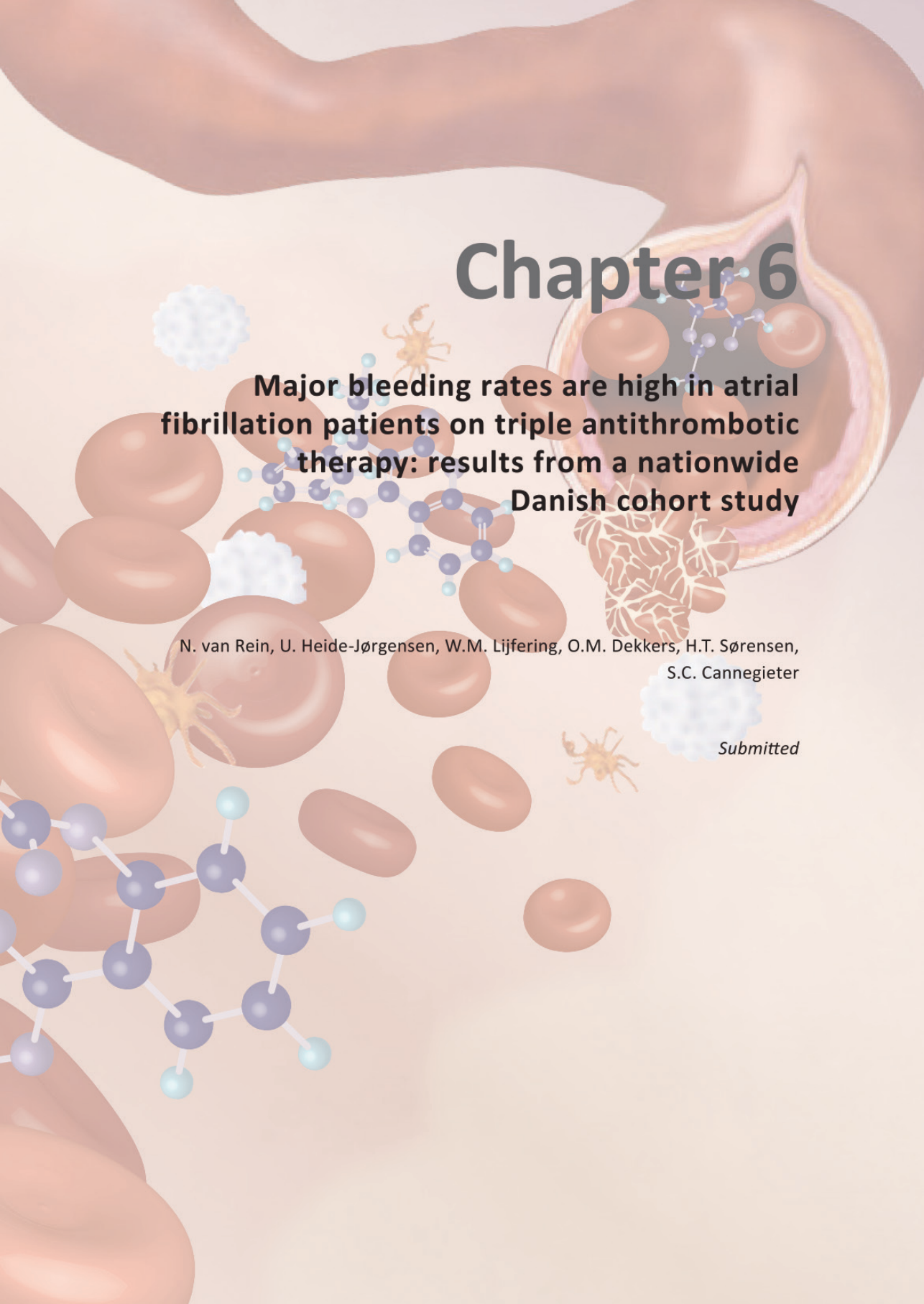
Risk and prevention of bleeding during anticoagulant treatment

Rein, N. van; Rein N. van



Chapter 6

Major bleeding rates are high in atrial fibrillation patients on triple antithrombotic therapy: results from a nationwide Danish cohort study

N. van Rein, U. Heide-Jørgensen, W.M. Lijfering, O.M. Dekkers, H.T. Sørensen, S.C. Cannegieter

Submitted

6

ABSTRACT

Background: Patients with atrial fibrillation generally require treatment with vitamin K antagonists (VKAs) and at times with additional platelet aggregation inhibitors. Data are scarce on bleeding rates in high-risk groups receiving combnation therapy, such as the elderly or patients with a high CHA_2DS_2-VASc score.

Methods: We conducted a nationwide cohort study of Danish atrial fibrillation patients aged 50 years or older. Treatments were ascertained from a prescription database. These included no anticoagulant treatment and treatment with VKAs, aspirin, clopidogrel, and combinations of anticoagulant drugs. Incidence rates (IRs) of major bleeding and hazard ratios were estimated, overall and stratified by treatment modality, age, CHA_2DS_2-VASc score, and comorbidity.

Results: We identified 216,109 patients with atrial fibrillation. Median age was 75 years and 48% were women. Over a total follow-up period of 854,914 patient-years (py), 24,414 major bleeds occurred [incidence rate (IR) 2.9/100 pys, 95% confidence interval (CI) 2.8-2.9/100 pys]. Compared with VKA monotherapy, adjusted hazard ratios of major bleeding were 1.52 (95% CI 1.37-1.69) for dual antiplatelet therapy, 1.78 (95% CI 1.71-1.86) for therapy with a VKA and an antiplatelet drug, and 3.73 (95% CI 3.23-4.31) for triple therapy. Subgroup analyses showed similar patterns. The IR for major bleeding was 11.9/100 pys among triple-therapy patients. Very high major bleeding rates occurred among patients over 90 years (IR 50.0/100 pys, 95% CI 24.4-91.8) and in patients with a CHA_2DS_2-VASc score over 6 (IR 20.0/100 pys, 95% CI 10.2-35.7).

Conclusions: Patients with atrial fibrillation on triple therapy experienced high rates of major bleeding compared with patients on dual therapy or monotherapy. The exceptionally high bleeding rates observed in patients on triple therapy over the age of 90 years or with a CHA_2DS_2-VASc score over 6 suggest that such therapy should be carefully considered in these patients.

INTRODUCTION

Persistent atrial fibrillation often requires long-term treatment with oral anticoagulants.[1] As patients with atrial fibrillation often have other underlying cardiovascular diseases, concurrent treatment with platelet inhibitors also may be indicated.[1,2] Previous research has shown that concurrent use of vitamin K antagonists (VKAs) with a single platelet inhibitor increases the risk of bleeding complications twofold to threefold compared with VKA monotherapy.[3] Triple therapy with VKA, aspirin, and clopidogrel has been associated with an almost fourfold increased risk of major bleeds compared with VKA monotherapy.[3] Although these relative risks are high, they do not provide sufficient information to assess clinical safety implications. For this, knowledge of absolute rates is needed, especially in patient groups with risk factors for major bleeding complications.[4] As well, sufficient numbers of patients are required to allow comparison of bleeding rates associated with several combinations of anticoagulant drugs.

We therefore conducted a cohort study in a nationwide setting (*i.e.*, the entire population of Denmark) to determine rates of major bleeds in patients with atrial fibrillation who used combinations of anticoagulant and antiplatelet drugs. Our approach took several high-risk groups into account.

METHODS

Setting and databases

The Danish National Health Service provides tax-funded medical care to all Danish residents.[5] The Danish Civil Registration System (CRS) issues a unique Civil Personal Register (CPR) number to all Danish residents at birth or upon immigration, which permits patient-level linkage of data among all Danish medical databases.[5] The data sources used in this study were the Danish National Patient Registry (DNPR)[5], the Danish Registry of Medicinal Product Statistics (DRMPS)[6], and the Danish Registry of Causes of Death.[7]

The DNPR is a nationwide registry containing information on all inpatient hospitalizations since 1977 and on all hospital specialist outpatient clinic and emergency room visits since 1995. Each record contains the patient's CPR number, dates of hospital inpatient and outpatient encounters, the discharge date (if applicable), and one or more discharge diagnoses, including a dedicated field for the primary diagnosis. Diagnoses were coded according to the *International Classification of Diseases, Eighth Revision* (ICD-8) from 1977 to 1993 and according to the *Tenth Revision* (ICD-10) thereafter.[8]

The nationwide DRMPS contains information on all prescriptions dispensed at community pharmacies in Denmark since 1995. All records contain the patient's CPR number, date of dispensing, quantity of drugs dispensed, and the Anatomical Therapeutic Chemical (ATC) code of the dispensed drug.[9]

The nationwide Danish Registry of Causes of Death contains information on all deaths in Denmark since 1875. Each record from 1994 on contains the deceased person's CPR number, date of death, and cause(s) of death classified by ICD-10 codes, including a code for the primary cause of death.[7]

Study population

The study included all patients in Denmark aged 50 years or older with a first-time primary or secondary hospital inpatient or outpatient discharge diagnosis of atrial fibrillation or flutter registered in the DNPR between 1 January 1995 and 31 December 2012. Younger patients were not included, as atrial fibrillation is rare in persons under age 50.[10] Patients with an atrial fibrillation diagnosis in an acute setting (*e.g.,* emergency room) were not eligible for inclusion. The diagnosis of atrial fibrillation and flutter has a positive predictive value of 99% in the DNPR.[11]

Exposure

Data on redeemed prescriptions for VKAs (warfarin and phenprocoumon), and platelet inhibitors (aspirin and clopidogrel) were obtained from the DRMPS using ATC codes (see Appendix 1 for codes). Patients were considered exposed starting on the day they filled a prescription for a VKA or platelet inhibitor. Length of exposure to VKAs was assumed to be 90 days per prescription, as drugs for chronic conditions are seldomly provided for more than three months in Denmark. Length of exposure to antiplatelet drugs was assumed to be one day per pill dispensed plus an extra 14 days as a wash-out period. The wash-out period was used to account for delay in picking up a prescribed drug from a pharmacy as well as the duration of action of individual drugs. Among the anticoagulant and antiplatelet drugs examined in this study, the only over-the-counter medicine is low-dose aspirin. However, patients treated long-term with low-dose aspirin usually receive a prescription to allow financial reimbursement, as reported in other studies.[3,12] Therefore aspirin use was included and coded as a prescription.

Based on medication use, seven categories of exposure were identified: no anticoagulant treatment; monotherapy with a VKA; monotherapy with aspirin; monotherapy with clopidogrel; dual therapy with a VKA and one antiplatelet drug (clopidogrel or aspirin); dual antiplatelet therapy with aspirin and clopidogrel; and triple therapy (VKA, aspirin, and clopidogrel).

Outcomes, comorbidities and comedications

Outcomes of interest were major bleeds (primary outcome), ischemic strokes, myocardial infarctions (MIs), and all-cause mortality (secondary outcomes). The DNPR and the Danish Registry of Causes of Death were used to ascertain outcomes, classified according to ICD-10 codes (see Appendix 1). Outcomes included both primary and secondary diagnoses recorded in the DNPR (excluding diagnoses made during

emergency room visits). The outcomes of fatal bleed, fatal ischemic stroke, and fatal MI were included only if the event was recorded as the primary cause of death in the Danish Registry of Causes of Death.

Diagnostic codes in the DNPR were used to identify comorbidities, defined as the presence, at any time, in a patient's record of ischemic heart disease, valvular heart disease, hypertension, MI, ischemic stroke, diabetes, liver disease, renal failure, malignancy, and previous major bleeds (see Appendix 1). Based on these diagnostic codes and clinical characteristics, we computed CHA_2DS_2-VASc scores. This score is based on age, sex, a history of congestive heart failure, hypertension, stroke/transient ischemic attack/thromboembolism, vascular disease, and diabetes mellitus.[13]

Use of anticoagulants during the 180 days preceding diagnosis of atrial fibrillation was ascertained from the DRMPS (see ATC codes in Appendix 1).

Statistical analysis

Patients were followed from the date of their atrial fibrillation diagnosis until occurrence of each of the study outcomes (major bleeding event, ischemic stroke, and MI), death or end of the study period (31 December 2013). When calculating follow-up time until a major bleed or another outcome, we did not consider the occurrence of the other outcomes. For example, when major bleeding events were studied, MIs were disregarded in the analysis even if a patient had an MI before the bleeding event.

Rates [incidence rates per 100 person-years (pys)] of the outcomes were estimated and further stratified by risk groups defined *a-priori* (*i.e.,* age in 10-year categories, CHA_2DS_2-VASc score, sex, previous ischemic heart disease, previous major bleeds, previous ischemic stroke, and previous MI). Exposure was considered as a time-dependent variable in all analyses.

In a secondary analysis, relative risk estimates of major bleeds were estimated for the different exposure groups using VKA monotherapy as the reference category. Hazard ratios (HRs) along with 95% confidence intervals (CIs) were estimated using a time-dependent Cox model. HRs were adjusted for the following confounding factors: sex and, as time-dependent variables, ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer. HRs were not estimated for secondary outcomes (*i.e.*, ischemic stroke, MI, and all-cause mortality), as confounding by indication for these outcomes would make such comparative results difficult to interpret. A sensitivity analysis was performed in which outcomes from the Danish Registry of Causes of Death were excluded. The rationale was that causes of death are more prone to misclassification than diagnoses and thus could influence the parameter estimates.

All analyses were performed using R version 2.15.2 (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/).

Table 1. Baseline characteristics of all patients in Denmark aged 50 years or older with a first-time primary or secondary hospital inpatient or outpatient discharge diagnosis of atrial fibrillation or flutter between 1 January 1995 and 31 December 2012, by type of therapy.

	All patients	No anticoagulant treatment	VKA monotherapy	Aspirin monotherapy	Clopidogrel monotherapy	Two Antiplatelet drugs	VKA+ Antiplatelet drug	Triple therapy
Patients	216,109	71,796	52,953	57,511	1962	3625	26,971	1291
Age, median (IQR)	75 (67-83)	75 (65-83)	72 (65-79)	80 (71-86)	78 (70-85)	77 (69-84)	74 (68-80)	74 (68-80)
Female sex	103,430 (48)	37,086 (52)	21,517 (41)	30,547 (53)	1025 (52)	2107 (58)	10,763 (40)	385 (30)
Comorbidities								
Ischemic heart disease	52,894 (24)	15,361 (21)	9396 (18)	21,578 (38)	1079 (55)	3203 (88)	11,190 (42)	1158 (90)
Valvular heart disease	17,961 (8)	4324 (6)	5006 (10)	4426 (8)	184 (9)	421 (12)	3432 (13)	168 (13)
Hypertension	66,318 (31)	17,168 (24)	15,091 (29)	19,467 (34)	1109 (57)	1,793 (50)	11,056 (41)	634 (49)
Diabetes	23,654 (11)	6689 (9)	4757 (9)	7163 (13)	321 (16)	670 (19)	3809 (14)	245 (19)
Liver disease	3686 (2)	1645 (2)	676 (1)	909 (2)	41 (2)	55 (2)	344 (1)	16 (1)
Renal failure	7405 (3)	2850 (4)	1085 (2)	2196 (4)	124 (6)	237 (7)	840 (3)	73 (6)
Malignancy	41,127 (19)	15,656 (22)	8271 (16)	11,530 (20)	464 (24)	695 (19)	4309 (16)	202 (16)
Previous ischemic stroke	32,327 (15)	7984 (11)	5718 (11)	11,080 (19)	980 (50)	851 (24)	5404 (20)	310 (24)
Previous myocardial infarction	36,124 (17)	8480 (12)	4979 (9)	12,134 (21)	716 (37)	2,649 (73)	6247 (24)	919 (71)
Previous major bleeds	26,887 (12)	9693 (14)	5022 (10)	7895 (14)	460 (23)	571 (16)	3081 (11)	165 (13)
Previous anticoagulant therapy								
VKA	31,368 (15)	2897 (4)	19,970 (38)	1044 (2)	57 (3)	60 (2)	7073 (26)	267 (21)
Aspirin	71,828 (33)	7101 (10)	5524 (10)	36,034 (63)	442 (23)	2384 (66)	19,487 (72)	856 (66)
Clopidogrel	4505 (2)	321 (0)	244 (1)	399 (1)	1097 (56)	1153 (32)	777 (3)	514 (40)

RESULTS

Characteristics

We identified 216,109 patients aged 50 years or older who were admitted to a hospital or who had an outpatient visit in a hospital clinic with a first-time diagnosis of atrial fibrillation between 1995 and 2013 (see Table 1). Median age was 75 years [interquartile range (IQR) 67-83 years] and 103,430 patients (48%) were women. The most common treatments were monotherapy with a VKA [52,953 patients (25%)] or aspirin [57,511 patients (27%)] or dual therapy with a VKA and an antiplatelet drug [26,971 patients (12%)]. Triple therapy was prescribed to 1962 patients (0.9%). The prevalence of a history of ischemic heart disease or a MI was highest among patients treated with aspirin and clopidogrel or with aspirin, clopidogrel, and a VKA (see Table 1).

Major bleeding by type of therapy

Median follow-up was three years (IQR 1-7 years), resulting in total follow-up time of 854,914 pys. A total of 24,414 major bleeds occurred during follow-up. Of these, 1141 (4.6%) were fatal. Major bleeding rates were lowest in patients not treated with an anticoagulant and increased with the number of anticoagulants or antiplatelet drugs used concurrently (incidence rates between 1.4 and 11.9 per 100 pys; see Table 2). Incidence rates and adjusted HRs for major bleeding, using VKA monotherapy as reference, were slightly lower in aspirin users than in VKA users, but higher in clopidogrel users. Compared with VKA monotherapy, adjusted HRs of major bleeding were 1.52 (95% CI 1.37-1.69) for dual antiplatelet therapy, 1.78 (95% CI 1.71-1.86) for therapy with both a VKA and an antiplatelet drug, and 3.73 (95% CI 3.23-4.31) for triple therapy.

Table 2. Incidence rate and hazard ratio of major bleeding associated with single, dual, and triple therapy.

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
No anticoagulant therapy	6147	310,859	2.0 (1.9-2.0)	0.81 (0.79-0.84)	0.82 (0.80-0.86)
VKA monotherapy	6070	249,559	2.4 (2.4-2.5)	reference	reference
Aspirin monotherapy	7409	271,917	2.7 (2.7-2.8)	1.12 (1.09-1.16)	0.93 (0.89-0.96)
Clopidogrel monotherapy	336	8427	4.0 (3.6-4.4)	1.62 (1.45-1.81)	1.11 (1.00-1.24)
Dual antiplatelet therapy	397	7296	5.4 (4.9-6.0)	2.06 (1.86-2.28)	1.52 (1.37-1.69)
VKA+ antiplatelet drug	3862	77,994	5.0 (4.8-5.1)	1.98 (1.90-2.06)	1.78 (1.71-1.86)
Triple therapy	193	1617	11.9 (10.3-13.7)	4.24 (3.67-4.89)	3.73 (3.23-4.31)

* Adjusted for sex and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.

Risk groups

Rates of major bleeding were lowest in the youngest age group (incidence rates between 0.7 and 9.6 per 100 pys) (see Table 3) and in the group with a CHA_2DS_2-VASc score of 0 (incidence rates between 0.6 and 2.6 per 100 pys) (see Table 4). As in the overall analysis, major bleeding rates increased with age and the number of anticoagulants used concurrently. For each 10-year increase in age, major bleeding rates in patients on triple therapy increased concurrently (9.6 per 100 pys for persons aged 50-59, 9.3 per 100 pys for persons aged 60-69, 12.6 per 100 pys for persons aged 70-79, 13.2 per 100 pys for persons aged 80-89, and 50.0 per 100 pys for those aged 90 and over). When incidence rates were contrasted with monotherapy as the reference group, the adjusted HRs closely followed the pattern of increased major bleeding risk with age. Similar results were found for the CHA_2DS_2-VASc scores. Absolute rates of major bleeds were highest in patients who used triple therapy and who had a CHA_2DS_2-VASc score above 6 (IR 20.0, 95% CI 10.2-35.7).

Table 3. Incidence rate and hazard ratio of major bleeding associated with single, dual, and triple therapy, stratified by age.

	Bleeds no.	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Age 50-59 yrs					
No anticoagulant therapy	271	40,093	0.7 (0.6-0.8)	0.55 (0.46-0.66)	0.62 (0.52-0.75)
VKA monotherapy	211	17,289	1.2 (1.1-1.4)	reference	reference
Aspirin monotherapy	156	15,614	1.0 (0.9-1.2)	0.85 (0.69-1.04)	0.84 (0.68-1.04)
Clopidogrel monotherapy	6	348	1.7 (0.7-3.6)	1.19 (0.49-2.90)	0.99 (0.41-2.42)
Dual antiplatelet therapy	14	426	3.3 (1.9-5.4)	2.27 (1.30-3.98)	1.83 (1.03-3.24)
VKA+ antiplatelet drug	112	4303	2.6 (2.2-3.1)	2.13 (1.69-2.68)	1.83 (1.45-2.32)
Triple therapy	11	114	9.6 (5.1-16.8)	6.75 (3.67-12.39)	5.35 (2.88-9.95)
Age 60-69 yrs					
No anticoagulant therapy	874	83,284	1.0 (1.0-1.1)	0.65 (0.59-0.71)	0.69 (0.63-0.76)
VKA monotherapy	1033	64,284	1.6 (1.5-1.7)	reference	reference
Aspirin monotherapy	687	53,125	1.3 (1.2-1.4)	0.80 (0.73-0.89)	0.79 (0.71-0.87)
Clopidogrel monotherapy	39	1532	2.5 (1.8-3.4)	1.57 (1.14-2.17)	1.22 (0.88-1.69)
Dual antiplatelet therapy	43	1557	2.8 (2.0-3.7)	1.62 (1.19-2.20)	1.29 (0.95-1.76)
VKA+ antiplatelet drug	637	20,014	3.2 (2.9-3.4)	1.95 (1.77-2.16)	1.72 (1.56-1.91)
Triple therapy	45	484	9.3 (6.9-12.3)	5.10 (3.78-6.88)	4.18 (3.08-5.66)
Age 70-79 yrs					
No anticoagulant therapy	1890	90,445	2.1 (2.0-2.2)	0.87 (0.81-0.92)	0.89 (0.83-0.94)
VKA monotherapy	2311	97,775	2.4 (2.3-2.5)	reference	reference
Aspirin monotherapy	1907	80,940	2.4 (2.3-2.5)	0.98 (0.92-1.04)	0.92 (0.86-0.98)

Table 3. (*Continued*)

	Bleeds no.	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Clopidogrel monotherapy	97	2610	3.7 (3.0-4.5)	1.49 (1.21-1.84)	1.16 (0.94-1.14)
Dual antiplatelet therapy	121	2462	4.9 (4.1-5.9)	1.89 (1.57-2.27)	1.47 (1.22-1.77)
VKA+ antiplatelet drug	1541	32,301	4.8 (4.5-5.0)	1.96 (1.84-2.09)	1.74 (1.63-1.86)
Triple therapy	86	684	12.6 (10.1-15.5)	4.71 (3.80-5.85)	3.87 (3.11-4.81)
Age 80-89 yrs					
No anticoagulant therapy	2366	77,094	3.1 (2.9-3.2)	0.83 (0.78-0.88)	0.84 (0.79-0.89)
VKA monotherapy	2252	64,053	3.5 (3.4-3.7)	reference	reference
Aspirin monotherapy	3378	93,034	3.6 (3.5-3.8)	0.98 (0.93-1.04)	0.95 (0.90-1.00)
Clopidogrel monotherapy	157	3094	5.1 (4.3-5.9)	1.34 (1.13-1.59)	1.15 (0.97-1.37)
Dual antiplatelet therapy	174	2367	7.4 (6.3-8.5)	1.92 (1.64-2.25)	1.61 (1.38-1.89)
VKA+ antiplatelet drug	1453	19,992	7.3 (6.9-7.6)	2.01 (1.88-2.15)	1.87 (1.74-2.00)
Triple therapy	42	317	13.2 (9.7-17.7)	3.32 (2.45-4.51)	2.82 (2.08-3.84)
Age > 90 years					
No anticoagulant therapy	746	19,942	3.7 (3.5-4.0)	0.81 (0.70-0.94)	0.84 (0.72-0.98)
VKA monotherapy	263	6158	4.3 (3.8-4.8)	reference	reference
Aspirin monotherapy	1281	29,204	4.4 (4.2-4.6)	0.99 (0.86-1.14)	1.02 (0.89-1.18)
Clopidogrel monotherapy	37	834	4.4 (3.2-6.1)	0.96 (0.66-1.38)	0.95 (0.66-1.38)
Dual antiplatelet therapy	45	485	9.3 (6.8-12.3)	1.80 (1.28-2.54)	1.72 (1.22-2.44)
VKA+ antiplatelet drug	119	1484	8.0 (6.7-9.6)	1.93 (1.55-2.41)	1.88 (1.41-2.35)
Triple therapy	9	18	50.0 (24.4-91.8)	9.34 (4.61-18.94)	8.43 (4.15-17.13)

* Adjusted for sex and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.

Compared with male patients, female patients had higher major bleeding rates (see Table 5). Patients with ischemic heart disease and patients who experienced a MI had similar rates of major bleeding. Rates were higher in patients with a history of ischemic stroke or a history of major bleeding. Results of the sensitivity analysis (see Appendix 2, Tables 1 to 4) were similar to those of the overall analysis.

Ischemic events and death

Rates of MI, ischemic stroke, and death increased with age and were highest among individuals who received clopidogrel monotherapy or two antiplatelet drugs with or without a VKA. Rates of ischemic stroke varied between 0.0 to 7.0 per 100 pys, rates of MIs varied between 0.0 to 14.2 per 100 pys, and death rates ranged from 0.0 to 55.0 per 100 pys (see Appendix 2 Figure 1).

Table 4. Incidence rate and hazard ratio of major bleeding associated with single, dual and triple therapy, stratified by CHA_2DS_2-VASc score.

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
CHA_2DS_2-VASc 0					
No anticoagulant therapy	156	26,955	0.6 (0.5-0.7)	0.57 (0.45-0.73)	0.55 (0.43-0.70)
VKA monotherapy	115	10,973	1.0 (0.9-1.3)	reference	reference
Aspirin monotherapy	59	7066	0.8 (0.6-1.1)	0.83 (0.61-1.14)	0.81 (0.59-1.11)
Clopidogrel monotherapy	0	30	NA	NA	NA
Dual antiplatelet therapy	0	6	NA	NA	NA
VKA+ antiplatelet drug	32	1238	2.6 (1.8-3.6)	2.34 (1.58-3.47)	2.35 (1.58-3.47)
Triple therapy	0	1	NA	NA	NA
CHA_2DS_2-VASc 1,2					
No anticoagulant therapy	1417	118,405	1.2 (1.1-1.3)	0.67 (0.62-0.72)	0.72 (0.67-0.77)
VKA monotherapy	1559	85,894	1.8 (1.7-1.9)	reference	reference
Aspirin monotherapy	1085	63,262	1.7 (1.6-1.8)	0.96 (0.89-1.04)	0.93 (0.86-1.00)
Clopidogrel monotherapy	27	1043	2.6 (1.7-3.7)	1.42 (0.97-2.08)	1.38 (0.94-2.02)
Dual antiplatelet therapy	27	984	2.7 (1.8-3.9)	1.33 (1.91-1.94)	1.59 (1.08-2.34)
VKA+ antiplatelet drug	612	17,802	3.4 (3.2-3.7)	1.81 (1.65-1.99)	1.87 (1.70-2.05)
Triple therapy	16	274	5.8 (3.5-9.3)	2.59 (1.58-4.24)	3.29 (2.00-5.42)
CHA_2DS_2-VASc 3,4					
No anticoagulant therapy	3144	126,358	2.5 (2.4-2.6)	0.95 (0.91-1.00)	0.93 (0.88-0.98)
VKA monotherapy	2921	113,539	2.6 (2.5-2.7)	reference	reference
Aspirin monotherapy	3854	134,483	2.9 (2.8-3.0)	1.10 (1.05-1.16)	1.01 (0.96-1.06)
Clopidogrel monotherapy	148	3511	4.2 (3.6-4.9)	1.59 (1.35-1.88)	1.39 (1.18-1.64)
Dual antiplatelet therapy	156	3064	5.1 (4.3-5.9)	1.76 (1.50-2.07)	1.64 (1.39-1.93)
VKA+ antiplatelet drug	1915	38,304	5.0 (4.8-5.2)	1.87 (1.76-1.98)	1.83 (1.72-1.94)
Triple therapy	84	808	10.4 (8.3-12.8)	3.80 (3.09-4.67)	3.99 (3.24-4.91)
CHA_2DS_2-VASc 5					
No anticoagulant therapy	897	26,593	3.4 (3.2-3.6)	0.94 (0.86-1.03)	0.92 (0.84-1.01)
VKA monotherapy	935	26,680	3.5 (3.3-3.7)	reference	Reference
Aspirin monotherapy	1484	43,266	3.4 (3.3-3.6)	0.96 (0.88-1.04)	0.90 (0.83-0.98)
Clopidogrel monotherapy	78	2075	3.8 (3.0-4.7)	1.03 (0.82-1.30)	0.90 (0.71-1.13)
Dual antiplatelet therapy	111	1764	6.3 (5.2-7.5)	1.64 (1.34-2.00)	1.48 (1.21-1.80)
VKA+ antiplatelet drug	784	13,389	5.9 (5.5-6.3)	1.62 (1.47-1.78)	1.57 (1.42-1.73)
Triple therapy	45	314	14.3 (10.6-19.0)	3.47 (2.57-4.68)	3.30 (2.44-4.46)

Table 4. (*Continued*)

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
CHA_2DS_2-VASc 6					
No anticoagulant therapy	416	9901	4.2 (3.8-4.6)	0.97 (0.85-1.11)	0.94 (0.82-1.08)
VKA monotherapy	419	9837	4.3 (3.9-4.7)	reference	reference
Aspirin monotherapy	704	18,364	3.8 (3.6-4.1)	0.89 (0.79-1.00)	0.86 (0.76-0.97)
Clopidogrel monotherapy	57	1240	4.6 (3.5-5.9)	1.05 (0.80-1.39)	0.97 (0.73-1.28)
Dual antiplatelet therapy	73	1080	6.8 (5.3-8.5)	1.48 (1.15-1.90)	1.37 (1.07-1.76)
VKA+ antiplatelet drug	383	5717	6.7 (6.1-7.4)	1.53 (1.34-1.76)	1.49 (1.30-1.72)
Triple therapy	28	170	16.5 (11.2-23.5)	3.39 (2.31-4.98)	3.13 (2.13-4.61)
CHA_2DS_2-VASc 7-9					
No anticoagulant therapy	117	2648	4.4 (3.7-5.3)	0.94 (0.73-1.21)	0.90 (0.70-1.17)
VKA monotherapy	121	2637	4.6 (3.8-5.5)	reference	reference
Aspirin monotherapy	223	5475	4.1 (3.6-4.6)	0.87 (0.70-1.09)	0.84 (0.67-1.05)
Clopidogrel monotherapy	26	528	4.9 (3.3-7.1)	1.03 (0.68-1.58)	0.98 (0.64-1.51)
Dual antiplatelet therapy	30	398	7.5 (5.2-10.6)	1.49 (1.00-2.23)	1.39 (0.92-2.08)
VKA+ antiplatelet drug	136	1545	8.8 (7.4-10.4)	1.84 (1.44-2.35)	1.76 (1.38-2.26)
Triple therapy	10	50	20.0 (10.2-35.7)	3.55 (1.85.6.79)	3.23 (1.68-6.20)

* Adjusted by sex and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.

DISCUSSION

Our study showed that the incidence rate of major bleeding increased with the number of prescribed anticoagulants. Nearly all groups treated with triple therapy experienced high rates of bleeding complications, up to 50.0 per 100 pys in the oldest age group. Relative risk estimates did not change greatly after adjustment for confounding factors, indicating that triple therapy was associated with a 2.8- to 8.4-fold increased risk of major bleeding complications compared with VKA monotherapy.

Major bleeding

We found that triple therapy was associated with a four-fold average increased risk of major bleeding, compared with VKA monotherapy. This was consistent across subgroups and agrees with the literature.[3] The clinical impact of relative risks depends on their absolute values. We expected that groups with a low baseline bleeding risk (*e.g.,* patients aged 50 to 60 years or with a CHA_2DS_2-VASc score of 1 to 2) would experience low rates of major bleeding complications during triple therapy. However,

Table 5. Incidence rate and hazard ratio of major bleeding associated with single, dual, and triple therapy, stratified by sex and by comorbidity.

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Female					
No anticoagulant therapy	2659	153,008	1.7 (1.7-1.8)	0.78 (0.74-0.82)	0.78 (0.74-0.82)
VKA monotherapy	2322	104,588	2.2 (2.1-2.3)	reference	reference
Aspirin monotherapy	3355	138,171	2.4 (2.3-2.5)	1.09 (1.04-1.15)	0.89 (0.84-0.94)
Clopidogrel monotherapy	135	4485	3.0 (2.5-3.6)	1.34 (1.13-1.60)	0.92 (0.77-1.09)
Dual antiplatelet therapy	159	3048	5.2 (4.5-6.1)	2.16 (1.84-2.54)	1.57 (1.33-1.85)
VKA+ antiplatelet drug	1328	27,786	4.8 (4.5-5.0)	2.07 (1.93-2.21)	1.91 (1.78-2.04)
Triple therapy	65	415	15.7 (12.2-19.8)	5.91 (4.62-7.57)	5.18 (4.04-6.64)
Male					
No anticoagulant therapy	3488	157,851	2.2 (2.1-2.3)	0.86 (0.82-0.90)	0.86 (0.82-0.90)
VKA monotherapy	3748	144,971	2.6 (2.5-2.7)	reference	reference
Aspirin monotherapy	4054	133,746	3.0 (2.9-3.1)	1.18 (1.13-1.24)	0.96 (0.92-1.00)
Clopidogrel monotherapy	201	3942	5.1 (4.4-5.8)	1.95 (1.69-2.25)	1.30 (1.13-1.50)
Dual antiplatelet therapy	238	4248	5.6 (4.9-6.3)	2.00 (1.75-2.28)	1.49 (1.31-1.71)
VKA+ antiplatelet drug	2534	50,208	5.0 (4.9-5.2)	1.91 (1.82-2.01)	1.74 (1.65-1.83)
Triple therapy	128	1202	10.6 (8.9-12.6)	3.60 (3.02-4.30)	3.33 (2.79-3.98)
Previous MI					
No anticoagulant therapy	948	33,594	2.8 (2.6-3.0)	0.86 (0.79-0.95)	0.86 (0.78-0.94)
VKA monotherapy	785	23,922	3.3 (3.1-3.5)	reference	reference
Aspirin monotherapy	1639	60,705	2.7 (2.6-2.8)	0.83 (0.77-0.91)	0.78 (0.71-0.85)
Clopidogrel monotherapy	122	2804	4.4 (3.6-5.2)	1.30 (1.08-1.58)	1.09 (0.90-1.32)
Dual antiplatelet therapy	254	4923	5.2 (4.6-5.8)	1.45 (1.26-1.67)	1.29 (1.12-1.49)
VKA+ antiplatelet drug	1148	21,649	5.3 (5.0-5.6)	1.59 (1.46-1.75)	1.59 (1.45-1.75)
Triple therapy	134	1052	12.7 (10.7-15.0)	3.35 (2.79-4.04)	3.47 (2.89-4.18)
Previous major bleed					
No anticoagulant therapy	1542	32,508	4.7 (4.5-5.0)	0.96 (0.89-1.04)	0.95 (0.88-1.03)
VKA monotherapy	1179	25,004	4.7 (4.5-5.0)	reference	reference
Aspirin monotherapy	1573	30,444	5.2 (4.9-5.4)	1.06 (0.99-1.15)	0.96 (0.89-1.04)
Clopidogrel monotherapy	114	1633	7.0 (5.8-8.4)	1.39 (1.15-1.69)	1.15 (0.95-1.40)
Dual antiplatelet therapy	87	1069	8.1 (6.6-10.0)	1.49 (1.20-1.85)	1.26 (1.01-1.57)
VKA+ antiplatelet drug	763	9297	8.2 (7.6-8.8)	1.67 (1.53-1.83)	1.61 (1.46-1.76)
Triple therapy	35	199	17.6 (12.4-24.2)	2.98 (2.13-4.18)	2.82 (2.01-3.96)

Table 5. (*Continued*)

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Previous ischemic stroke					
No anticoagulant therapy	1236	32,084	3.9 (3.6-4.1)	1.17 (1.08-1.26)	1.08 (1.00-1.17)
VKA monotherapy	1329	40,909	3.2 (3.1-3.4)	reference	reference
Aspirin monotherapy	2040	52,283	3.9 (3.7-4.1)	1.19 (1.11-1.27)	1.05 (0.97-1.12)
Clopidogrel monotherapy	170	4108	4.1 (3.6-4.8)	1.24 (1.05-1.45)	1.10 (0.93-1.29)
Dual antiplatelet therapy	155	2318	6.7 (5.7-7.8)	1.95 (1.65-2.31)	1.69 (1.43-2.01)
VKA+ antiplatelet drug	1100	17,573	6.3 (5.9-6.6)	1.86 (1.72-2.01)	1.80 (1.66-1.95)
Triple therapy	50	313	16.0 (12.0-20.9)	4.12 (3.10-5.47)	3.86 (2.90-5.13)
Ischemic heart disease					
No anticoagulant therapy	2165	81,222	2.7 (2.6-2.8)	0.88 (0.83-0.94)	0.86 (0.81-0.91)
VKA monotherapy	2059	68,794	3.0 (2.9-3.1)	reference	reference
Aspirin monotherapy	3396	125,011	2.7 (2.6-2.8)	0.90 (0.85-0.95)	0.83 (0.78-0.87)
Clopidogrel monotherapy	214	5188	4.1 (3.6-4.7)	1.34 (1.17-1.55)	1.09 (0.95-1.26)
Dual antiplatelet therapy	337	6429	5.2 (4.7-5.8)	1.58 (1.40-1.77)	1.41 (1.25-1.58)
VKA+ antiplatelet drug	2195	44,540	4.9 (4.7-5.1)	1.60 (1.51-1.70)	1.59 (1.50-1.69)
Triple therapy	185	1539	12.0 (10.4-13.9)	3.42 (2.94-3.98)	3.58 (3.07-4.16)

*Adjusted for age at baseline, sex, and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.

this was not the case, as major bleeding rates were at least 5.8 per 100 pys. One explanation is that triple therapy causes major bleeding. An alternate explanation may be that the indication for this therapy, *i.e.,* high risk of atherothrombosis, is also associated with a high risk of bleeding.[14] All other subgroups experienced very high major bleeding rates (at least 9.3 per 100 pys) while receiving triple therapy. Bleeding rates gradually increased with age, as is well known. Bleeding rates also increased with higher CHA_2DS_2-VASc scores, which is to be expected since elements of the score, such as age, diabetes mellitus, hypertension, and a history of ischemic stroke, are risk factors for bleeding.[14]

We also observed that female patients experienced higher major bleeding rates than male patients, in contrast to the findings of previous studies.[14] This makes it likely that there is an alternate explanation, such as confounding, for the sex difference in bleeding rates.

High major bleeding rates also were observed among patients on triple therapy with ischemic heart disease or a history of a major bleeding or ischemic event. In addition, patients with a history of major bleeding or an ischemic stroke experienced higher rates

of major bleeding than patients with a history of MI or with ischemic heart disease. The reason may be that ischemic strokes and major bleeds are risk factors for future major bleeding. This has not been reported for ischemic heart disease or history of MI.[14]

Clinical implications

The high rates of major bleeding found among patients receiving triple therapy raises the question whether concomitant use of three anticoagulants is advisable. However, risk factors for ischemic events and major bleeding overlap[15], making it hard to distinguish which patients are at high risk for major bleeding, but not at risk for ischemic events, and vice versa. In addition, due to confounding by indication, this non-randomized study does not permit evaluation of the effectiveness of combinations of antithrombotic drugs (*i.e.*, medication could have been indicated due to high risk of thromboembolic outcomes). Still, two important findings in our study were that among patients receiving triple therapy, half of those aged over 90 years experienced a major bleed per year and that patients with a CHA_2DS_2-VASc scores of 7 to 9 had a bleeding rate of 20.0 per 100 pys. These very high bleeding rates suggest that triple therapy may be contraindicated in these groups.

Strengths and limitations

This population-based cohort study contained data from over 200,000 patients with large numbers of outcome events, making the results robust and generalizable to the currently treated population and allowing multiple subgroup analyses. A limitation is its reliance on dispensed prescriptions as recorded in a pharmacy registry, as filled prescriptions do not imply that patients actually took the medications. Still, if patients did not take their medications, results would have been diluted. The rates and risk estimates of bleeding complications would likely have been higher if patients had been compliant. Another limitation is the study's observational design, which precludes strong recommendations about optimal treatment choices for patients. Another potential limitation is that ICD codes do not distinguish between paroxysmal, persistent, and permanent atrial fibrillation[16], and these specific diagnoses may have influenced choice of treatment. In addition, only bleeding events that resulted in hospital admissions or were fatal were considered major. This may have resulted in underestimation of rates of major bleeding.

CONCLUSION

This study showed that patients with atrial fibrillation on triple therapy experienced a high rate of major bleeding. Some subgroups, such as patients over 90 years of age and patients with a CHA_2DS_2-VASc of 7 to 9, had very high bleeding rates, suggesting that triple therapy should be carefully considered in these patients.

REFERENCES

1. Lansberg MG, O'Donnell MJ, Khatri P, et al. Antithrombotic and thrombolytic therapy for ischemic stroke: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* Feb 2012;141(2 Suppl):e601S-636S.
2. Paikin JS, Wright DS, Crowther MA, Mehta SR, Eikelboom JW. Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. *Circulation.* May 11 2010;121(18):2067-2070.
3. Hansen ML, Sorensen R, Clausen MT, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Archives of internal medicine.* Sep 13 2010;170(16):1433-1441.
4. Levine MN, Raskob G, Beyth RJ, Kearon C, Schulman S. Hemorrhagic complications of anticoagulant treatment: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* Sep 2004;126(3 Suppl):287S-310S.
5. Schmidt M, Schmidt SA, Sandegaard JL, Ehrenstein V, Pedersen L, Sorensen HT. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical epidemiology.* 2015;7:449-490.
6. Kildemoes HW, Sorensen HT, Hallas J. The Danish National Prescription Registry. *Scandinavian journal of public health.* Jul 2011;39(7 Suppl):38-41.
7. Helweg-Larsen K. The Danish Register of Causes of Death. *Scandinavian journal of public health.* Jul 2011;39(7 Suppl):26-29.
8. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scandinavian journal of public health.* Jul 2011;39(7 Suppl):30-33.
9. Gaist D, Sorensen HT, Hallas J. The Danish prescription registries. *Danish medical bulletin.* Sep 1997;44(4):445-448.
10. van Rein N, Cannegieter SC, le Cessie S, et al. Statins and Risk of Bleeding: An Analysis to Evaluate Possible Bias Due to Prevalent Users and Healthy User Aspects. *American journal of epidemiology.* May 15 2016;183(10):930-936.
11. Frost L, Vukelic Andersen L, Vestergaard P, Husted S, Mortensen LS. Trends in risk of stroke in patients with a hospital diagnosis of nonvalvular atrial fibrillation: National Cohort Study in Denmark, 1980-2002. *Neuroepidemiology.* 2006;26(4):212-219.
12. Sorensen R, Hansen ML, Abildstrom SZ, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet.* Dec 12 2009;374(9706):1967-1974.
13. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* Feb 2010;137(2):263-272.
14. Schulman S, Beyth RJ, Kearon C, Levine MN, American College of Chest P. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest

Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* Jun 2008;133(6 Suppl):257S-298S.

15. Lip GY, Lane DA, Buller H, Apostolakis S. Development of a novel composite stroke and bleeding risk score in patients with atrial fibrillation: the AMADEUS Study. *Chest.* Dec 2013;144(6):1839-1847.
16. Sundboll J, Adelborg K, Munch T, et al. Positive predictive value of cardiovascular diagnoses in the Danish National Patient Registry: a validation study. *BMJ open.* Nov 18 2016;6(11):e012832.

APPENDIX 1.

Diagnosis and pharmaceutical codes used in the study

Study population - Danish National Registry of Patients
Atrial fibrillation ICD-10 code 148

Baseline drug use - Danish Registry of Medicinal Product Statistics
Warfarin ATC code B01AA03
Phenprocoumon ATC code B01AA04
Aspirin ATC code B01AC06
Clopidogrel ATC code B01AC04

Baseline comorbidities - Danish National Registry of Patients
Ischemic heart disease ICD-10 code I20-I25; ICD-8 code 409-415
Valvular heart disease ICD-10 code I34-I37; ICD-8 code 393-398, 424
Heart failure ICD-10 code I50; ICD-8 code 427.0, 427.1
Hypertension ICD-10 code I10-I15; ICD-8 code 399-405
Diabetes ICD-10 code E10-E14; ICD-8 code 249, 250
Liver disease ICD-10 code K70-K77, R16 and R17; ICD-8 code 570-573, 782.8, 785.1, 785.2
Renal failure ICD-10 code N17-N19 and R34; ICD-8 code 403, 404, 579-585
Malignancy ICD-10 code C00-C97; ICD-8 code 139-240
Systemic embolism ICD-10 code I26 and I74; ICD-8 code 444, 450
Ischemic stroke ICD-10 code I63-I66, I69.3 and I69.4; ICD-8 code 431, 439
Myocardial infarction ICD-10 code I21; ICD-8 code 410
Major bleed ICD-10 code D62, I60-I62, I69.0, I69.1, I69.2, J94.2, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K28.0, K28.2, K28.4, K28.6, K92.0, K92.1, K92.2, N02, R04, R31, S06.4, S06.5 and S06.6; ICD-8 code 430, 431, 531.0, 531.2, 532.0, 532.2, 533.0, 534.0, 534.2, 783.0, 783.1, 784.5, 785.7, 789.3

Exposure - Danish Registry of Medicinal Product Statistics
Warfarin ATC code B01AA03
Phenprocoumon ATC code B01AA04
Aspirin ATC code B01AC06
Clopidogrel ATC code B01AC04

Outcomes - Danish National Registry of Patients and Danish Registry of Causes of Death
Major bleeds ICD 10 codes D62, I60-I62, I69.0, I69.1, I69.2, J94.2, K25.0, K25.2, K25.4, K25.6, K26.0, K26.2, K26.4, K26.6, K27.0, K27.2, K28.0, K28.2, K28.4, K28.6, K92.0, K92.1, K92.2, N02, R04, R31, S06.4, S06.5 and S06.6
Ischemic stroke ICD-10 code I63
Myocardial infarction ICD-10 code I21

APPENDIX 2

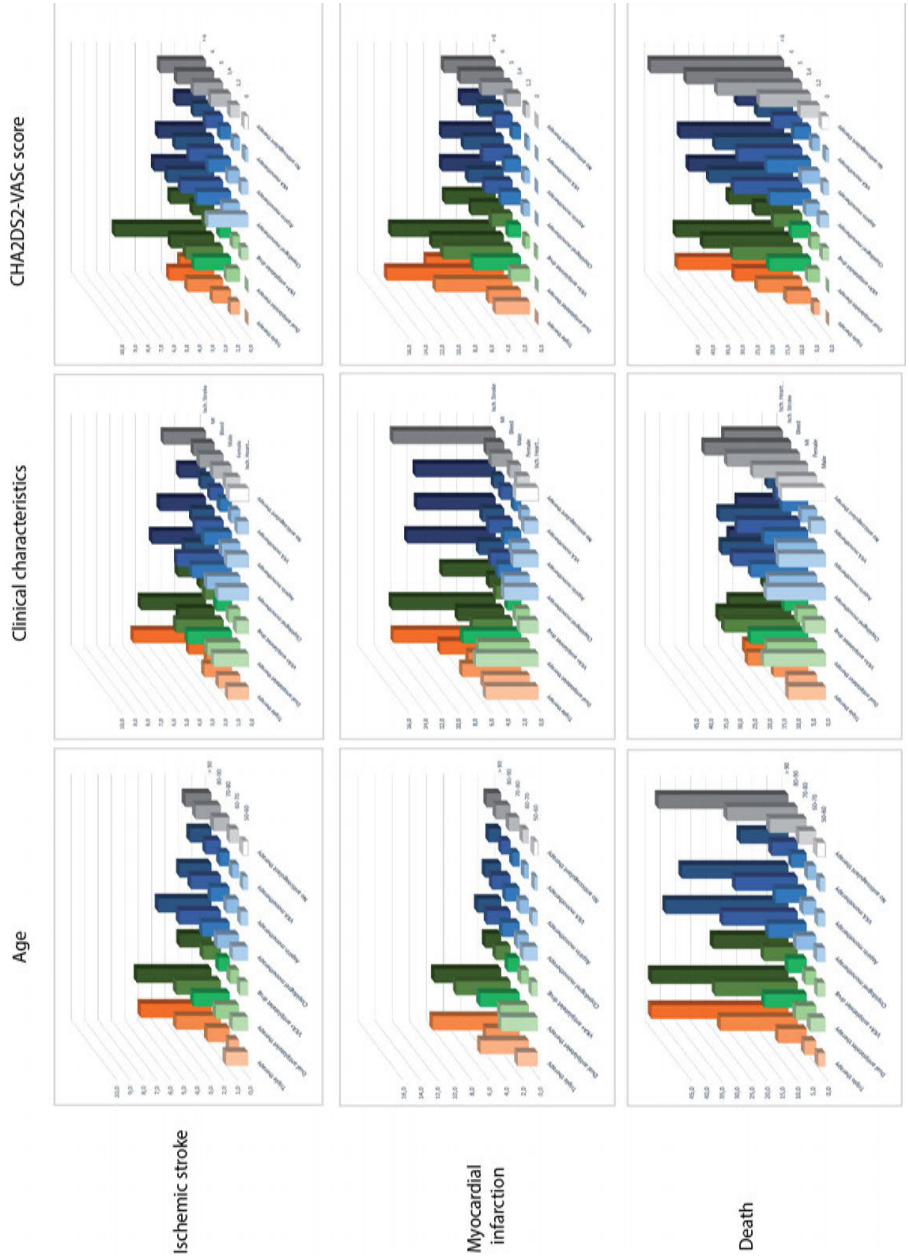


Figure 1. Incidence rates per 100 person-years of secondary outcomes by subgroups

Table 1. Sensitivity analysis excluding cause of death: incidence rate and hazard ratio of non-fatal major bleeding associated with single, dual, and triple therapy.

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
No anticoagulant therapy	5775	310,859	1.9 (1.8-1.9)	0.79 (0.76-0.82)	0.80 (0.77-0.83)
VKA monotherapy	5883	249,559	2.4 (2.3-2.4)	reference	reference
Aspirin monotherapy	6961	271,917	2.6 (2.5-2.6)	1.09 (1.05-1.13)	0.90 (0.87-0.94)
Clopidogrel monotherapy	311	8427	3.7 (3.3-4.1)	1.55 (1.38-1.74)	1.08 (0.96-1.21)
Dual antiplatelet therapy	380	7296	5.2 (4.7-5.7)	2.04 (1.84-2.26)	1.51 (1.36-1.68)
VKA+ antiplatelet drug	3771	77,994	4.8 (4.7-5.0)	2.00 (1.92-2.08)	1.80 (1.72-1.87)
Triple therapy	192	1617	11.9 (10.2-13.7)	4.36 (3.78-5.04)	3.82 (3.30-4.42)

* Adjusted for sex and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.

Table 2. Sensitivity analysis excluding cause of death: incidence rate of non-fatal major bleeding associated with single, dual, and triple therapy, stratified by age.

	Bleeds no.	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Age 50-59 yrs					
No anticoagulant therapy	259	40,093	0.65 (0.57-0.73)	0.55 (0.46-0.66)	0.62 (0.52-0.75)
VKA monotherapy	210	17,289	1.21 (1.06-1.39)	reference	reference
Aspirin monotherapy	153	15,614	0.98 (0.83-1.15)	0.85 (0.69-1.04)	0.84 (0.68-1.04)
Clopidogrel monotherapy	5	348	1.44 (0.53-3.19)	1.19 (0.49-2.90)	0.99 (0.41-2.42)
Dual antiplatelet therapy	13	426	3.05 (1.70-5.09)	2.27 (1.30-3.98)	1.83 (1.03-3.24)
VKA+ antiplatelet drug	110	4203	2.62 (2.16-3.14)	2.13 (1.69-2.68)	1.83 (1.45-2.32)
Triple therapy	11	114	9.65 (5.07-16.77)	6.75 (3.67-12.39)	5.35 (2.88-9.95)
Age 60-69 yrs					
No anticoagulant therapy	832	83,284	1.00 (0.93-10.69)	0.65 (0.59-0.71)	0.69 (0.63-0.76)
VKA monotherapy	1009	64,284	1.57 (1.48-1.67)	reference	reference
Aspirin monotherapy	657	53,125	1.24 (1.15-1.33)	0.80 (0.73-0.89)	0.79 (0.71-0.87)
Clopidogrel monotherapy	38	1532	2.48 (1.78-3.37)	1.57 (1.14-2.17)	1.22 (0.88-1.69)
Dual antiplatelet therapy	43	1557	2.76 (2.02-3.69)	1.62 (1.19-2.20)	1.29 (0.95-1.76)
VKA+ antiplatelet drug	625	20,014	3.12 (2.89-3.38)	1.95 (1.77-2.16)	1.72 (1.56-1.91)
Triple therapy	45	484	9.30 (6.86-12.33)	5.10 (3.78-6.88)	4.18 (3.08-5.66)
Age 70-79 yrs					
No anticoagulant therapy	1811	90,445	2.00 (1.91-2.10)	0.86 (0.81-0.92)	0.89 (0.83-0.94)
VKA monotherapy	2253	97,775	2.30 (2.21-2.40)	reference	reference
Aspirin monotherapy	1829	80,940	2.26 (2.16-2.37)	0.98 (0.92-1.04)	0.92 (0.86-0.98)
Clopidogrel monotherapy	91	2610	3.49 (2.82-4.26)	1.49 (1.21-1.84)	1.16 (0.94-1.44)
Dual antiplatelet therapy	117	2462	4.75 (3.95-5.67)	1.89 (1.57-2.27)	1.47 (1.22-1.77)
VKA+ antiplatelet drug	1503	32,301	4.65 (4.42-4.89)	1.96 (1.84-2.09)	1.74 (1.63-1.86)
Triple therapy	86	684	12.57 (10.12-15.45)	4.71 (3.80-5.85)	3.87 (3.11-4.81)
Age 80-89 yrs					
No anticoagulant therapy	2217	77,094	2.88 (2.76-3.00)	0.83 (0.78-0.88)	0.84 (0.79-0.89)
VKA monotherapy	2171	64,053	3.39 (3.25-3.53)	reference	reference
Aspirin monotherapy	3154	93,034	3.39 (3.27-3.51)	0.98 (0.93-1.04)	0.95 (0.90-1.00)
Clopidogrel monotherapy	144	3094	4.65 (3.94-5.46)	1.34 (1.13-1.59)	1.15 (0.97-1.37)
Dual antiplatelet therapy	169	2367	7.14 (3.12-8.28)	1.92 (1.64-2.25)	1.61 (1.38-1.89)
VKA+ antiplatelet drug	1416	19,992	7.08 (6.72-7.46)	2.01 (1.88-2.15)	1.87 (1.74-2.00)
Triple therapy	42	317	13.25 (9.67-17.74)	3.32 (2.45-4.51)	2.82 (2.07-3.84)

Table 2. (*Continued*)

	Bleeds no.	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Age ≥ 90 yrs					
No anticoagulant therapy	656	19,942	3.29 (3.05-3.55)	0.81 (0.70-0.94)	0.84 (0.72-0.98)
VKA monotherapy	240	6158	3.90 (3.43-4.41)	reference	reference
Aspirin monotherapy	1168	29,204	4.00 (3.78-4.23)	0.99 (0.86-1.14)	1.02 (0.89-1.18)
Clopidogrel monotherapy	33	843	3.91 (2.74-5.43)	0.96 (0.66-1.38)	0.95 (0.66-1.38)
Dual antiplatelet therapy	38	485	7.84 (5.62-10.64)	1.80 (1.28-2.54)	1.72 (1.22-2.44)
VKA+ antiplatelet drug	117	1484	7.88 (6.55-9.41)	1.93 (1.55-2.41)	1.88 (1.51-2.35)
Triple therapy	8	18	44.44 (20.64-84.40)	9.34 (4.61-18.94)	8.43 (4.15-17.13)

* Adjusted by sex and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.

Table 3. Sensitivity analysis excluding cause of death: incidence rate of non-fatal major bleeding associated with single, dual, and triple therapy, stratified by sex and by comorbidity.

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Female					
No anticoagulant therapy	2456	153,008	1.61	0.75 (0.71-0.79)	0.75 (0.71-0.79)
VKA monotherapy	2237	104,588	2.14	reference	reference
Aspirin monotherapy	3122	138,171	2.26	1.05 (1.00-1.11)	0.86 (0.82-0.92)
Clopidogrel monotherapy	122	4485	2.72	1.26 (1.05-1.51)	0.88 (0.73-1.06)
Dual antiplatelet therapy	151	3048	4.95	2.14 (1.81-2.52)	1.57 (1.33-1.86)
VKA+ antiplatelet drug	1292	27,786	4.65	2.09 (1.95-2.24)	1.93 (1.80-2.07)
Triple therapy	64	415	15.42	6.10 (4.75-7.82)	5.34 (4.16-6.87)
Male					
No anticoagulant therapy	3319	157,851	2.10	0.84 (0.80-0.88)	0.84 (0.80-0.88)
VKA monotherapy	3646	144,971	2.51	reference	reference
Aspirin monotherapy	3839	133,746	2.87	1.15 (1.10-1.20)	0.94 (0.89-0.98)
Clopidogrel monotherapy	189	3942	4.79	1.89 (1.63-2.18)	1.26 (1.09-1.46)
Dual antiplatelet therapy	229	4248	5.39	1.98 (1.73-2.26)	1.48 (1.29-1.69)
VKA+ antiplatelet drug	2479	50,208	4.94	1.93 (1.83-2.03)	1.74 (1.66-1.84)
Triple therapy	128	1202	10.65	3.70 (3.10-4.41)	3.40 (2.85-4.07)
Previous MI					
No anticoagulant therapy	902	33,594	2.69	0.84 (0.77-0.93)	0.84 (0.76-0.92)
VKA monotherapy	765	23,922	3.20	reference	reference
Aspirin monotherapy	1547	60,705	2.55	0.81 (0.74-0.88)	0.76 (0.69-0.83)
Clopidogrel monotherapy	115	2804	4.10	1.26 (1.04-1.53)	1.07 (0.88-1.30)
Dual antiplatelet therapy	241	4923	4.90	1.41 (1.22-1.63)	1.27 (1.10-1.47)
VKA+ antiplatelet drug	1122	21,649	5.18	1.60 (1.46-1.75)	1.60 (1.46-1.76)
Triple therapy	134	1052	12.74	3.46 (2.87-4.16)	3.60 (2.99-4.33)
Previous bleed					
No anticoagulant therapy	1446	32,508	4.45	0.93 (0.86-1.00)	0.92 (0.85-1.00)
VKA monotherapy	1148	25,004	4.59	reference	reference

Table 3. (*Continued*)

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
Aspirin monotherapy	1482	30,444	4.87	1.03 (0.95-1.11)	0.94 (0.87-1.01)
Clopidogrel monotherapy	109	1633	6.67	1.37 (1.12-1.66)	1.15 (0.94-1.40)
Dual antiplatelet therapy	86	1069	8.04	1.51 (1.21-1.88)	1.29 (1.03-1.61)
VKA+ antiplatelet drug	746	9297	8.02	1.68 (1.53-1.84)	1.61 (1.47-1.77)
Triple therapy	35	199	17.59	3.07 (2.19-4.30)	2.89 (2.06-4.06)
Previous ischemic stroke					
No anticoagulant therapy	1135	32,084	3.54	1.11 (1.03-1.21)	1.04 (0.96-1.12)
VKA monotherapy	1279	40,909	3.13	reference	reference
Aspirin monotherapy	1842	52,283	3.52	1.11 (1.04-1.20)	0.99 (0.92-1.07)
Clopidogrel monotherapy	154	4108	3.75	1.17 (0.99-1.38)	1.04 (0.88-1.23)
Dual antiplatelet therapy	150	2318	6.47	1.97 (1.66-2.33)	1.71 (1.44-2.03)
VKA+ antiplatelet drug	1075	17,573	6.12	1.89 (1.74-2.05)	1.82 (1.68-1.98)
Triple therapy	50	313	15.97	4.30 (3.24-5.71)	4.00 (3.01-5.32)
Ischemic heart disease					
No anticoagulant therapy	2043	81,222	2.52	0.85 (0.80-0.91)	0.84 (0.79-0.89)
VKA monotherapy	2001	68,794	2.91	reference	reference
Aspirin monotherapy	3213	125,011	2.57	0.88 (0.83-0.93)	0.81 (0.76-0.85)
Clopidogrel monotherapy	197	5188	3.80	1.27 (1.10-1.47)	1.05 (0.90-1.21)
Dual antiplatelet therapy	321	6429	4.99	1.55 (1.37-1.74)	1.39 (1.23-1.56)
VKA+ antiplatelet drug	2142	44,540	4.81	1.61 (1.52-1.71)	1.59 (1.50-1.69)
Triple therapy	184	1539	11.96	3.52 (3.02-4.10)	3.66 (3.14-4.26)

* Adjusted for sex and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.

Table 4. Sensitivity analysis excluding cause of death: incidence rate of non-fatal major bleeding associated with single, dual, and triple therapy, stratified by CHA_2DS_2-VASc score.

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
CHA_2DS_2-VASc 0					
No anticoagulant therapy	151	26,955	0.56	0.57 (0.44-0.72)	0.54 (0.42-0.69)
VKA monotherapy	113	10,973	1.03	reference	reference
Aspirin monotherapy	56	7066	0.79	0.80 (0.58-1.11)	0.78 (0.57-1.08)
Clopidogrel monotherapy	0	30	NA	NA	NA
Dual antiplatelet therapy	0	6	NA	NA	NA
VKA+ antiplatelet drug	32	1238	2.58	2.39 (1.61-3.54)	2.39 (1.61-3.55)
Triple therapy	0	1	NA	NA	NA
CHA_2DS_2-VASc 1,2					
No anticoagulant therapy	1342	118,405	1.13	0.65 (0.60-0.70)	0.70 (0.65-0.75)
VKA monotherapy	1522	85,894	1.77	reference	reference
Aspirin monotherapy	1033	63,262	1.63	0.93 (0.86-1.01)	0.90 (0.83-0.98)
Clopidogrel monotherapy	26	1043	2.49	1.40 (0.95-2.07)	1.36 (0.92-2.01)
Dual antiplatelet therapy	27	984	2.74	1.36 (0.93-1.99)	1.62 (1.10-2.38)
VKA+ antiplatelet drug	602	17,802	3.38	1.83 (1.66-2.01)	1.88 (1.71-2.07)
Triple therapy	16	274	5.84	2.66 (1.63-4.36)	3.34 (2.03-5.51)
CHA_2DS_2-VASc 3,4					
No anticoagulant therapy	2954	126,358	2.34	0.92 (0.87-0.97)	0.90 (0.86-0.95)
VKA monotherapy	2841	113,539	2.50	reference	reference
Aspirin monotherapy	3646	134,483	2.71	1.07 (1.02-1.12)	0.99 (0.94-1.04)
Clopidogrel monotherapy	150	3511	4.27	1.55 (1.31-1.83)	1.36 (1.15-1.62)
Dual antiplatelet therapy	151	3064	4.93	1.75 (1.49-2.06)	1.62 (1.38-1.92)
VKA+ antiplatelet drug	1876	38,304	4.90	1.88 (1.78-2.00)	1.83 (1.73-1.94)
Triple therapy	94	808	11.63	3.92 (3.19-4.81)	4.04 (3.28-4.98)
CHA_2DS_2-VASc 5					
No anticoagulant therapy	831	26,593	3.12	0.91 (0.83-1.01)	0.89 (0.81-0.98)
VKA monotherapy	893	26,680	3.35	reference	reference
Aspirin monotherapy	1376	43,266	3.18	0.93 (0.86-1.01)	0.88 (0.81-0.96)
Clopidogrel monotherapy	73	3075	2.37	1.01 (0.80-1.28)	0.89 (0.70-1.13)
Dual antiplatelet therapy	106	1764	6.01	1.64 (1.34-2.00)	1.48 (1.20-1.81)
VKA+ antiplatelet drug	758	13,389	5.66	1.64 (1.49-1.80)	1.58 (1.43-1.74)
Triple therapy	45	314	14.33	3.63 (2.69-4.91)	3.41 (2.52-4.62)

Table 4. (*Continued*)

	Bleeds (no.)	Exposure time (py)	Incidence rate per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
CHA_2DS_2-VASc 6					
No anticoagulant therapy	393	9901	3.97	0.96 (0.84-1.11)	0.94 (0.81-1.08)
VKA monotherapy	399	9837	4.06	reference	reference
Aspirin monotherapy	650	18,364	3.54	0.86 (0.76-0.98)	0.84 (0.74-0.95)
Clopidogrel monotherapy	51	1239	4.12	0.99 (0.74-1.33)	0.92 (0.69-1.23)
Dual antiplatelet therapy	66	1080	6.11	1.41 (1.09-1.83)	1.31 (1.00-1.71)
VKA+ antiplatelet drug	370	5717	6.47	1.56 (1.35-1.80)	1.51 (1.31-1.74)
Triple therapy	27	170	15.88	3.46 (2.34-5.13)	3.17 (2.17-4.70)
CHA_2DS_2-VASc 7-9					
No anticoagulant therapy	104	2648	3.93	0.88 (0.67-1.15)	0.85 (0.65-1.12)
VKA monotherapy	115	2637	4.36	reference	reference
Aspirin monotherapy	200	5475	3.65	0.82 (0.65-1.04)	0.80 (0.63-1.01)
Clopidogrel monotherapy	21	528	3.98	0.88 (0.55-1.41)	0.85 (0.53-1.36)
Dual antiplatelet therapy	30	398	7.54	1.59 (1.06-2.37)	1.48 (0.99-2.23)
VKA+ antiplatelet drug	133	1545	8.61	1.90 (1.48-2.44)	1.82 (1.41-2.34)
Triple therapy	10	50	20.00	3.83 (2.00-7.34)	3.47 (1.80-6.67)

* Adjusted by sex and the following comorbidities: ischemic heart disease, valvular heart disease, liver disease, kidney failure, and cancer.