10.1161/CIRCULATIONAHA.118.036248

Major Bleeding Rates in Atrial Fibrillation Patients on Single, Dual, or Triple Antithrombotic Therapy: Results from a Nationwide Danish Cohort Study

Running Title: *van Rein et al.; High Major Bleeding Rates During Triple Therapy*

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Abstract

Background: Patients with atrial fibrillation generally require anticoagulant therapy, and at times therapy with additional platelet aggregation inhibitors. Data are scarce on bleeding rates in high-risk groups receiving combination 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 vitamine K antagonists (VKAs), direct oral anticoagulants (DOACs), platelet inhibitors, and combinations of antithrombotic drugs. Incidence rates (IRs) of major bleeding and hazard ratios were estimated overall, and also stratified by treatment modality, age, CHA_2DS_2-VASc score, and comorbidity. Major bleeding was defined as bleeding requiring hospitalization or causing death.

Results: We identified 272,315 patients with atrial fibrillation. Median age was 75 years (interquartile range 67-83) and 47% were women. Over a total follow-up period of 1,373,131 patient-years (PYs), 31,459 major bleeds occurred [incidence rate (IR) 2.3/100 PYs, 95% confidence interval (CI) 2.3-2.3/100 PYs]. Compared with VKA monotherapy, adjusted hazard ratios of major bleeding were 1.13 (95% CI 1.06-1.19) for dual antiplatelet therapy, 1.82 (95% CI 1.76-1.89) for therapy with a VKA and an antiplatelet drug, 1.28 (95% CI 1.13-1.44) for therapy of a DOAC with an antiplatelet drug, 3.73 (95% CI 3.23-4.31) for VKA triple therapy and 2.28 (95% CI 1.67-3.12) for DOAC triple therapy. Subgroup analyses showed similar patterns. The IR for major bleeding was 10.2/100 PYs among triple-therapy patients. Very high major bleeding rates occured among patients on triple therapy aged > 90 years (IR 22.8/100 PYs) or with a CHA_2DS_2-VASc score over 6 (IR 17.6/100 PYs) or with a history of major bleeding (IR 17.5/100 PYs).

Conclusions: Patients with atrial fibrillation on triple therapy experienced high rates of major bleeding compared with patients on dual therapy or monotherapy. The 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 or with a history of a major bleeding warrants careful consideration of such therapy in these patients.

Key Words: Anticoagulants; Hemorrhage; Atrial Fibrillation; Antiplatelet Drug; Cohort Study

Clinical Perspective

What is new?

- This study showed that patients with atrial fibrillation on VKA and DOAC triple therapy experienced a high rate of major bleeding across all subgroups.
- Bleeding rates were similar between patients who received VKA and DOAC triple therapy.
- Some subgroups, such as patients over 90 years of age or patients with a CHA_2DS_2-VASc of 7 to 9 or with a history of a major bleeding, had very high major bleeding rates.

What are the clinical implications?

- The 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 or with a history of a major bleeding warrant careful weighing of the high bleeding risk with the risk of thrombotic events in these patients.
- The high bleeding rates in all subgroups of patients on VKA and DOAC triple therapy emphasize that the duration of triple therapy should be as short as possible.

Introduction

Patients with atrial fibrillation often require long-term treatment with oral anticoagulants such as vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs) [1]. As these patients 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 VKAs with a single platelet inhibitor is associated with a twofold to threefold higher risk of bleeding complications as compared with VKA monotherapy [3]. Triple therapy with VKA, aspirin, and clopidogrel has been associated with an almost fourfold higher 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]. In addition, information is scarce on bleeding rates during combined use of DOAC and antiplatelet drugs, which has become more prevalent in recent years. For this, sufficient numbers of patients are required to allow comparison of bleeding rates associated with several combinations of antithrombotic 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.

Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure. Such disclosure would conflict with the regulations for use of Danish health care data.

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 2015. 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), DOACs (dabigatran, rivaroxaban and apixaban) and platelet inhibitors (aspirin, clopidogrel, dipyridamole, prasugrel and ticagrelor) were obtained from the DRMPS using ATC codes (see Supplemental Material). Antithrombotic drug exposure was considered as a time-dependent variable. Patients were considered exposed starting on the day they filled a prescription for an antithrombotic drug. Length of exposure to VKAs was assumed to be 90 days per prescription, as drugs for chronic conditions are seldom provided for more than three months at a time in Denmark. Length of exposure to DOACs and antiplatelet drugs was based on the number of pills collected divided by two in case of twice-daily dosing (*i.e.* for dabigatran, apixaban, ticagrelor, and dipyridamole) and divided by one in case of once-daily dosing (all other antithrombotic drugs). On top of this period, we added 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 was low-dose aspirin. However, patients receiving

long-term treatment with low-dose aspirin usually obtain a prescription to permit financial reimbursement, as reported in other studies [3, 12]. Therefore aspirin use was included and coded as a prescription.

Based on medication use, ten categories of exposure were identified: no antithrombotic treatment; monotherapy with a VKA; monotherapy with a DOAC; monotherapy with aspirin; monotherapy with another antiplatelet drug; dual therapy with a VKA and one antiplatelet drug; dual therapy with a DOAC and one antiplatelet drug; dual antiplatelet therapy; VKA triple therapy (VKA and two antiplatelet drugs); and DOAC triple therapy (DOAC and two antiplatelet drugs).

Outcomes, comorbidities and comedications

Outcomes of interest were major bleeds (primary outcome), ischemic strokes, myocardial infarctions (MIs), and all-cause mortality (secondary outcomes). In short, all major bleeds, ischemic strokes, and myocardial infarctions that led to a hospital admission or that were fatal were outcomes of interest. The DNPR and the Danish Registry of Causes of Death were used to ascertain outcomes, classified according to ICD-10 codes (see Supplemental Material). 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. 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 (see the Supplemental Material) [13].

Receipt of at least one filled prescription of antithrombotic agents within 180 days preceding the AF diagnosis was ascertained from the DRMPS and considered as baseline use (see ATC codes in the Supplemental Material).

Statistical analysis

Patients were followed from the date of their atrial fibrillation diagnosis until occurrence of the outcome of interest for a given analysis (major bleeding event, ischemic stroke, or MI), death or end of the study period (31 December 2015). In calculating follow-up time until a major bleed or another outcome, we did not consider the occurrence of the other outcomes. For example, if a patient experienced both an ischemic stroke and a major bleeding event, we calculated separate follow-up times for each analysis. Thus all follow-up from the diagnosis of atrial fibrillation to the first major bleeding event was included in the analysis of major bleeding, and all follow-up until the first ischemic stroke was included in the ischemic stroke analysis.

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). In addition, bleeding rates were stratified by single, double and triple therapy and by weeks from AF diagnosis. Incidence rates per week were calculated by dividing the number of major bleeds in a week by the total follow-up time in that particular week multiplied by 100. 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. Additional sensitivity analyses were performed in which only major bleedings which were primary hospital diagnoses or primary causes of death were considered. This allowed us to ascertain whether the combination of primary and secondary bleeding diagnoses yielded results similar to the results for primary hospital diagnoses alone. In another sensitivity analysis, major bleeding was divided into intracranial bleeding and other major bleeding.

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/). The study was approved by the Danish Data Protection Agency, record number 2015-57-0002, and Aarhus University, record number 2016-051-000001, serial number 818. In Denmark, registry-based research does not require approval from an ethics committee or informed consent from patients.

Results

Characteristics

We identified 272,315 patients aged 50 years or older who were admitted to a hospital or who had a outpatient visit in a hospital clinic with a first-time diagnosis of atrial fibrillation between 1995 and 2015 (see Table 1). Median age was 75 years [interquartile range (IQR) 67-83 years], 19,458 (7%) patients were above 90 years of age, and 128,825 patients (47%) were women. The median CHA_2DS_2-VASc score was 3 (IQR 2-4) and 27,306 patients (10%) had a CHA_2DS_2-VASc score of 6 or more. The most common treatments were monotherapy with a VKA [59,141 patients (22%)] or aspirin [60,827 patients (22%)] or dual therapy with a VKA and an antiplatelet drug [31,539 patients (12%)]. Dipyridamole was used by 9656 patients (4%), and P2Y12 antagonists were used by 14,289 patients (5%), of whom 13,439 used clopidogrel (5%), 89 used prasugrel (0.03%), and 922 used ticagrelor (0.3%). VKA triple therapy was prescribed to 4069 patients (1%) and DOAC triple therapy to 886 patients (0.3%). The prevalence of a history of ischemic heart disease or an MI was highest among patients treated with dual antiplatelet therapy or with VKA triple therapy or DOAC triple therapy (see Table 1).

Major bleeding by type of therapy

Median follow-up was four years (IQR 2-8 years), resulting in total follow-up time of 1,373,131 PYs. A total of 31,459 major bleeds occurred during follow-up. Of these, 995 (3.2%) were fatal. Major bleeding rates were lowest in patients not treated with an antithrombotic agents and increased with the number of anticoagulants or antiplatelet drugs used concurrently (incidence rates between 1.3 and 10.4 per 100 PYs; see Table 2). Major bleeding rates were highest within the first month after AF diagnosis (see Supplemental Material Figure 1). Incidence rates and adjusted HRs for major bleeding, using VKA monotherapy as reference, were lower in DOAC

users than in VKA users, and higher in ticagrelor users as compared with other antiplatelet users (see Supplemental Material Table 1). Compared with VKA monotherapy, adjusted HRs of major bleeding were 1.13 (95% CI 1.06-1.19) for dual antiplatelet therapy, 1.82 (95% CI 1.76-1.89) for therapy with both a VKA and an antiplatelet drug, 1.28 (95% CI 1.13-1.44) for therapy with both a DOAC and an antiplatelet drug, 3.13 (95% CI 2.84-3.45) for VKA triple therapy, and 2.28 (95% CI 1.67-3.12) for DOAC triple therapy. Intracranial bleeding rates were between 0.4 and 1.4 per 100 PYs for users of antithrombotic agents and were higher among patients who used VKAs as compared with patients who used DOACs (Table 2). The sensitivity analysis that included only primary diagnoses of major bleeding yielded results similar to those of the main analysis (see Supplemental Material Table 2).

Risk groups

Rates of major bleeding were lowest in the youngest age group (incidence rates between 0.6 and 10.1 per 100 PYs) (see Figure 1A, Figure 2, and Supplemental Material Table 3) and in the group with a CHA_2DS_2-VASc score of 0 (incidence rates between 0.4 and 2.7 per 100 PYs) (see Figure 1B, Figure 3, and Supplemental Material Table 4). As in the overall analysis, major bleeding rates increased with age and the number of antithrombotic agents used simultaneously. Major bleeding rates in patients on VKA triple therapy increased with each 10-year increase in age (10.1 per 100 PYs for patients aged 50-59, 7.4 per 100 PYs for patients aged 60-69, 9.8 per 100 PYs for patientsaged 70-79, 13.7 per 100 PYs for patients aged 80-89, and 21.9 per 100 PYs for those aged 90 and over). The results of the DOAC triple therapy group followed the same trend as the VKA triple therapy group (unknown for patients aged 50-59, 2.9 per 100 PYs for patients aged 60-69, 8.6 per 100 PYs for patients aged 70-79, 12.5 per 100 PYs for patients aged 80-89, and 25.1 per 100 PYs for those aged 90 and over). When incidence rates were contrasted

with VKA monotherapy as the reference group, the adjusted HRs closely followed the pattern of higher 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 VKA triple therapy and who had a CHA_2DS_2-VASc score above 6 (IR 17.1, 95% CI 11.3-24.9).

Compared with male patients, female patients had higher major bleeding rates (see Figure 1C, Figure 4, and Supplemental Material Table 5). Patients with ischemic heart disease and patients who experienced an 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 in which outcomes from the Danish Registry of Causes of Death were excluded (see the Supplemental Material Table 2 and 6 to 8) 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 platelet inhibitor monotherapy or two antiplatelet drugs with or without a VKA or DOAC. Rates of ischemic stroke varied between 0.0 to 8.1 per 100 PYs, rates of MIs varied between 0.0 to 15.1 per 100 PYs, and death rates ranged from 0.0 to 43.3 per 100 PYs (see Supplemental Material Figure 2, 3, and 4).

Discussion

Our study showed that the incidence rate of major bleeding increased with the number of prescribed antithrombotic agents. Nearly all groups treated with triple therapy experienced high rates of bleeding complications, up to 25 per 100 PYs in the oldest age group. Relative risk estimates did not change greatly after adjustment for confounding factors, indicating that DOAC

triple therapy was associated with a 1.2- to 3.9- fold and VKA triple therapy was associated with a 2.4- to 5.4-fold higher risk of major bleeding complications compared with VKA monotherapy.

Major bleeding

We found that VKA triple therapy was associated with a three-fold average higher risk of major bleeding, compared with VKA monotherapy, which agrees with the literature [3]. As compared with the study by Hansen *et al.*, we found lower incidence rates of bleeding events. The lower bleeding rates may be explained by the difference in the definition of exposure duration, which was based on the average dosage from previous prescriptions in the Hansen *et al.* study, while we assumed that patients used VKAs for 90 days and that the duration of use of other drugs was based on the recommended dosage with an additional washout period. In addition to the literature, we found that DOAC triple therapy is associated with similar bleeding risks as compared with VKA triple therapy and that incidence rates of bleeding events among triple therapy users were high across all subgroups. We also found that treatment regimens with a VKA were associated with higher rates of intracranial bleeding than other treatments. A possible explanation is that VKAs cause more intracranial bleeding than other anticoagulants, as previously described [14]. An alternate explanation may be confounding by indication, as, for example, DOACs are contra-indicated in patients with kidney failure.

The clinical impact of relative risks depends on their absolute values. Results showed that patients who received DOAC triple therapy had similar major bleeding rates as compared with groups with VKA triple therapy. In addition, 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, this was not the case, as major bleeding rates were at least 5.1 per 100 PYs in these groups. 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 [15]. All other subgroups experienced very high major bleeding rates while receiving VKA or DOAC 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 [15].

We also observed that female patients experienced higher major bleeding rates than male patients, in contrast to the findings of previous studies [15]. This makes it likely that there is an alternate explanation, such as confounding, for the sex difference in bleeding rates.

High major bleeding rates were also 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 [15].

Clinical implications

The high rates of major bleeding found among patients receiving triple therapy raises the question whether concomitant use of three antithrombotic drugs is advisable. However, risk factors for ischemic events and major bleeding overlap [16], 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, these high bleeding rates emphasize that treatment with triple therapy should be as short as possible. In addition, three important findings in our study were that among patients receiving triple therapy: 22-25 patients per 100 PYs of those aged over 90 years experienced a major bleed. A recent study suggested that patients over 85 years have the highest absolute benefit of oral anticoagulants [17]. This may be true for monotherapy, but the results of this study emphasize that the bleeding risk is unacceptably high in patients over 90 years using triple therapy. Patients with a CHA_2DS_2-VASc scores of 7 to 9 and patients with a history of major bleeding had a bleeding rate of 17 per 100 PYs. These very high bleeding rates must be carefully weighed against the prevention of thrombo-embolic events in these groups.

Strengths and limitations

This population-based cohort study contained data from over 250,000 patients with large numbers of outcome events, making the results robust and generalizable to the currently treated population and allowing multiple subgroup analyses. The main limitation of the study is the observational design, in which the assessment of safety was made in isolation from an assessment of efficacy. Therefore, our results alone cannot guide clinical decision-making and should preferably be confirmed by a clinical trial. A downside is that such a trial would have to be very large, which may make this study the best evidence possible. Another limitation is that while the overall sample size is large, many of the subgroups are relatively small, limiting the statistical power to explore all possible associations. A limitation is the reliance on dispensed prescriptions as recorded in a pharmacy registry, as filled prescriptions do not imply that patients actually took the medication. Still, if patients did not take their medication, 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 that platelet inhibitors were considered as one drug group in all analyses, although the drugs are used for different indications and individual drugs may have different bleeding risks. It was beyond the scope of this study to directly compare antiplatelet drugs in terms of efficacy and safety outcomes. Still, we included the overall safety outcomes and length of use to give an indication of these numbers. In addition, only bleeding events that resulted in hospital admissions or were fatal were considered major. This is not completely consistent with the International Society of Thrombosis and Haemostasis criteria for major bleeding and may have led to underestimation of rates of major bleeding. Another limitation is that we were unable to stratify major bleeding rates by a bleeding risk score, such as the HAS BLED score, as variables such as alcohol use and labile INR were unavailable. Finally, this is an observational study in which residual confounding could have played a role in the results it yielded, *i.e.*, patients at high risk of major bleeding may not have received triple therapy. This might have resulted in an underestimation of the relative risk estimates.

Conclusion

This study showed that patients with atrial fibrillation on VKA and DOAC 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 and with a history of a major bleeding, had very high bleeding rates, suggesting that triple therapy should be carefully considered in these patients.

Sources of Funding

Hartstichting (2011 T12), Center for Translational Molecular Medicine (01 C-201) and

Hartstichting (99.165).

Disclosures

None.

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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 2015, by type of therapy.

		No	Monotherapy				Dual therapy			Triple therapy	
	All	anticoag.				Other	Dual	VKA+	DOAC+		
	patients	treatment	VKA	DOAC	Aspirin	Antiplatelets	Antiplatelet*	Antiplatelet*	Antiplatelet*	VKA	DOAC
General characteristics											
Patients	272,315	79,194	59,141	14,201	60,827	4227	10,687	31,539	5966	4069	886
Age	75 (67-83)	74 (64-83)	72 (65-79)	73 (67-81)	79 (70-86)	79 (71-86)	80 (71-86)	75 (68-81)	77 (70-84)	75 (68-81)	77 (70-83)
Female sex	128,825 (47)	40,883 (52)	24,240 (41)	6657 (47)	32,125 (53)	2140 (51)	5067 (47)	12,536 (40)	2701 (45)	1427 (35)	375 (42)
CHA_2DS_2-VASc	3 (2-4)	3 (1-4)	2 (1-4)	3 (2-4)	3 (2-4)	4 (3-5)	4 (3-5)	3 (2-4)	4 (3-5)	4 (3-5)	4 (3-5)
Comorbidities											
IHD	81,025 (30)	16,182 (20)	10,522 (18)	2144 (15)	24,306 (40)	1821 (43)	6154 (58)	13,717 (43)	2547 (43)	2480 (61)	491 (55)
Valv. heart dis.	23,221 (9)	4621 (6)	5784 (10)	837 (6)	4963 (8)	380 (9)	1010 (9)	4288 (14)	587 (10)	494 (12)	83 (9)
Hypertension	93,468 (34)	19,791 (25)	17,961 (30)	5778 (41)	21,410 (35)	2402 (57)	5422 (51)	13,583 (43)	3560 (60)	2194 (54)	561 (63)
Diabetes	31,503 (12)	7212 (9)	5482 (9)	1365 (10)	7896 (13)	712 (17)	1864 (17)	4716 (15)	1093 (18)	737 (18)	168 (19)
Liver disease	5095 (2)	2059 (3)	818 (1)	245 (2)	1048 (2)	112 (3)	181 (2)	433 (1)	102 (2)	57 (1)	17 (2)
Renal failure	10,643 (4)	3420 (4)	1487 (3)	279 (2)	2682 (4)	336 (8)	665 (6)	1192 (4)	203 (3)	250 (6)	29 (3)
Malignancy	55,186 (20)	18,367 (23)	9961 (17)	3029 (21)	12,770 (21)	1056 (25)	2236 (21)	5238 (17)	1327 (22)	708 (17)	182 (21)
Previous											
iCVA	43,200 (16)	8033 (10)	6080 (10)	1779 (13)	8758 (14)	2546 (60)	5746 (54)	5664 (18)	1492 (25)	2089 (51)	475 (54)
MI	47,194 (17)	9269 (12)	5722 (10)	754 (5)	14,055 (23)	1080 (26)	4609 (43)	7883 (25)	1223 (20)	1820 (45)	335 (38)
Major bleeds	40,425 (15)	12,059 (15)	6861 (12)	1999 (14)	9672 (16)	1116 (26)	2140 (20)	4333 (14)	1101 (18)	682 (17)	153 (17)
Receipt of at least one filled prescription within 180 preceding the atrial fibrillation diagnosis											
VKA	40,308 (15)	3600 (5)	24,314 (41)	232 (2)	1360 (2)	97 (2)	150 (1)	9285 (29)	55 (1)	710 (17)	8 (1)
DOAC	6483 (2)	457 (1)	152 (0)	4430 (31)	96 (0)	13 (0)	20 (0)	49 (0)	962 (16)	6 (0)	86 (10)
Aspirin	88,455 (32)	4181 (5)	3447 (6)	817 (6)	39,727 (65)	618 (15)	7714 (72)	22,980 (73)	4377 (73)	3092 (76)	730 (82)
Antiplatelet	18,175 (7)	650 (1)	572 (1)	301 (2)	855 (1)	2929 (69)	5815 (54)	2117 (7)	1105 (19)	2601 (64)	670 (76)

* Antiplatelet represents aspirin as well as other antiplatelet drugs.

Continuous variables denoted as median (interquartile range), categorical variables as number (%)

Anticoag: anticoagulant; DOAC: direct oral anticoagulant; iCVA: ischemic cerebrovascular accident; IHD: ischemic heart disease; no: number; MI: myocardial infarction; valv. heart dis.: valvular heart disease; VKA: vitamin K antagonist

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

	Bleeds (no.)	Exposure time (PY)	per 100 py (95% CI)	Hazard ratio (95% CI)	Hazard ratio* (95% CI)
All major bleeding					
No anticoagulant therapy	6830	495,735	1.4 (1.3-1.4)	0.60 (0.58-0.62)	0.55 (0.53-0.57)
VKA monotherapy	7768	337,273	2.3 (2.3-2.4)	reference	reference
DOAC monotherapy	1077	49,075	2.2 (2.1-2.3)	0.89 (0.83-0.94)	0.84 (0.79-0.90)
Aspirin monotherapy	8049	316,186	2.5 (2.5-2.6)	1.09 (1.05-1.12)	0.98 (0.95-1.01)
Platelet inhibitor monotherapy	720	21,278	3.4 (3.1-3.6)	1.44 (1.34-1.56)	1.03 (0.95-1.11)
Dual antiplatelet therapy	1505	39,824	3.8 (3.6-4.0)	1.58 (1.49-1.67)	1.13 (1.06-1.19)
VKA+ antiplatelet drug	4769	100,259	4.8 (4.6-4.9)	1.98 (1.91-2.05)	1.82 (1.76-1.89)
DOAC+ antiplatelet drug	272	6843	4.0 (3.5-4.5)	1.47 (1.30-1.66)	1.28 (1.13-1.44)
VKA triple therapy	429	4130	10.4 (9.4-11.4)	3.73 (3.39-4.12)	3.13 (2.84-3.45)
DOAC triple therapy	40	454	8.8 (6.4-11.9)	2.79 (2.04-3.81)	2.28 (1.67-3.12)
Intracranial bleeding					
No anticoagulant therapy	1441	495,735	0.3 (0.3-0.3)	0.50 (0.46-0.53)	0.48 (0.45-0.52)
VKA monotherapy	1992	337,273	0.6 (0.6-0.6)	reference	reference
DOAC monotherapy	224	49,075	0.5 (0.4-0.5)	0.73 (0.64-0.84)	0.66 (0.57-0.75)
Aspirin monotherapy	1326	316,186	0.4 (0.4-0.4)	0.71 (0.66-0.76)	0.68 (0.63-0.73)
Platelet inhibitor monotherapy	146	21,278	0.7 (0.6-0.8)	1.15 (0.97-1.36)	0.73 (0.61-0.86)
Dual antiplatelet therapy	288	39,824	0.7 (0.6-0.8)	1.20 (1.06-1.35)	0.73 (0.64-0.84)
VKA+ antiplatelet drug	875	100,259	0.9 (0.8-0.9)	1.44 (1.33-1.55)	1.35 (1.25-1.47)
DOAC+ antiplatelet drug	39	6843	0.6 (0.4-0.8)	0.86 (0.62-1.18)	0.73 (0.53-1.01)
VKA triple therapy	57	4130	1.4 (1.1-1.8)	2.03 (1.56-2.64)	1.61 (1.23-2.10)
DOAC triple therapy	4	454	0.9 (0.3-2.1)	1.17 (0.44-3.12)	0.90 (0.34-2.40)
Other major bleeding					
No anticoagulant therapy	5389	495,735	1.1 (1.1-1.1)	0.64 (0.62-0.66)	0.58 (0.56-0.61)
VKA monotherapy	5776	337,273	1.7 (1.7-1.8)	reference	reference
DOAC monotherapy	853	49,075	1.7 (1.6-1.9)	0.94 (0.87-1.01)	0.89 (0.83-0.96)
Aspirin monotherapy	6723	316,186	2.1 (2.1-2.2)	1.22 (1.18-1.26)	1.08 (1.04-1.12)
Platelet inhibitor monotherapy	574	21,278	2.7 (2.5-2.9)	1.54 (1.42-1.68)	1.12 (1.03-1.22)
Dual antiplatelet therapy	1217	39,824	3.1 (2.9-3.2)	1.71 (1.61-1.82)	1.26 (1.18-1.34)
VKA+ antiplatelet drug	3894	100,259	3.9 (3.8-4.0)	2.16 (2.07-2.25)	1.96 (1.88-2.04)
DOAC+ antiplatelet drug	233	6843	3.4 (3.0-3.9)	1.68 (1.47-1.91)	1.41 (1.24-1.61)
VKA triple therapy	372	4130	9.0 (8.1-10.0)	4.30 (3.88-4.78)	3.58 (3.22-3.99)
DOAC triple therapy	36	454	7.9 (5.6-10.9)	3.32 (2.39-4.60)	2.67 (1.93-3.71)

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

CI: confidence interval; DOAC: direct oral anticoagulant; no: number ; PY: patient-years; VKA: vitamin K antagonist

Figure Legends

Figure 1. Incidence rates per 100 person-years of major bleeds by age (A), CHA_2DS_2-VASc score (B), and sex and comorbidity (C).

A: Incidence rates per 100 person-years of major bleeds by age.

B: Incidence rates per 100 person-years of major bleeds by CHA_2DS_2-VASc score.

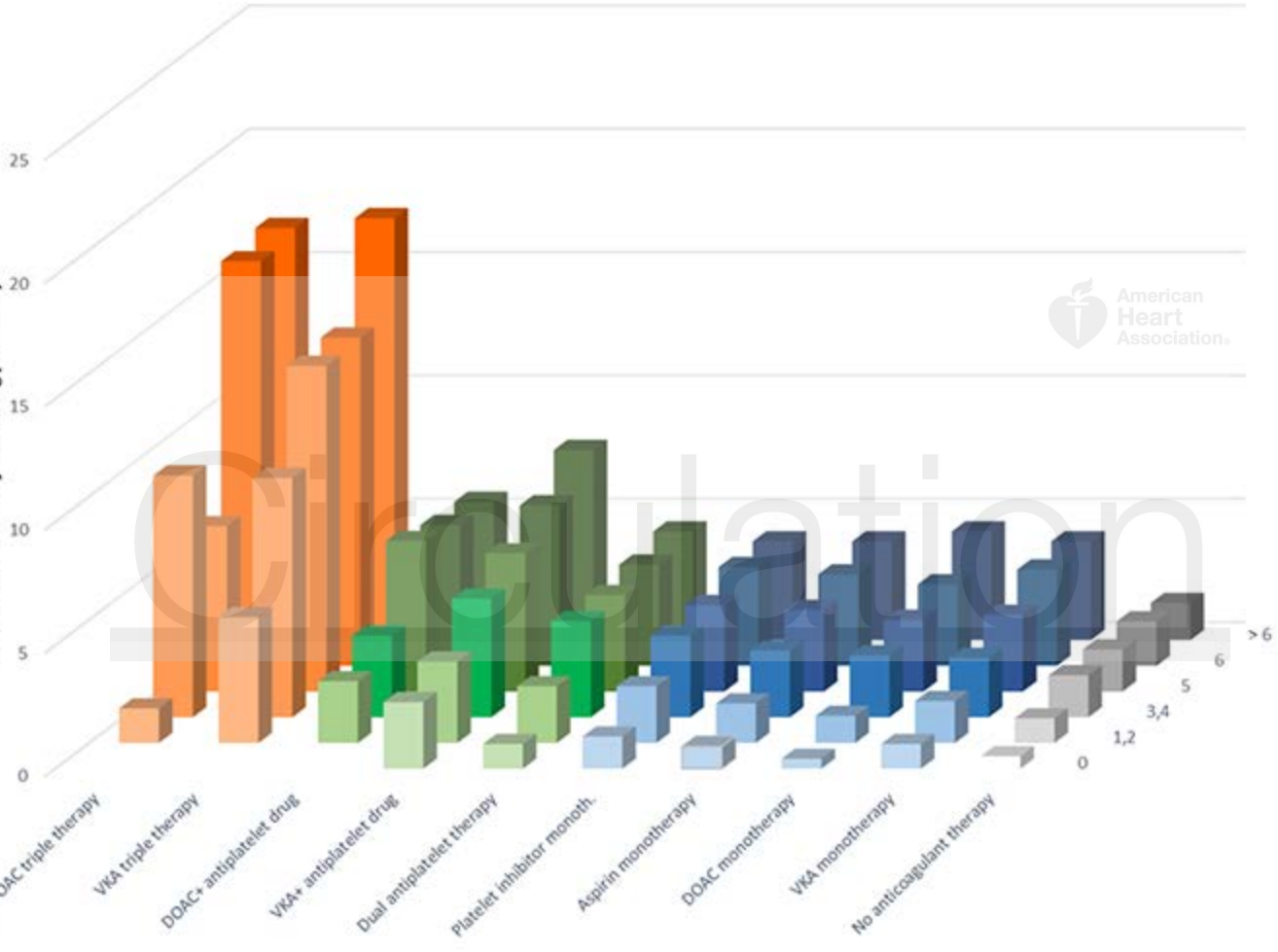
C: Incidence rates per 100 person-years of major bleeds by sex and by comorbidity.

Figure 2. Incidence rate and hazard ratio of major bleeding associated with single, dual, and triple therapy, stratified by age. Dashed lines represent incidence rate of reference group (VKA monotherapy). * Adjusted by sex and the following comorbidities: ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, kidney failure, and cancer; CI: confidence interval; DOAC: direct oral anticoagulant; no: number ; VKA: vitamin K antagonist

Figure 3. Incidence rate and hazard ratio of major bleeding associated with single, dual and triple therapy, stratified by CHA2DS2-VASc score. Dashed lines represent incidence rate of reference group (VKA monotherapy). * Adjusted by sex and the following comorbidities: ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, kidney failure, and cancer

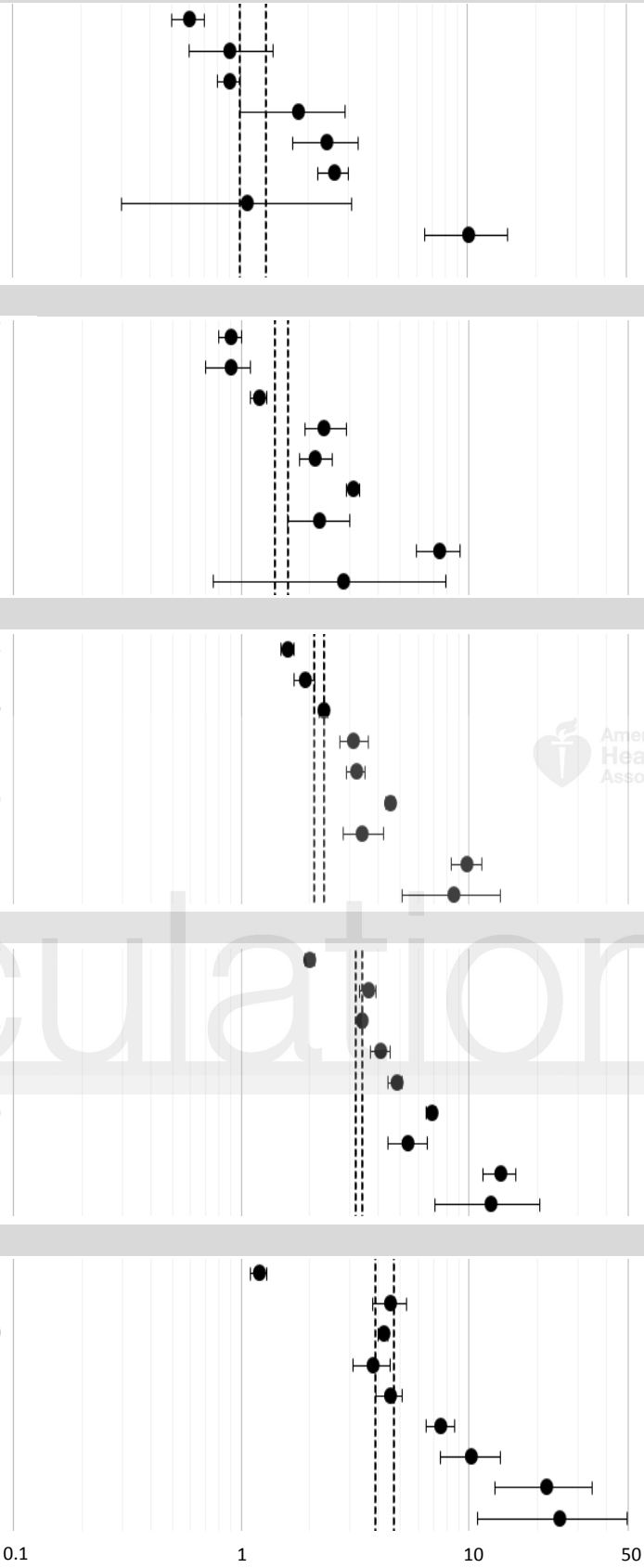
** Numbers were censored from the manuscript due to small numbers and patient confidentiality; CI: confidence interval; DOAC: direct oral anticoagulant; monoth: monotherapy; no: number; VKA: vitamin K antagonist

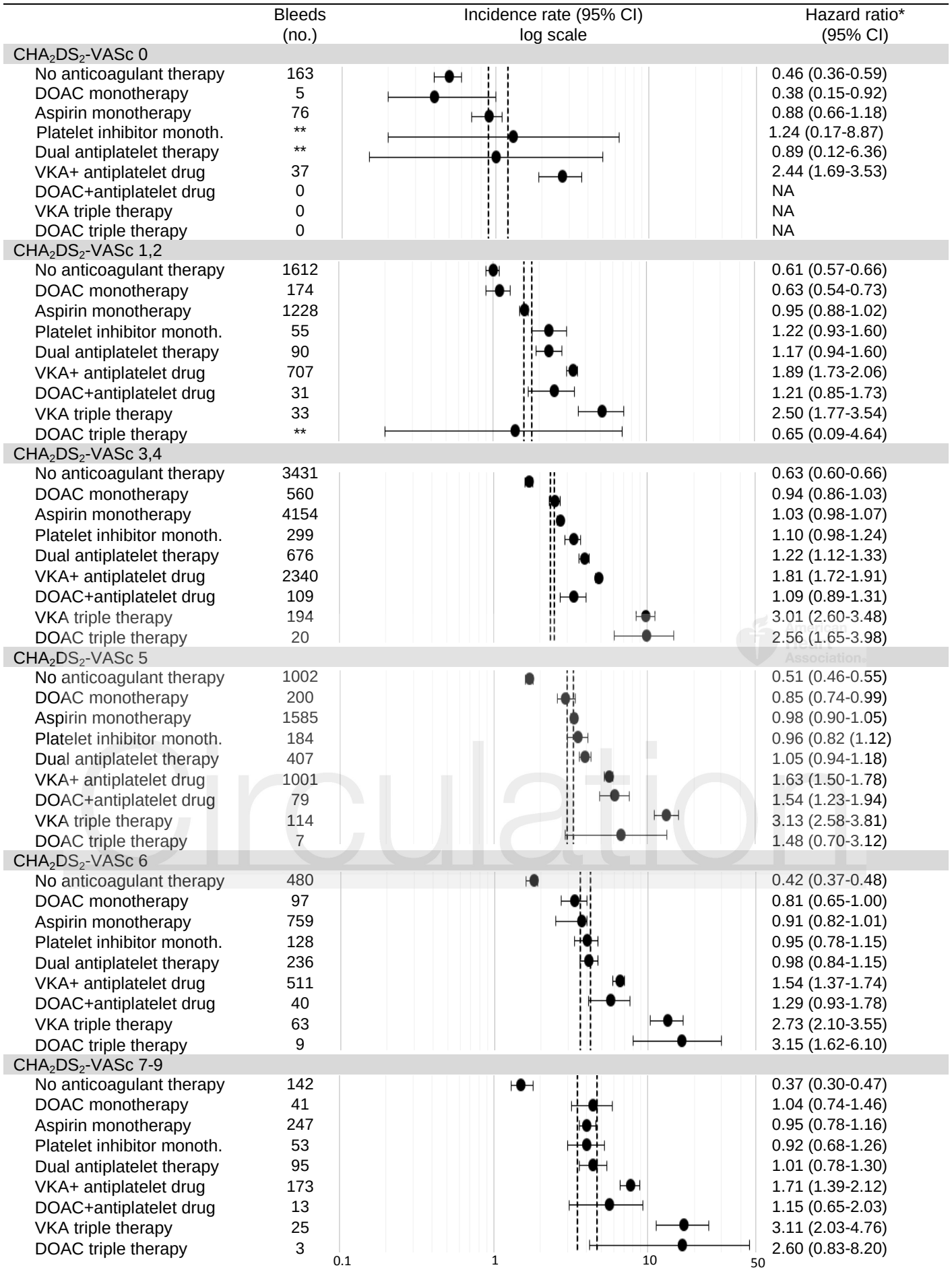
Figure 4. Incidence rate and hazard ratio of major bleeding associated with single, dual, and triple therapy, stratified by sex and by comorbidity. Dashed lines represent incidence rate of reference group (VKA monotherapy). *Adjusted by sex and the following comorbidities: ischemic heart disease, valvular heart disease, diabetes, hypertension, liver disease, kidney failure, and cancer; CI: confidence interval; DOAC: direct oral anticoagulant; monoth: monotherapy; no: number; VKA: vitamin K antagonist



C

	Bleeds no.	Incidence rate (95% CI) log scale	Hazard ratio* (95% CI)
Age 50-59 yrs			
No anticoagulant therapy	303		0.63 (0.53-0.75)
DOAC monotherapy	22		0.77 (0.50-1.19)
Aspirin monotherapy	165		0.83 (0.67-1.01)
Platelet inhibitor monoth.	13		1.10 (0.63-1.94)
Dual antiplatelet therapy	32		1.37 (0.94-2.01)
VKA+ antiplatelet drug	129		1.82 (1.46-2.27)
DOAC+ antiplatelet drug	3		0.75 (0.24-2.36)
VKA triple therapy	22		5.42 (3.45-8.50)
DOAC triple therapy	0		NA
Age 60-69 yrs			
No anticoagulant therapy	1017		0.65 (0.60-0.71)
DOAC monotherapy	111		0.81 (0.72-0.90)
Aspirin monotherapy	808		0.98 (0.93-1.04)
Platelet inhibitor monoth.	80		1.05 (0.90-1.21)
Dual antiplatelet therapy	131		1.02 (0.92-1.14)
VKA+ antiplatelet drug	775		1.75 (1.65-1.86)
DOAC+ antiplatelet drug	37		1.14 (0.93-1.42)
VKA triple therapy	81		2.87 (2.45-3.36)
DOAC triple therapy	3		2.36 (1.44-2.86)
Age 70-79 yrs			
No anticoagulant therapy	2142		0.73 (0.69-0.77)
DOAC monotherapy	353		0.81 (0.72-0.90)
Aspirin monotherapy	2155		0.98 (0.93-1.04)
Platelet inhibitor monoth.	194		1.05 (0.90-1.21)
Dual antiplatelet therapy	376		1.02 (0.92-1.14)
VKA+ antiplatelet drug	1889		1.75 (1.65-1.86)
DOAC+ antiplatelet drug	88		1.14 (0.93-1.42)
VKA triple therapy	167		2.87 (2.45-3.36)
DOAC triple therapy	16		2.36 (1.44-2.86)
Age 80-89 yrs			
No anticoagulant therapy	2587		0.57 (0.54-0.61)
DOAC monotherapy	459		0.97 (0.87-1.07)
Aspirin monotherapy	3501		0.99 (0.94-1.04)
Platelet inhibitor monoth.	325		1.04 (0.92-1.17)
Dual antiplatelet therapy	753		1.20 (1.10-1.30)
VKA+ antiplatelet drug	1809		1.85 (1.75-1.97)
DOAC+ antiplatelet drug	102		1.24 (1.01-1.51)
VKA triple therapy	143		2.88 (2.43-3.42)
DOAC triple therapy	14		2.19 (1.29-3.70)
Age ≥ 90 years			
No anticoagulant therapy	781		0.30 (0.27-0.34)
DOAC monotherapy	132		0.94 (0.77-1.15)
Aspirin monotherapy	1420		0.94 (0.84-1.05)
Platelet inhibitor monoth.	108		0.87 (0.71-1.08)
Dual antiplatelet therapy	213		1.00 (0.85-1.19)
VKA+ antiplatelet drug	167		1.60 (1.34-1.92)
DOAC+ antiplatelet drug	42		1.82 (1.32-2.51)
VKA triple therapy	16		3.72 (2.25-6.14)
DOAC triple therapy	7		3.87 (1.83-8.19)





	Bleeds (no.)	Incidence rate (95% CI) log scale	Hazard ratio* (95% CI)
Female			
No anticoagulant therapy	2914		0.53 (0.50-0.56)
DOAC monotherapy	437		0.76 (0.69-0.85)
Aspirin monotherapy	3635		0.95 (0.91-1.00)
Platelet inhibitor monoth.	314		0.93 (0.83-1.05)
Dual antiplatelet therapy	526		1.06 (0.97-1.15)
VKA+ antiplatelet drug	1623		1.92 (1.81-2.05)
DOAC+antiplatelet drug	121		1.48 (1.23-1.78)
VKA triple therapy	137		3.45 (2.90-4.10)
DOAC triple therapy	15		2.29 (1.38-3.81)
Male			
No anticoagulant therapy	3916		0.58 (0.56-0.60)
DOAC monotherapy	640		0.88 (0.81-0.96)
Aspirin monotherapy	4414		1.00 (0.96-1.04)
Platelet inhibitor monoth.	406		1.09 (0.99-1.21)
Dual antiplatelet therapy	880		1.17 (1.09-1.26)
VKA+ antiplatelet drug	3146		1.76 (1.68-1.84)
DOAC+antiplatelet drug	151		1.11 (0.94-1.30)
VKA triple therapy	292		2.96 (2.63-3.34)
DOAC triple therapy	25		2.20 (1.49-3.27)
Previous MI			
No anticoagulant therapy	1017		0.48 (0.44-0.53)
DOAC monotherapy	142		0.94 (0.79-1.12)
Aspirin monotherapy	1916		0.84 (0.78-0.90)
Platelet inhibitor monoth.	210		1.04 (0.89-1.20)
Dual antiplatelet therapy	541		1.16 (1.05-1.29)
VKA+ antiplatelet drug	1485		1.67 (1.54-1.80)
DOAC+antiplatelet drug	85		1.25 (1.00-1.56)
VKA triple therapy	257		3.61 (3.14-4.14)
DOAC triple therapy	22		2.47 (1.61-3.77)
Previous major bleed			
No anticoagulant therapy	2144		0.61 (0.57-0.64)
DOAC monotherapy	346		0.84 (0.75-0.94)
Aspirin monotherapy	2186		1.00 (0.94-1.06)
Platelet inhibitor monoth.	264		0.98 (0.86-1.11)
Dual antiplatelet therapy	414		1.02 (0.91-1.14)
VKA+ antiplatelet drug	1306		1.69 (1.58-1.82)
DOAC+antiplatelet drug	80		1.05 (0.84-1.31)
VKA triple therapy	125		2.76 (2.30-3.32)
DOAC triple therapy	13		2.01 (1.16-3.47)
Previous ischemic stroke			
No anticoagulant therapy	1314		0.54 (0.50-0.58)
DOAC monotherapy	332		0.92 (0.82-1.04)
Aspirin monotherapy	1746		1.17 (1.09-1.25)
Platelet inhibitor monoth.	434		0.98 (0.88-1.09)
Dual antiplatelet therapy	999		1.06 (0.98-1.15)
VKA+ antiplatelet drug	1312		1.71 (1.59-1.84)
DOAC+antiplatelet drug	77		1.11 (0.88-1.40)
VKA triple therapy	177		2.41 (2.06-2.81)
DOAC triple therapy	17		1.92 (1.19-3.11)
Ischemic heart disease			
No anticoagulant therapy	2368		0.51 (0.48-0.54)
DOAC monotherapy	361		0.85 (0.76-0.95)
Aspirin monotherapy	3855		0.87 (0.83-0.91)
Platelet inhibitor monoth.	392		0.99 (0.89-1.11)
Dual antiplatelet therapy	851		1.12 (1.03-1.21)
VKA+ antiplatelet drug	2803		1.64 (1.55-1.72)
DOAC+antiplatelet drug	160		1.19 (1.01-1.39)
VKA triple therapy	353		3.38 (3.02-3.78)
DOAC triple therapy	33		2.51 (1.78-3.54)