA		11.7%	12.2%	9.9%
Myocardial infarction >30 days before index		35.7%	35.1%	31.1%
Peripheral artery disease		16.3%	14.5%	14.3%
Heart failure		60.9%	49.9%	43.5%
Mechanical heart valve		3.4%	3.9%	3.2%
Pacemaker/ICD		17.2%	17.1%	12.9%
Hypertension		80.9%	80.8%	79.0%
Diabetes		34.4%	32.7%	32.2%
Cancer within 3 years		11.1%	10.8%	9.6%
Anaemia		25.0%	17.3%	11.9%
Chronic kidney disease		15.2%	12.3%	8.5%
Liver disease		1.3%	1.4%	1.2%
Dementia		4.3%	2.6%	1.0%
Frequent falls		7.2%	5.8%	3.0%
Drugs dispensed within 4 months before up to one week after hospital discharge				
Beta blocker		82.7%	88.6%	91.3%
Digoxin		21.2%	19.0%	16.5%
Class 1 anti-arrhythmic		0.8%	0.8%	1.2%
Class 3 anti-arrhythmic		3.9%	5.9%	5.9%
ACE-inhibitor		43.2%	50.7%	56.6%
ARB		28.0%	29.6%	32.3%
Diuretic		69.3%	62.2%	51.9%
Statin		52.2%	73.4%	89.5%
NSAID		1.6%	3.6%	4.6%
Proton pump inhibitor		34.2%	42.9%	48.0%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

Table 8. Baseline characteristics - combinations including dabigatran

		Dabigatran monotherapy (n=64)	Dabigatran+ 1 antiplatelet (n=74)	Dabigatran+ ≥2 antiplatelets (n=65)
Procedure	No PCI	98.4%	60.8%	30.8%
	PCI without stent	1.6%	2.7%	4.6%
	PCI with stent	-	36.5%	64.6%
Duration of AF,[A] years	mean	3.5±4.7	3.3±4.4	3.4±5.1
	median	1.3	0.8	0.7
Demography				
Female sex		60.9%	44.6%	27.7%
Age, years	mean	78.6±9.9	76.3±9.4	73.2±8.8
	median	81	78	74
	Q1-Q3	70-86	69-83	68-80
Living alone		51.6%	48.7%	36.9%
University level studies		25.0%	21.6%	23.1%
Income (1000 SEK), median		174	166	192
Immigrant[B]		17.2%	10.8%	20.0%
Medical history				
CHA_2DS_2-VASc score	mean	5.0±1.7	4.7±1.8	4.4±1.6
	median	5	4	4
	Q1-Q3	4-6	3-6	3-6
HASBLED score	mean	2.3±1.1	2.9±0.9	3.0±0.8
	median	2	3	3
	Q1-Q3	2-3	2-3	3-3
Hospitalized with bleeding		18.8%	13.5%	12.3%
Intracranial		1.6%	1.4%	1.5%
Gastrointestinal		14.1%	6.8%	12.3%
Urogenital		7.8%	13.5%	10.8%
Other		7.8%	4.1%	4.6%
Thromboembolic event		28.1%	18.9%	27.7%
Ischaemic stroke		17.2%	12.2%	18.5%
Unspecified stroke		7.8%	5.4%	6.2%
Systemic embolism		7.8%	2.7%	1.5%
TIA		1.6%	6.8%	15.4%
Myocardial infarction >30 days before index		23.4%	21.6%	29.2%
Peripheral artery disease		9.4%	8.1%	20.0%
Heart failure		29.7%	40.5%	33.9%
Mechanical heart valve		1.6%	1.4%	1.5%
Pacemaker/ICD		9.4%	8.1%	6.2%
Hypertension		81.3%	67.6%	76.9%
Diabetes		18.8%	31.1%	26.2%
Cancer within 3 years		6.3%	10.8%	13.9%
Anaemia		18.8%	13.5%	9.2%
Chronic kidney disease		4.7%	1.4%	1.5%
Liver disease		-	2.7%	-
Dementia		7.8%	2.7%	3.1%
Frequent falls		9.4%	2.7%	3.1%
Drugs dispensed within 4 months before up to one week after hospital discharge				
Beta blocker		81.3%	89.2%	83.1%
Digoxin		20.3%	28.4%	9.2%
Class 1 anti-arrhythmic		-	1.4%	1.5%
Class 3 anti-arrhythmic		6.3%	2.7%	9.2%
ACE-inhibitor		29.7%	54.1%	47.7%
ARB		28.1%	27.0%	38.5%
Diuretic		45.3%	50.0%	38.5%
Statin		56.3%	83.8%	90.8%
NSAID		9.4%	9.5%	6.2%
Proton pump inhibitor		31.3%	43.2%	43.1%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

Table 9. Baseline characteristics - combinations including rivaroxaban

		Rivaroxaban monotherapy (n=92)	Rivaroxaban+ 1 antiplatelet (n=117)	Rivaroxaban+ ≥2 antiplatelets (n=99)
Procedure	No PCI	100%	75.2%	29.3%
	PCI without stent	-	5.1%	2.0%
	PCI with stent	-	19.7%	68.7%
Duration of AF,[A] years	mean	2.7±3.6	2.7±4.0	3.1±4.8
	median	0.7	0.5	0.2
Demography				
Female sex		52.2%	40.2%	34.3%
Age, years	mean	80.5±9.1	77.8±9.0	74.0±7.3
	median	83	80	74
	Q1-Q3	77-87	73-84	69-79
Living alone		70.7%	51.3%	40.4%
University level studies		19.6%	19.7%	15.2%
Income (1000 SEK), median		162	174	175
Immigrant[B]		19.6%	19.7%	15.2%
Medical history				
CHA_2DS_2-VASc score	mean	5.1±1.7	5.0±1.7	4.6±1.8
	median	5	5	5
	Q1-Q3	4-6	4-6	3-6
HASBLED score	mean	2.2±0.8	3.1±0.8	3.0±0.8
	median	3	3	3
	Q1-Q3	3-4	3-4	3-3
Hospitalized with bleeding		21.7%	11.1%	11.1%
Intracranial		2.2%	4.3%	2.0%
Gastrointestinal		12.0%	4.3%	5.1%
Urogenital		12.0%	8.6%	10.1%
Other		9.8%	1.7%	4.0%
Thromboembolic event		23.9%	24.8%	21.2%
Ischaemic stroke		16.3%	19.7%	12.1%
Unspecified stroke		1.1%	6.0%	3.0%
Systemic embolism		2.2%	2.6%	1.0%
TIA		8.7%	6.8%	9.1%
Myocardial infarction >30 days before index		29.4%	29.1%	29.3%
Peripheral artery disease		8.7%	13.7%	11.1%
Heart failure		52.2%	35.9%	42.4%
Mechanical heart valve		1.1%	-	1.0%
Pacemaker/ICD		17.4%	8.6%	15.2%
Hypertension		75.0%	80.3%	79.8%
Diabetes		19.6%	39.3%	33.3%
Cancer within 3 years		14.1%	11.1%	12.1%
Anaemia		29.4%	9.4%	11.1%
Chronic kidney disease		5.4%	5.1%	7.1%
Liver disease		2.2%	1.7%	1.0%
Dementia		7.6%	4.3%	3.0%
Frequent falls		8.7%	6.8%	3.0%
Drugs dispensed within 4 months before up to one week after hospital discharge				
Beta blocker		90.2%	90.6%	91.9%
Digoxin		10.9%	14.5%	14.1%
Class 1 anti-arrhythmic		-	0.9%	-
Class 3 anti-arrhythmic		2.2%	6.0%	5.1%
ACE-inhibitor		32.6%	46.2%	57.6%
ARB		30.4%	35.9%	28.3%
Diuretic		58.7%	50.4%	48.5%
Statin		42.4%	76.1%	87.9%
NSAID		1.1%	3.4%	7.1%
Proton pump inhibitor		39.1%	39.3%	56.6%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

Table 10. Baseline characteristics - combinations including apixaban

		Apixaban monotherapy (n=243)	Apixaban+ 1 antiplatelet (n=369)	Apixaban+ ≥2 antiplatelets (n=209)
Procedure	No PCI	96.7%	77.2%	35.4%
	PCI without stent	1.7%	3.8%	3.8%
	PCI with stent	1.7%	19.0%	60.8%
Duration of AF,[A] years	mean	2.8±4.7	2.3±3.8	2.8±4.3
	median	0.4	0.1	0.1
Demography				
Female sex		54.7%	46.1%	32.5%
Age, years	mean	80.7±10.4	79±4	77.1±8.9
	median	83	81	78
	Q1-Q3	75-89	73-87	71-84
Living alone		63.0%	55.0%	53.6%
University level studies		14.8%	16.5%	25.8%
Income (1000 SEK), median		163	166	174
Immigrant[B]		13.2%	11.1%	14.8%
Medical history				
CHA_2DS_2-VASc score	mean	5.1±1.6	5.0±1.7	4.8±1.8
	median	5	5	5
	Q1-Q3	4-6	4-6	3-6
HASBLED score	mean	2.3±1.0	3.2±0.8	3.1±0.8
	median	2	3	3
	Q1-Q3	2-3	3-4	3-4
Hospitalized with bleeding		18.1%	17.1%	12.0%
Intracranial		4.1%	4.9%	1.4%
Gastrointestinal		11.1%	9.2%	9.6%
Urogenital		9.1%	7.9%	9.6%
Other		5.8%	6.5%	3.8%
Thromboembolic event		26.3%	26.6%	23.0%
Ischaemic stroke		18.5%	18.7%	15.3%
Unspecified stroke		4.9%	7.1%	6.2%
Systemic embolism		1.7%	1.6%	0.5%
TIA		9.1%	8.4%	10.1%
Myocardial infarction >30 days before index		23.9%	24.1%	29.2%
Peripheral artery disease		9.9%	14.4%	12.4%
Heart failure		42.8%	36.9%	37.8%
Mechanical heart valve		1.2%	0.5%	1.0%
Pacemaker/ICD		13.6%	11.9%	9.1%
Hypertension		79.8%	78.1%	79.4%
Diabetes		23.5%	25.8%	30.1%
Cancer within 3 years		9.9%	8.1%	10.1%
Anaemia		25.5%	17.6%	12.9%
Chronic kidney disease		8.2%	10.6%	8.1%
Liver disease		2.1%	0.8%	1.4%
Dementia		3.7%	4.9%	1.9%
Frequent falls		10.3%	8.1%	7.2%
Drugs dispensed within 4 months before up to one week after hospital discharge				
Beta blocker		87.2%	87.8%	93.8%
Digoxin		14.8%	10.3%	11.5%
Class 1 anti-arrhythmic		0.8%	1.1%	0.5%
Class 3 anti-arrhythmic		5.8%	3.3%	3.4%
ACE-inhibitor		35.0%	47.4%	56.9%
ARB		29.2%	29.3%	31.6%
Diuretic		52-3%	52.6%	53.1%
Statin		50.6%	71.3%	90.9%
NSAID		5.8%	7.3%	7.7%
Proton pump inhibitor		37.0%	39.8%	54.6%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

Table 11. Baseline characteristics - combinations including any NOAC

		NOAC monotherapy (n=399)	NOAC+ 1 antiplatelet (n=560)	NOAC+ ≥2 antiplatelets (n=373)
Procedure	No PCI	97.7%	74.6%	33.0%
	PCI without stent	1.3%	3.9%	3.5%
	PCI with stent	1.0%	21.4%	63.5%
Duration of AF,[A] years	mean	2.9±4.4	2.5±3.9	3.0±4.6
	median	0.6	0.2	0.2
Demography				
Female sex		55.1%	44.6%	32.2%
Age, years	mean	80.3±10.0	78.7±9.5	75.6±8.7
	median	83	80	76
	Q1-Q3	75-87	73-86	70-82
Living alone		62.9%	53.4%	47.2%
University level studies		17.5%	17.9%	22.5%
Income (1000 SEK), median		164	169	177
Immigrant[B]		15.3%	12.9%	15.8%
Medical history				
CHA2DS2-VASc score	mean	5.1±1.6	4.9±1.7	4.7±1.8
	median	5	5	5
	Q1-Q3	4-6	4-6	3-6
HASBLED score	mean	2.3±1.0	3.2±1.0	3.1±0.8
	median	2	3	3
	Q1-Q3	2-3	3-4	3-4
Hospitalized with bleeding		19.1%	15.4%	11.8%
Intracranial		3.3%	4.3%	1.6%
Gastrointestinal		11.8%	7.9%	8.9%
Urogenital		9.5%	8.8%	9.9%
Other		7.0%	5.2%	4.0%
Thromboembolic event		26.1%	25.2%	23.3%
Ischaemic stroke		17.8%	18.0%	15.0%
Unspecified stroke		4.5%	6.6%	5.4%
Systemic embolism		2.8%	2.0%	0.8%
TIA		7.8%	7.9%	10.7%
Myocardial infarction >30 days before index		25.1%	24.8%	29.2%
Peripheral artery disease		9.5%	13.4%	13.4%
Heart failure		42.9%	37.1%	38.3%
Mechanical heart valve		1.0%	0.5%	1.1%
Pacemaker/ICD		13.8%	10.7%	10.2%
Hypertension		79.0%	77.1%	79.1%
Diabetes		21.8%	29.3%	30.3%
Cancer within 3 years		10.3%	9.1%	11.3%
Anaemia		25.3%	15.4%	11.8%
Chronic kidney disease		7.0%	8.2%	6.7%
Liver disease		1.8%	1.3%	1.1%
Dementia		5.3%	4.5%	2.4%
Frequent falls		9.8%	7.1%	5.4%
Drugs dispensed within 4 months before up to one week after hospital discharge				
Beta blocker		87.0%	88.6%	91.4%
Digoxin		14.8%	13.6%	11.8%
Class 1 anti-arrhythmic		0.5%	1.1%	0.5%
Class 3 anti-arrhythmic		5.0%	3.8%	4.8%
ACE-inhibitor		33.6%	48.0%	55.5%
ARB		29.3%	30.4%	31.9%
Diuretic		52.6%	51.8%	49.3%
Statin		49.6%	73.9%	90.1%
NSAID		5.3%	6.8%	7.2%
Proton pump inhibitor		36.6%	40.2%	53.1%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

Table 12. Baseline characteristics - combinations with antiplatelets only

		One antiplatelet (n=2,770)	Two antiplatelets (n=3,805)	Three antiplatelets (n=181)
Procedure	No PCI	91.7%	62.2%	65.2%
	PCI without stent	0.8%	2.4%	5.0%
	PCI with stent	7.5%	35.4%	29.8%
Duration of AF,[A]	mean	4.3±4.6	4.4±4.6	4.3±4.4
years	median	2.8	3.1	3.3
Demography				
Female sex		49.4%	39.7%	32.6%
Age, years	mean	83.3±9.5	78.8±10.7	77.6±9.2
	median	85	81	78
	Q1-Q3	78-90	72-87	71-85
Living alone		64.8%	58.0%	46.4%
University level studies		11.5%	14.1%	16.0%
Income (1000 SEK), median		152	161	171
Immigrant[B]		13.4%	13.8%	10.5%
Medical history				
CHA_2DS_2-VASc score	mean	5.5±1.6	4.8±1.8	5.6±1.7
	median	5	5	6
	Q1-Q3	4-7	4-6	5-7
HASBLED score	mean	3.4±1.0	3.1±1.0	3.6±0.9
	median	3	3	3
	Q1-Q3	3-4	3-4	3-4
Hospitalized with bleeding		22.7%	16.2%	16.6%
Intracranial		4.7%	3.6%	5.0%
Gastrointestinal		13.3%	9.1%	12.2%
Urogenital		10.7%	9.3%	11.1%
Other		7.3%	5.7%	3.9%
Thromboembolic event		31.7%	22.8%	50.3%
Ischaemic stroke		22.6%	14.9%	36.5%
Unspecified stroke		9.0%	5.3%	15.5%
Systemic embolism		2.4%	2.0%	2.2%
TIA		10.6%	9.3%	22.7%
Myocardial infarction >30 days before index		38.0%	35.4%	40.9%
Peripheral artery disease		17.0%	14.2%	21.0%
Heart failure		53.4%	40.7%	46.4%
Mechanical heart valve		1.2%	1.4%	2.2%
Pacemaker/ICD		12.2%	10.3%	9.4%
Hypertension		78.3%	75.6%	86.2%
Diabetes		30.7%	29.1%	42.0%
Cancer within 3 years		13.5%	11.2%	21.0%
Anaemia		30.3%	18.4%	23.2%
Chronic kidney disease		16.6%	11.4%	21.0%
Liver disease		1.8%	1.7%	2.2%
Dementia		10.5%	6.2%	5.5%
Frequent falls		15.1%	8.8%	7.2%
Drugs dispensed within 4 months before up to one week after hospital discharge				
Beta blocker		77.5%	85.8%	90.6%
Digoxin		12.5%	10.2%	6.1%
Class 1 anti-arrhythmic		0.4%	0.7%	1.1%
Class 3 anti-arrhythmic		2.7%	3.4%	2.2%
ACE-inhibitor		38.8%	50.3%	51.4%
ARB		21.1%	25.6%	31.5%
Diuretic		62.2%	52.2%	63.5%
Statin		44.8%	73.0%	76.8%
NSAID		5.1%	7.3%	6.6%
Proton pump inhibitor		44.2%	40.2%	47.5%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

Table 13. Baseline characteristics - combinations including any oral anticoagulant (warfarin or NOAC) with or without addition of antiplatelet drugs.

		OAC monotherapy (n=1,863)	OAC+ 1 antiplatelet (n=2,499)	OAC+ ≥2 antiplatelets (n=2,185)
Procedure	No PCI	97.4%	73.6%	32.8%
	PCI	2.6%	26.4%	67.2%
Duration of AF,[A] years	mean	4.8±4.8	4.1±4.7	3.9±4.7
	median	3.4	2.2	2.0
Demography				
Female sex		49.4%	41.1%	28.1%
Age, years	mean	81.2±8.7	78.9±9.0	75.4±8.5
	median	83	80	76
	Q1-Q3	77-87	73-86	70-82
Living alone		59.3%	52.5%	45.5%
University level studies		13.3%	15.5%	18.3%
Income (1000 SEK), median		160	168	181
Immigrant[B]		12.6%	13.1%	13.7%
Medical history				
CHA_2DS_2-VASc score	mean	5.5±1.6	5.2±1.7	4.7±1.7
	median	5	5	5
	Q1-Q3	4-7	4-6	4-6
HASBLED score	mean	2.4±1.0	3.2±0.9	3.1±0.9
	median	2	3	3
	Q1-Q3	2-3	3-4	3-4
Hospitalized with bleeding		19.7%	16.1%	12.2%
Intracranial		3.0%	2.8%	1.7%
Gastrointestinal		11.1%	9.0%	8.3%
Urogenital		11.4%	9.7%	9.8%
Other		7.6%	5.9%	4.4%
Thromboembolic event		32.5%	29.0%	23.7%
Ischaemic stroke		23.7%	19.6%	15.2%
Unspecified stroke		7.4%	6.2%	4.8%
Systemic embolism		3.1%	2.2%	1.7%
TIA		10.8%	11.2%	10.1%
Myocardial infarction >30 days before index		33.4%	32.8%	30.8%
Peripheral artery disease		14.8%	14.3%	14.1%
Heart failure		57.0%	47.0%	42.6%
Mechanical heart valve		2.8%	3.1%	2.8%
Pacemaker/ICD		16.5%	15.7%	12.5%
Hypertension		80.5%	80.0%	79.0%
Diabetes		31.7%	31.9%	31.9%
Cancer within 3 years		10.9%	10.4%	9.8%
Anaemia		25.1%	16.9%	11.9%
Chronic kidney disease		13.4%	11.4%	8.2%
Liver disease		1.4%	1.4%	1.1%
Dementia		4.5%	3.0%	1.2%
Frequent falls		7.8%	6.1%	3.4%
Drugs dispensed within 4 months before up to one week after hospital discharge				
Beta blocker		83.6%	88.6%	91.4%
Digoxin		19.8%	17.8%	15.7%
Class 1 anti-arrhythmic		0.7%	0.8%	1.1%
Class 3 anti-arrhythmic		4.1%	5.4%	5.7%
ACE-inhibitor		41.1%	50.1%	56.4%
ARB		28.3%	29.7%	32.3%
Diuretic		65.7%	59.8%	51.5%
Statin		51.6%	73.5%	89.6%
NSAID		2.4%	4.3%	5.1%
Proton pump inhibitor		34.7%	42.3%	48.8%

[A]Time since first recorded diagnosis of AF in the Patient register. [B]Born abroad.

10.3 Outcome data

Hospitalization for major/fatal bleeding occurred at an overall rate of 7.3 per 100 years at risk; rehospitalization for a new ACS episode (18.1 per 100 years at risk); ischaemic stroke or systemic embolism (4.1 per 100 years at risk) and death from any cause (19.4 per 100 years at risk). These are overall rates, irrespective of treatment received. Outcomes related to received treatments are found on the following pages.

It is not meaningful to compare the bleeding rates in this study with those in adjudicated studies like the ROCKET trial where "major and non-major clinically relevant bleedings" occurred at rates of 14.9 and 14.5% annually in the rivaroxaban and warfarin cohort, respectively, and "major bleedings" at 3.1% for both rivaroxaban and warfarin. The Swedish registries are not suited for detection of so-called “non-major clinically relevant bleedings”.

The same definitions of bleeding events cannot be used in registry studies and in prospective interventional trials. An important difference is that in clinical trials patients are actively asked if there were any bleeding complications, while registry studies have to rely on recorded diagnoses of bleeding events.

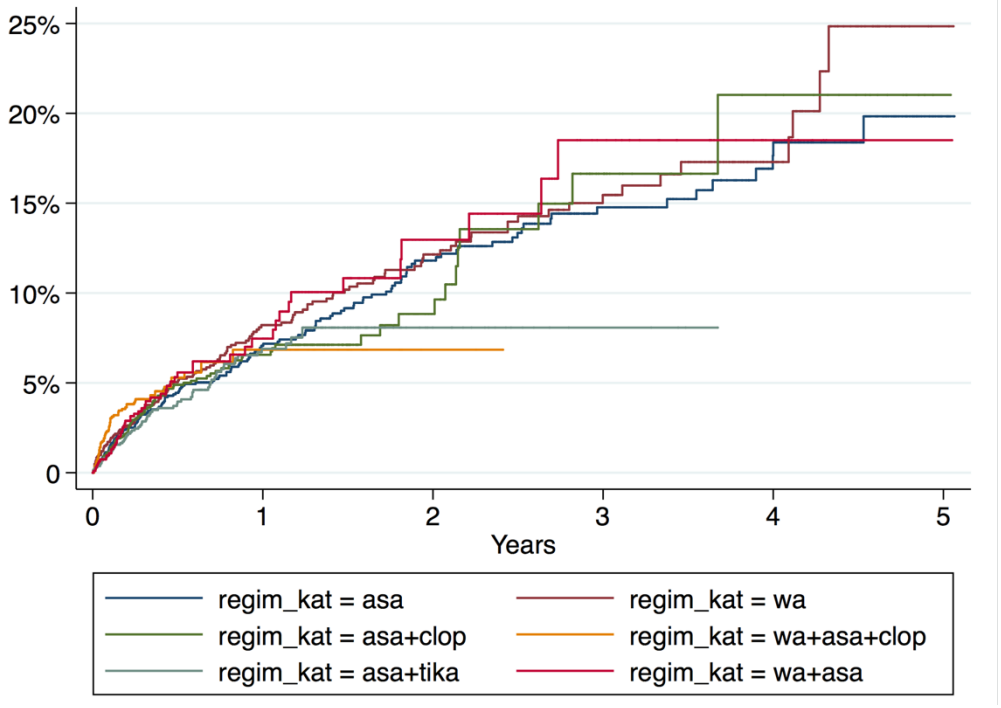
In a previous validation study of bleeding events in the Swedish registries it was found that bleeding diagnoses that were associated with an overnight hospital stay carried acceptable positive and negative predictive values as to be useful for research purposes. In contrast, diagnoses made in open care were often related to follow up for previous bleeds that were no longer active, therefore these diagnoses were less reliable. The bleeding rates among AF patients on rivaroxaban or warfarin in the recent interim Rivaroxaban PASS report was about 3.0–3.5% based on data from the same registers and using a similar study protocol. In the present study on ACS patients, bleeding rates were about twice as high. Thus it is clear that AF patients with ACS constitute a high-risk subpopulation.

Although the number of patients with events are quite large (bleedings, 717; new ACS, 1,616; stroke/systemic embolism, 410; all-cause mortality, 1,964), the large number of drug combinations and interventions makes most sub-groups too small to make comparisons statically significant. Analysing the outcomes for all 94 drug combinations observed at baseline is not feasible. Therefore only the most frequently used combinations, and each of the oral anticoagulants in monotherapy, with the addition of one or two or more antiplatelets are shown in the tables below. Likewise, patients have been analysed according to intervention group and in total.

There is ample room for confounding by indication, i.e. the prescribing doctors decide which treatment should be given based on information about patient risk, of which not all is accessible second-hand from diagnostic codes and other registry information. More aggressive regimens may for instance be better at preventing relapse of ACS and stroke; however, if these regimens are predominantly only used for patients whom the prescribing doctors believe to be at a higher risk of such events compared with other patients, the outcome for that combination may appear to be inefficient or even worse than milder alternatives given to patients at lower risk.

10.3.1 Main bleeding endpoint

(A



(B)

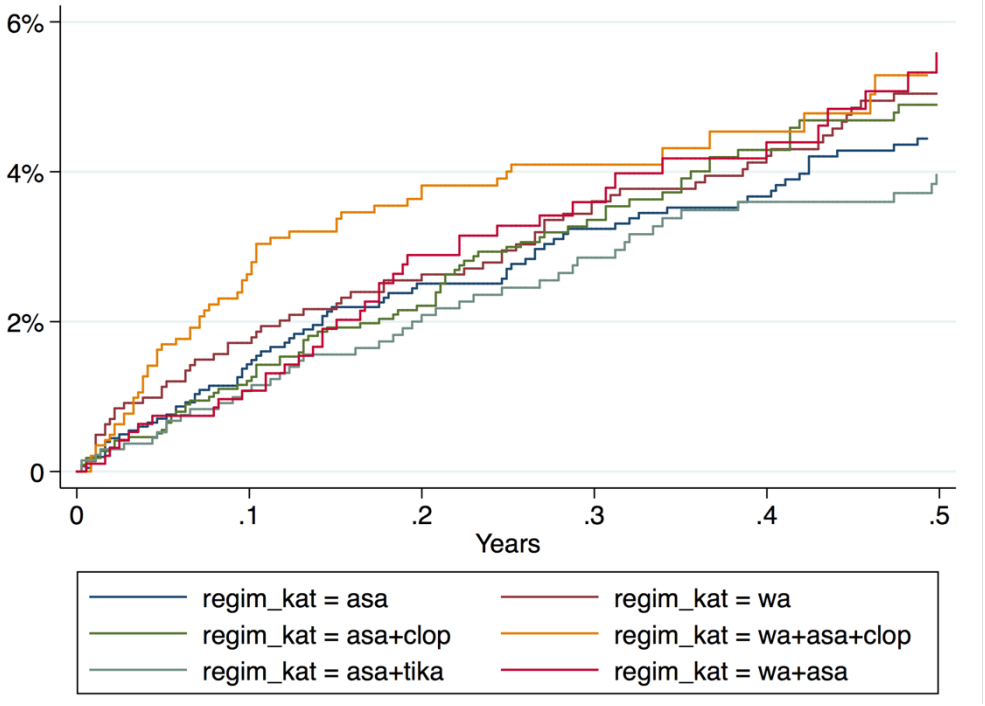


Figure 3. (A) Main bleeding endpoint for the most commonly used treatment regimens (B) Main bleeding endpoint for the most commonly used treatment regimens during the first 6 months.

Table 14. Main bleeding endpoint - the most common antithrombotic drug combinations

	All events=577		No PCI events=449		PCI without stent events=14		PCI with stent events=106	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
asa n=2,162 events=150	6.1 (5.2-7.2)	reference[A]	6.3 (5.3-7.4)	reference[A]	0	*reference[B]*	3.7 (1.2-11.3)	reference[A]
asa+clop n=2,242 events=103	7.3 (6.0-8.9)	1.13 (0.87-1.46)	8.3 (6.6-10.4)	1.12 (0.84-1.49)	7.1 (2.3-22.1)	-	5.4 (3.7-8.1)	1.25 (0.37-4.29)
asa+tika n=1,355 events=67	6.9 (5.4-8.8)	1.42 (1.04-1.94)	10.7 (7.5-15.2)	1.77 (1.19-2.65)	15.5 (6.4-37.1)	-	4.8 (3.4-6.8)	1.22 (0.35-4.20)
warfarin n=1,464 events=133	6.7 (5.7-8.0)	1.27 (1.00-1.61)	6.7 (5.6-8.0)	1.23 (0.96-1.57)	4.3 (0.6-30.3)	-	10.3 (3.9-27.4)	2.33 (0.51-10.64)
wa+asa n=971 events=55	8.4 (6.5-11.0)	1.49 (1.08 -2.04)	8.3 (6.3-10.9)	1.42 (1.02-1.99)	10.7 (6.4-37.1)	-	9.1 (2.3-36.5)	2.21 (0.36-4.20)
wa+asa+clop n=1,446 events=61	11.4 (8.9-14.7)	1.86 (1.34-2.59)	14.6 (9.2-23.2)	1.95 (1.18-3.25)	9.2 (2.3-36.7)	-	10.6 (7.8-14.3)	1.83 (0.54-6.26)

[A]Multivariable adjustment for age (continuous), sex, duration of AF, previous hospitalization with bleeding diagnosis, anaemia, chronic kidney disease, diabetes, alcohol index, baseline use of NSAID or PPI.

[B]13 patients had aspirin monotherapy after a PCI without a stent and none experienced a bleeding event. Since aspirin was the chosen comparator, it was not possible to calculate hazard ratios for this subcohort.

Baseline characteristics for these patients are presented in Table 6

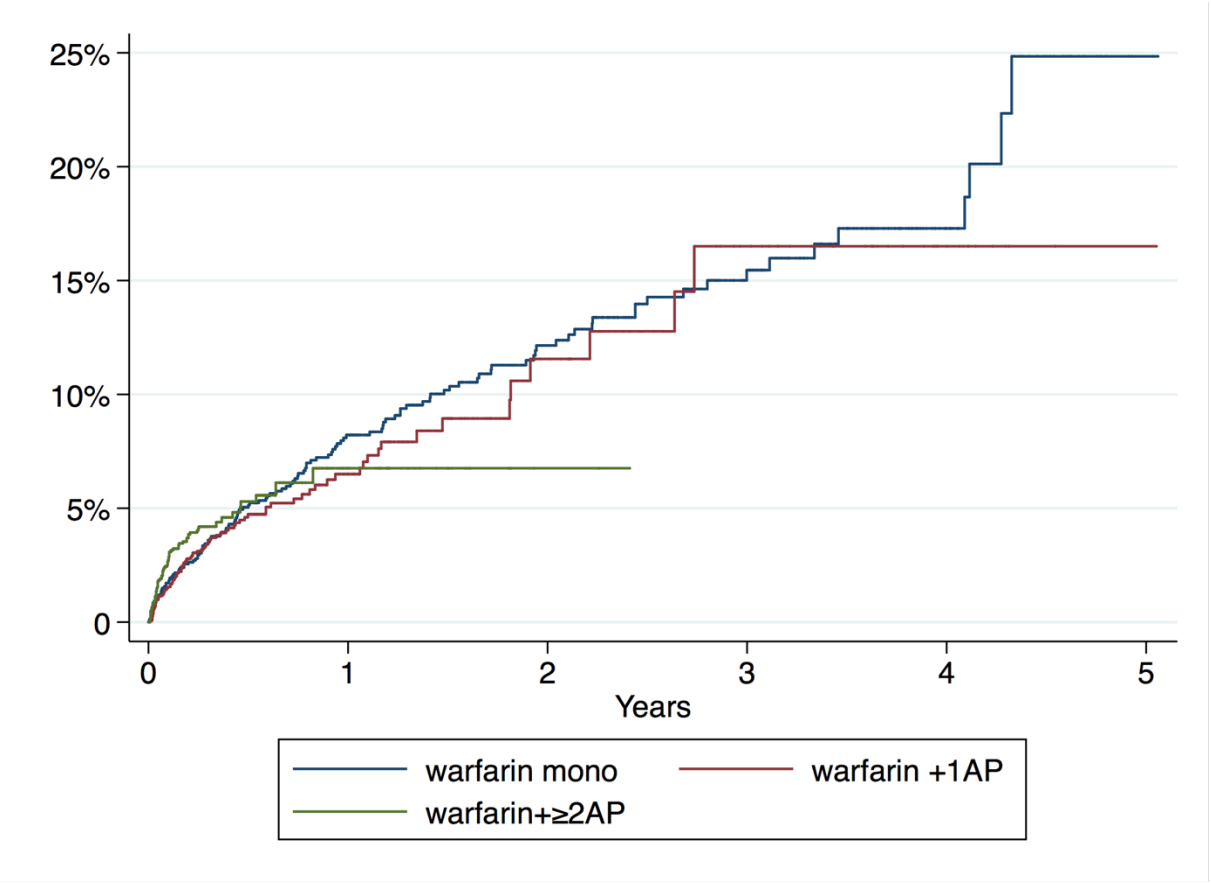


Figure 4. Main bleeding endpoint with combinations including warfarin

Table 15. Main bleeding endpoint - combinations including warfarin

	All (events=295)		No PCI (events=216)		PCI without stent (events=9)		PCI with stent (events=70)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
wa alone n=1,464 events=133	6.7 (5.7-8.0)	reference[A]	6.7 (5.6-8.0)	reference[A]	4.3 (0.6-30.3)	*reference[B]*	10.3 (3.9-27.4)	*reference[C]*
wa+1AP n=1,939 events=91	7.8 (6.4-9.6)	1.07 (0.81-1.42)	8.1 (6.4-10.3)	1.08 (0.79-1.49)	11.7 (5.2-25.9)	*2.77 (0.32-24.24)*	6.3 (4.0-10.0)	*0.45 (0.15-1.39)*
wa+≥2AP n=1,812 events=71	12.0 (9.5-15.1)	1.53 (1.09-2.14)	14.7 (9.7-22.3)	1.56 (0.96-2.54)	8.7 (2.2-34.9)	*1.33 (0.11-16.51)*	11.2 (8.4-14.9)	*0.65 (0.22-1.93)*

[A]Multivariable adjustment for age, sex, duration of AF, previous hospitalization with bleeding diagnosis, anaemia, chronic kidney disease, diabetes, alcohol index, baseline use of NSAID or PPI.

[B]Adjustment only for age due to the low number of endpoint events.

[C]Multivariable analysis with reduced set of covariates due to low number of events. Adjustment for age, sex, previous hospitalization with bleeding diagnosis, anaemia, chronic kidney disease, diabetes and baseline use of NSAID.

Baseline characteristics for these patients are presented in Table 7.

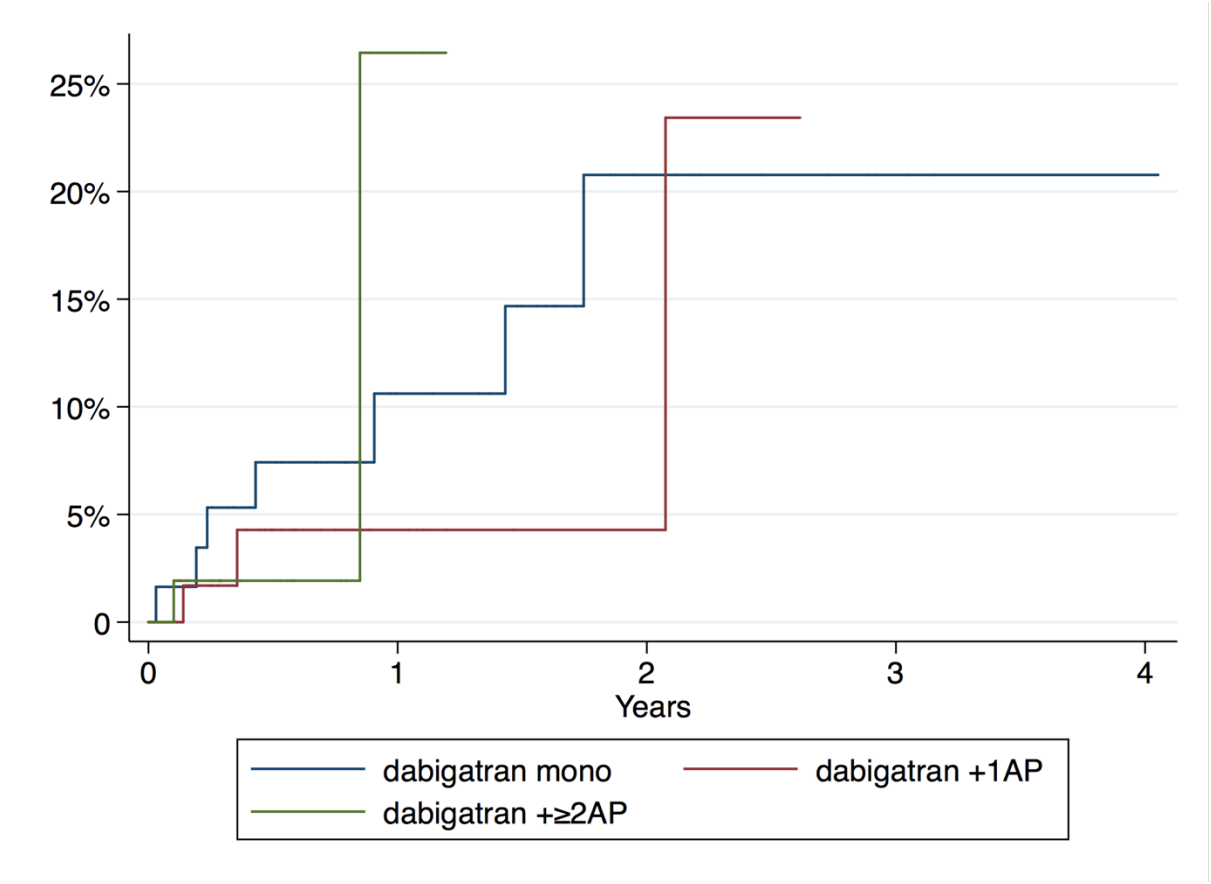


Figure 5. Main bleeding endpoint with combinations including dabigatran

Table 16. Main bleeding endpoint - combinations including dabigatran

	All (events=12)		No PCI (events=12)		PCI without stent (no events)		PCI with stent (no events)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
dabi alone n=64 events=7	10.0 (4.8-21.1)	*reference*[A]	10.0 (4.8-21.1)	*reference*[A]	0-	*reference*[B]	0	*reference*[B]
dabi+1AP n=74 events=3	7.3 (2.3-22.5)	*0.74 (0.18-3.12)*	11.7 (3.8-36.3)	*1.14 (0.28-4.69)*	0	-	0	-
dabi+≥2AP n=65 events=2	9.9 (2.5-39.5)	*1.05 (0.18-6.27)*	37.6 (9.4-150.2)	*3.55 (0.63-19.91)*	0	-	0	-

[A]Due to the low number of events adjustment was only made for age
[B]No events. Multivariable adjustments not possible
Baseline characteristics for these patients are presented in Table 8

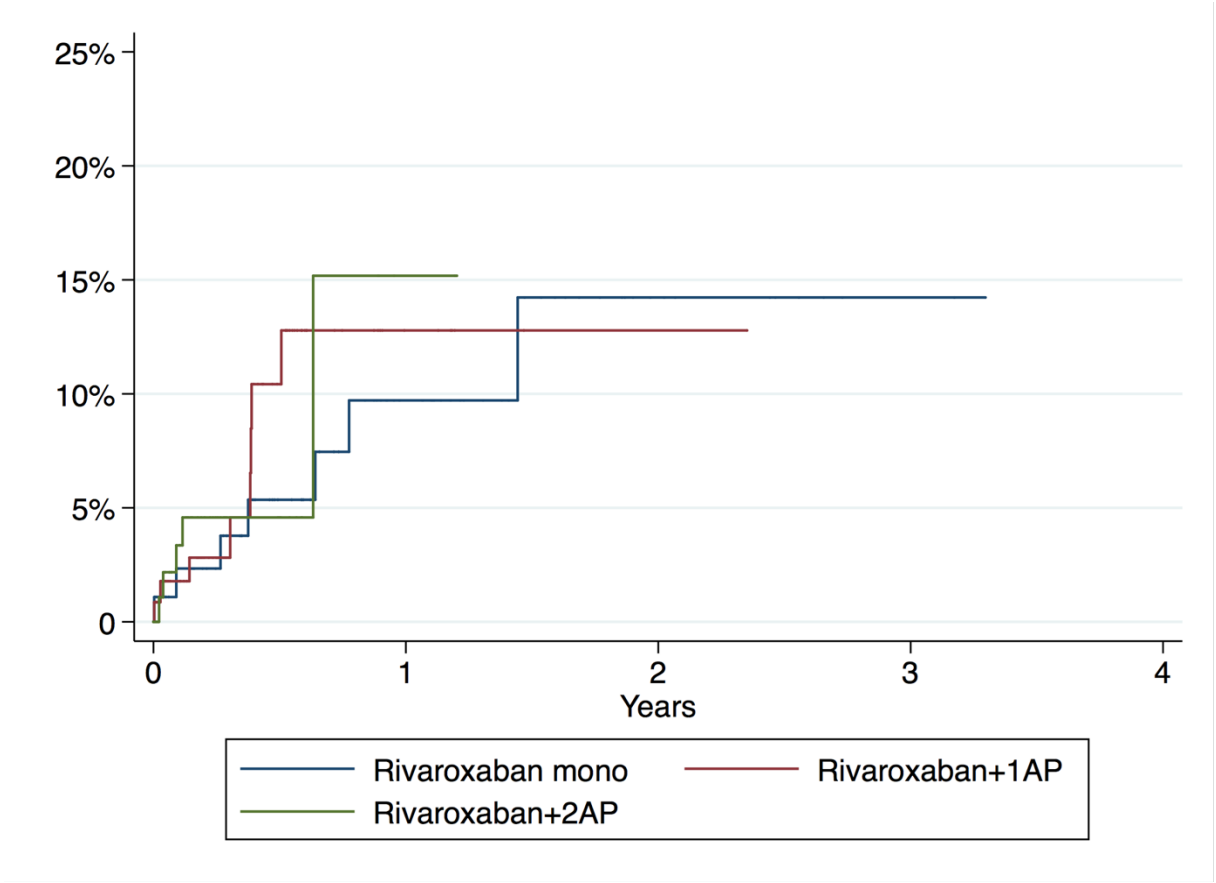


Figure 6. Main bleeding endpoint with combinations including rivaroxaban

Table 17. Main bleeding endpoint with combinations including rivaroxaban

	All (events=20)		No PCI (events=12)		PCI without stent (events=2)		PCI with stent (events=6)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
riva alone n=92 events=7	8.9 (4.2-18.6)	*reference*[A]	8.9 (4.2-18.6)	*reference*[B]	0	*reference*[C]	0	*reference*[C]
riva+1AP n=117 events=8	16.3 (8.2-32.6)	*1.76 (0.59-5.21)*	9.2 (3.0-28.5)	*1.10 (0.26-4.65)*	86.6 (21.6-346.1)	-	21.4 (6.9-66.3)	-
riva+≥2AP n=99 events=5	15.4 (6.4-36.9)	*2.07 (0.56-7.61)*	21.9 (5.5-87.6)	*3.53 (0.62-20.16)*	0	-	13.0 (4.2-40.3)	-

[A]Adjustment only for age and previous bleed due to the low number of endpoint events.
[B]Adjustment only for age due to the low number of endpoint events.
[C]Multivariable adjustments not possible.
Baseline characteristics for these patients are presented in Table 9.

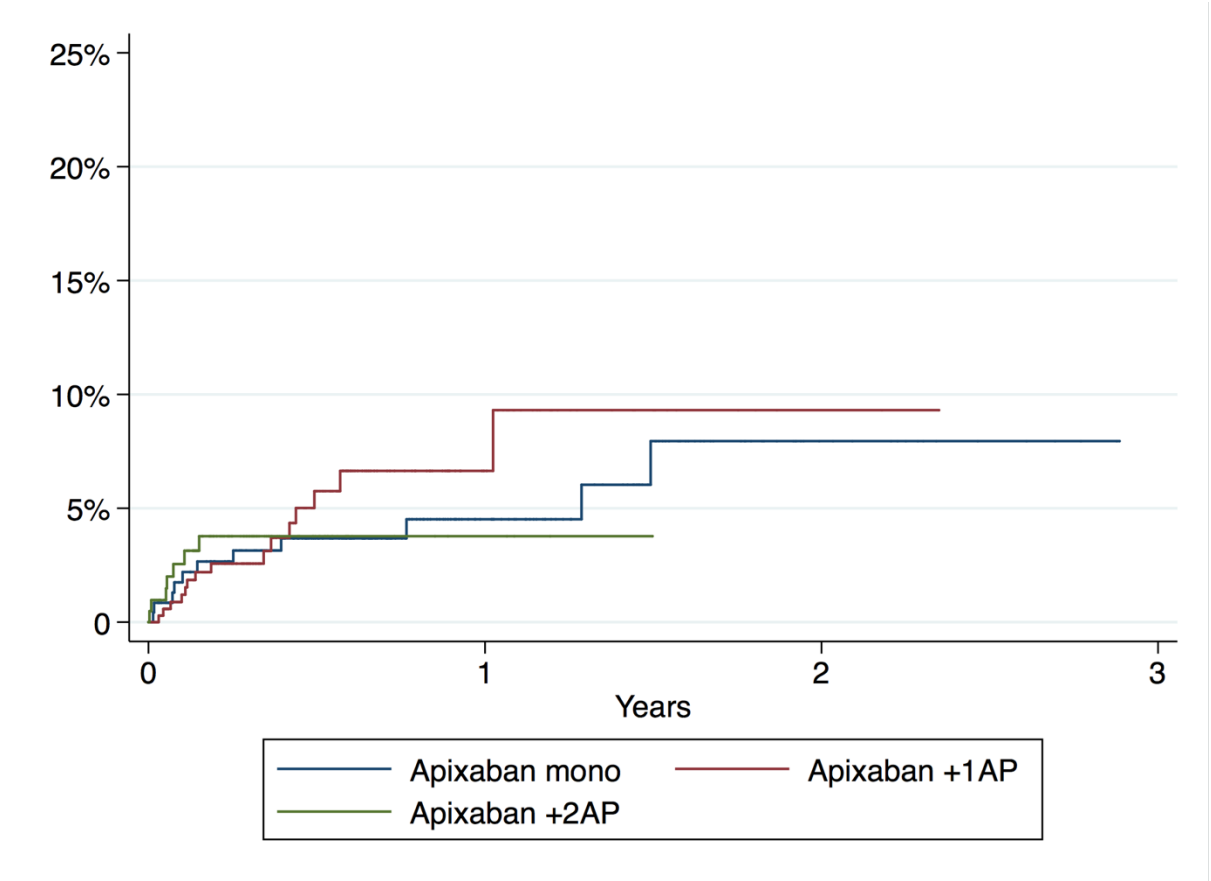


Figure 7. Main bleeding endpoint with combinations including apixaban

Table 18. Main bleeding endpoint with combinations including apixaban

	All (events=33)		No PCI (events=23)		PCI without stent (no events)		PCI with stent (events=10)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
apixa alone n=243 events=11	5.1 (2.8-9.3)	*reference*[A]	5.3 (3.0-9.7)	*reference*[B]	0	*reference*[C]	0	*reference*[D]
apixa+1AP n=369 events=15	9.3 (5.6-15.4)	*1.46 (0.65-3.28)*	9.9 (5.5-17.9)	*1.43 (0.60-3.44)*	0	-	9.1 (3.4-24.2)	-
apixa+≥2AP n=209 events=7	11.5 (5.5-24.1)	*1.68 (0.60-4.68)*	5.4 (0.8-38.3)	*0.74 (0.09-6.00)*	0	-	15.2 (6.8-33.8)	-

[A]Adjustment only for age, sex and previous bleed due to the low number of endpoint events.
[B]Adjustment only for age and previous bleed due to the low number of endpoint events.
[C]No events. Multivariable adjustments not possible.
[D]No events in the reference category and also too few events for multivariable analysis.
Baseline characteristics for these patients are presented in Table 10

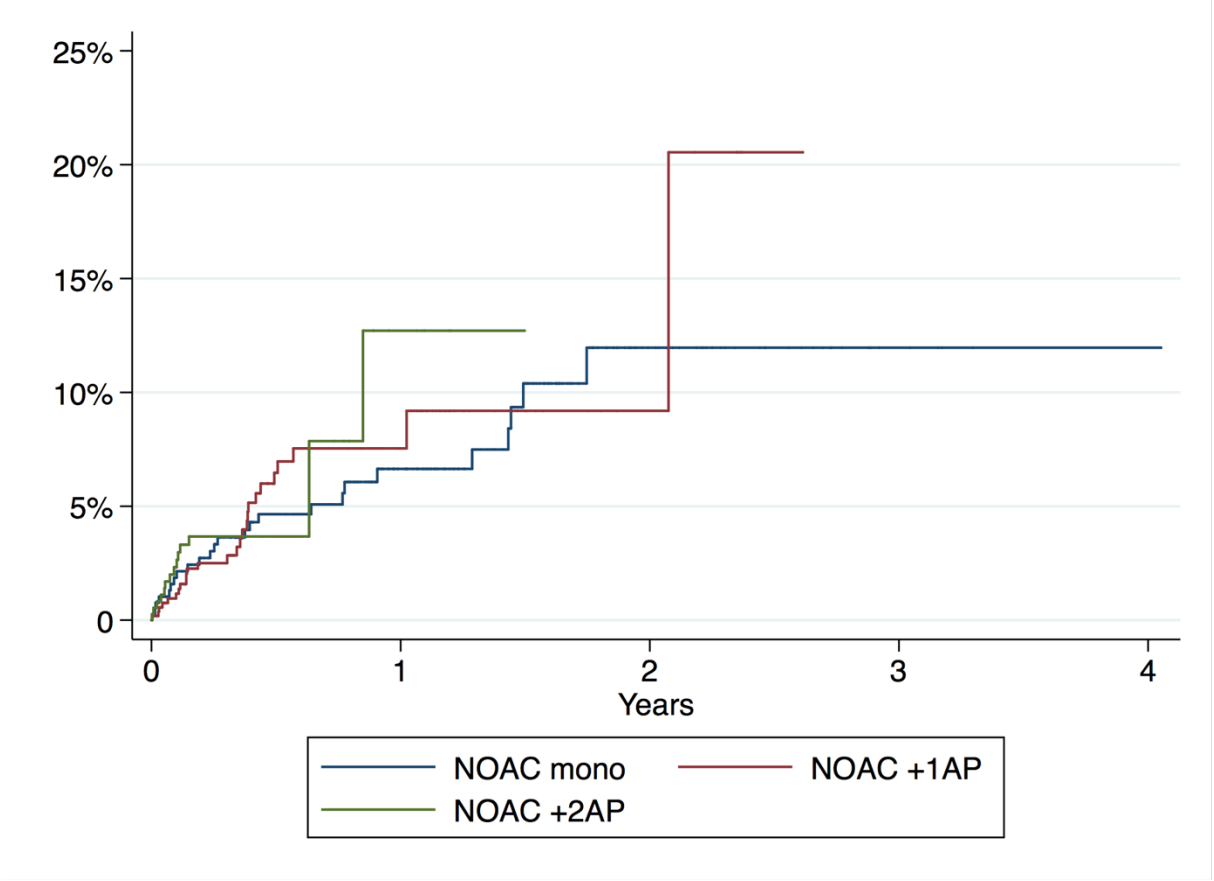


Figure 8. Main bleeding endpoint with combinations including any NOAC

Table 19. Main bleeding endpoint with combinations including any NOAC

	All (events=65)		No PCI (events=47)		PCI without stent (events=2)		PCI with stent (events=16)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
NOAC alone n=399 events=25	6.9 (4.7-10.2)	*reference*[A]	7.1 (4.8-10.4)	*reference*[B]	0	*reference*[C]	0	*reference*[D]
NOAC+1AP n=560 events=26	10.3 (7.0-15.1)	*1.39 (0.77-2.51)*	10.1 (6.3-16.2)	*1.33 (0.74-2.40)*	18.2 (4.6-72.9)	-	9.7 (4.6-20.3)	-
NOAC+≥2AP n=373 events=14	12.3 (7.3-20.8)	*1.81 (0.86-3.80)*	15.2 (6.3-36.4)	*1.69 (0.81-3.52)*	0	-	11.7 (6.1-22.5)	-

[A]Multivariable analysis with reduced set of covariates due to low number of events. Adjustment for age, sex, previous hospitalization with bleeding diagnosis, anaemia, chronic kidney disease and diabetes.
[B]Adjustment for age, sex, previous hospitalization with bleeding diagnosis and chronic kidney disease.
[C]Multivariable adjustments not possible.
[D]No events in the reference category and also too few events for multivariable analysis.
Baseline characteristics for these patients are presented in Table 1

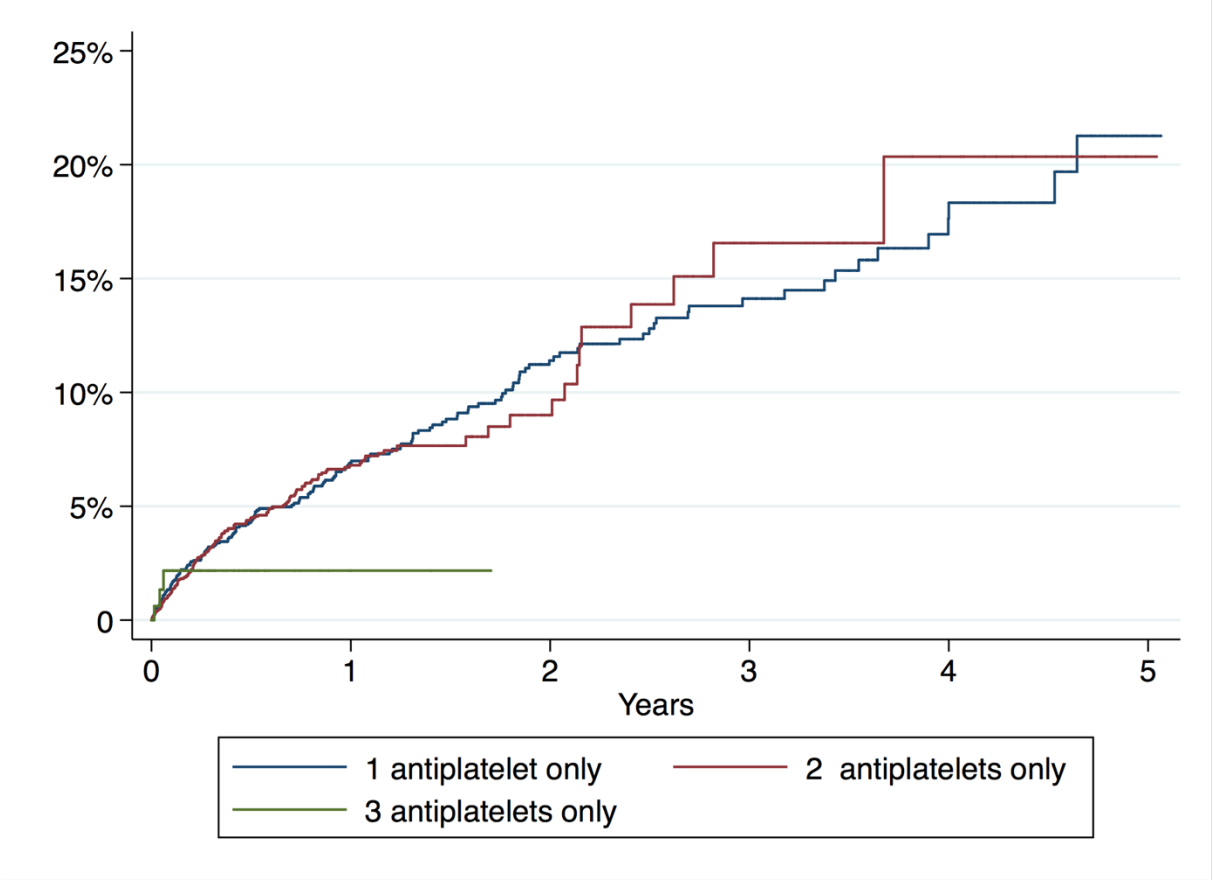


Figure 9. Main bleeding endpoint with combinations including only antiplatelets

Table 20. Main bleeding endpoint with combinations including only antiplatelets

	All (events=357)		No PCI (events=278)		PCI without stent (events=9)		PCI with stent (events=70)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
1 AP n=2,770 events=176	6.2 (5.3-7.2)	reference[A]	6.2 (5.4-7.3)	reference[A]	0	*reference[B]*	6.0 (3.2-11.2)	*reference[C]*
2 AP n=3,805 events=178	7.3 (6.3-8.4)	1.19 (0.95-1.50)	8.9 (7.4-10.8)	1.25 (0.97-1.61)	10.4 (5.2-20.7)	-	5.3 (4.1-6.8)	*0.98 (0.49-1.95)*
3 AP n=181 events=3	9.0 (2.9-27.9)	1.01 (0.32-3.19)	4.4 (0.6-31.5)	0.50 (0.07-3.59)	174.8 (24.6-1240.6)	-	9.7 (1.4-68.9)	*0.96 (0.12-7.58)*

[A]Mulitivariable adjustment for age, sex, duration of AF, previous hospitalization with bleeding diagnosis, anaemia, chronic kidney disease, diabetes, alcohol index, baseline use of NSAID or PPI.

[B]No events in the reference category and also too few events for multivariable analysis. The extremely high rate in the group with three antiplatelet drugs was due one single patient and a cumulative time at risk of only 209 days for all 9 patients in this box.

[C]Multivariable analysis with reduced set of covariates due to low number of events. Adjustment for age, sex, previous hospitalization with bleeding diagnosis, anaemia, chronic kidney disease, diabetes and baseline use of NSAID.

Baseline characteristics for these patients are presented in Table 12.

Table 21. Main bleeding endpoint - combinations with any OAC/NOAC

	All n=6,547 events=360		**No PCI n=4,371 events=263**		**PCI n=2,176 events=97**	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
OAC alone n=1,863 events=158	6.8 (5.8-7.9)	reference	6.8 (5.8-7.9)	reference	7.1 (2.9-17.0)	reference
OAC+1AP n=2,499 events=117	8.3 (6.9-9.9)	1.13 (0.87-1.46)	8.4 (6.8-10.5)	1.12 (0.84-1.48)	7.8 (5.6-11.0)	0.78 (0.30-2.06)
OAC+≥2AP n=2,185 events=85	12.0 (9.7-14.9)	1.57 (1.16-2.14)	14.8 (10.1-21.5)	1.63 (1.06-2.56)	11.1 (8.5-14.3)	0.88 (0.34-2.32)

10.3.2 New hospitalization for ACS

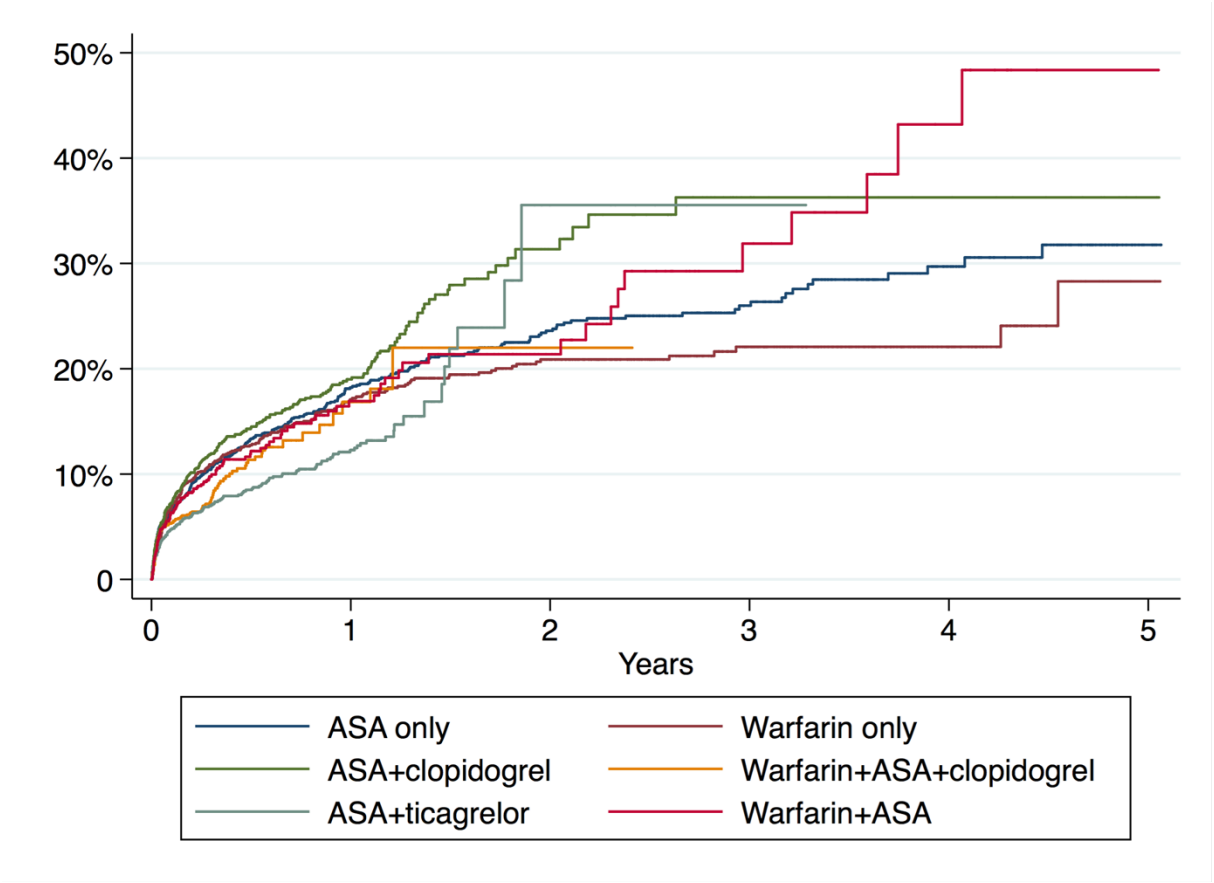


Figure 10. New hospitalization for ACS with the most common regimens

Table 22A. New hospitalization for ACS - the most common regimens

	All (events=1,301)		No PCI (events=1,043)		PCI without stent (events=29)		PCI with stent (events=229)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95%CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
asa n=2,162 events=340	15.4 (13.8-17.1)	reference[A]	15.6 (14.0-17.3)	reference[A]	17.4 (6.5-46.3)	*reference[B]*	9.6 (4.6-20.2)	reference[A]
asa+clop n=2,242 events=330	27.0 (24.3-30.1)	1.24 (1.06-1.45)	32.9 (29.1-37.2)	1.25 (1.05-1.48)	21.2 (10.1-44.5)	*1.07 (0.30-3.77)*	16.8 (13.3-21.3)	1.75 (0.78-3.90)
asa+tika n=1,355 events=143	15.7 (13.3-18.5)	0.94 (0.76-1.16)	23.9 (18.7-30.5)	1.11 (0.84-1.46)	22.5 (10.7-47.2)	*0.93 (0.26-3.35)*	11.8 (9.4-14.9)	1.32 (0.58-3.00)
warfarin n=1,464 events=236	13.1 (11.6-14.9)	0.91 (0.77-1.08)	13.1 (11.5-14.9)	0.90 (0.75-1.06)	8.8 (2.2-35.1)	*0.53 (0.09-2.93)*	19.3 (8.7-43.0)	1.86 (0.62-5.60)
wa+asa n=971 events=127	21.7 (18.2-25.8)	1.04 (0.85-1.29)	22.9 (19.2-27.3)	1.04 (0.84-1.28)	10.1 (3.3-31.)	*0.51 (0.11-2.37)*	5.4 (0.8-38.5)	0.51 (0.06-4.26)
wa+asa+clop n=1,446 events=125	25.0 (20.9-29.7)	0.95 (0.76-1.19)	41.7 (31.4-55.6)	1.22 (0.88-1.67)	30.6 (13.7-68.1)	*0.96 (0.24-3.78)*	16.9 (13.4-21.4)	1.51 (0.66-3.45)

[A]Multivariable adjustment for age, sex, previous myocardial infarction, peripheral artery disease, heart failure, diabetes, chronic kidney disease, baseline use of beta blocker or a statin.

[B]Because of few events, adjustment was only made for age, previous myocardial infarction and diabetes.

Baseline characteristics for these patients was presented in Table 6.

Comment: The Kaplan–Meier graph shows a very high relapse rate during the first few months, after which it stabilizes. Thus, the risk is not proportional throughout the exposed period. Moreover, the curves for the different regimens cross indicating that the risk doesn´t change in the same way for all drugs. (This is relevant for the following figures and tables about ACS recurrence). This is not ideal for Cox regression procedures. Table 22B shows the results of three different regression models using the exactly the same covariates for the adjustments:

Table 22B. Sensitivity analysis, three regression models

	All (events=1,301)		
	Cox HR (95% CI)	**Weibull HR (95% CI)**	**Logistic OR (95% CI)**
asa n=2,162 events=340	reference	reference	reference
asa+clop n=2,242 events=330	1.24 (1.06-1.45)	1.29 (1.10-1.51)	0.90 (0.76-1.07)
asa+tika n=1,355 events=143	0.94 (0.76-1.16)	0.98 (0.79-1.21)	0.70 (0.56-0.88)
warfarin n=1,464 events=236	0.91 (0.77-1.08)	0.91 (0.77-1.07)	1.02 (0.85-1.22)
wa+asa n=971 events=127	1.04 (0.85-1.29)	1.08 (0.88-1.33)	0.79 (0.63-0.99)
wa+asa+clop n=1,446 events=125	0.95 (0.76-1.19)	1.02 (0.82-1.27)	0.52 (0.41-0.66)

Table 22B shows the results of three regression models. To the left is the original Cox regression based on non-violation of the proportional hazards assumption, in the middle a parametric Weibull regression which is not dependent on the proportional hazards assumption and to the right, a logistic regression which disregards time at risk. Looking at the results, the logistic regression seems most in line with what one would expect, with more aggressive antithrombotic treatment associated with lower risk of recurrent ACS. However, this is a heavily biased result. The more aggressive combinations are used for a shorter duration than monotherapies, as can be seen from Tables 4 and 5. Assuming that the risk of relapse is the same per time unit for all six regimens in Table 22B, regimens with short exposure would generate fewer failures and thus appear to be better than regimens used for longer periods.

Consider the similarity in order when regimens are arranged according to increasing odds ratios and according to median treatment durations:

wa+asa+clop (OR 0.52), asa+tika (OR 0.70), wa+asa (OR 0.79), asa+clop (OR 0.90), asa (OR 1.00), warfarin (OR 1.02)

wa+asa+clop (110 days), asa+clop (150 days), wa+asa (156 days), asa+tika (311 days) , asa (399 days), warfarin (403 days)

Logistic regression does therefore not appear to be a useful alternative.

The estimates obtained with the Cox and Weibull regressions are similar, but the Weibull method has the advantage of accepting that risk may change over time. The Cox method was specified in the study protocol (pp 9 and 16) and will therefore be used for the main analyses, with supplementary Weibull regressions as sensitivity analyses when the Kaplan–Meier curves show gross deviations from the proportional hazards assumption.

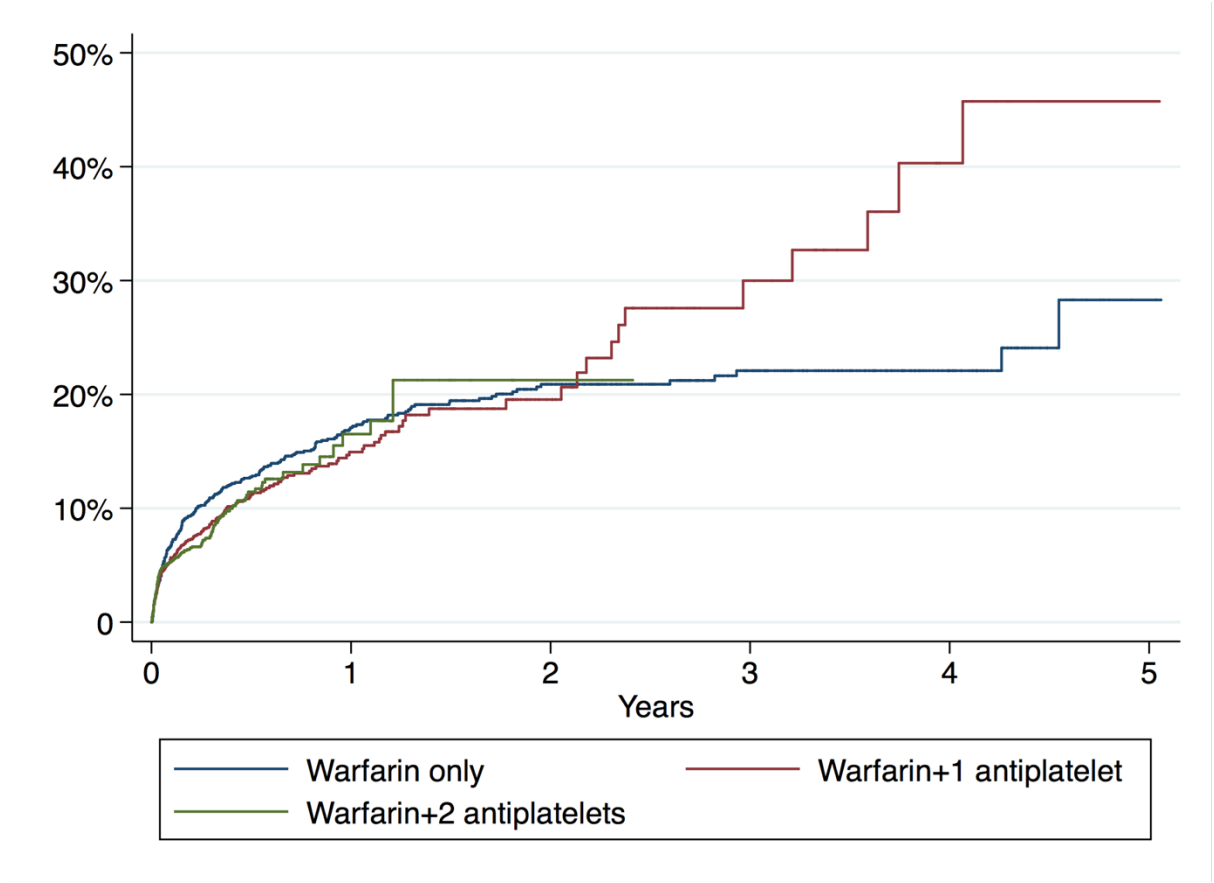


Figure 11. New hospitalization for ACS - warfarin combination

Table 23A. New hospitalization for ACS - combinations including warfarin

	All (events=595)		No PCI (events=457)		PCI without stent (events=15)		PCI with stent (events=123)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
wa alone n=1,464 events=236	13.1 (11.6-14.9)	reference[A]	13.1 (11.5-14.9)	reference[A]	8.8 (2.2-35.1)	*reference[B]*	19.3 (8.7-43.0)	reference[A]
wa+1AP n=1,939 events=213	20.1 (17.5-22.9)	1.00 (0.82-1.22)	22.7 (19.5-26.5)	1.05 (0.85-1.29)	13.7 (6.5-28.7)	*1.44 (0.27-7.58)*	14.1 (10.3-19.3)	0.57 (0.23-1.38)
wa+≥2AP n=1,812 events=146	26.0 (22.1-30.6)	0.99 (0.79-1.26)	44.6 (34.8-57.2)	1.32 (0.97-1.78)	28.9 (13.0-64.4)	*2.13 (0.36-12.50)*	19.4 (15.6-24.3)	0.65 (0.27-1.58)

[A]Multivariable adjustment for age, sex, previous myocardial infarction, peripheral artery disease, heart failure, diabetes, chronic kidney disease, baseline use of beta blocker or a statin.
[B]Because of few events, adjustment was only made for age.
Baseline characteristics for these patients are presented in Table 7.

Table 23B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	**No PCI HR (95% CI)**	**PCI without stent HR (95% CI)**	**PCI with stent HR (95% CI)**
wa alone n=1,464 events=236	reference[A]	reference[A]	*reference[B]*	reference[A]
wa+1AP n=1,939 events=213	1.08 (0.89-1.31)	1.14 (0.93-1.40)	*1.38 (0.28-6.86)*	0.61 (0.25-1.46)
wa+≥2AP n=1,811 events=146	1.11 (0.88-1.40)	1.53 (1.14-2.07)	*2.17 (0.40-11.85)*	0.66 (0.28-11.57)

In these tables regarding warfarin regimens, and in the following tables concerning NOACs, there is a tendency to observe a higher risk for a recurrent ACS episode with more aggressive antithrombotic treatment, despite adjustments for treatment duration. The unadjusted event rates also tend to be higher with combination treatment than with monotherapy. This could be an effect of confounding by indication as discussed above. The dichotomous covariates available for adjustment do not fully reflect the severity of disease.

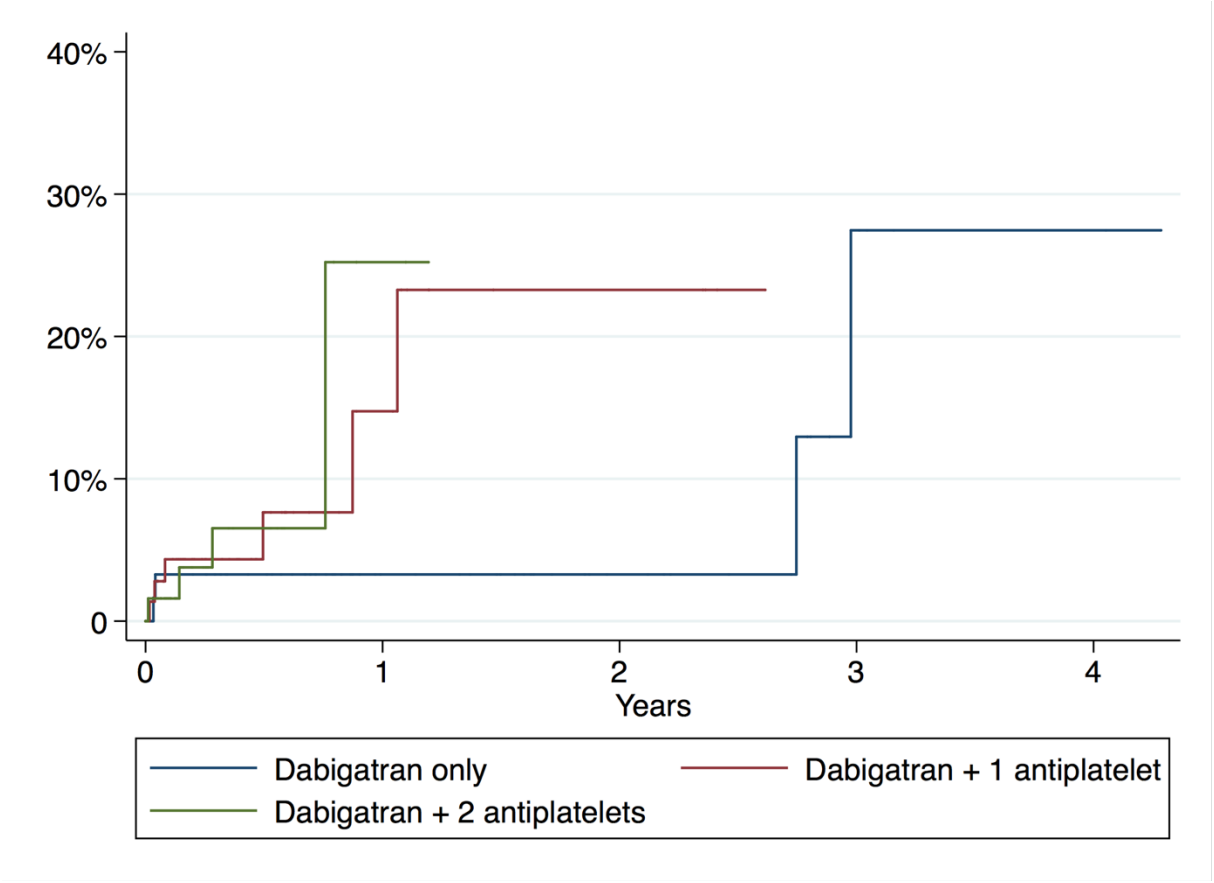


Figure 12. New hospitalization for ACS - combinations including dabigatran

Table 24A. New hospitalization for ACS - combinations including dabigatran

	All (events=14)		No PCI (events=8)		PCI without stent (events=2)		PCI with stent (events=4)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
dabi alone n=64 events=4	4.9 (1.9-13.2)	*reference*[A]	3.7 (1.2-11.5)	*reference*[A]	2435 (343-17826)	*reference*[B]	0	*reference*[C]
dabi+1AP n=74 events=6	15.5 (7.0-34.4)	*3.90 (0.75-20.19)*	12.1 (3.9-37.4)	*6.28 (0.63-63.09)*	468 (66-3324)	-	14.6 (3.7-58.4)	-
dabi+≥2AP n=65 events=4	20.8 (7.8-55.4)	*3.62 (0.58-22.51)*	43.4 (10.8-173.3)	*13.90 (1.10-176.26)*	0	-	14.1 (3.5-56.5)	-

[A]Because of few events, adjustment was only made for age.
[B]Multivariable adjustments not possible. The dabi alone group consisted of just one individual who was readmitted for ACS after 14 days. The dabi+1AP group consisted of two individuals of whom one was readmitted for ACS after 29 days. The extremely high event rates are thus due to very short follow-up, rather than to high number of events.
[C]Multivariable adjustments not possible.
Baseline characteristics for these patients are presented in Table 8.

Table 24B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	No PCI HR (95% CI)	PCI without stent HR (95% CI)	PCI with stent HR (95% CI)
dabi alone n=64 events=4	*reference*[A]	*reference*[A]	*reference*[B]	*reference*[C]
dabi+1AP n=74 events=6	*2.37 (0.63-8.54)*	*3.09 (0.55-17.17)*	-	-
dabi+≥2AP n=65 events=4	*2.62 (0.57-12.08)*	*11.58 (1.51-89.08)*	-	-

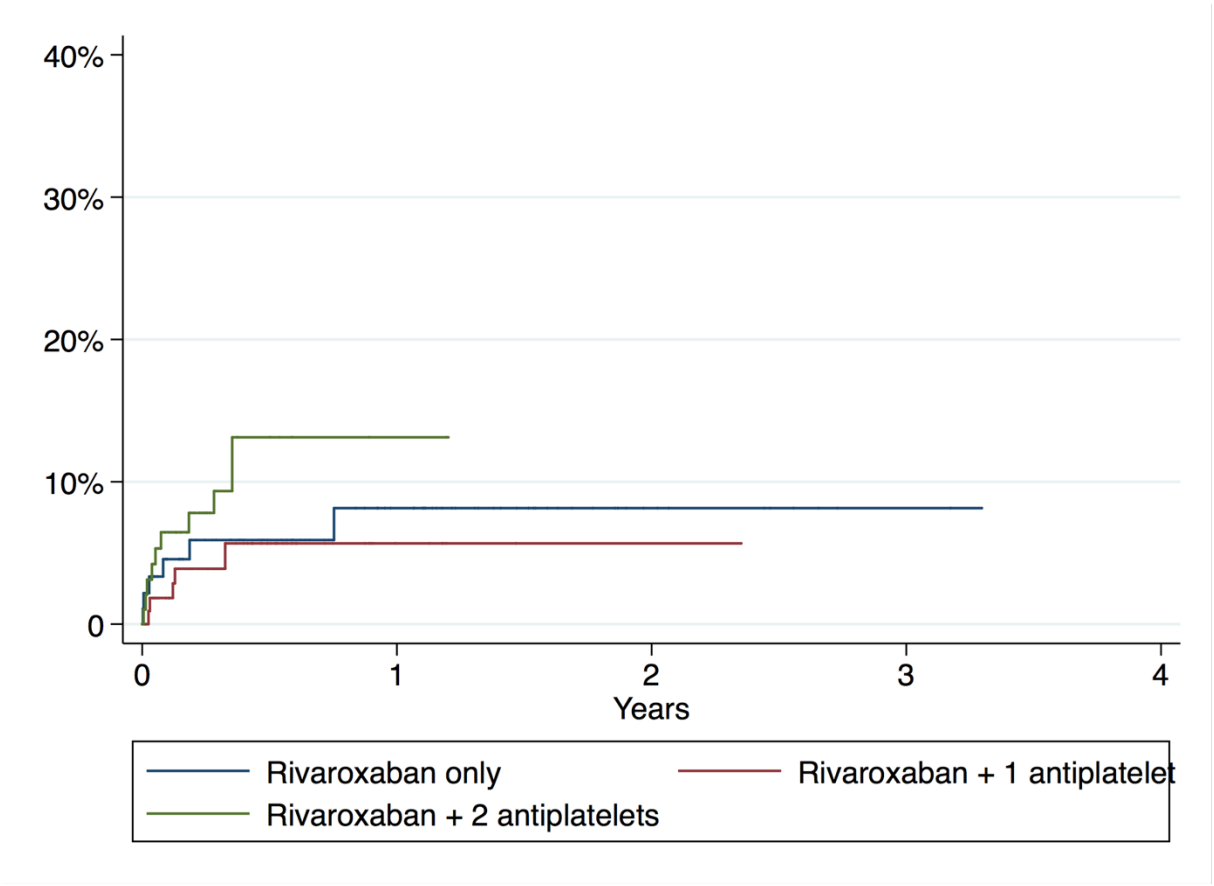


Figure 13. New hospitalization for ACS - combinations including rivaroxaban

Table 25A. New hospitalization for ACS - combinations including rivaroxaban

	All (events=20)		No PCI (events=15)		PCI without stent (no events)		PCI with stent (events=5)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
riva alone n=92 events=6	7.4 (3.3-16.5)	*reference*[A]	7.4 (3.3-16.5)	*reference*[B]	0	*reference*[C]	0	*reference*[C]
riva+1AP n=117 events=5	10.1 (4.2-24.2)	*0.92 (0.27-3.09)*	12.3 (4.6-32.8)	*0.91 (0.25-3.31)*	0	*	6.9 (1.0-48.6)	-
riva+≥2AP n=99 events=9	29.5 (15.3-56.8)	*2.90 (0.91-9.24)*	65.9 (27.4-158.4)	*4.92 (0.98-17.86)*	0	*	17.7 (6.7-42.3)	-

[A]Because of few events, adjustment was only made for age and previous myocardial infarction.
[B]Because of few events, adjustment was only made for age. There were only eight individuals using riva+2APs. Their aggregated time at risk was 7.5 years. Five of them were rehospitalized for ACS after a mean interval of only 44 days. Hence the very high event rate in this box.
[C]Multivariable adjustments not possible.
Baseline characteristics for these patients are presented in Table 9.

Table 25B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	**No PCI HR (95% CI)**	**PCI without stent HR (95% CI)**	**PCI with stent HR (95% CI)**
riva alone n=92 events=6	*reference*[A]	*reference*[B]	*reference*[C]	*reference*[C]
riva+1AP n=117 events=5	*1.11 (0.33-3.72)*	*1.09 (0.30-3.95)*	-	-
riva+≥2AP n=99 events=9	*3.71 (1.17-11.78)*	*6.19 (1.72-22.35)*	-	-

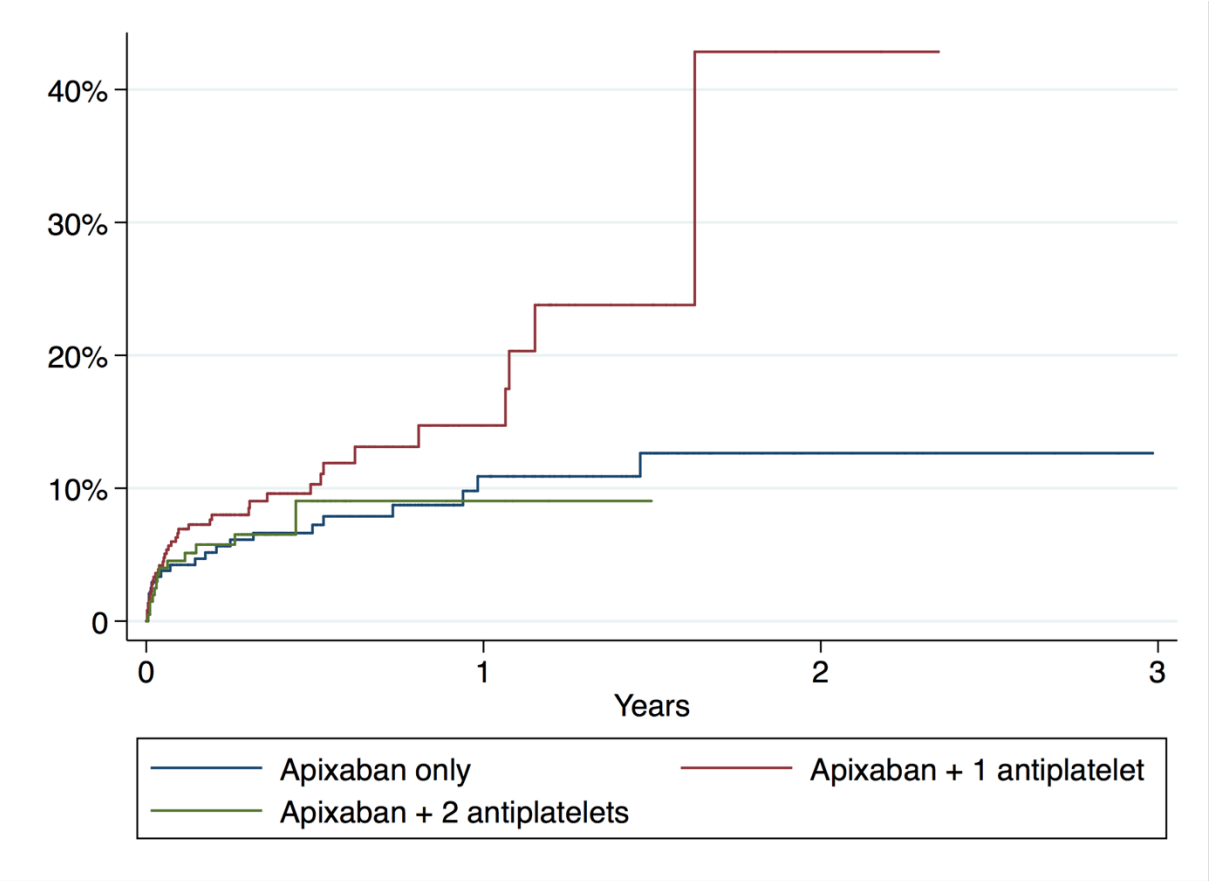


Figure 14. New hospitalization for ACS - apixaban combinations

Table 26A. New hospitalization for ACS - combinations including apixaban

	All (events=73)		No PCI (events=59)		PCI without stent (events=3)		PCI with stent (events=11)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
apixa alone n=243 events=21	10.4 (6.8-15.9)	*reference*[A]	10.8 (7.0-16.6)	*reference*[B]	0	*reference*[C]	0	*reference*[C]
apixa+1AP n=369 events=39	25.4 (18.6-34.8)	*1.68 (0.96-2.92)*	30.6 (21.6-43.2)	*1.78 (0.99-3.19)*	32.3 (8.1-129.0)	-	11.7 (4.9-28.2)	-
apixa+≥2AP n=209 events=13	22.3 (13.0-38.4)	*1.16 (0.56-2.41)*	35.3 (15.9-78.7)	*1.46 (0.56-3.80)*	35.8 (5.0-254.5)	-	15.6 (7.0-34.7)	-

[A]Multivariable adjustment with reduced set of covariates due to low number of events. Adjustment for age, sex, previous myocardial infarction, peripheral artery disease, heart failure, diabetes, chronic kidney disease.
[B]Multivariable adjustment for age, sex, previous myocardial infarction, peripheral artery disease, diabetes, chronic kidney disease.
[C]Multivariable adjustments not possible.
Baseline characteristics for these patients are presented in Table 10.

Table 26B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	No PCI HR (95% CI))	PCI without stent HR (95% CI)	PCI with stent HR (95% CI)
apixa alone n=243 events=21	*reference*[A]	*reference*[B]	*reference*[C]	*reference*[C]
apixa+1AP n=369 events=39	*1.64 (0.95-2.83)*	*1.74 (0.99-3.07)*	-	-
apixa+≥2AP n=209 events=13	*1.14 (0.56-2.32)*	*1.43 (0.56-3.65)*	-	-

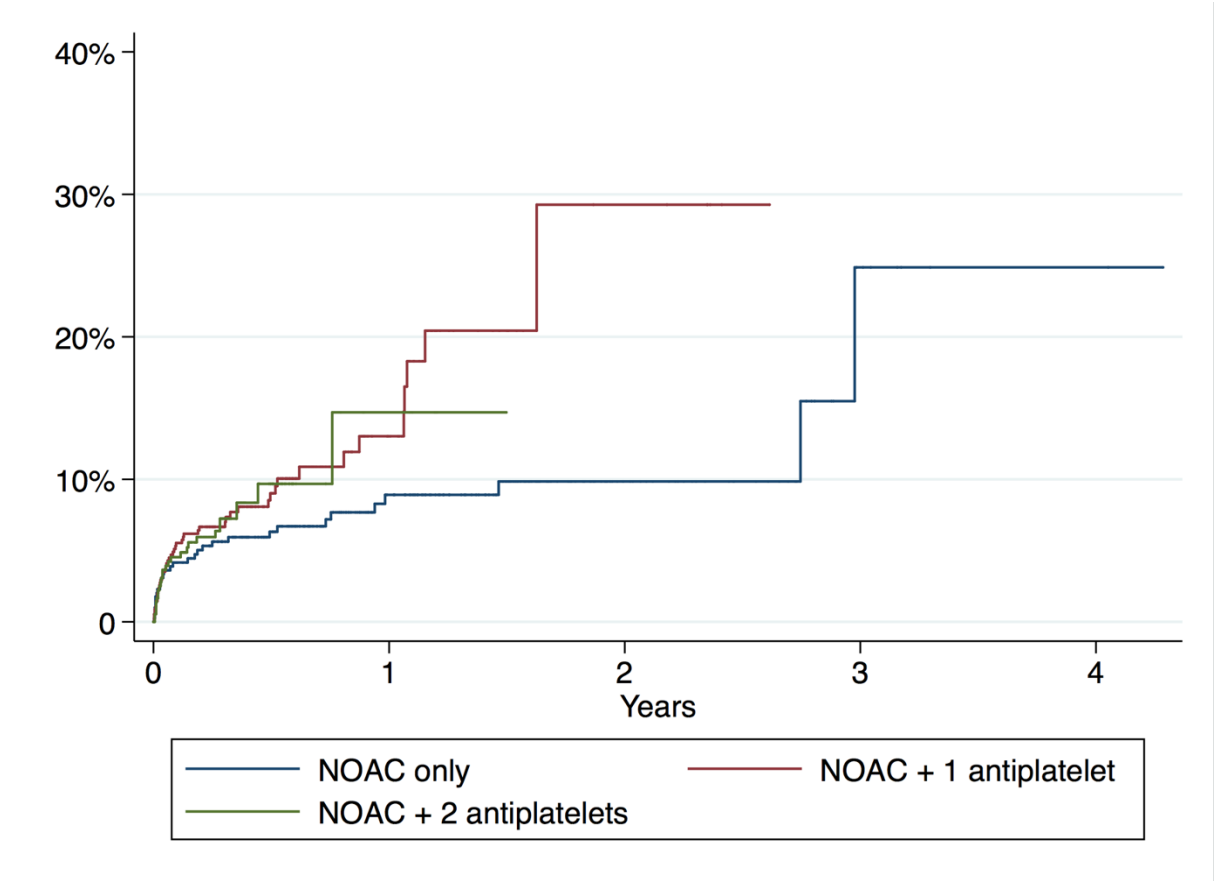


Figure 15. New hospitalization for ACS - NOAC combinations

Table 27A. New hospitalization for ACS - combinations including any NOAC

	All (events=107)		No PCI (events=82)		PCI without stent (events=5)		PCI with stent (events=20)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
NOAC alone n=399 events=31	8.5 (6.0-12.1)	reference[A]	8.4 (5.9-12.1)	reference[A]	21.4 (3.0-151.9)	*reference[B]*	0	*reference[C]*
NOAC+1AP n=560 events=50	20.7 (15.7-27.3)	1.74 (1.07-2.83)	24.1 (17.6-32.9)	1.88 (1.12-3.15)	33.7 (10.9-104.4)	-	11.3 (5.6-22.6)	-
NOAC+≥2AP n=373 events=26	24.1 (16.4-35.4)	1.61 (0.89-2.89)	44.6 (25.9-76.7)	2.39 (1.17-4.88)	28.0 (3.9-198.7)	-	16.0 (9.1-28.1)	-

[A]Multivariable adjustment for age, sex, previous myocardial infarction, peripheral artery disease, heart failure, diabetes, chronic kidney disease, baseline use of beta blocker or a statin.
[B]Too few events for multivariable adjustments
[C]Multivariable adjustments not possible.
Baseline characteristics for these patients are presented in Table 11.

Table 27B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	**No PCI HR (95% CI)**	**PCI without stent HR (95% CI)**	**PCI with stent HR (95% CI)**
NOAC alone n=398 events=	reference[A]	reference[A]	*reference[B]*	*reference[C]*
NOAC+1AP n=560 events=	1.69 (1.06-2.70)	1.82 (1.11-3.00)	-	-
NOAC+≥2AP n=373 events=	1.59 (0.91-2.81)	2.40 (2.00-4.79)	-	-

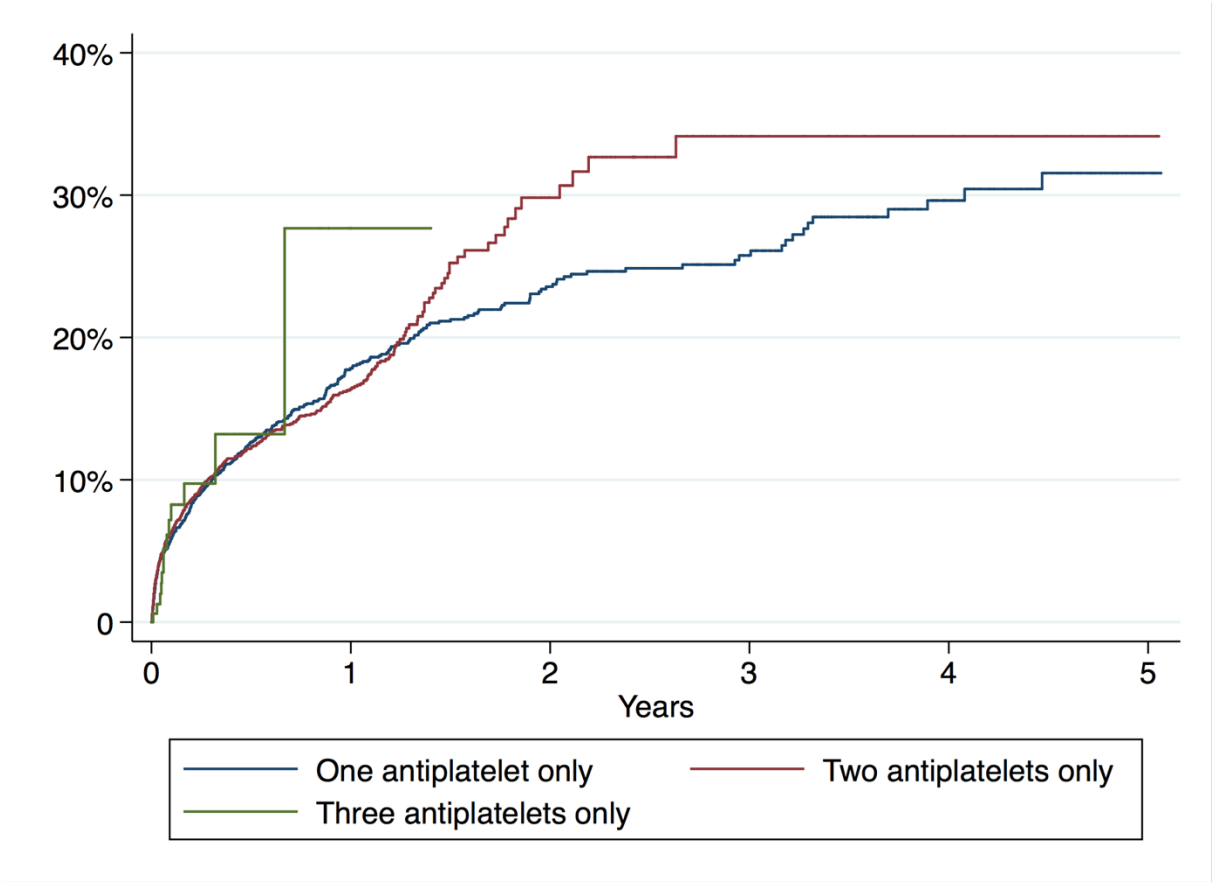


Figure 16. New hospitalization for ACS - antiplatelet regimens alone

Table 28A. New hospitalization for ACS - combinations including antiplatelet drugs only

	All (events=914)		No PCI (events=727)		PCI without stent (events=19)		PCI with stent (events=168)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
1 AP n=2,770 events=404	15.7 (14.2-17.3)	reference[A]	15.9 (14.3-17.5)	reference[A]	19.9 (8.3-47.7)	*reference[B]*	12.3 (7.8-19.3)	reference[A]
2 AP n=3,805 events=497	22.7 (20.7-24.7)	1.23 (1.07-1.42)	31.2 (28.0-34.7)	1.29 (1.11-1.51)	20.9 (12.4-35.2)	*0.76 (0.27-2.13)*	13.9 (11.8-16.4)	1.42 (0.87-2.33)
3 AP n=181 events=13	42.0 (24.4-72.4)	1.14 (0.65-1.99)	50.0 (26.9-92.8)	1.17 (0.62-2.21)	0	-	29.3 (9.5-90.9)	1.45 (0.42-4.97)

[A]Multivariable adjustment for age, sex, previous myocardial infarction, peripheral artery disease, heart failure, diabetes, chronic kidney disease, baseline use of beta blocker or a statin.

[B]Because of few events, adjustment was only made for age and previous myocardial infarction.

Table 28B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	No PCI HR (95% CI)	PCI without stent HR (95% CI)	PCI with stent HR (95% CI)
1 AP n=2,770 events=404	reference[A]	reference[A]	*reference[B]*	reference[A]
2 AP n=3,805 events=497	1.26 (1.09-1.45)	1.35 (1.16-1.58)	*0.77 (0.27-2.17)*	1.39 (0.85-2.26)
3 AP n=181 events=13	1.22 (0.70-2.14)	1.28 (0.68-2.40)	-	1.48 (0.43-5.05)

Table 29. New hospitalization for ACS - combinations with any OAC/NOAC

	All n=6,547 events=702		**No PCI n=4,371 events=539**		**PCI n=2,176 events=163**	
	Events per 100 yrs at risk	**HR (95% CI)**	**Events per 100 yrs at risk**	**HR (95% CI)**	**Events per 100 yrs at risk**	**HR (95% CI)**
OAC alone n=1,863 events=267	12.3 (11.0-13.9)	reference	12.3 (10.9-13.9)	reference	14.4 (7.5-27.7)	reference
OAC+1AP n=2,499 events=263	20.2 (17.9-22.8)	1.09 (0.91-1.30)	23.0 (20.0-26.3)	1.13 (0.94-1.37)	14.0 (10.8-18.1)	0.72 (0.35-1.48)
OAC+≥2AP n=2,185 events=172	25.7 (22.1-29.9)	1.07 (0.86-1.33)	44.6 (35.6-55.9)	1.44 (1.10-1.90)	19.4 (15.9-23.6)	0.81 (0.40-1.67)

10.3.3 Ischaemic stroke or systemic embolism

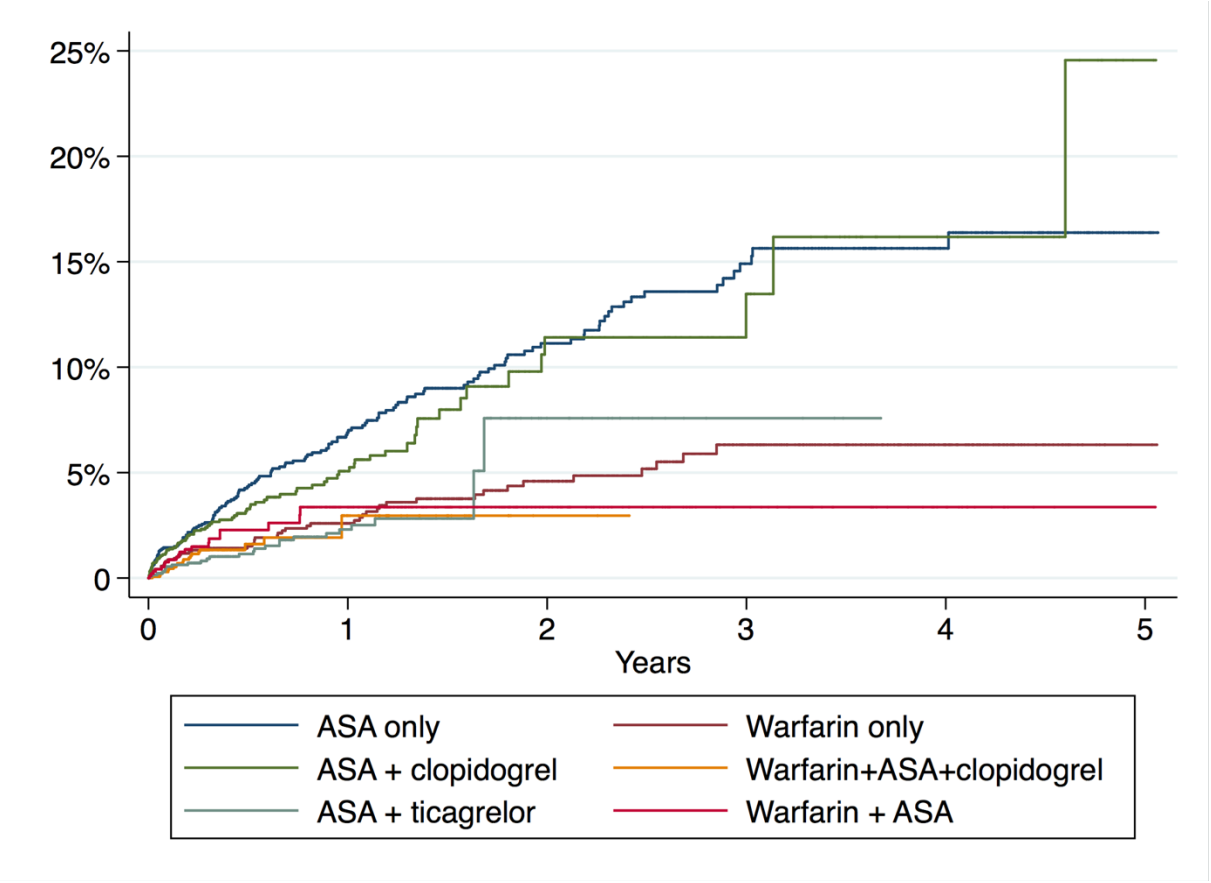


Figure 17. Ischaemic stroke or systemic embolism with the most common regimens

Table 30. Ischaemic stroke or systemic embolism - with the most common regimens

	All (events=342)		No PCI (events=290)		PCI without stent (events=5)		PCI with stent (events=47)	
	Events per 100 years at risk	**Multivar HR(95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
asa n=2,162 events=145	5.8 (5.0-6.9)	reference[A]	5.9 (5.0-7.0)	reference[A]	4.1 (0.6-29.0)	*reference[B]*	4.7 (1.8-12.6)	reference[A]
asa+clop n=2,242 events=86	6.1 (5.0-7.6)	0.97 (0.73-1.27)	7.2 (5.6-9.2)	0.95 (0.70-1.29)	4.9 (1.2-19.6)	-	4.1 (2.6-6.4)	0.84 (0.26-2.70)
asa+tika n=1,355 events=25	2.5 (1.7-3.8)	0.59 (0.38-0.93)	3.7 (2.1-6.7)	0.65 (0.35-1.21)	0	-	2.1 (1.3-3.6)	0.53 (0.15-1.86)
warfarin n=1,464 events=47	2.3 (1.8-3.1)	0.42 (0.30-0.58)	2.4 (1.8-3.1)	0.41 (0.29-0.58)	0	-	2.6 (0.4-18.2)	0.59 (0.06-5.46)
wa+asa n=971 events=20	3.0 (1.9-4.6)	0.48 (0.30-0.78)	3.3 (2.1-5.0)	0.49 (0.30-0.79)	0	-	0	-
wa+asa+clop n=1,446 events=19	3.5 (2.2-5.5)	0.60 (0.36-0.99)	6.3 (3.2-12.7)	0.82 (0.40-1.71)	9.0 (2.2-35.9)	-	2.3 (1.2-4.4)	0.43 (0.12-1.60)

[A]Multivariable adjustment for age, sex, previous ischaemic stroke, systemic embolism or TIA, hypertension, heart failure, diabetes, vascular disease, i.e. the constituent factors of the CHA_2DS_2-VASc stroke risk stratification scheme.
[B]Too few events for multivariable adjustments.
Baseline characteristics for these patients are presented in Table 6.

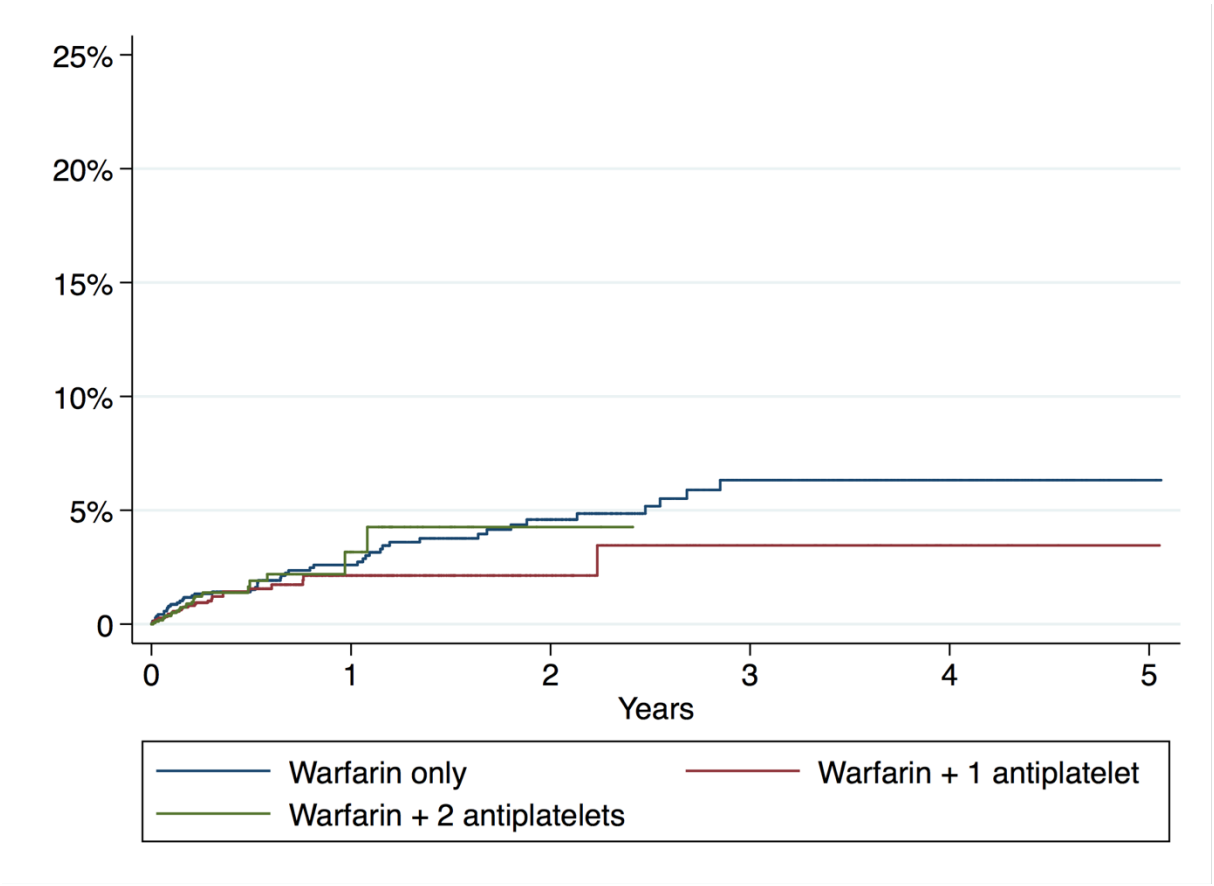


Figure 18. Ischaemic stroke or systemic embolism - combinations including warfarin

Table 31. Ischaemic stroke or systemic embolism - combinations including warfarin

	All (events=97)		No PCI (events=80)		PCI without stent (events=2)		PCI with stent (events=15)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
wa alone n=1,464 events=47	2.3 (1.8-3.1)	reference[A]	2.4 (1.8-3.1)	reference[A]	0	*reference[B]*	2.6 (0.4-18.2)	*reference[C]*
wa+1AP n=1,939 events=26	2.2 (1.5-3.2)	0.79 (0.48-1.31)	2.6 (1.7-4.0)	0.87 (0.51-1.48)	0	-	1.3 (0.5-3.5)	*0.56 (0.05-6.57)*
wa+≥2AP n=1,812 events=24	4.0 (2.7-5.9)	1.38 (0.78-2.41)	7.9 (4.5-13.8)	2.09 (1.05-4.16)	8.5 (2.1-34.2)	-	2.3 (1.2-4.3)	*0.92 (0.08-10.91)*

[A]Multivariable adjustment for age, sex, previous ischaemic stroke, systemic embolism or TIA, hypertension, heart failure, diabetes, previous myocardial infarction/peripheral artery disease (="vascular disease") i.e. the constituent risk factors of the CHA_2DS_2-VASc scheme.
[B]Too few events for multivariable adjustment.
[C]Because of few events, adjustment was only made for age.
Baseline characteristics for these patients are presented in Table 7.

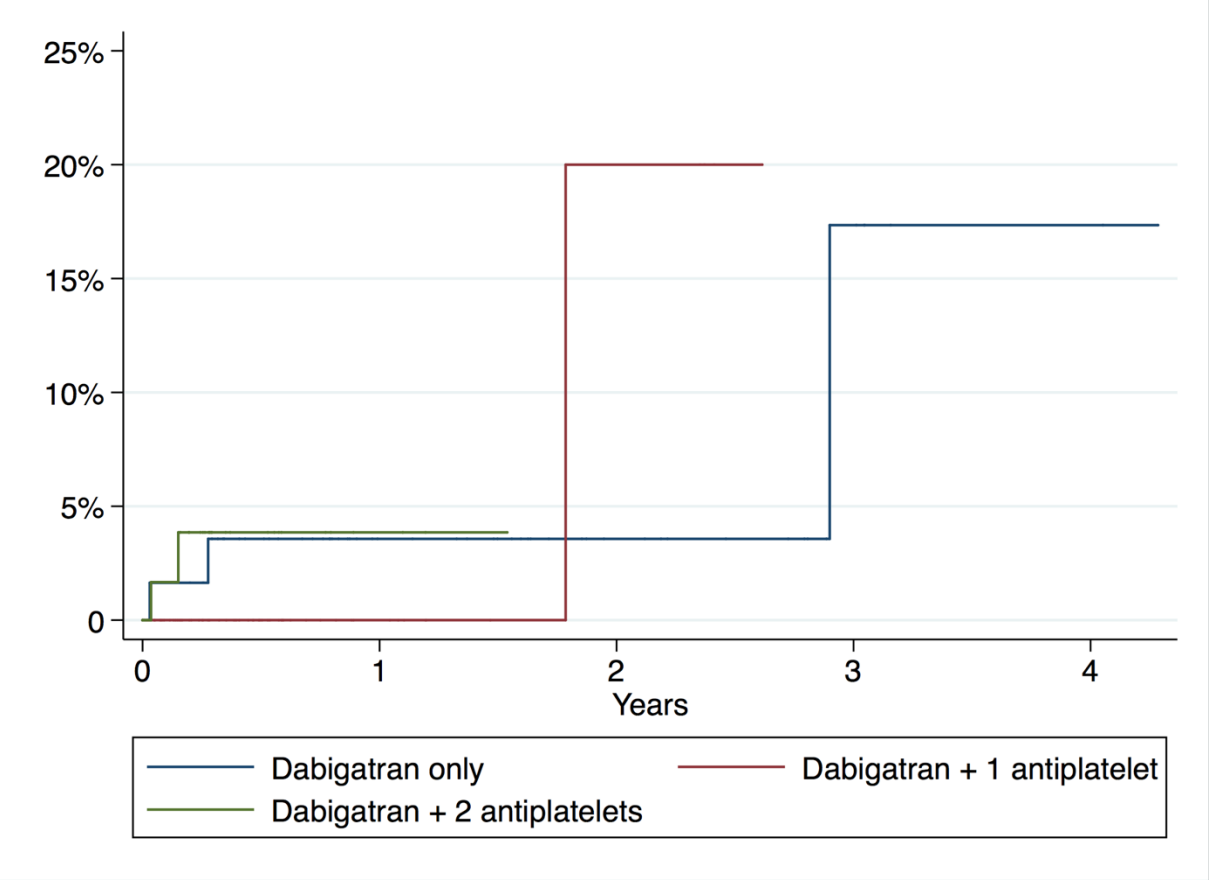


Figure 19. Ischaemic stroke or systemic embolism - dabigatran combinations

Table 32. Ischaemic stroke or systemic embolism - dabigatran combinations

	All (events=6)		No PCI (events=5)		PCI without stent (no events)		PCI with stent (events=1)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
dabi alone n=64 events=3	3.7 (1.2-11.6)	*reference*[A]	3.7 (1.2-11.6)	*reference*[A]	0	*reference*[A]	0	*reference*[A]
dabi+1AP n=74 events=1	2.4 (0.3-17.3)	-	3.9 (0.6-27.9)	-	0	-	0	-
dabi+≥2AP n=65 events=2	9.8 (2.4-39.0)	-	16.7 (2.4-118.5)	-	0	-	7.1 (1.0-50.6)	-

[A]Because of few events, no adjustment were possible.
Baseline characteristics for these patients are presented in Table 8.

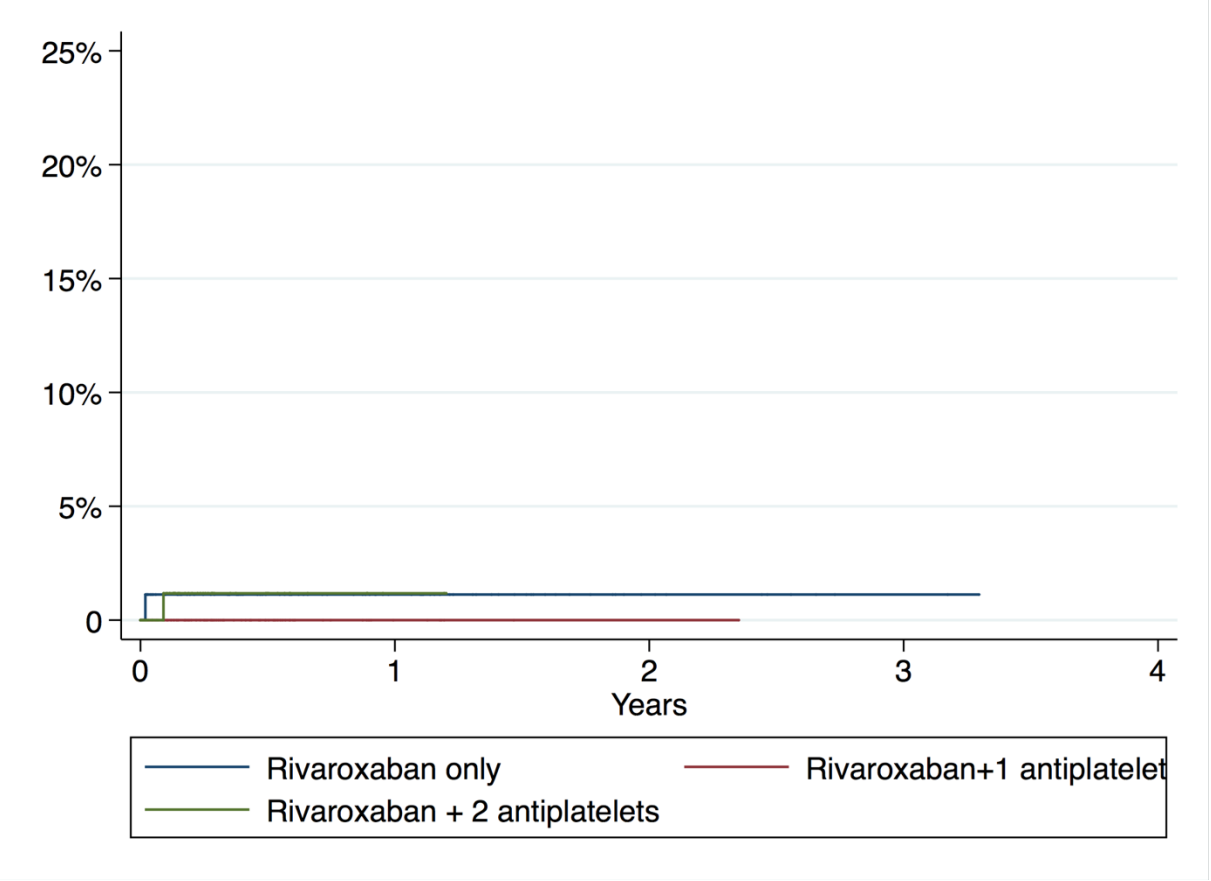


Figure 20. Ischaemic stroke or systemic embolism - rivaroxaban combinations

Table 33. Ischaemic stroke or systemic embolism - rivaroxaban combinations

	All (events=2)		No PCI (events=1)		PCI without stent (no events)		PCI with stent (events=1)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
riva alone n=92 events=1	1.2 (0.2-8.7)	*reference*[A]	1.2 (0.2-8.7)	*reference*[A]	0	*reference*[A]	0	*reference*[A]
riva+1AP n=117 events=0	0	-	0	-	0	-	0	-
riva+≥2AP n=99 events=1	3.0 (0.4-21.3)	-	0	-	0	-	4.3 (0.6-30.2)	-

[A]Because of few events, no adjustment were possible.
Baseline characteristics for these patients are presented in Table 9.

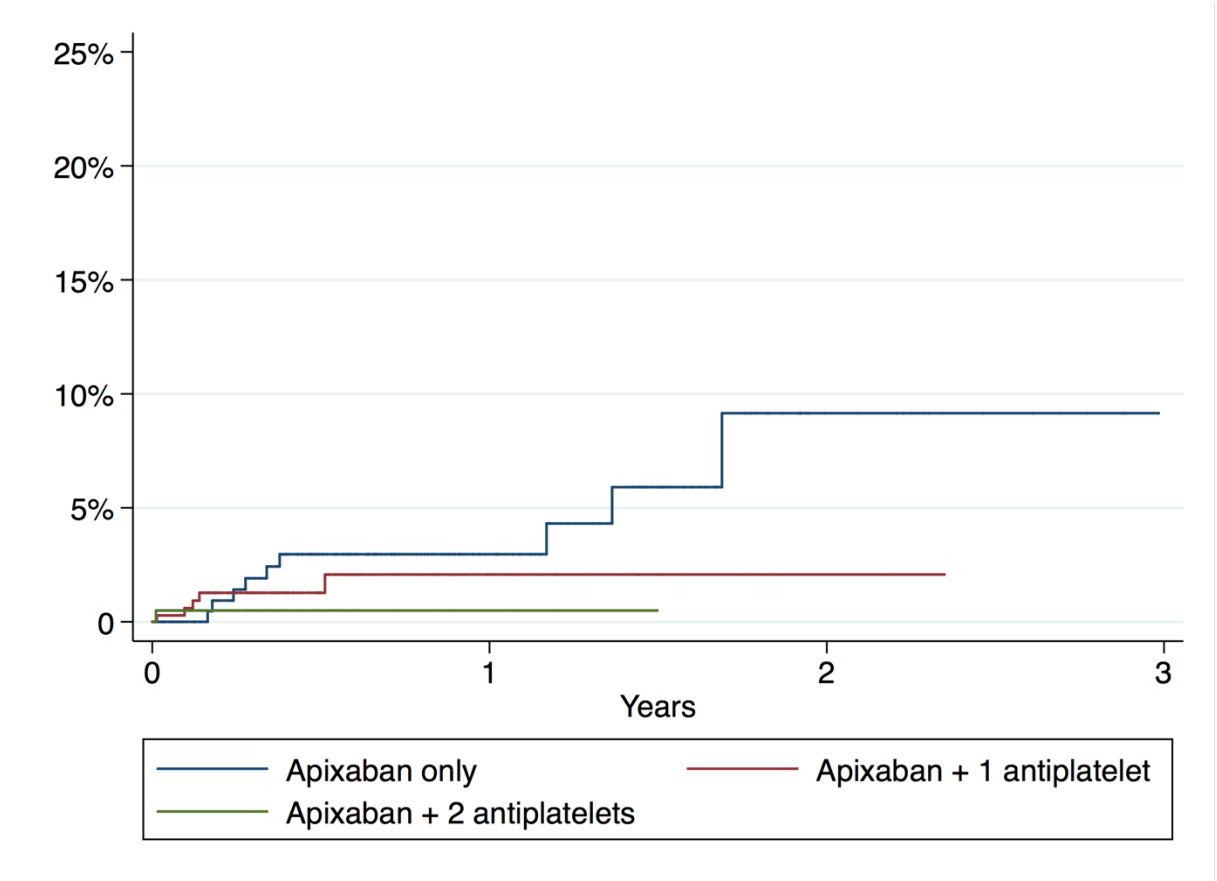


Figure 21. Ischaemic stroke or systemic embolism - apixaban combinations

Table 34. Ischaemic stroke or systemic embolism - apixaban combinations

	All (events=15)		No PCI (events=13)		PCI without stent (no events)		PCI with stent (events=2)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
apixa alone n=243 events=9	4.2 (2.2-8.1)	*reference*[A]	4.4 (2.3-8.4)	*reference*[A]	0	*reference*[B]	0	*reference*[B]
apixa+1AP n=369 events=5	3.0 (1.3-7.3)	*0.62 (0.20-1.95)*	2.7 (0.9-8.3)	*0.53 (0.14-2.2)*	0	-	4.5 (1.1-18.0)	-
apixa+≥2AP n=209 events=1	1.6 (0.2-11.5)	*0.28 (0.03-2.32)*	5.4 (0.8-38.5)	*0.94 (0.11-7.97)*	0	-	0	-

[A]Because of few events, adjustment was only made for age.
[B]Because of few events, no adjustment were possible.
Baseline characteristics for these patients are presented in Table 11.

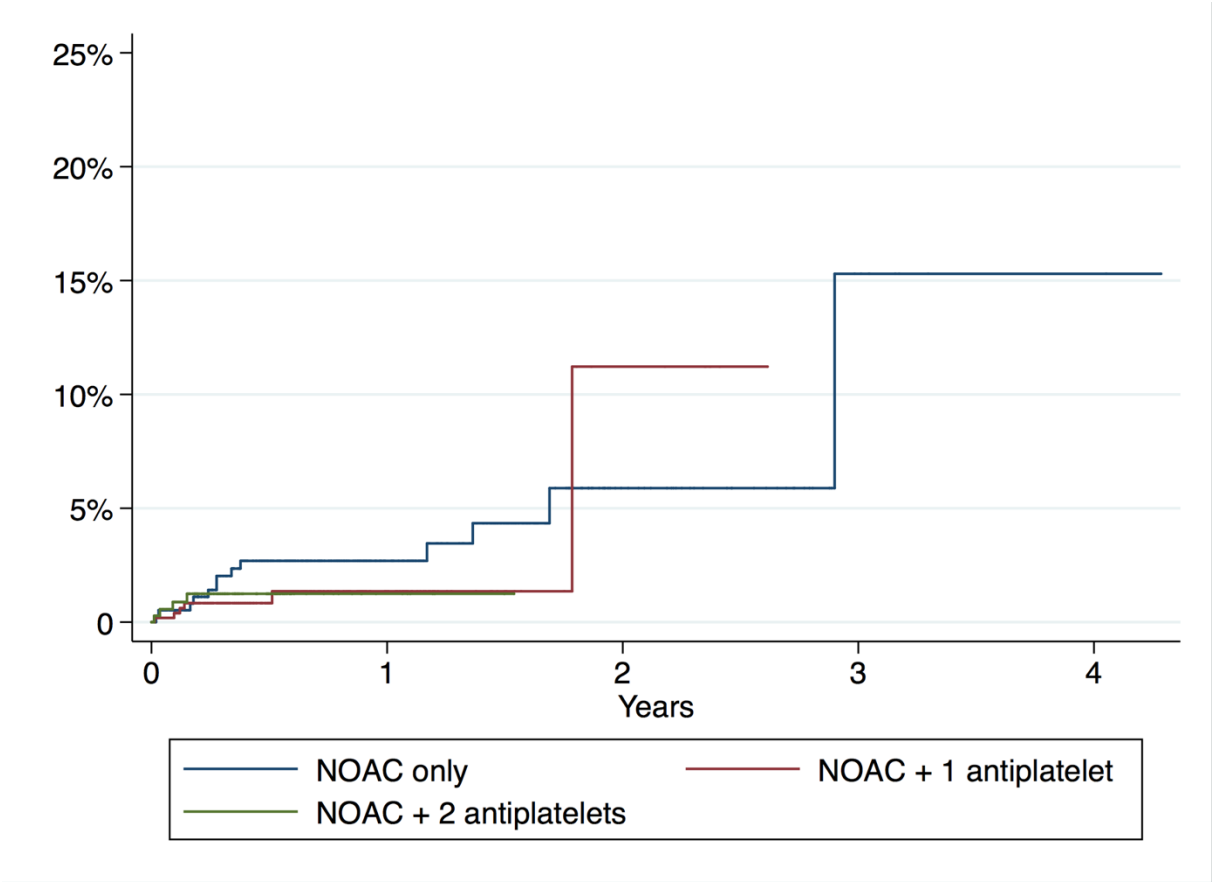


Figure 22. Ischaemic stroke or systemic embolism - NOAC combinations

Table 35. Ischaemic stroke or systemic embolism - combinations including any NOAC

	All (events=23)		No PCI (events=19)		PCI without stent (no events)		PCI with stent (events=4)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
NOAC alone n=399 events=13	3.5 (2.0-6.0)	*reference*[A]	3.5 (2.1-6.1)	*reference*[A]	0	*reference*[B]	0	*reference*[C]
NOAC+1AP n=560 events=6	2.3 (1.1-5.2)	*0.52 (0.19-1.43)*	2.3 (0.9-6.2)	*0.49 (0.15-1.56)*	0	-	2.7 (0.7-10.9)	-
NOAC+≥2AP n=373 events=4	3.5 (1.3-9.2)	*0.71 (0.21-2.39)*	5.9 (1.5-23.6)	*0.89 (0.19-4.24)*	0	-	2.6 (0.6-10.2)	-

[A]Adjustment was only made for age and previous ischaemic stroke/systemic embolism/ TIA because of few endpoint events.
[B]No adjustments because there were no events.
[C]Adjustments not possible

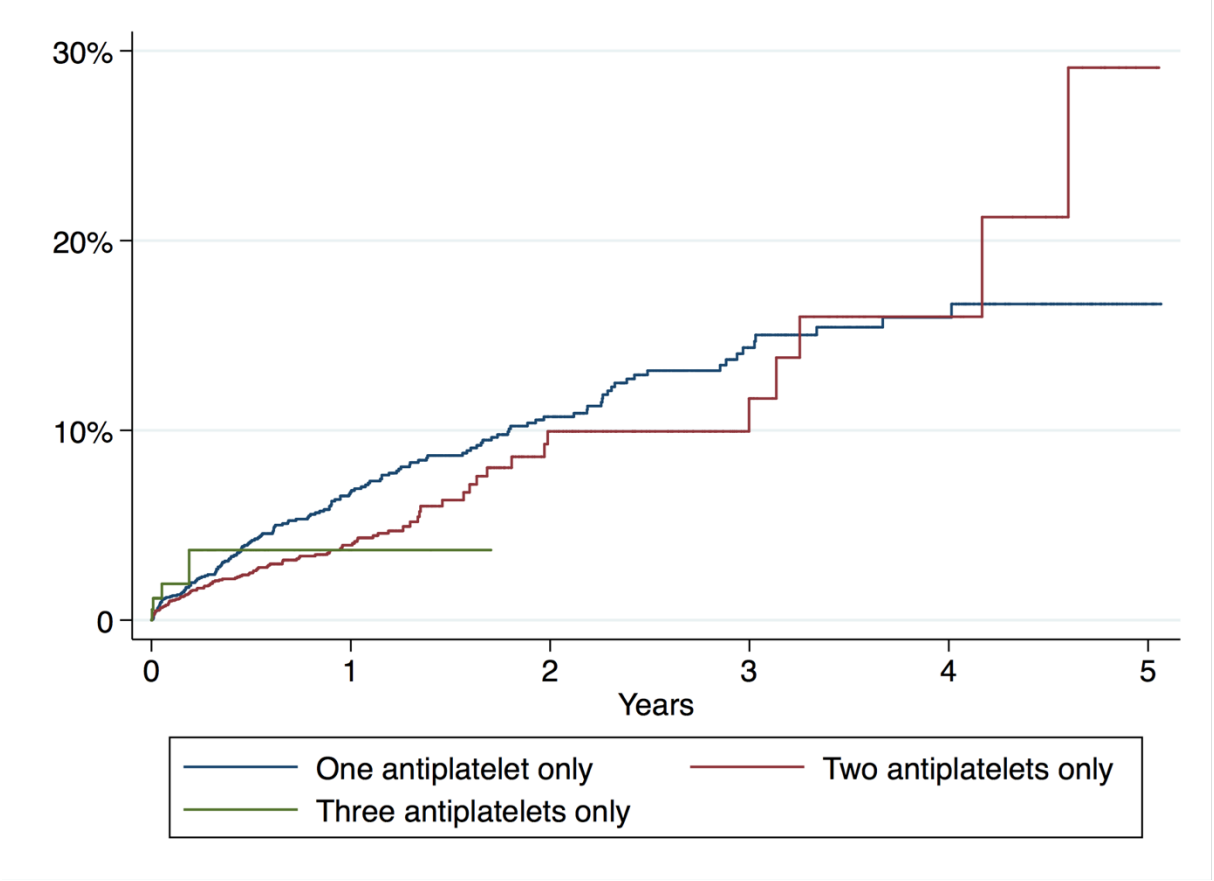


Figure 23. Ischaemic stroke or systemic embolism - antiplatelet regimens alone

Table 36. Ischaemic stroke or systemic embolism - antiplatelet drugs only

	All (events=290)		No PCI (events=243)		PCI without stent (events=5)		PCI with stent (events=42)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
1 AP n=2,770 events=167	5.8 (5.0-6.7)	reference[A]	5.8 (5.0-6.8)	reference[A]	3.6 (0.5-25.7)	*reference[B]*	5.3 (2.7-10.1)	*reference[C]*
2 AP n=3,805 events=119	4.8 (4.0-5.8)	0.96 (0.75-1.24)	6.6 (5.4-8.2)	1.01 (0.76-1.33)	3.8 (1.2-11.9)	-	2.9 (2.1-4.1)	*0.71 (0.32-1.56)*
3 AP n=181 events=4	12.0 (4.5-32.0)	1.45 (0.53-3.96)	13.4 (4.3-41.5)	1.36 (0.43-4.31)	187.3 (26.4-1329.7)	-	0	-

[A]Multivariable adjustment for age, sex, previous ischaemic stroke, systemic embolism or TIA, hypertension, heart failure, diabetes and "vascular disease", i.e. the constituent factors of the CHA_2DS_2-VASc stroke risk stratification scheme.

[B]No adjustments possible because of few events. The extremely high incidence rate among patients without stents was based on one patient who had a stroke after one day of the time at risk (= on day 8 after hospital discharge for ACS).

[C]Adjustment was only made for age, previous ischaemic stroke/systemic embolism/TIA, hypertension and diabetes because of few endpoint events.

Table 37. Ischaemic stroke or systemic embolism - combinations with any OAC/NOAC

	All n=6,547 events=120		**No PCI n=4,371 events=99**		**PCI n=2,176 events=21**	
	Events per 100 yrs at risk	**HR (95% CI)**	**Events per 100 yrs at risk**	**HR (95% CI)**	**Events per 100 yrs at risk**	**HR (95% CI)**
OAC alone n=1,863 events=60	2.5 (1.9-3.2)	reference	2.5 (2.0-3.3)	reference	1.4 (0.2-9.9)	reference
OAC+1AP n=2,499 events=32	2.2 (1.6-3.1)	0.73 (0.46-1.14)	2.6 (1.8-3.8)	0.77 (0.48-1.24)	1.4 (0.6-3.0)	0.90 (0.10-8.59)
OAC+≥2AP n=2,185 events=28	3.9 (2.7-5.6)	1.20 (0.72-2.00)	7.5 (4.4-12.7)	1.74 (0.93-3.27)	2.6 (1.5-4.4)	1.56 (0.16-15.01)

10.3.4 Death from any cause

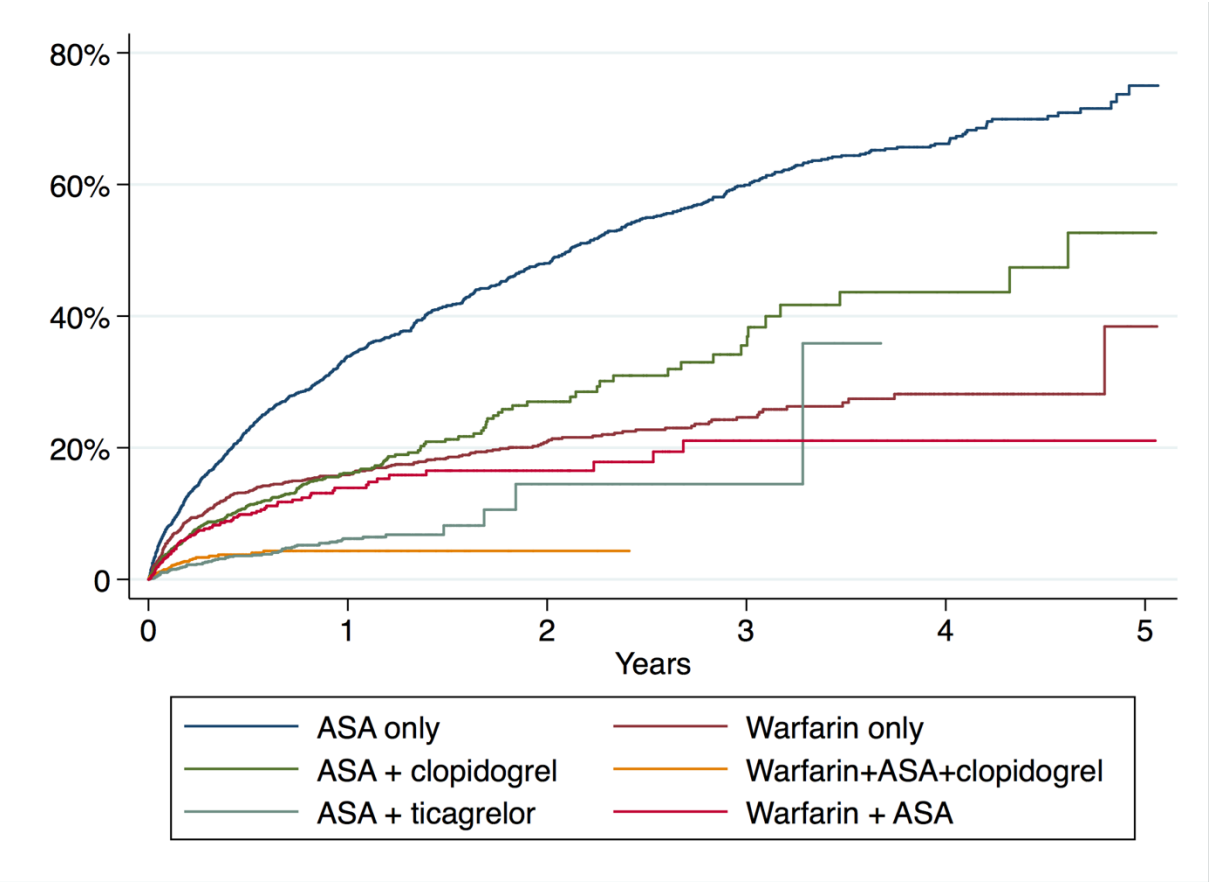


Figure 24. Death from any cause - the most common regimens

Table 38A. Death from any cause - the most common regimens

	All (events=1,646)		No PCI (events=1,522)		PCI without stent (events=22)		PCI with stent (events=102)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
asa n=2,162 events=879	34.5 (32.3-36.9)	reference[A]	35.1 (32.8-37.5)	reference[A]	28.2 (13.4-59.1)	*reference[B]*	19.5 (12.1-31.4)	*reference[C]*
asa+clop n=2,242 events=286	19.8 (17.6-22.2)	0.64 (0.56-0.74)	26.1 (23.0-29.6)	0.67 (0.58-0.78)	16.4 (7.8-34.4)	*0.47 (0.27-0.81)*	7.6 (5.5-10.5)	*0.57 (0.50-0.66)*
asa+tika n=1,355 events=65	6.6 (5.2-8.4)	0.40 (0.31-0.52)	13.8 (10.2-18.8)	0.52 (0.38-0.72)	5.7 (1.4-23.0)	*0.26 (0.13-0.49)*	3.4 (2.2-5.1)	*0.33 (0.25-0.43)*
warfarin n=1,464 events=268	13.0 (11.5-14.7)	0.47 (0.41-0.54)	13.1 (11.6-14.8)	0.46 (0.40-0.53)	8.3 (2.1-33.4)	*0.52 (0.21-1.29)*	9.6 (3.6-25.5)	*0.44 (0.39-0.51)*
wa+asa n=971 events=101	14.8 (12.2-18.0)	0.55 (0.45-0.68)	15.5 (12.7-18.9)	0.54 (0.44-0.67)	6.4 (1.6-25.4)	*0.46 (0.16-1.38)*	9.1 (2.3-36.4)	*0.48 (0.39-0.60)*
wa+asa+clop n=1,446 events=47	8.6 (6.4-11.4)	0.38 (0.28-0.51)	18.7 (12.6-27.9)	0.57 (0.38-0.87)	8.9 (2.2-35.6)	*0.30 (0.15-0.57)*	5.3 (3.4-8.1)	*0.30 (0.22-0.40)*

[A]Multivariable adjustment for age, sex, living alone, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, valvular disease, pacemaker/ICD, hypertension, diabetes, myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer within 3 years, alcohol index, dementia, hospitalization for fall accidents ≥twice, baseline use of statin, digoxin or diuretic. All of these 20 cofactors, with the exception of sex, had a statistically significant association with mortality in univariate analyses.

[B]Adjustment only for age and frequent falls because of few events.

[C]Adjustment for age, sex, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, hypertension, diabetes, myocardial infarction, cancer within 3 years and hospitalization for fall accidents ≥twice (i.e. adjustment for one cofactor for every ten endpoint events).

Baseline characteristics for these patients was presented in Table 6.

Table 38B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	No PCI HR (95% CI)	PCI without stent HR (95% CI)	PCI with stent HR (95% CI)
asa n=2,162 events=879	reference[A]	reference[A]	*reference[B]*	*reference[C]*
asa+clop n=2,242 events=286	0.65 (0.56-0.74)	0.68 (0.59-0.79)	*0.56* *(0.20-1.62)*	*0.42* *(0.23-0.76)*
asa+tika n=1,355 events=65	0.40 (0.31-0.51)	0.53 (0.38-0.72)	*0.31* *(0.06-1.64)*	*0.24* *(0.12-0.47)*
warfarin n=1,464 events=268	0.47 (0.41-0.54)	0.46 (0.40-0.53)	*0.35* *(0.07-1.69)*	*0.46* *(0.15-1.39)*
wa+asa n=971 events=101	0.56 (0.45-0.69)	0.55 (0.45-0.69)	*0.29* *(0.06-1.45)*	*0.35* *(0.08-1.57)*
wa+asa+clop n=1,446 events=47	0.39 (0.29-0.53)	0.61 (0.40-0.92)	*0.53* *(0.10-2.85)*	*0.24* *(0.12-0.47)*

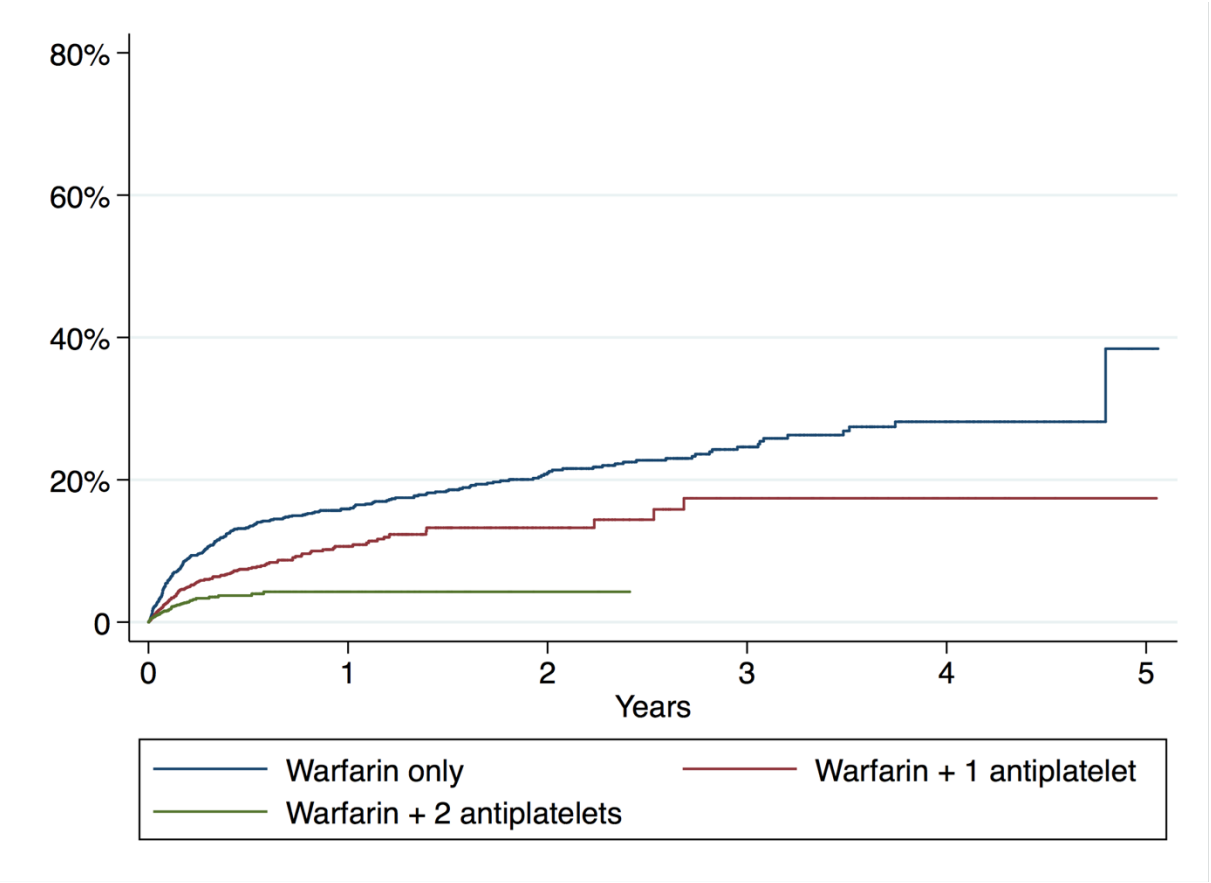


Figure 25. Death from any cause - warfarin combinations

Table 39A. Death from any cause - warfarin combinations

	All (events=470)		No PCI (events=418)		PCI without stent (events=8)		PCI with stent (events=44)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
wa alone n=1,464 events=268	13.0 (11.5-14.7)	reference[A]	13.1 (11.6-14.8)	reference[A]	8.3 (2.1-33.4)	*reference[B]*	9.6 (3.6-25.5)	*reference[C]*
wa+1AP n=1,939 events=148	12.3 (10.5-14.5)	0.82 (0.67-1.02)	15.2 (12.7-18.0)	0.90 (0.72-1.12)	7.3 (2.7-19.4)	*1.00 (0.16-6.13)*	5.3 (3.2-8.6)	*0.39 (0.12-1.24)*
wa+≥2AP n=1,812 events=54	8.8 (6.8-11.5)	0.60 (0.43-0.82)	17.9 (12.4-26.0)	0.84 (0.56-1.27)	8.5 (2.1-33.9)	*1.23 (0.13-11.75)*	5.6 (3.7-8.3)	*0.32 (0.10-1.03)*

[A]Multivariable adjustment for age, sex, living alone, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, valvular disease, pacemaker/ICD, hypertension, diabetes, myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer within 3 years, alcohol index, dementia, hospitalization for fall accidents ≥twice, baseline use of statin, digoxin or diuretic.
[B]Adjustment for age only because of few events.
[C]Adjustment for age, heart failure, diabetes and frequent falls only.
Baseline characteristics for these patients are presented in Table 7.

Table 39B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	No PCI HR (95% CI)	PCI without stent HR (95% CI)	PCI with stent HR (95% CI)
wa alone n=1,464 events=268	reference[A]	reference[A]	*reference[B]*	reference[A]
wa+1AP n=1,939 events=148	0.91 (0.74-1.12)	1.00 (0.81-1.25)	*0.95 (0.16-5.56)*	0.41 (0.14-1.26)
wa+≥2AP n=1,812 events=54	0.70 (0.51-0.96)	0.99 (0.66-1.49)	*1.11 (0.13-9.36)*	0.37 (0.12-1.11)

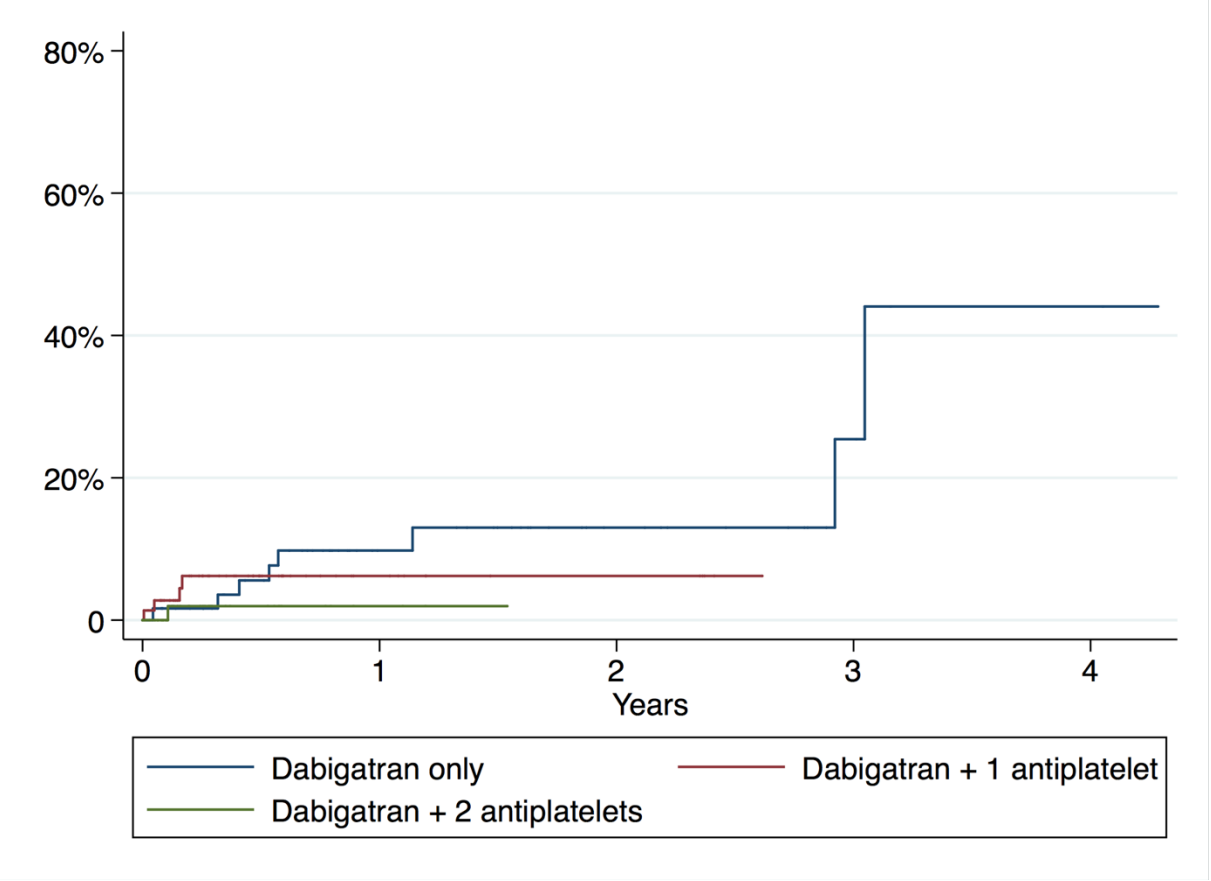


Figure 26. Death from any cause - dabigatran combinations

Table 40A. Death from any cause - dabigatran combinations

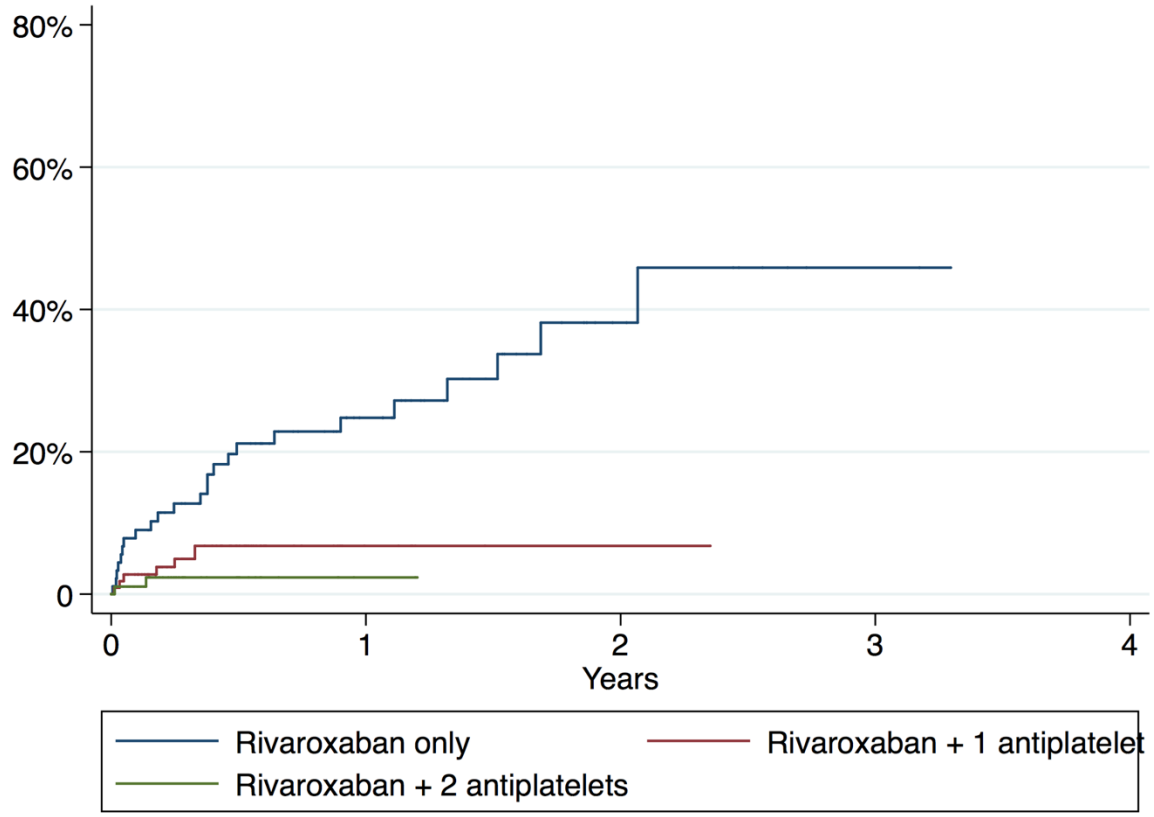
	All (events=13)		No PCI (events=13)		PCI without stent (no events)		PCI with stent (no events)	
	Events per 100 years at risk	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**	**Events per 100 years at risk**	**Multivar HR (95% CI)**
dabi alone n=64 events=8	9.8 (4.9-19.6)	*reference*[A]	9.8 (4.9-19.6)	*reference*[A]	0	*reference*[B]	0	*reference*[B]
dabi+1AP n=74 events=4	9.6 (3.6-25.5)	*1.08 (0.28-4.13)*	15.2 (5.7-40.6)	*1.87 (0.49-7.15)*	0	-	0	-
dabi+≥2AP n=65 events=1	4.8 (0.7-33.9)	*0.48 (0.05-4.48)*	16.6 (2.3-117.9)	*1.60 (0.18-14.42)*	0	-	0	-

[A]Adjustment for age only because of few events.
[B]No adjustments because there were no events.
Baseline characteristics for these patients are presented in Table 8.

Table 40B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	**No PCI HR (95% CI)**	**PCI without stent HR (95% CI)**	**PCI with stent HR (95% CI)**
dabi alone n=64 events=8	*reference*[A]	*reference*[A]	*reference*[B]	*reference*[B]
dabi+1AP n=74 events=4	*1.10 (0.30-4.05)*	*1.79 (0.49-6.55)*	-	-
dabi+≥2AP n=65 events=1	*0.53 (0.06-4.88)*	*1.57 (0.18-13.73)*	-	-

Figure 27. Death from any cause - rivaroxaban combinations



The unadjusted mortality among patients on rivaroxaban monotherapy in Figure 27 is based on 92 patients with a median age of 83 years of whom none had a PCI procedure. Baseline characteristics of these 92 patients are presented in Table 9.

Table 41A. Death from any cause - rivaroxaban combinations

	All (events=32)		No PCI (events=30)		PCI without stent (events=1)		PCI with stent (events=1)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
riva alone n=92 events=24	29.2 (19.6-43.5)	*reference*[A]	29.2 (19.6-43.5)	*reference*[A]	0	*reference*[B]	0	*reference*[B]
riva+1AP n=117 events=6	11.2 (5.3-26.4)	*0.48 (0.19-1.24)*	15.1 (6.3-36.2)	*0.54 (0.19-1.48)*	40.0 (5.6-284.1)	-	0	-
riva+≥2AP n=99 events=2	6.0 (1.5-23.9)	*0.26 (0.05-1.20)*	10.6 (1.5-75.4)	*0.41 (0.05-3.15)*	0	-	4.2 (0.6-29.9)	-

[A]Adjustment for age, heart failure and frequent falls only.
[B]Adjustment not possible.
Baseline characteristics for these patients was presented in Table 8.

Table 41B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	**No PCI HR (95% CI)**	**PCI without stent HR (95% CI)**	**PCI with stent HR (95% CI)**
riva alone n=92 events=24	*reference*[A]	*reference*[A]	*reference*[B]	*reference*[B]
riva+1AP n=117 events=6	*0.48 (0.19-1.20)*	*0.53 (0.19-1.42)*	-	-
riva+≥2AP n=99 events=2	*0.26 (0.06-1.19)*	*0.41 (0.05-3.13)*	-	-

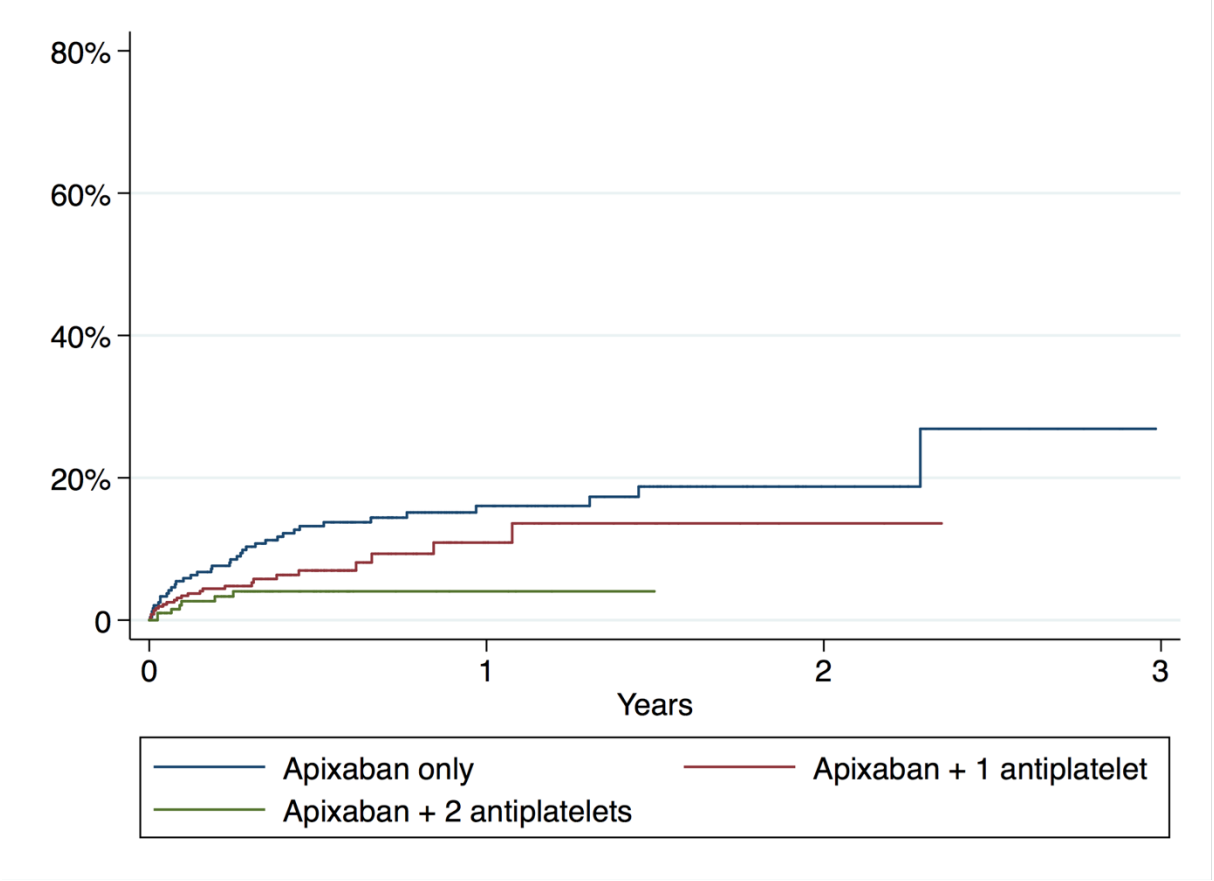


Figure 28. Death from any cause - apixaban combinations

Table 42A. Death from any cause - apixaban combinations

	All (events=68)		No PCI (events=63)		PCI without stent (no events)		PCI with stent (events=5)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
apixa alone n=243 events=37	16.9 (12.3-23.4)	*reference*[A]	17.6 (12.8-24.3)	*reference*[A]	0	*reference*[B]	0	*reference*[B]
apixa+1AP n=369 events=24	14.4 (9.7-21.5)	*0.70 (0.41-1.19)*	20.1 (13.4-30.3)	*0.79 (0.46-1.36)*	0	-	2.2 (0.3-15.8)	-
apixa+≥2AP n=209 events=7	11.3 (5.4-23.7)	*0.45 (0.20-1.06)*	16.2 (5.2-50.2)	*0.40 (0.12-1.35)*	0	-	9.9 (3.7-26.3)	-

[A]Adjusted for age, sex, heart failure, previous myocardial infarction, diabetes, cancer and frequent falls only.
[B]Adjustment not possible.
Baseline characteristics for these patients are presented in Table 9.

Table 42B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	**No PCI HR (95% CI)**	**PCI without stent HR (95% CI)**	**PCI with stent HR (95% CI)**
apixa alone n=243 events=37	*reference*[A]	*reference*[A]	*reference*[B]	*reference*[B]
apixa+1AP n=369 events=24	*0.73 (0.43-1.23)*	*0.81 (0.48-1.39)*	-	-
apixa+≥2AP n=209 events=7	*0.49 (0.21-1.13)*	*0.42 (0.13-1.42)*	-	-

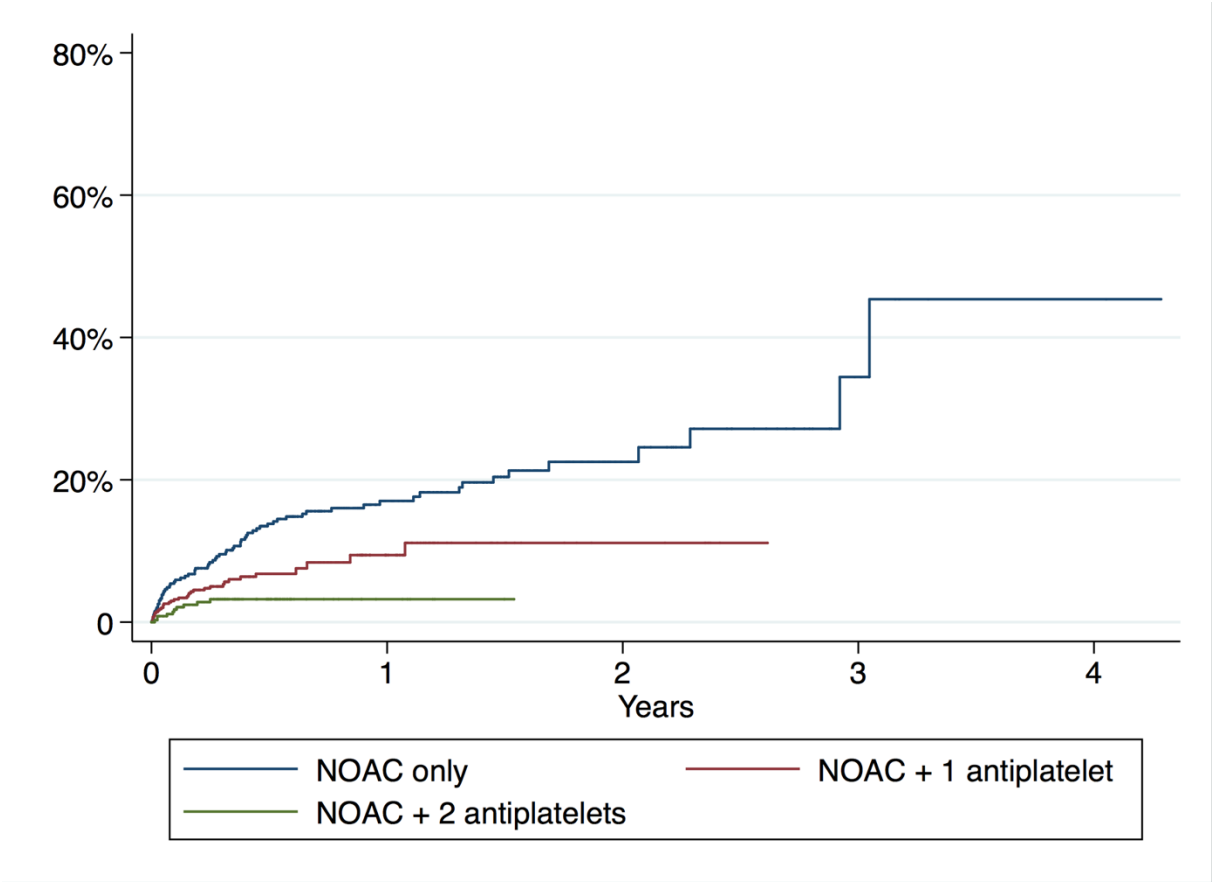


Figure 29. Death from any cause - combinations with any NOAC

Table 43A. Death from any cause - combinations with any NOAC

	All (events=113)		No PCI (events=106)		PCI without stent (events=1)		PCI with stent (events=6)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
NOAC alone n=399 events=69	18.0 (14.3-22.8)	reference[A]	18.5 (14.6-23.4)	*reference[B]*	0	*reference[C]*	0	*reference[C]*
NOAC+1AP n=560 events=34	13.1 (9.4-18.4)	0.63 (0.41-0.98)	18.4 (13.0-26.0)	*0.75 (0.49-1.17)*	9.0 (1.3-63.7)	-	1.4 (0.2-9.6)	-
NOAC+≥2AP n=373 events=10	8.6 (4.6-16.0)	0.41 (0.20-0.82)	14.7 (6.1-35.4)	*0.51 (0.20-1.28)*	0	-	6.4 (2.6-15.3)	-

[A]Adjustment for age, sex, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, hypertension, diabetes, myocardial infarction, cancer within 3 years, alcohol index and hospitalization for fall accidents ≥twice (i.e. adjustment for one cofactor for every ten endpoint events).
[B]Adjustment for age, sex, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, hypertension, diabetes, myocardial infarction, cancer within 3 years and hospitalization for fall accidents ≥ twice.
[C]Adjustment not possible.
Baseline characteristics for these patients are presented in Table 10.

Table 43B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	**No PCI HR (95% CI)**	**PCI without stent HR (95% CI)**	**PCI with stent HR (95% CI)**
NOAC alone n=399 events=69	reference[A]	*reference[B]*	*reference[C]*	*reference[C]*
NOAC+1AP n=560 events=34	0.66 (0.43-1.01)	*0.77 (0.50-1.19)*	-	-
NOAC+≥2AP n=373 events=10	0.43 (0.22-0.86)	*0.53 (0.21-1.34)*	-	-

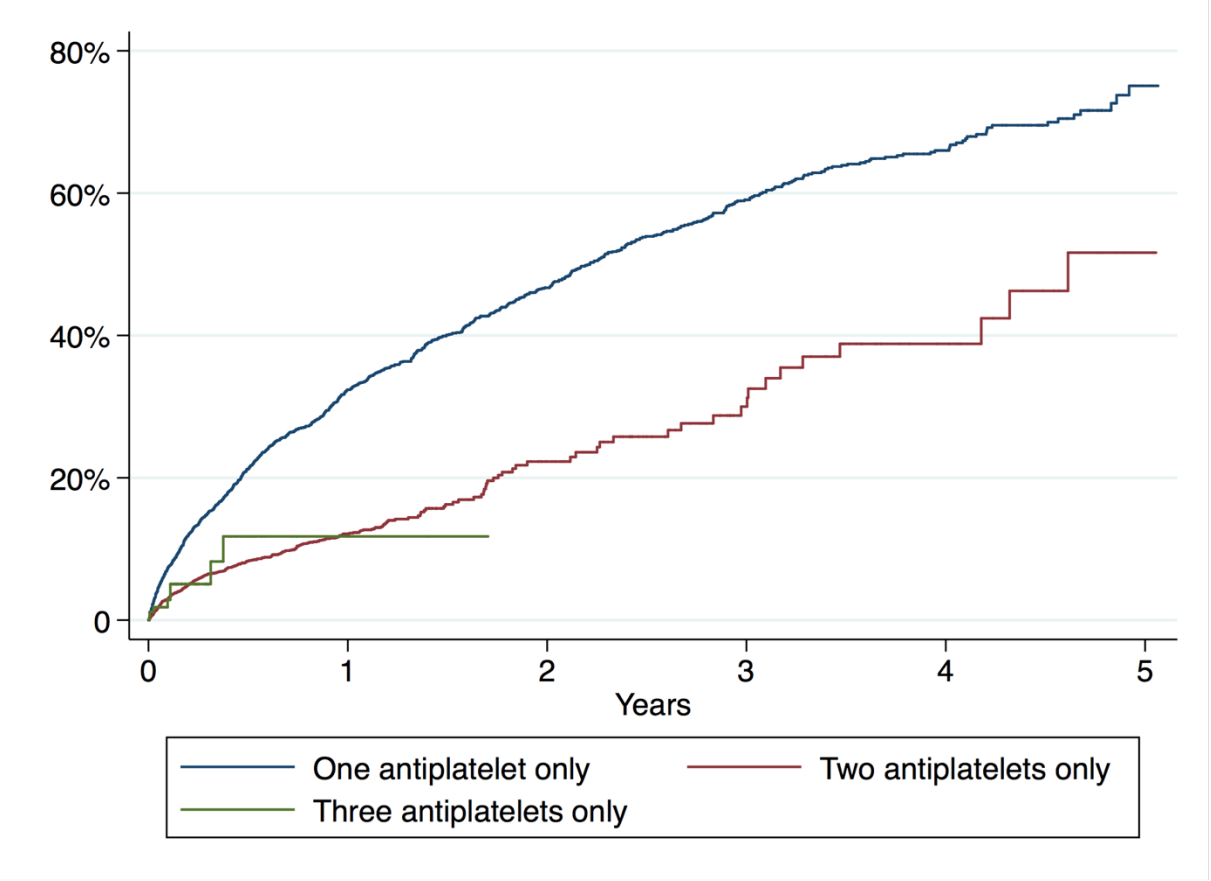


Figure 30. Death from any cause - combinations with antiplatelets only

Patients using only one antiplatelet drug had higher mortality than patients using two or more. This may be due to selection bias and/or to beneficial effects of drug combination treatment.

Table 44A. Death from any cause - combinations with antiplatelets only

	All (events=1,381)		No PCI (events=1,280)		PCI without stent (events=17)		PCI with stent (events=84)	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
1 AP n=2,770 events=1,004	33.9 (31.9-36.0)	reference[A]	35.3 (33.1-37.5)	reference[A]	25.0 (11.9-52.5)	*reference[B]*	13.7 (9.2-20.4)	*reference[C]*
2 AP n=3,805 events=369	14.7 (13.3-16.3)	0.64 (0.56-0.73)	23.4 (20.9-26.2)	0.69 (0.60-0.79)	12.4 (6.7-23.1)	*0.69 (0.25-1.87)*	5.1 (4.0-6.6)	*0.61 (0.36-1.03)*
3 AP n=181 events=8	23.6 (11.8-47.3)	0.66 (0.33-1.32)	30.7 (14.7-64.5)	0.69 (0.33-1.45)	0	-	9.6 (1.4-68.3)	*0.67 (0.09-5.07)*

[A]Adjustment for age, sex, living alone, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, valvular disease, pacemaker/ICD, hypertension, diabetes, myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer within 3 years, alcohol index, dementia, hospitalization for fall accidents ≥twice, baseline use of statin, digoxin or diuretic.

[B]Adjustment only for age and frequent fall accidents.

[C]Adjustment for age, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, previous myocardial infarction, diabetes, cancer within 3 years and frequent falls.

Table 44B. Alternative Weibull regression with the same covariates

	All HR (95% CI)	No PCI HR (95% CI)	PCI without stent HR (95% CI)	PCI with stent HR (95% CI)
1 AP n=2,770 events=1,004	reference[A]	reference[A]	*reference[B]*	*reference[C]*
2 AP n=3,805 events=369	0.63 (0.55-0.71)	0.69 (0.60-0.79)	*0.62 (0.23-1.67)*	*0.53 (0.32-0.87)*
3 AP n=181 events=8	0.68 (0.34-1.37)	0.71 (0.34-1.50)	-	*0.65 (0.09-4.95)*

Table 45. Death from any cause - combinations with any OAC/NOAC

	OAC alone n=3,492 events=337		**OAC+1AP n=3,158 events=182**		**OAC+≥2AP n=2,904 events=64**	
	Events per 100 yrs at risk	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**	**Events per 100 yrs at risk**	**Multivar HR (95% CI)**
No PCI n=4,371 events=524	14.0 (12.5-15.6)	reference[A]	15.7 (13.5-18.3)	reference[A]	17.4 (12.3-24.4)	reference[A]
PCI n=2,176 events=59	8.1 (3.6-18.0)	1.05 (0.46-2.38)	5.0 (3.3-7.5)	0.50 (0.31-0.79)	5.8 (4.0-8.2)	0.53 (0.31-0.90)

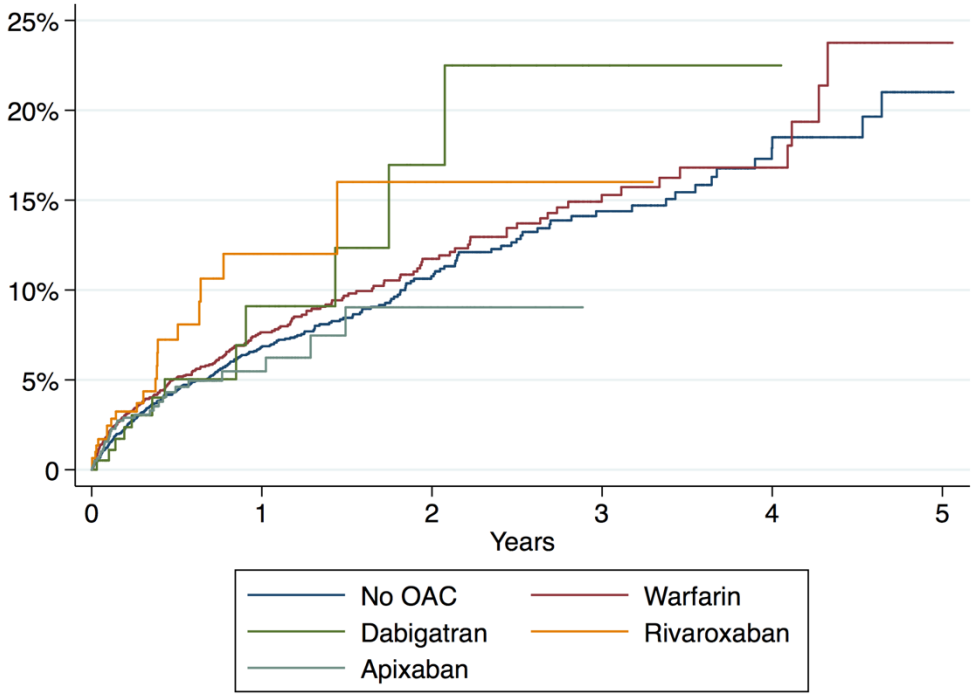
[a]Adjustment for age, sex, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, hypertension, diabetes, myocardial infarction, cancer within 3 years, alcohol index and hospitalization for fall accidents ≥twice (i.e. adjustment for one cofactor for every ten endpoint events).

10.4 Main results

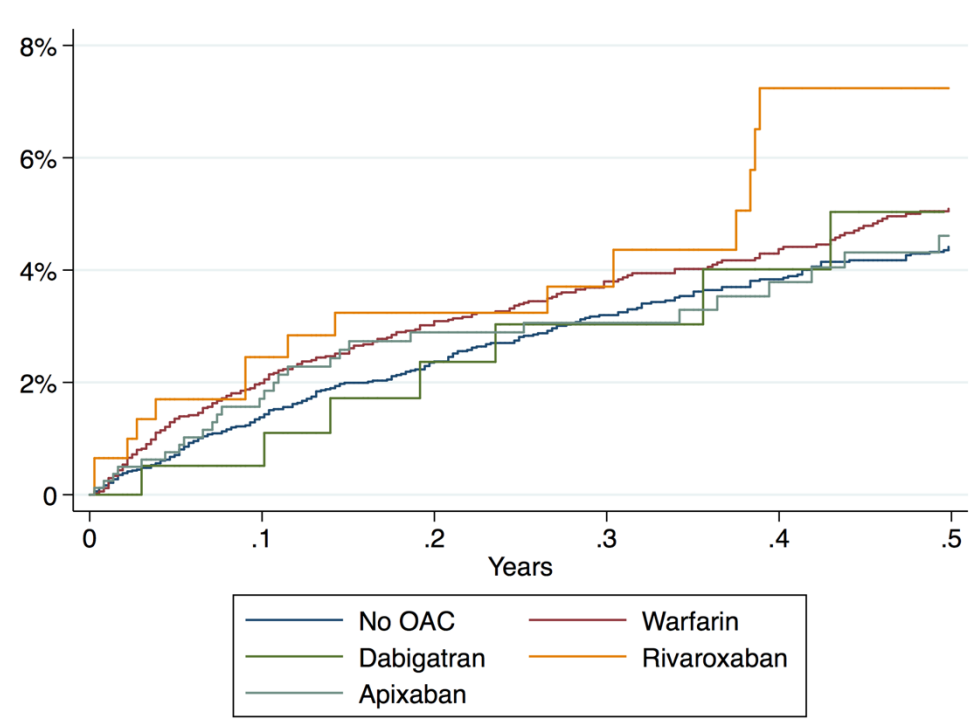
Described in Section 10.3 (Outcome data).

10.5 Other analyses

10.5.1 Unadjusted comparison of outcomes with other oral anticoagulants



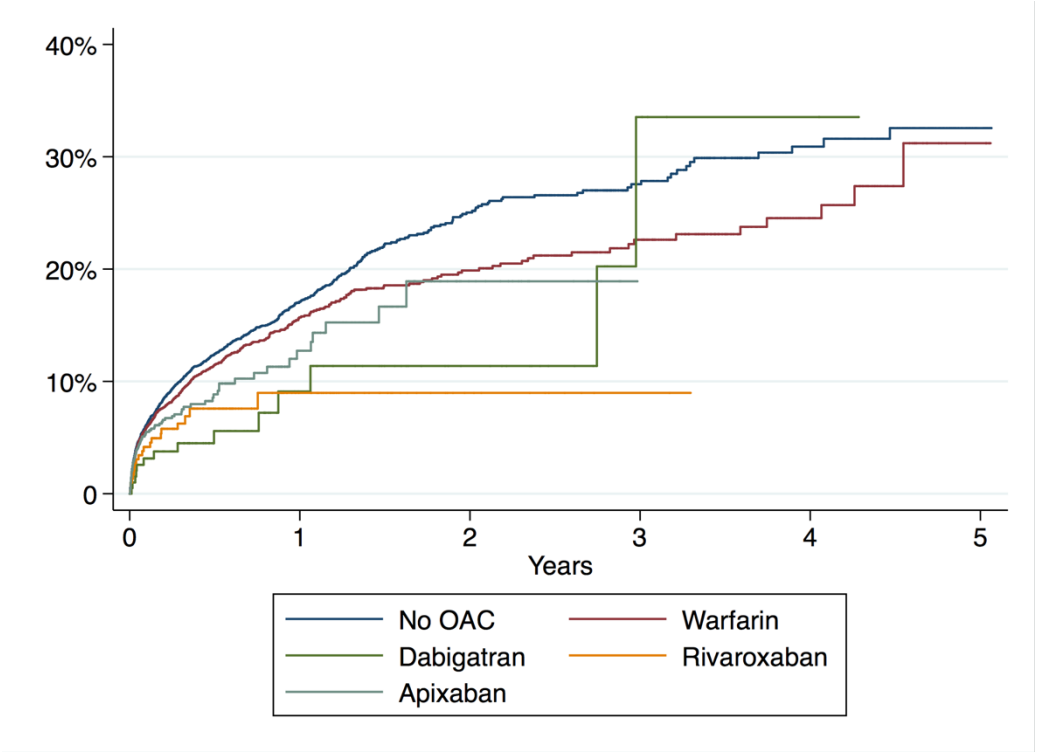
(A)



(B)

Figure 31. (A) Major bleeding endpoint (B) Major bleeding endpoint during the first 6 months

(A)



(B)

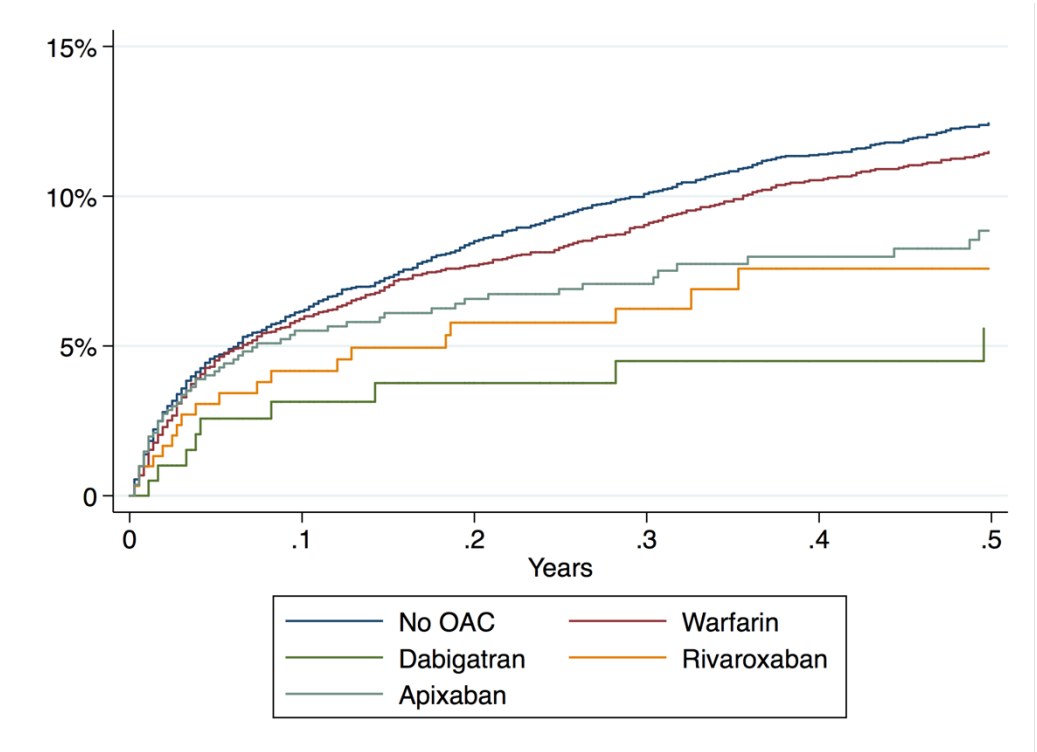
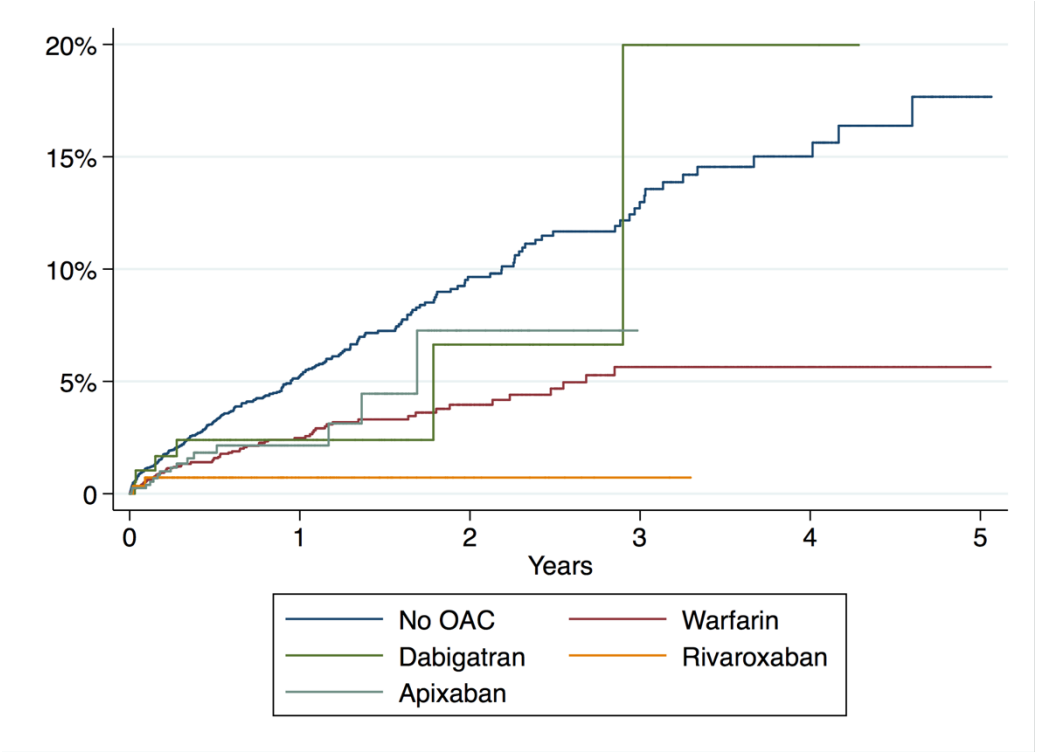


Figure 32. (A) Hospitalization for new ACS episode (B) Hospitalization for new ACS episode during the first 6 months

(A)



(B)

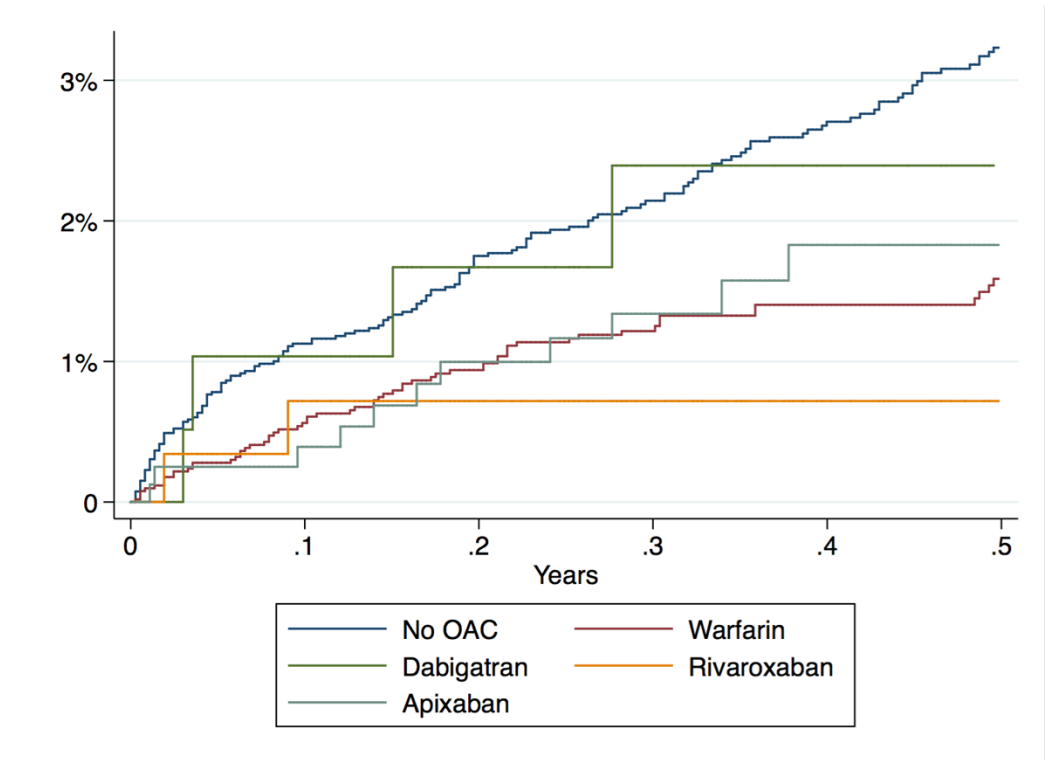
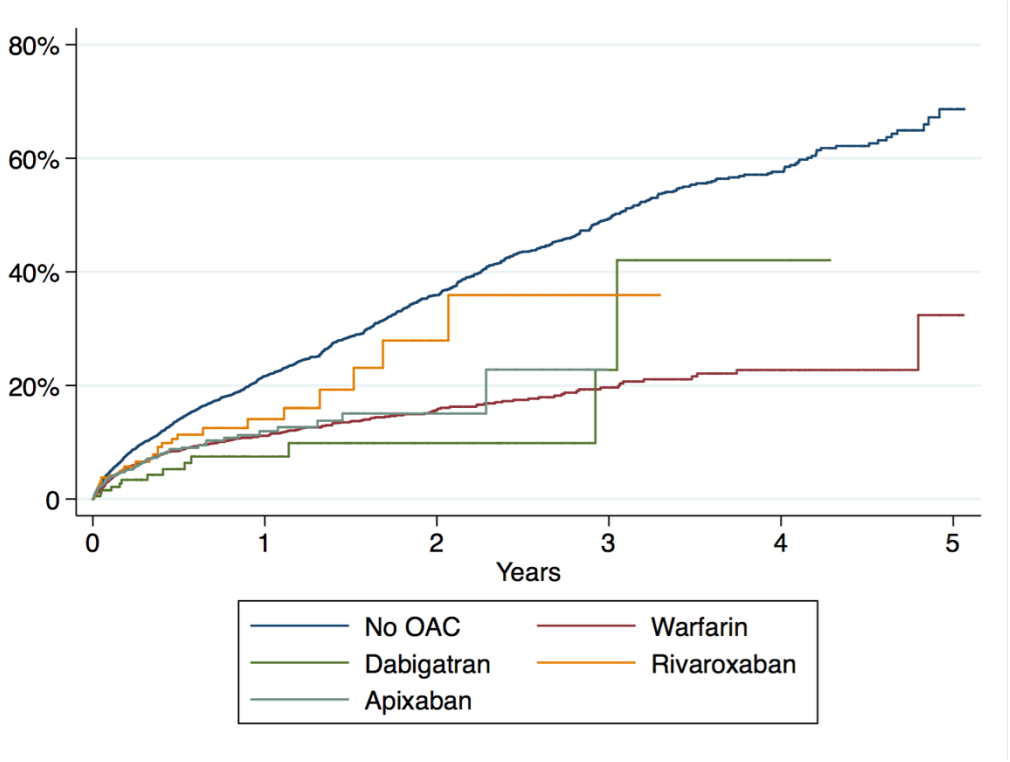


Figure 33. (A) Ischaemic stroke or systemic embolism (B) Ischaemic stroke or systemic embolism during the first 6 months

(A)



(B)

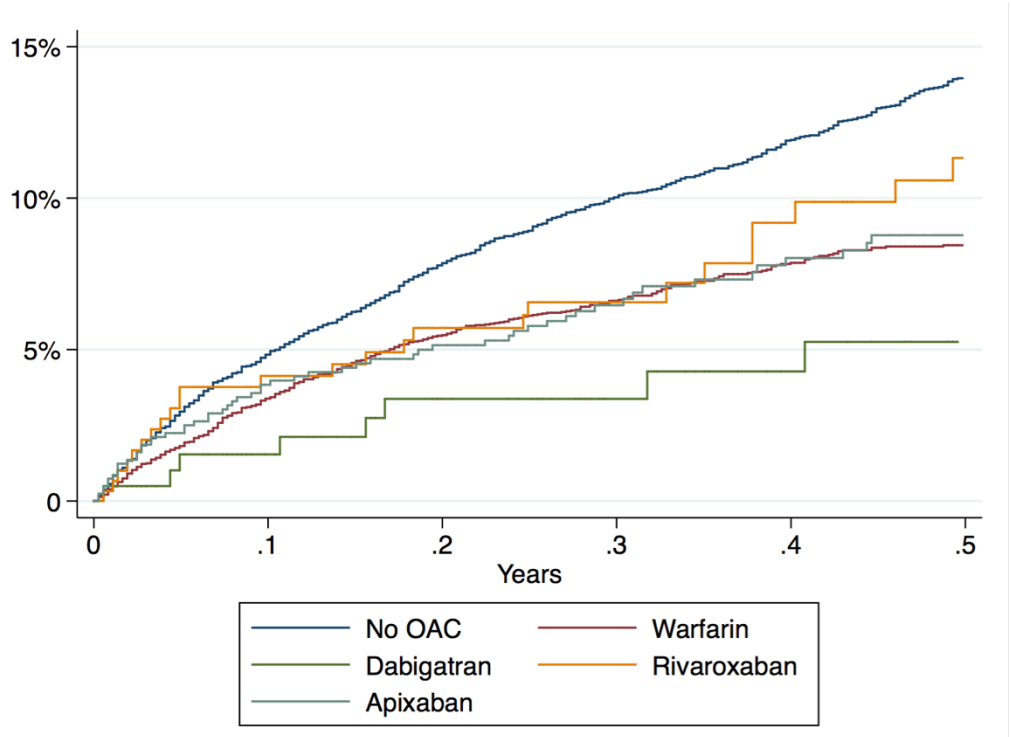


Figure 34. (A) Death from any cause (B) Death from any cause during the first 6 months

Table 46. Adjusted comparisons between rivaroxaban and warfarin - main bleeding endpoint

	All						Propensity score matched subset[A]					
	n	Cum events	Cum years at risk	Events per 100 yrs at risk	Cox (95% CI)	Weibull (95% CI)	n	Cum events	Cum years at risk	Events per 100 yrs at risk	Cox (95% CI)	Weibull (95% CI)
Warfarin	5,215	295	3,736	7.9 (7.0-8.9)	reference[B]	reference[B]	304	11	202	5.5 (3.0-9.8)	reference[C]	reference[C]
Rivaroxaban	308	20	160	12.5 (8.0-19.3)	1.57 (0.99-2.48)	1.57 (0.99-2.47)	304	20	159	12.5 (8.1-19.5)	1.96 (0.94-4.09)	2.07 (0.99-4.33)

[A]Differences between the rivaroxaban and warfarin cohorts before and after propensity score matching is shown in Table 52.
[B]Multivariable adjustment for age, sex, duration of AF, previous hospitalization with bleeding diagnosis, anaemia, chronic kidney disease, diabetes, alcohol index, baseline use of NSAID or PPI.
[C]Univariate without further adjustments.

Table 47. Individual bleeding diagnoses among rivaroxaban treated patients

Pat nr	Sex	Age	Regimen	Main diagnosis	Secondary bleeding diagnoses	Comment
1	F	95	riva 20 mg	Maelena	-	Transfusion. Previously hospitalized for GI-bleeding
2	M	76	riva 15 mg +tika	Caecal cancer	Gastric ulcer with bleeding (as 3rd secondary diagnosis)	
3	M	74	riva 15 mg +clop	Mitral insufficiency	Anemia (10th secondary diagnosis), Duodenal ulcer with bleeding (as 18th and last secondary diagnosis)	Transfusion and dialysis. Both renal failure and heart failure.
4	M	72	riva 20 mg +asa+clop	GI-bleed, unspecified	-	Gastroscopy and coloscopy
5	F	78	riva 15 mg +asa+clop	Nosebleed		Tamponade applied
6	F	85	riva 15 mg	Haematemesis	-	Transfusion. Dementia with gastrostomy.
7	F	79	riva 20 mg +clop	Haematuria	Cancer in the bladder	Transfusion. CHADSVASC 8, HASBLED 5
8	M	74	riva 20 mg +asa+clop	Gastric ulcer with bleeding	-	Transfusion.
9	F	79	riva 15 mg +asa+clop	Nosebleed	-	Tamponade applied. Transfusion Diabetes and chronic kidney disease.
10	M	82	riva 20 mg	Duodenal ulcer without bleeding	Anaemia after major bleeding (3rd secondary),	Lung cancer (1st secondary diagnosis)
11	M	70	riva 15 mg +asa+clop	Other gastritis	Iron defiency anaemia secondary to chronic blood loss (1st secondary)	Endoscopic electrocoagulation in the ventrice
12	F	84	riva 20 mg +clop	Iron defiency anaemia secondary to chronic blood loss	-	Transfusion. Gastroscopy. Coloscopy.
13	F	72	riva 15 mg +asa	Nosebleed	-	Tamponade applied.
14	M	87	riva 15 mg +clop	Maelena	-	Gastroscopy. Rectoscopy.
15	M	76	riva 15 mg +tika	GI-bleed, unspecified	Benign tumour of the colon	Endoscopic polypectomy in the rectum
16	F	88	riva 15 mg	Acute renal failure	Chronic gastric ulcer without bleeding (6th secondary), anaemia after major bleeding (7th secondary)	Transfusion. Gastroscopy with biopsy. Coloscopy.
17	F	81	riva 15mg +tika	Subdural bleeding	-	Bladder cancer. **DIED IN HOSPITAL.**
18	F	80	riva 15 mg	Chronic obstructive pumonary disease	Anaemia, unspecified (1st secondary) Diverticulosis of colon (8th secondary) GI-bleed, unspecified (9th secondary)	Sigmoidoscopy
19	F	89	riva 20 mg	Pertrochanteric fracture of the hip	GI-bleed, unspecified (4th secondary)	Hip surgery with fixation. Transfusion. Previously hospitalized with bleeding diagnosis.
20	M	83	riva 20 mg	Atrial fibrillation (as underlying cause of death)	Intracerebral bleeding as first contributory cause of death	**DIED OUT OF HOSPITAL**

Table 48. Adjusted comparisons between rivaroxaban and warfarin - new hospitalization for ACS

	All						Propensity score matched subset					
	n	Cum events	Cum years at risk	Events per 100 yrs at risk	Cox (95% CI)	Weibull (95% CI)	n	Cum events	Cum years at risk	Events per 100 yrs at risk	Cox (95% CI)	Weibull (95% CI)
Warfarin	5,215	595	3,420	17.4 (16.1-18.9)	reference[A]	reference[A]	304	29	188	15.4 (10.7-22.2)	reference[B]	reference[B]
Rivaroxaban	308	20	161	12.4 (8.0-19.3)	0.66 (0.42-1.02)	0.67 (0.43-1.05)	304	20	160	12.5 (8.1-19.4)	0.71 (0.40-1.26)	0.73 (0.41-1.29)

[A]Adjustment for age, sex, previous myocardial infarction, peripheral artery disease, heart failure, diabetes, chronic kidney disease, baseline use of beta blocker or a statin.
[B]Univariate without further adjustments.

Table 49. Adjusted comparisons between rivaroxaban and warfarin - ischaemic stroke or systemic embolism

	All						Propensity score matched subset					
	n	Cum events	Cum years at risk	Events per 100 yrs at risk	Cox (95% CI)	Weibull (95% CI)	n	Cum events	Cum years at risk	Events per 100 yrs at risk	Cox (95% CI)	Weibull (95% CI)
Warfarin	5,215	97	3,813	2.5 (2.1-3.1)	reference[A]	reference[A]	304	3	207	1.4 (0.5-4.5)	reference[B]	reference[B]
Rivaroxaban	308	2	165	1.2 (0.3-4.8)	0.48 (0.12-1.94)	0.49 (0.12-1.99)	304	2	164	1.2 (0.3-4.9)	0.73 (0.12-4.39)	0.75 (0.13-4.51)

[A]Adjustment for age, sex, previous ischaemic stroke, systemic embolism or TIA, hypertension, heart failure, diabetes, vascular disease.
[B]Univariate without further adjustments.

Table 50. Adjusted comparisons between rivaroxaban and warfarin - death from any cause

	All						Propensity score matched subset					
	n	**Cum events**	**Cum years at risk**	**Events per 100 yrs at risk**	**Cox (95% CI)**	**Weibull (95% CI)**	**n**	**Cum events**	**Cum years at risk**	**Events per 100 yrs at risk**	**Cox (95% CI)**	**Weibull (95% CI)**
Warfarin	5,215	470	3,875	12.1 (11.1-13.3)	reference[A]	reference[A]	304	31	208	14.9 (10.5-21.2)	reference[B]	reference[B]
Rivaroxaban	308	32	166	19.3 (13.6-27.2)	1.67 (1.16-2.39)	1.72 (1.20-2.47)	304	30	165	18.2 (12.7-26.0)	1.09 (0.66-1.80)	1.09 (0.66-1.81)

[A]Adjustment for age, sex, living alone, ischaemic or haemorrhagic stroke, chronic kidney disease, heart failure, valvular disease, pacemaker/ICD, hypertension, diabetes, myocardial infarction, peripheral artery disease, chronic obstructive pulmonary disease, cancer within 3 years, alcohol index, dementia, hospitalization for fall accidents ≥twice, baseline use of statin, digoxin or diuretic.

[B]Univariate without further adjustments.

Comment: The mortality in the rivaroxaban cohort was related to bleeding in two of 32 cases. One was an 83 year old male using rivaroxaban in monotherapy who died from an intracerebral haemorrhage after 234 days on treatment, and the other was a 81 year old woman with post-stroke dementia who was using rivaroxaban in combination with ticagrelor and died with a diagnosis of subdural bleed and brain compression 10 days after initiating treatment. The individual causes of death for patients on rivaroxaban treatment are presented in Table 45.

Table 51. Individual causes of death among rivaroxaban treated patients

Pat nr	Sex	Age	Regimen	Underlying cause of death	First contributing cause of death	Bleed
1	M	83	riva	heart failure	heart failure	
2	M	79	riva+clop	pancreatic cancer	pancreatic cancer	
3	M	83	riva	chronic ischaemic heart disease	heart failure	
4	F	68	riva	permanent AF	embolic stroke	
5	F	85	riva	chronic ischaemic heart disease	heart arrest (sic!)	
6	F	90	riva	chronic ischaemic heart disease	heart failure	
7	F	84	riva	chronic obstructive pulmonary disease	respiratory insufficiency	
8	M	75	riva+asa	ruptured aortic aneurysm	heart arrest (sic!)	
9	F	86	riva	acute ischaemic heart disease	acute respiratory insufficiency	
10	F	87	riva	B-cell lymphoma	-	
11	M	81	riva+asa+clop	atherosclerotic heart disease	acute ischaemic heart disease	
12	F	87	riva	acute myocardial infarction	heart arrest (sic!)	
13	F	77	riva+asa+clop	other undefined cause of death	other undefined cause of death	
14	F	88	riva	stroke, unspecified	stroke, unspecified	
15	F	94	riva	hypetensive heart disease with chf	heart failure	
16	F	82	riva	unspecified dementia	shock, unspecified	
17	M	81	riva	chronic ischaemic heart disease	heart failure	
18	F	87	riva	acute myocardial infarction	heart failure	
19	F	87	riva	diabetes mellitus type 2	heart arrest (sic!)	
20	M	84	riva	late effects of cerebrovascular disease	heart failure	
21	M	83	riva	Alzheimer's disease	Alzheimer's disease	
23	F	84	riva	unspecified dementia	fatigue	
24	F	80	riva	pancreatic cancer	pancreatic cancer	
24	M	72	riva+clop	heart failure	heart failure	
25	F	84	riva+clop	chronic obstructive pulmonary disease	pneumonia	
26	M	83	riva	permanent AF	intracerebral bleed, unspecified	x
27	M	72	riva+tika	localized brain atrophy	pneumonia	
28	F	88	riva	septicaemia, unspecified	-	
29	F	81	riva+tika	subdural bleeding	compression of the brain	x
30	M	89	riva	permanent AF	renal failure, unspecified	
31	M	92	riva	acute myocardial infarction	heart failure	
32	F	78	riva	chronic obstructive pulmonary disease	respiratory insufficiency, unspecified	

Table 52. Baseline characteristics before and after PS-matching

		Before PS-matching			After PS-matching		
		Rivaroxaban (n=308)	Warfarin (n=5,209)	p-value	Rivaroxaban (n=304)	Warfarin (n=304)	p-value
Procedure	No PCI	67.9%	66.0%	0.755	67.8%	64.1%	0.626
	PCI without stent	2.6%	3.1%		2.6%	2.6%	
	PCI with stent	29.6%	31.0%		29.6%	33.2%	
AFduration, years [A]	mean	2.8±4.2	4.7±4.8	**<0.001**	2.8±4.1	3.1±4.0	0.260
	median	0.5	3.1		0.5	1.3	
Demography							
Female sex		41.9%	37.8%	0.150	41.8%	47.4%	0.165
Age, years	mean	77.4±8.9	78.4±8.8	**0.036**	77.4±8.9	77.4±9.4	0.886
	median	78	80		78	79	
	Q1-Q3	72-84	73-85		72-84	71-84	
Living alone		53.6%	51.4%	0.461	54.0%	54.0%	1.000
University level studies		18.2%	15.0%	0.153	17.8%	14.8%	0.801
Income (1000 SEK), median		170	169	0.726	170	168	0.490
Immigrant		18.2%	12.8%	**0.007**	17.4%	17.8%	0.915
Medical history							
CHA_2DS_2-VASc score	mean	4.9±1.8	5.1±1.7	**0.022**	4.9±1.8	4.9±1.6	0.903
	median	5	5		5	5	
	Q1-Q3	4-6	4-6		4-6	4-6	
HASBLED score	mean	2.8±1.0	3.0±1.0	**0.048**	2.8±1.0	2.8±0.9	0.581
	median	3	3		3	3	
	Q1-Q3	2-3	2-4		2-3	2-3	
Hospitalized with bleeding		14.3%	15.9%	0.447	14.1%	10.9%	0.220
Intracranial		2.9%	2.3%	0.455	3.0%	1.3%	0.161
Gastrointestinal		6.8%	9.4%	0.135	6.6%	7.6%	0.635
Urogenital		10.1%	10.4%	0.849	9.9%	9.5%	0.891
Other		4.9%	6.0%	0.412	4.6%	3.6%	0.540
Thromboembolic event		23.4%	29.0%	**0.033**	23.4%	23.6%	0.924
Ischaemic stroke		16.2%	19.9%	0.119	16.5%	17.4%	0.746
Unspecified stroke		3.6%	6.2%	0.060	3.6%	5.3%	0.325
Systemic embolism		2.0%	2.4%	0.613	2.0%	1.6%	0.761
TIA		8.1%	11.2%	0.092	7.9%	8.2%	0.882
Myocardial infarction >30 days before index		29.2%	33.9%	0.092	29.6%	26.3%	0.366
Peripheral artery disease		11.4%	14.9%	0.086	11.2%	11.8%	0.799
Heart failure		42.9%	50.7%	**0.007**	43.1%	39.1%	0.323
Mechanical heart valve		0.7%[B]	3.5%	**0.007**	0.3%	0.7%	0.563
Pacemaker/ICD		13.3%	15.7%	0.261	13.2%	9,5%	0.160
Hypertension		78.6%	80.2%	0.485	70.0%	79.3%	0.921
Diabetes		31.5%	33.0%	0.584	31.9%	29.3%	0.481
Cancer within 3 years		12.3%	10.4%	0.293	12.5%	11.2%	0.616
Anaemia		15.9%	17.6%	0.452	15.8%	18.4	0.389
Chronic kidney disease		5.8%	11.8%	**0.002**	5.9%	4.6%	0.468
Liver disease		1.6%	1.3%	0.635	1.6%	1.6%	1.000
Dementia		4.9%	2.5%	**0.013**	4.3%	4.9%	0.699
Frequent falls		6.2%	5.2%	0.480	6.3%	6.3%	1.000
Drugs dispensed within 4 months before up to one week after hospital discharge							
Beta blocker		90.9%	87.9%	0.112	91.5%	89.8%	0.487
Digoxin		13.3%	18.7%	**0.017**	13.5%	11.5%	0.462
Class 1 anti-arrhythmic		0.3%	0.9%	0.289	0.3%	0.3%	1.000
Class 3 anti-arrhythmic		4.6%	5.3%	0.547	4.6%	3.3%	0.405
ACE-inhibitor		45.8%	50.6%	0.101	46.1%	44.1%	0.625
ARB		31.8%	30.1%	0.524	31.9%	34.5%	0.491
Diuretic		52.3%	60.6%	**0.004**	52.3%	53.6%	0.745
Statin		69.8%	73.1%	0.214	70.7%	69.7%	0.790
NSAID		3.9%	3.4%	0.640	4.0%	2.6%	0.363
Proton pump inhibitor		44.8%	42.2%	0.371	44.7%	46.1%	0.745

[A]Years since first diagnosis of AF.

[B] Two riva patients had mechanical heart valves at index. The first was an 80 year old male on riva 15mg + asa + clopidogrel initiated in May 2015 who survived the observation period without events. The other was an 83 year old male using riva 20mg initiated in August 2015 who died from an intracerebral bleeding. This latter patient remained in the propensity score matched cohort.

Tests for diffferences between groups were made with Chi2 test for cathegorical variables, and with Wilcoxon's rank sum test for continuous variables. In the context of comparing mean values, the CHA2DS2-VASc and HASBLED scores were treated as continuous.

10.6 Safety data (Adverse events/adverse reactions)

As per the EMA Guideline on Good Pharmacovigilance Practices (Module VI–Management and reporting of adverse reactions to medicinal products), for non-interventional study designs that are based on secondary use of data, individual reporting of adverse reactions is not required. No expedited reporting of adverse events or reactions is required.

11. Discussion

11.1 Key results

There was a great diversity in treatments given to AF patients who had ACS-episodes. The most common regimes did not include an oral anticoagulant, in contrast to current national and international guideline recommendations. Dual antiplatelet therapy, the standard treatment for ACS patients without AF, is frequently used for AF patients as well.

Elderly and frail patients, at high risk for both bleeds and thromboses, generally received less aggressive antithrombotic drug regimens than younger and healthier patients. This complicated the interpretation of outcome data. Differences in bleeding rates between high risk and low risk patients were attenuated by the choice of antithrombotic regimen, while differences regarding ischaemic stroke and reinfarction may have been exaggerated for the same reason. The diversity of regimens made most of the groups including a NOAC too small for valid comparisons of the benefits or risks associated with individual regimens.

11.2 Limitations

There is a possibility for unmeasured confounders for bleeding affecting the data, e.g. inadequate or missing recording of ethnicity, alcohol intake or over-the-counter use of some medications. Confounding by indication is also probable e.g. patients with renal failure are more likely to receive warfarin than other OACs. Some unmeasured confounding may have occurred due to missing or imprecisely reported and recorded information, i.e. on alcohol consumption, smoking or drug abuse; however, as the study has a descriptive nature capture of these data is not relevant for addressing the research questions.

Data in the registries are mostly binary, while risk is a continuum. For example, a diagnosis of hypertension will cover both patients with borderline hypertension and malignant hypertension, although the impact on the prognosis is very different. In patients with poor health, in whom many different diagnoses could be used at discharge, competition between diagnoses is likely to lead to omission of less severe or acute diagnoses that would have been listed in patients with fewer concomitant diseases. Over-reporting of disease is uncommon, whereas under-reporting is very common, especially for life style related conditions like obesity or alcoholism. Thus, risk scores according to CHA_2DS_2-VASc are likely to represent underestimates of the true scores.

Information on prescriptions dispensed but not used, and about drugs used by hospitalized patients, are not captured. The information about the exposure to warfarin will be inexact due to the highly varying dosages of warfarin. There is no standard dose from which the time the

dispensed drug quantity can be calculated. The interval between refill purchases is only a surrogate for this, which will be less precise in patients with few refills and short follow up than in patients with many refills and long follow-up. Therefore, interpretation of differences in outcomes related to analysed treatment regimens involving warfarin should be made with caution considering that the exposure to warfarin will be determined using a different method than other antithrombotic drugs.

The study findings may not be representative for other countries as this study is based on Swedish data only; however, it might be applicable to other Scandinavian settings with similar health systems. The findings could also be extrapolated to at least several other European settings with similar population structure and treatment approaches. Besides, the study is representative for Sweden as it captures the entire population.

11.3 Interpretation

11.4 Generalizability

12. Other information

13. Conclusion

This study shows that there is no single standard therapy for patients with AF who also have an episode of ACS. As many as 93 different treatment combinations were identified from drug dispensings occurring up to 7 days after hospital discharge. The number of regimens increases further if different dose strengths, durations of treatment and drug sequences are considered. An impact of current guideline recommendations regarding this patient group was difficult to detect. There is little or no scientific evidence regarding the benefit or harm for the majority of these regimens.

There were clear differences between patients given different regimens; more potent antithrombotic regimens were generally given to younger and healthier patients with lower perceived bleeding risks. Elderly patients with higher perceived bleeding risk were more often given regimens consisting of only antiplatelet drugs and no oral anticoagulation. It was not possible to determine which treatment regimen was better or worse because of selection biases and undocumented reasons why doctors preferred one treatment over the other. Neutralizing effects could be observed where high risk patients with low risk drug combinations had bleeding rates similar to those of low risk patients using high risk drug combinations.

The most common treatment among patients with ACS and AF was dual antiplatelet therapy, the standard treatment for ACS patients without AF, indicating that the awareness of the need for oral anticoagulation in this patient population was not adequately recognized by prescribing doctors.

14. References

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15. Appendices

Annex 1. List of stand-alone documents

Annex 2. Additional information

Table 53. Details of the specific codes behind the main bleeding outcome

Code	Meaning	Number
I60	Subarachnoid haemorrhage	8
I61	Intracerebral haemorrhage	65
I62	Sub- and epidural haemorrhages	44
S064	Traumatic epidural haemorrhages	1
S065	Traumatic subdural haemorrhages	47
S066	Traumatic subarachnoid haemorrhages	26
K226	Gastro-oesophageal laceration-haemorrhage syndrome (Boerhave)	4
K250	Gastric ulcer - Acute with haemorrhage	35
K252	Gastric ulcer - Acute with both haemorrhage and perforation	2
K254	Gastric ulcer - Chronic or unspecified with haemorrhage	4
K256	Gastric ulcer - Chronic or unspecified with both haemorrhage and perforation	-
K260	Duodenal ulcer - Acute with haemorrhage	33
K262	Duodenal ulcer - Acute with both haemorrhage and perforation	-
K264	Duodenal ulcer - Chronic or unspecified with haemorrhage	2
K266	Duodenal ulcer - Chronic or unspecified with both haemorrhage and perforation	-
K270	Unspecified peptic ulcer - Acute with haemorrhage	4
K272	Unspecified peptic ulcer - Acute with both haemorrhage and perforation	-
K274	Unspecified peptic ulcer - Chronic or unspecified with haemorrhage	1
K276	Unspecified peptic ulcer - Chronic or unspecified with both haemorrhage and perforation	-
K280	Gastrojejunal ulcer - Acute with haemorrhage	-
K282	Gastrojejunal ulcer - Acute with both haemorrhage and perforation	-
K284	Gastrojejunal ulcer - Chronic or unspecified with haemorrhage	-
K286	Gastrojejunal ulcer - Chronic or unspecified with both haemorrhage and perforation	-
K290	Acute haemorrhagic gastritis	12
K625	Haemorrhage of anus and rectum	38
K661	Haemoperitoneum	-
K920	Haematemesis	21
K921	Melaena	63
K922	Unspecified gastrointestinal haemorrrhage	279
I850	Oesophageal varices with bleeding	2
I983	Oesophageal varices with bleeding in diseases classified elsewhere	-
N02	Recurrent and persistent haematuria	1
R319	Unspecified haematuria	209
N939	Abnormal uterine and vaginal bleeding, unspecified	-
N950	Postmenopausal bleeding	10
N501A	Unspecified bleeding in the male genital organs	-
H113	Conjunctival haemorrhage	-
H313	Choroidal haemorrhage and rupture	-
H356	Retinal haemorrhage	1
H431	Vitreous haemorrhage	6
H450	Vitreous haemorrhage in diseases classified elsewhere	-
H922	Otorraghia	-
I312	Haemopericardium	6
J942	Haemothorax	7
M250	Haemarthrosis	4
R04	Epistaxis, haemothysis and other haemorrhages from the respiratory passsages	123
R58	Haemorrhage not otherwise specified	20
D500	Iron deficiency anaemia secondary to blood loss (chronic)	43
D629	Acute posthaemorrhagic anaemia	127

Table 54. Definitions of medical history: events of interest and concomitant diseases

Covariate	ICD-10 or procedure code beginning with
Intracerebral bleed[A]	**I60-61, I690-I691**
Intracranial bleed	I60-62, S064-066 , I690-692
Gastrointestinal bleed	I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922
Urogenital bleed	N02, R319, N950, **N939, N501A**
Other bleed	**H113, H313, H356,** H431, **H450, H922, I312, J942, M250,** R04, R58, **D500,** D629, **T810, Z513,** procedure code DR029, **DR033**
anybleedhosp	**overnight stay with I60-62, S064-066 , I690-692, I850, I983, K226, K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K284, K286, K290, K625, K661, K920, K921, K922, N02, R319, N950, N939, N501A, H113, H313, H356, H431, H450, H922, I312, J942, M250, R04, R58, D500, D629, T810, Z513, procedure code DR029, DR033**
Ischaemic stroke	I63, I693
Unspecified stroke	I64, I694
Systemic emboli	I74
TIA	G45
Thromboembolism	I63-64, I693-694, I74, G45
Anaemia	D50-64
Coagulation or platelet defect	D65-69
Chronic kidney disease (CKD)	N18-19, procedure codes DR016, DR024, KAS00, KAS10, KAS20
Liver disease	K70-77, procedure codes JJB, JJC
Heart failure	I50,I110,I130,I132,I255,K761,I42-43
Hypertension	I10-15
Diabetes	E10-14 or use of antidiabetic drug (ATC codes beginning with A10)
Myocardial infarction	**I21, I22, I252**
Peripheral artery disease	**I70-73**
Vascular disease	I21, I22, I252, I70-73 (as in CHA_2DS_2-VASc)
Mitral stenosis	I342, I050, I052, Q232
Mechanical heart valve	Z952
Other valvular disease	I34-39, I05-08, Q22-23
Pacemaker or ICD	Z950, Z450, procedure code FPE
Thyroid disease	**E00-07 , E890**
COPD	J43-44
Asthma	J45-46
Cancer	Chapter C except C44 (basalioma) within preceding 3 years
Alcohol index[a]	E244, F10, G312, G621, G721, I426, K292, K70, K860, O354, P043, Q860, T51, Y90-91, Z502, Z714
Dementia	F00-03, F051, G300-301, G308-309
Frequent faller	≥2 hospitalizations with diagnosis W00-19 or R296
CHA_2DS_2-VASc score	1 point each for: heart failure, hypertension, age 65-74 years, diabetes, vascular disease, female sex and 2 points each for age ≥75 years and thromboembolism

[A]A set of codes used by the Swedish Board of Health and Welfare for annual reporting alcohol related mortality in the population.

TIA, transient ischemic attack; ICD, implantable cardioverter defibrillator; COPD, chronic obstructive pulmonary disease.

Additions to the protocol marked in bold.