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Circulation. published online January 27, 2014;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539

DOI: 10.1161/CIRCULATIONAHA.113.004834

Antiplatelet Therapy for Stable Coronary Artery Disease in Atrial Fibrillation Patients on Oral Anticoagulant: A Nationwide Cohort Study

Running title: *Lamberts et al.; AF patients with stable CAD*

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Journal Subject Codes: Anticoagulants:[184] Coumarins, Treatment:[122] Secondary prevention, Treatment:[118] Cardiovascular pharmacology, Etiology:[3] Acute coronary syndromes, Etiology:[8] Epidemiology

DOI: 10.1161/CIRCULATIONAHA.113.004834

Abstract

***Background*—**Optimal long-term antithrombotic treatment of patients with coexisting atrial fibrillation (AF) and stable coronary artery disease (CAD) is unresolved and commonly a single antiplatelet agent is added to oral anticoagulation. We investigated the effectiveness and safety of adding antiplatelet therapy to vitamin K antagonist (VKA) in AF patents with stable CAD.

***Methods and Results*—**AF patients with stable CAD (defined as 12 months from an acute coronary event) between 2002-2011 were identified. Subsequent risk of cardiovascular events and serious bleeding (requiring hospitalization) events were examined with adjusted Cox regression models according to ongoing antithrombotic therapy. A total of 8,700 patients were included (mean age 74.2 years; 38% females). During a mean follow-up of 3.3 years, crude incidence rates were 7.2, 3.8 and 4.0 events per 100 person-years for myocardial infarction/coronary death, thromboembolism and serious bleeding, respectively. Relative to VKA monotherapy, the risk of myocardial infarction/coronary death was similar for VKA plus aspirin (HR 1.12 [0.94-1.34]) or VKA plus clopidogrel (HR 1.53 [0.93-2.52]). The risk of thromboembolism was comparable in all regimens including VKA, while the risk of bleeding increased when aspirin (HR 1.50 [1.23-1.82]) or clopidogrel (HR 1.84 [1.11-3.06]) was added to VKA.

***Conclusions*—**In AF patients with stable CAD, adding antiplatelet therapy on top of VKA is not associated with a reduction in risk of recurrent coronary events or thromboembolism, while risk of bleeding is significantly increased. The common practice of adding antiplatelet therapy to oral VKA anticoagulation in patients with AF and stable CAD warrants reassessment.

Key words: atrial fibrillation, myocardial infarction, bleeding, antithrombotic, stroke

DOI: 10.1161/CIRCULATIONAHA.113.004834

Introduction

Optimal long-term antithrombotic treatment of patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) is unresolved, and common practice is to add antiplatelet therapy to oral anticoagulation (OAC). The cornerstone of AF treatment should include OAC if one or more stroke risk factors (such as vascular disease) are present[1], while initial preventive treatment after myocardial infarction (MI) or percutaneous coronary intervention (PCI) consists of drugs for platelet anti-aggregation.[2] American and European consensus documents (Level C evidence) recommend adding two antiplatelet drugs on top of vitamin K antagonist (VKA) arbitrarily from 1 month to 1 year after an acute coronary event depending on degree of severity, type of stent implanted, and presumed bleeding risk.[3, 4] The risk of serious bleeding with multiple antithrombotic drugs is raised substantially[5, 6], even with only short-term initial therapy[7]. For this reason, one antiplatelet should be removed when the risk of recurrent coronary event and stent thrombosis has declined, and VKA alone is now recommended in AF patients who are greater than one year from an acute coronary event or revascularization procedure.[8] New data also suggest that MI risk could actually increase with multiple antiplatelets added on top of OAC treatment.[9]

Both the need for additional antiplatelet after the vulnerable period and the timing of VKA monotherapy are unknown. In 'real-life' AF patients surviving an acute coronary event, we investigated ongoing antithrombotic treatment and risk of new coronary events, thromboembolism and serious bleeding. We tested the hypothesis that long-term antithrombotic treatment with only VKA after 12 months with stable CAD compared to adding a single antiplatelet agent to VKA results in fewer serious bleeding events but without an additional cost of increased risk of recurrent coronary events or thromboembolism.

Methods

Databases

From nationwide Danish administrative registries, we extracted information on healthcare and drug utilization that could be linked on the individual level to each resident.[10] All admissions to hospitals are recorded by the National Patient Registry and provided by International Classification of Diseases (ICD) coding (ICD-8 until 1994 and ICD-10 onwards). Diagnoses of MI (predictive value 94%)[11], AF (predictive value 99%)[12] and ischemic stroke (predictive value 97%)[13] have been validated, and bleeding diagnoses have shown a positive predictive value of 89-99% in hospital databases.[14] The Danish Registry of Medicinal Product Statistics (national prescription registry) provides data on number of tablets, the strength and the date of dispensing for all prescribed drugs classified according to the Anatomical Therapeutic Classification (ATC). Vital status and causes of death are obtainable through the civil registration system and the National Causes of Death Registry, respectively. The latter provides information from physicians on both the primary and potential contributing causes of death also according to the ICD-10 classification. All ICD and ATC codes used in the study are listed in **Supplemental Table 1** and **Supplemental Table 2**.

Population

All AF patients hospitalized for either MI or PCI between January 1, 2001 and December 31, 2011 were identified. To be eligible for inclusion, no subsequent hospitalization for MI, unstable or stable angina within 360 days was allowed (**Figure 1**). Patients with AF and stable CAD, defined as 360 days from index coronary event (MI/PCI), were followed from 2002 through the end of the study period on December 31st 2011. Only patients prescribed antithrombotic therapy were included. To ensure no recent MI/PCI episode occurred prior to an AF diagnosis, patients

who were registered with any MI or PCI within 360 days prior to their MI/PCI hospitalization were also excluded.[7]

Antithrombotic treatment regimens

We defined the following antithrombotic treatment regimens: single antiplatelet therapy (aspirin or clopidogrel), VKA monotherapy (warfarin or phenprocoumon), dual antiplatelet therapy (aspirin and clopidogrel), VKA plus single antiplatelet (either aspirin or clopidogrel), and VKA plus dual antiplatelet therapy., We calculated drug availability at any given time from claimed prescriptions, as previously described [5-7]. A daily dosage was calculated for up to three prescription claims, allowing the daily dose (for VKA only) to change with prescriptions claimed. A fixed dosing regimen was used for aspirin (75, 100 and 150 mg) and clopidogrel (75 mg). Treatment at the date of inclusion was defined as baseline treatment.

Outcomes

Effectiveness outcomes were defined as MI/coronary death and fatal/nonfatal thromboemblism. Thromboembolism included ischaemic stroke and systemic arterial embolism. The principal safety outcome was fatal/nonfatal bleeding. A secondary outcome of all-cause death was also defined. Nonfatal events were obtained from admissions in the National Patient Registry, and fatal events were recorded from National Causes of Death Register. The diagnoses (e.g. intracranial bleeding, gastrointestinal bleeding, anemia from bleeding) to characterize 'serious bleeding' has previously been used.[5-7] This category of serious bleeding would include most ISTH (International Society of Thrombosis and Haemostasis) major and clinically relevant non-major bleeds, although all events required hospitalisation.[15] For additional insight, we also categorized death from bleeding as fatal bleeding directly and as death within 30 days from a nonfatal bleeding admission. A composite outcome of MI, thromboembolism, bleeding and all-

cause mortality was also defined.

Concomitant treatment and comorbidity

Prescription claims 180 days prior to inclusion defined concomitant pharmocotherapy, and comorbidities were determined from any preceding diagnosis as previously described[16]. The CHA_2DS_2–VASc (Congestive heart failure, hypertension, Age>75, Diabetes mellitus, Stroke, Vascular disease, Age 65-75, and female Sex) and modified HAS-BLED (Hypertension, Abnormal renal/liver function, Stroke/thromboembolism, Bleeding history, Labile INR [international normalized ratio], Elderly [age>65 years], Drug consumption/alcohol abuse) scores were calculated. For HAS-BLED, data on labile INR was unavailable and use of antiplatelet therapy was omitted from the HAS-BLED score because it is an explanatory variable. The scores have been shown to accurately predict risk of thromboembolism and bleeding in the Danish population.[17]

Statistical analyses

Characteristics according to antithrombotic treatment at inclusion are expressed as percentages or as means and standard deviations (SD). Rates were all crude incidence rates, calculated by the the number of events per 100 person-years with 95% CI (confidence interval). The risk of outcomes associated with antithrombotic treatment was estimated by means of time-dependent Cox proportional-hazards models, with adjustment for changes in exposure (based on prescription claims) during follow-up. VKA as monotherapy was used as reference. All models were adjusted for age, gender, inclusion year and MI/PCI status at index event, pharmacotherapy and comorbidity (including factors comprising the CHA_2DS_2-VASc and HAS-BLED scores). Unadjusted estimates were also reported for the main models. To assess if the risk of our effectiveness or safety outcomes changed over time, we performed landmark analyses for

periods of 0-2 years and >2 years from inclusion in a Cox model for each outcome. Due to low numbers, only aspirin monotherapy, dual antiplatelet, VKA plus aspirin and VKA plus clopidogrel were explored. We also decided to report risks for patients that had a previous PCI performed at their index event to assess if longer term outcomes differed for patients receiving invasive intervention (considered "low-risk" patients) compared to patients receiving only pharmacotherapy (considered "high-risk" patients). We performed a sensitivity analysis as suggested by Schneeweiss for assessing the impact of a potential unmeasured confounder for regimens of VKA and VKA plus aspirin as these were the most prevalent regimens including VKA and assessing the relation of adding antiplatelet to VKA was our main purpose.[18] All patients were followed to death or the end of the study period (December 31, 2011). We tested for fulfilment of proportional hazards assumption, linearity of continuous variables and lack of interactions for the Cox models, and no significant deviations from the assumptions were found. A two-sided P value of less than 0.05 was considered to indicate statistical significance. Data were analysed with SAS 9.2 (SAS Institute Corp, Cary, NC) and Stata 11.0 (StataCorp, College Station, TX).

Ethics

Ethical approval is not required for register-based studies in Denmark. The Danish Data protection agency approved the study (reference no. 2007-58-0015 / I.suite no. 00916 GEH-2010-001). Anonymized data were made available to us so individuals could not be identified.

Results

In 8,700 AF patients with stable CAD (mean age 74.2, SD 10.4; 38% female) included in the study, a total of 3,243 (37%) were treated with VKA at inclusion (**Table 1**). Selection of the

study population is shown in **Figure 1**. A total of 28,947 person-years were accumulated, and groups contributing most with time-at-risk were aspirin monotherapy (45%), VKA plus aspirin (26%), and VKA monotherapy (14%). **Figure 2** shows the crude incidence rates of MI/coronary death after the index coronary event.

Risk of myocardial infarction/coronary death, thromboembolism and serious bleeding during follow-up

Within a mean follow-up of 3.3 years, 3,457 (40%) died. The number of events coded as MI/coronary death, thromboembolism and serious bleeding were 1,978 (23%), 1,040 (12.0%) and 1,061 (12%), respectively. Corresponding crude incidence rates were 7.2, 3.8 and 4.0 events per 100 person-years. **Table 2** shows the numbers and crude incidence rates for each outcome according to antithrombotic treatment group. Crude incidence rates of MI/coronary death were similar for VKA and VKA plus aspirin but higher for VKA plus dual antiplatelet therapy. Adjusted HRs for all outcomes are illustrated in **Figure 3A-D**. Relative to VKA monotherapy, there was no decrease in risk of MI/coronary death associated with use of VKA plus single antiplatelet (either aspirin or clopidogrel), and a higher risk with dual antiplatelet therapy with or without VKA. A comparable risk of thromboembolism was present for regimens including VKA, while non-VKA therapies were associated with greater risk compared to VKA monotherapy. Bleeding risk was greater in those who also took antiplatelets (either aspirin or clopidogrel). Aspirin monotherapy showed a decrease in bleeding risk while clopidogrel (with or without aspirin) showed comparable bleeding risk compared to VKA as monotherapy. The unadjusted HR estimates are provided as supplementary material (**Supplemental Table 3**), and resemble the adjusted analyses. The combined outcome of MI, thromboembolism, bleeding and all-cause mortality showed no beneficial effect of VKA plus a single antiplatelet compared to VKA

monotherapy (**Table 3**).

Previous PCI, landmark analyses, death from bleeding and sensitivity analysis

For 3,393 patients with previous PCI, 512 (15%), 291 (9%) and 370 (11%) events of MI/coronary death, thromboembolism and serious bleeding occured, respectively. In patients with previous PCI, the crude rate of MI/coronary death was 4.5 per 100 person-years while the corresponding crude rate in non-invasively treated patients was 9.1 per 100 person-years. A similar 2-fold greater rate was present for thromboembolism in non-PCI treated (4.7 events per 100 person-years) compared to PCI treated patients (2.8 events per 100 person-years). In the adjusted Cox models, the risks resembled those from the main analysis with comparable risk of thrombosis between VKA with and without single antiplatelet therapy, while bleeding risk was greater in those who also took an antiplatelet (either aspirin or clopidogrel). For further details of risks for PCI and non-PCI treated patients, please see **Supplemental Table 4**. The risk of MI/coronary death and thromboembolism was consistent and similar between VKA and VKA plus single antiplatelet therapy in periods of 0-2 and >2 years (**Supplemental Figure 1A-C**). Of 951 patients admitted with a nonfatal bleeding episode, 507 died (53%) while in the 7,749 patients not experiencing bleeding, 2,950 died (38%), corresponding to a HR 2.14 (1.94-2.37). No significant difference was observed of death from bleeding between VKA and VKA plus single antiplatelet, and only VKA plus dual antiplatelet therapy was associated with significantly increased risk in death from bleeding (**Supplemental Table 5**). When estimating the impact of an unmeasured confounder, we found that a potential confounder should be three times more prevalent in the exposed group (VKA + aspirin) and be associated with a three-fold increase in risk of the outcome to explain a beneficial effect of VKA + aspirin compared to VKA concerning the outcome of MI. Regarding outcomes of thromboembolism, serious bleeding and all-cause

death, corresponding analyses indicated that an unmeasured confounder should be very unevenly distributed in the groups with a very strong association towards VKA plus aspirin therapy, and also be very strongly associated with the outcome.

Discussion

In this nationwide observational study, the addition of antiplatelet therapy to VKA in patients with AF and stable CAD was not associated with any benefit while serious bleeding was significantly increased. Therapies only including antiplatelet drugs (and not VKA therapy) were associated with an increased risk of all-cause death, with an appreciable risk of bleeding with the combination of aspirin and clopidogrel therapy. The study suggests that monotherapy with VKA may be the best choice in patients with AF and stable CAD.

Randomized clinical trials have demonstrated that treatment with single and dual antiplatelet therapy is valuable after an MI and after a PCI procedure.[19, 20] There is also evidence from randomized trials for the benefit of long-term VKA therapy in selected patients with AF.[21] We and others have previously examined the use of single and multiple antithrombotic therapies after a recent coronary event.[6, 22, 23] However, there is lack of evidence for optimal long-term antithrombotic treatment strategy in patients with AF and stable CAD.

The ineffectiveness of dual antiplatelet therapy on recurrent MI risk compared to VKA monotherapy is somewhat unexpected and was also present in patients treated with PCI. Due to the non-randomized design of the study, this association could be based on the assumption that antiplatelet users were found ineligible for treatment with VKA and INR monitoring, and most likely comprise a group with a poorer outcome profile. A possible mechanistic explanation is that increased thrombogenesis in AF could play a role. AF has often been described as a

prothrombotic state, and while underlying mechanisms are not fully understood, clots (including coronary) in these patients could be fibrin rich (rather than platelet rich) leading to a more protective effect of anticoagulation.[24] The ACTIVE W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events) included patients with AF (with approximately 18% with a previous MI), and a sub analysis on risk of MI showed more events for aspirin plus clopidogrel (n=36) compared to VKA (n=23).[25] The increased relative risk of 1.58 is in accordance with our findings (HR 2.24). In the non-acute setting, our data suggest that VKA is at least as effective as dual antiplatelet therapy in preventing coronary events. Results from a recent controlled trial in a similar population (WOEST, What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing), found a significant increased risk of death and numerical more events of MI in VKA plus dual antiplatelet (aspirin and clopidogrel) compared to VKA plus clopidogrel therapy[9]. Our data support these findings, i.e. that antiplatelet therapy alone or added on top of VKA is not associated with further protection against thrombosis. However, as an observational study a causal treatment effect cannot be established. Further studies are warranted to explore this potential contradictory effect of antiplatelet therapy in anticoagulated patients.

Although the Thrombosis Prevention Trial focused on primary prevention of coronary events in high-risk subjects comparing the effect of low-intensity warfarin against aspirin, the investigators concluded that warfarin per se reduced fatal coronary events compared to aspirin but the combination of both was most effective in primary prevention of ischemic heart disease.[26] The Warfarin-Aspirin Reinfarction (WARIS) II study investigated the effect of aspirin, warfarin or both for secondary prevention after MI, and found warfarin alone or with aspirin to be superior to aspirin alone for a combined endpoint of death, nonfatal reinfarction and stroke.[22]

However, when comparing warfarin versus warfarin plus aspirin, no difference in either the combined endpoint or in event-free survival was demonstrated. For only reinfarctions, there was a significant protective effect of warfarin monotherapy and warfarin plus aspirin compared to aspirin only, but no analyses on reinfarctions were given for warfarin versus warfarin plus aspirin. This latter issue is important in patients with coronary artery disease and co-existing AF where oral anticoagulant is needed for thromboprophylaxis, and warfarin could also protect against MI.

We confirmed previous results for inadequacy of single or dual antiplatelets compared to VKA[25], and furthermore showed that any addition of antiplatelets to VKA did not result in additional thromboembolic protection. Notably, bleeding risk was increased with more intense antithrombotic treatment, and in accordance with previous studies we found a significant increase for VKA plus single antiplatelet relative to VKA only.[27] In peripheral artery disease, the combination of VKA plus aspirin had no benefit on thromboembolism but substantially increased the risk of major bleeding.[28] Although a bleeding episode raised subsequent risk of death more than two-fold, we did not find a difference in death from bleeding when adding a single antiplatelet to VKA. Hence, adding an antiplatelet agent to VKA agents does not add any benefit concerning preventing thrombosis but, notably, is associated with an increased risk of bleeding.

Long-term secondary prevention of CAD with aspirin is recommended in most patients (without AF). Still, interpretation of data on aspirin use in primary prevention has linked aspirin to poorer prognosis and associated aspirin with sudden death, hence masking MI events[29, 30]. Also, the main benefit of aspirin on mortality post-MI is seen early (<30 days) after which the event free survival curves for aspirin and placebo are comparable.[19] However, many of these

older studies were in the era prior to contemporary management of acute coronary syndrome with early coronary intervention and use of stents and other secondary prevention measures such as statins, renin-angiotensin system inhibitors etc. For the primary outcomes, crude rates were lower in patients treated with PCI compared to non-PCI treated. In either group, the findings from the adjusted analyses resembled those from the main analyses. Also, the protective effect of VKA on thrombosis was unchanged after two years compared to VKA plus a single antiplatelet agent.

For the indication of stroke prophylaxis in AF, all approved new oral anticoagulants (e.g. apixiban, rivaroxiban, dabigatran) show similar or better overall effect compared to VKA.[31] Even with these new anticoagulants, combination therapy is associated with greater bleeding risk and no appreciable effect on thromboembolism.[32] Whether these new anticoagulants can replace VKA in AF patients with co-existing CAD is unknown and further investigation is warranted. Of note, recent data support dabigatran could increase MI risk compared to warfarin.[33]

Clinical implications

While the current study is purely observational, some of the conclusions are backed by a subgroup analysis of the ACTIVE W trial and the recent WOEST trial described above. Given that there is no evidence of benefit from long-term combination of VKA with platelet inhibition, but certainty of some risk with bleeding, we find that using VKA only in patients with AF, an indication for VKA and stable CAD is a valid consideration.

Strengths and limitations

This observational nationwide study includes real-life unselected cohort of patients with AF and CAD, which is often characterized by being at higher risk for adverse events compared to controlled trials which often apply restrictive inclusions criteria for subjects that make

extrapolation to everyday patients difficult.[34] Furthermore we did have the ability to continually update ongoing antithrombotic treatment, and thus also investigate therapies given in day-to-day practice, which do not necessarily adhere to guidelines. Diagnoses of MI, AF and ischemic stroke have shown high validity in the registries. Confounding-by-indication, i.e. patients at higher risk are treated with more intense antithrombotic therapy, could be present, and patients treated with aspirin plus clopidogrel with or without VKA were at higher risk of MI/coronary death and all-cause death. As our findings were consistent (adjusted and unadjusted main and landmark analyses) and we controlled for a wide range of known risk factors, we do not believe this alters our interpretation of an overall beneficial effect of VKA versus VKA plus single antiplatelet therapy. Possible unmeasured confounders were smoking status, body mass index, information on coronary anatomy, type of AF (i.e. paroxysmal, persistent, or permanent), INR values and patient/physician preference for VKA therapy. The estimation of the impact of a potential unmeasured confounder on the outcomes investigated suggests that such a confounder very unlikely alone could have driven the results. The registry holds no data on type of stent implanted. Over-the-counter aspirin was not registered but as patients are financial reimbursed with prescribed aspirin and persistence to aspirin is high in MI patients in Denmark[66], such use is unlikely to affect our conclusions.

Conclusions

In AF patients with stable CAD, adding antiplatelet therapy (either aspirin or clopidogrel) on top of VKA is not associated with a greater reduction in risk of recurrent coronary events or thromboembolism, while risk of bleeding is significantly increased. Thus, VKA might be considered as monotherapy for AF patients after 12 months of a coronary event among patients

with stable CAD. The common practice of adding antiplatelet therapy to oral anticoagulation in patients with AF and stable CAD warrants reassessment.

Funding Sources: Dr. Lamberts is supported by an unrestricted grant from Department of Cardiology, Gentofte University Hospital. Dr. Gislason is supported by an unrestricted clinical research scholarship from the Novo Nordisk Foundation.

Conflict of Interest Disclosures: None.

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DOI: 10.1161/CIRCULATIONAHA.113.004834

Table 1. Patient characteristics at inclusion according to antithrombotic treatment

Characteristics	Not including VKA			Including VKA			
	Aspirin (3,273)	**Clopidogrel (417)**	**Aspirin plus clopidogrel (1,767)**	**VKA (950)**	**VKA plus aspirin (1,471)**	**VKA plus clopidogrel (322)**	**VKA plus aspirin plus clopidogrel (500)**
Females	1,494 (46)	161 (39)	659 (37)	360 (38)	460 (31)	96 (30)	101 (20)
Age (years (SD*))	76.1 (10.9)	73.4 (10.9)	73.0 (10.8)	73.2 (10.0)	73.6 (9.0)	72.6 (8.1)	71.0 (8.4)
Previous MI	2,858 (87)	279 (67)	1,159 (66)	804 (85)	1,104 (75)	141 (44)	211 (42)
With PCI performed†	259 (9)	83 (30)	495 (43)	57 (79)	170 (15)	77 (55)	108 (51)
With stent implantation†	210 (7)	73 (26)	424 (37)	44 (5)	134 (12)	70 (50)	96 (45)
Previous PCI without MI	415 (13)	138 (33)	608 (34)	146 (15)	367 (25)	181 (56)	289 (58)
With stent implantation†	288 (69)	124 (90)	561 (92)	112 (77)	255 (69)	168 (93)	272 (94)
CHA_2DS_2-VASc§							
Low (score 0)‡	24 (1)	10 (2)	28 (2)	7 (1)	12 (1)	0 (0)	6 (1)
Intermediate (score 1)	130 (4)	34 (8)	120 (7)	42 (4)	62 (4)	19 (6)	38 (8)
High (score ≥2)	3,119 (95)	373 (89)	1,619 (92)	901 (95)	1,397 (95)	303 (94)	456 (91)
HAS-BLED§							
Low (score 0-1)	900 (28)	102 (24)	506 (29)	237 (25)	315 (21)	55 (17)	106 (21)
Intermediate (score 2)	1,325 (40)	163 (39)	677 (38)	380 (40)	658 (45)	135 (42)	218 (44)
High (score ≥3)	1,048 (32)	152 (37)	584 (33)	333 (35)	498 (34)	132 (41)	176 (35)
Pharmacotherapy							
RAS inhibitors‖	1,643 (50)	229 (55)	1,109 (63)	537 (57)	951 (65)	236 (73)	351 (70)
Statins	1,747 (53)	310 (74)	1,453 (82)	495 (52)	1,070 (73)	283 (88)	439 (88)
Beta-blockers	2,151 (66)	296 (71)	1,345 (76)	628 (66)	1,122 (76)	264 (82)	419 (84)
Loop-diuretics	1,690 (52)	186 (45)	756 (43)	517 (54)	804 (55)	166 (52)	242 (48)
Spironolactone	453 (14)	52 (12)	221 (13)	182 (19)	273 (19)	51 (16)	99 (20)
Thiazide	530 (16)	63 (15)	287 (16)	145 (15)	214 (15)	59 (18)	86 (17)
Digoxin	907 (28)	92 (22)	321 (18)	92 (22)	622 (42)	145 (45)	189 (38)
Prednisolone	295 (9)	43 (10)	145 (8)	74 (8)	91 (6)	17 (5)	35 (7)
Proton pump inhibitors	840 (26)	158 (38)	484 (27)	194 (20)	310 (21)	73 (23)	112 (22)
NSAID#	506 (16)	70 (17)	271 (15)	128 (13)	187 (13)	47 (15)	67 (13)

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Comorbidity							
Ischemic stroke	527 (16)	74 (18)	251 (14)	171 (18)	278 (19)	58 (18)	67 (13)
Diabetes mellitus	473 (14)	76 (18)	288 (16)	117 (12)	241 (16)	60 (19)	113 (23)
Arterial embolism	54 (2)	9 (2)	30 (2)	13 (1)	30 (2)	7 (2)	13 (3)
Peripheral arterial disease	371 (11)	49 (12)	194 (11)	94 (10)	164 (11)	35 (11)	51 (10)
Alcohol-related diseases	152 (5)	28 (7)	117 (7)	50 (5)	63 (4)	13 (4)	28 (6)
Liver disease	57 (2)	9 (2)	29 (2)	21 (2)	29 (2)	9 (3)	8 (2)
Chronic renal disease	266 (8)	33 (8)	121 (7)	97 (10)	102 (7)	22 (7)	29 (6)
Previous bleeding	735 (22)	127 (30)	356 (20)	240 (25)	314 (21)	87 (27)	120 (24)
Hypertension	1,921 (59)	264 (63)	1,212 (69)	607 (64)	1,054 (72)	254 (79)	401 (80)
Malignancy	500 (15)	53 (13)	267 (15)	159 (17)	197 (13)	51 (16)	77 (15)
Congestive heart failure	966 (30)	106 (25)	403 (23)	317 (33)	478 (32)	102 (32)	148 (30)

Cells are numbers (rounded column percent). * standard deviation, † group percentages given, ‡ includes patients because PCI was not included in the score, § CHA_2DS_2-VASc, HAS-BLED, please see manuscript text, || renin-angiotensin system, # non-steroidal anti-inflammatory drug.

DOI: 10.1161/CIRCULATIONAHA.113.004834

Table 2. Comparison of antithrombotic treatment and risk of effectiveness and safety outcomes.

Treatment	Duration in person- years†	Mean treatment‡ (days)	MI*/coronary death		Thromboembolism		Serious bleeding		All-cause death	
			No.	Crude rate [95% CI]§	No.	Crude rate [95% CI]§	No.	Crude rate [95% CI]§	No.	Crude rate [95% CI]§
VKA plus aspirin plus clopidogrel	264	102	16	7.8 [4.8-12.7]	9	3.6 [1.9-6.9]	25	10.1 [6.8-14.9]	33	12.5 [8.9-17.6]
VKA plus clopidogrel	262	163	17	4.4 [4.8-11.8]	11	4.6 [2.6-8.3]	17	7.0 [4.4-11.3]	27	10.3 [7.1-15.0]
VKA plus aspirin	7,509	809	339	4.7 [4.2-5.2]	167	2.3 [2.0-2.7]	371	5.2 [4.7-5.8]	535	7.1 [6.5-7.8]
VKA	4,107	544	188	4.7 [4.1-5.4]	118	3.0 [2.5-3.6]	147	3.9 [3.3-4.6]	350	8.5 [7.7-9.5]
Aspirin plus clopidogrel	1,332	195	119	11.5 [9.6-13.7]	80	6.6 [5.3-8.3]	56	4.4 [3.4-5.7]	214	16.1 [14.1-18.4]
Clopidogrel	667	236	55	9.0 [6.9-11.7]	35	5.8 [4.1-8.0]	31	4.9 [3.5-7.0]	100	15.0 [12.3-18.2]
Aspirin	13,079	732	1,048	8.4 [7.9-8.9]	533	4.3 [3.9-4.7]	356	2.9 [2.6-3.2]	1,764	13.5 [12.9-14.1]

All rates are crude incidence rates (events per 100 person-years); * myocardial infarction, † Total time-at-risk until death, ‡ Treatment is set as time-varying variable, and reported data is given as mean without standard deviation due to right-censoring, § confidence interval

Table 3. Risk of the combined outcome of MI, thromboembolism, bleeding and all-cause mortality

Treatment	Number of events	Crude rate	Unadjusted HR [95% CI]*	Adjusted HR [95% CI]*
VKA plus aspirin plus clopidogrel	39	20.8	1.33 [0.96-1.84]	1.70 [1.22-2.36]
VKA plus clopidogrel	39	19.0	1.28 [0.92-1.77]	1.42 [1.02-1.97]
VKA plus aspirin	298	13.8	1.00 [0.90-1.12]	1.15 [1.03-1.29]
VKA	490	13.8	Reference	Reference
Aspirin plus clopidogrel	243	26.3	1.71 [1.46-2.00]	1.63 [1.39-1.91]
Clopidogrel	111	20.4	1.43 [1.16-1.75]	1.29 [1.04-1.59]
Aspirin	2,222	19.4	1.39 [1.26-1.53]	1.35 [1.22-1.49]

All rates are crude incidence rates (events per 100 person-years). Adjusted analyses were controlled for gender, age, inclusion year, PCI status, pharmacotherapy and comorbidity (including factors comprising the CHA_2DS_2-VASc and HAS-BLED scores. *HR, hazard ratio; CI, confidence interval

DOI: 10.1161/CIRCULATIONAHA.113.004834

Figure Legends:

Figure 1. Overview of the study population**.** Myocardial infarction includes nonfatal myocardial infarction. Abbreviations: VKA, vitamin K antagonists.

Figure 2. Crude incidence rates of myocardial infarction/coronary death over time**.** Crude incidence rates of myocardial infarction/coronary death in atrial fibrillation patients after an episode of myocardial infarction or coronary intervention (index event). The study included patients at 360 days from the index event with stable coronary artery disease (i.e. no admission of myocardial infarction, unstable angina or stable angina defined stable coronary artery disease). The rate is calculated every 15 days for the first 720 days, and then every 30 days onwards. The estimate at day 1440 includes all remaining events.

Figure 3. Risk of myocardial infarction/coronary death, thromboembolism, bleeding and all-cause death. Forest plots show adjusted HRs with error bars indicating 95% CI. Abbreviations: VKA, vitamin K antagonist.

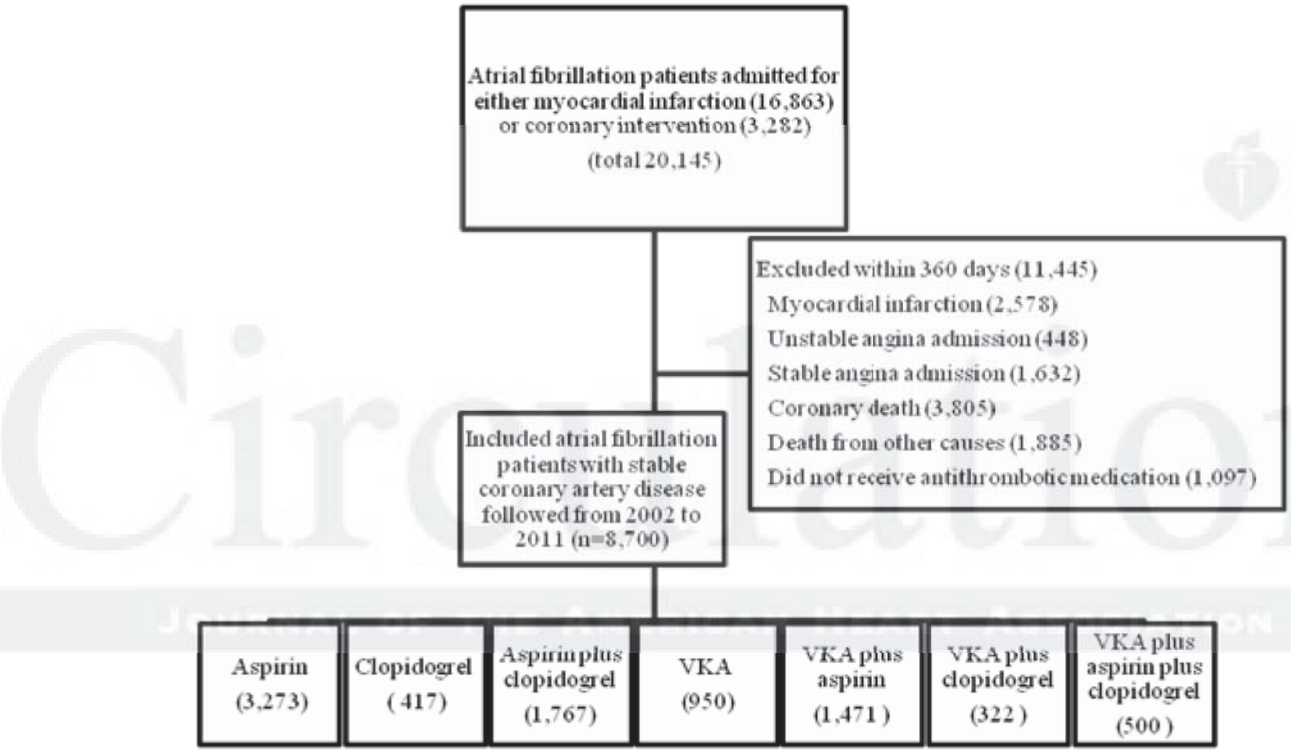

Figure 1

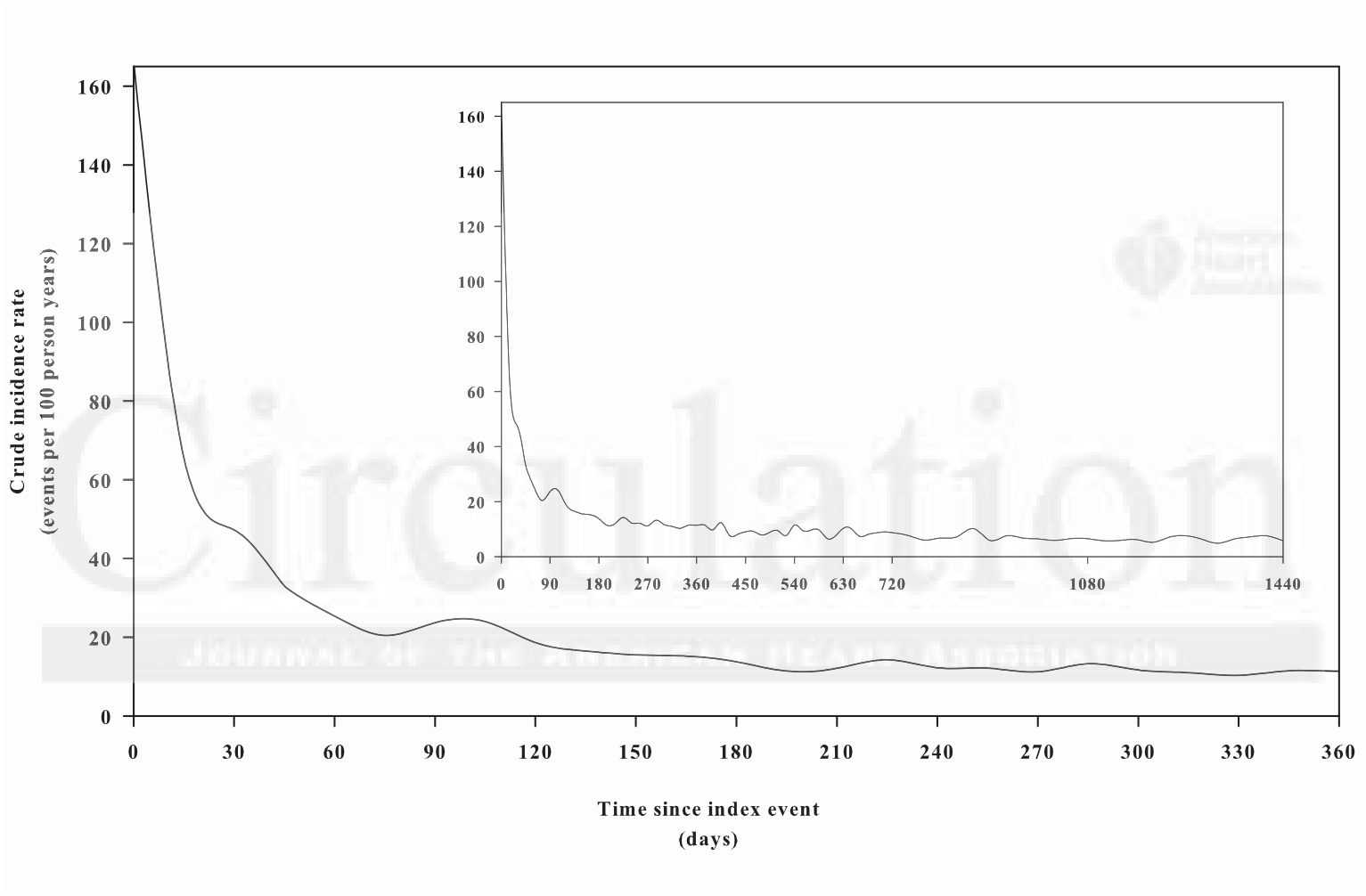

Figure 2

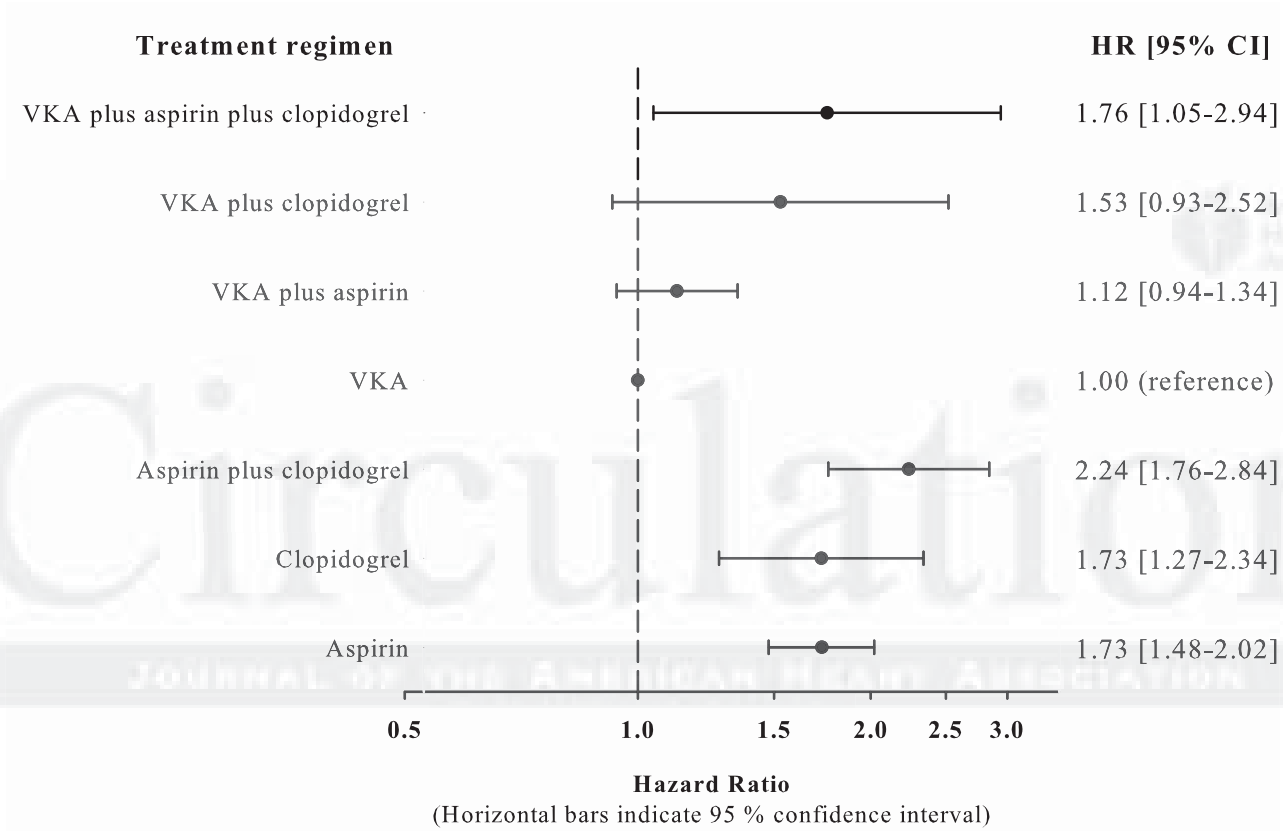

Figure 3A

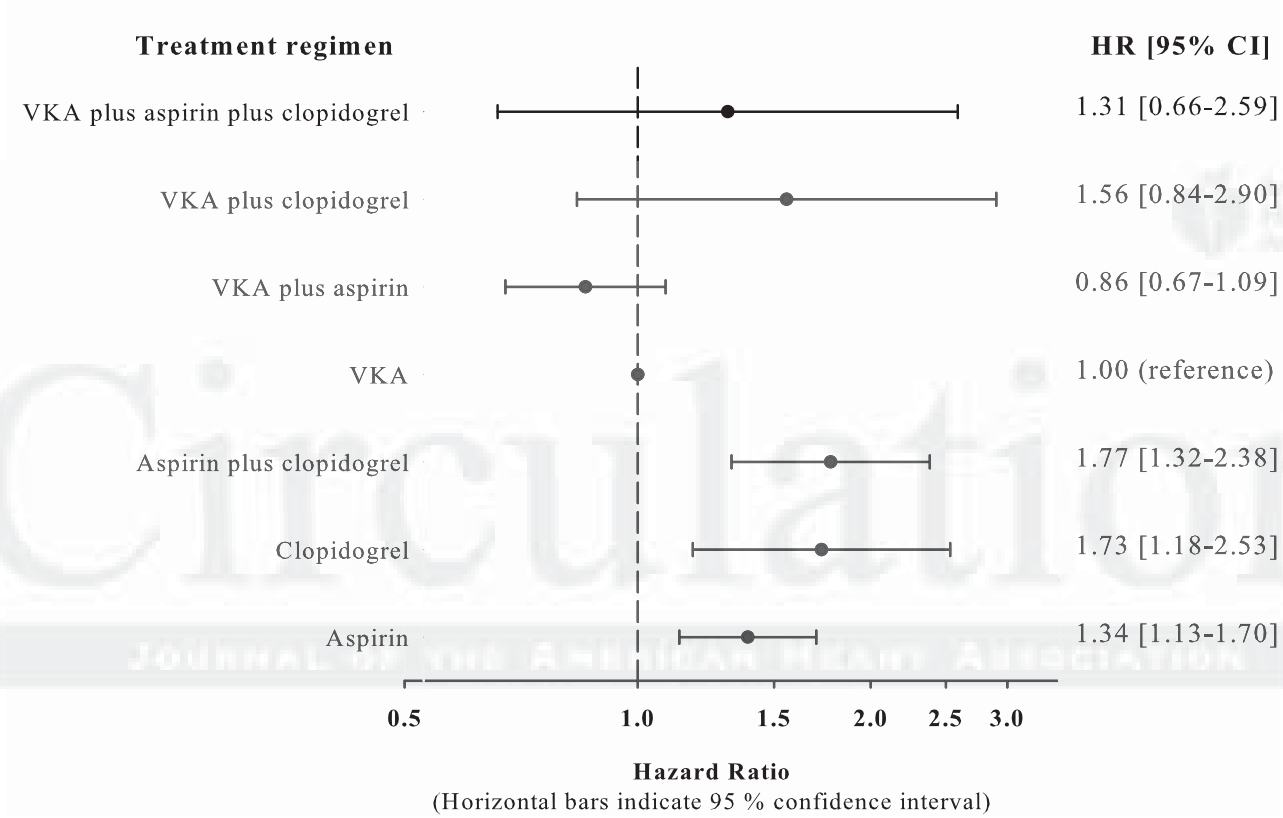

Figure 3B

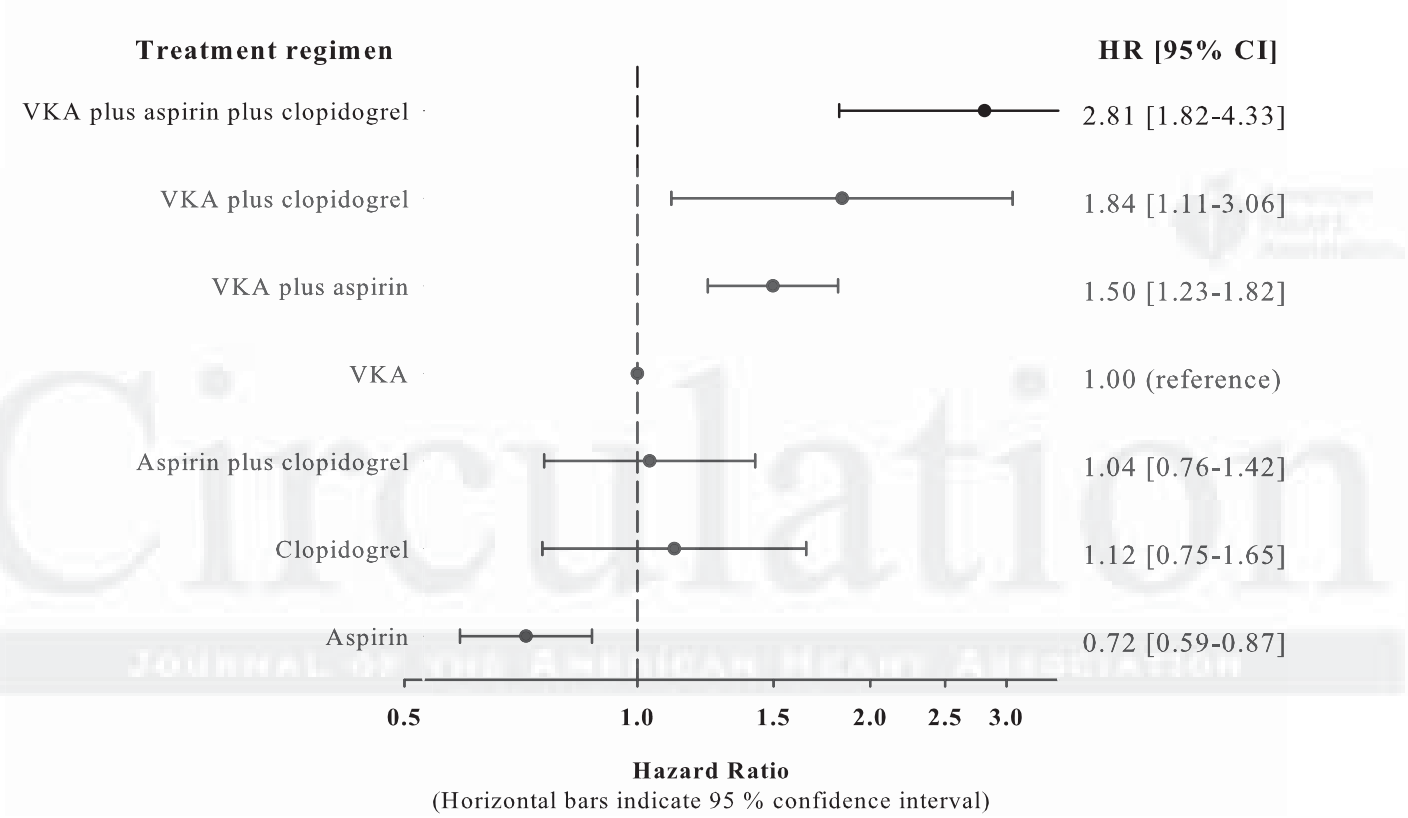

Figure 3C

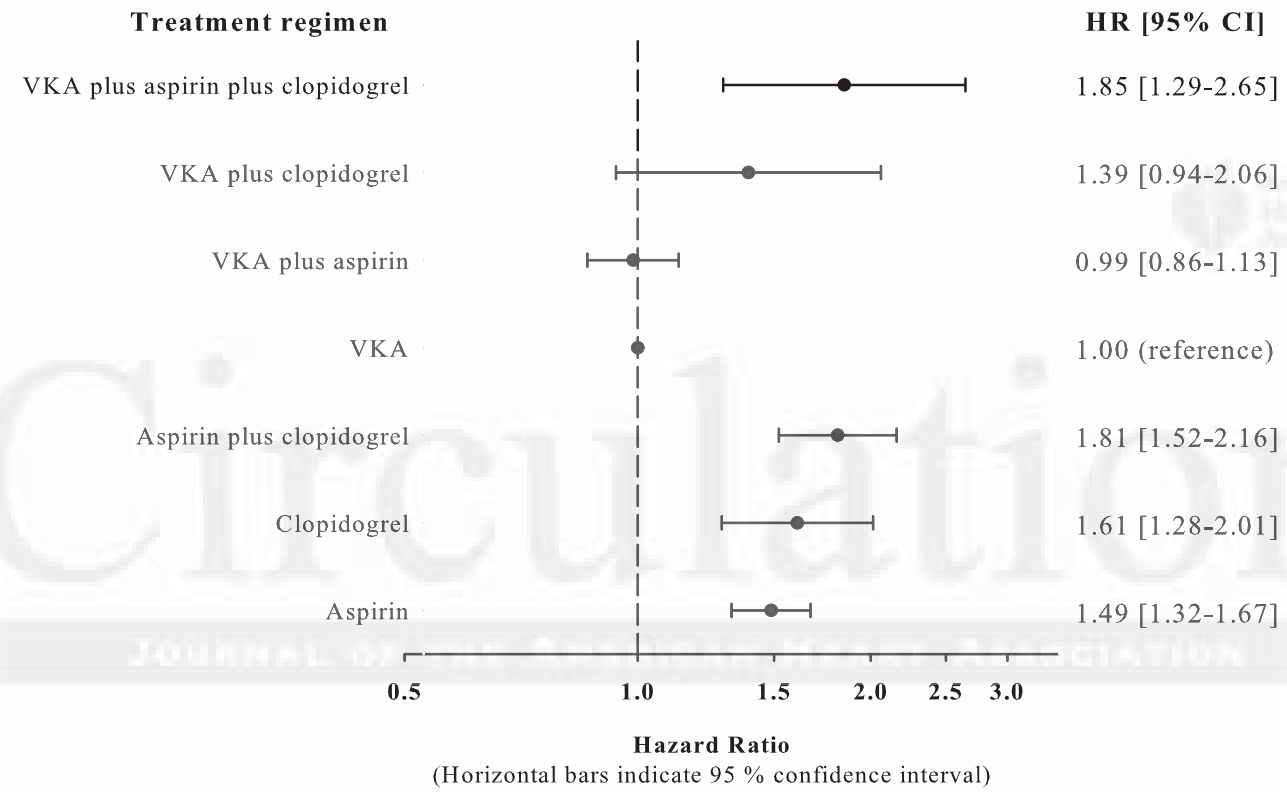

Figure 3D

SUPPLEMENTAL MATERIAL

Supplemental Table 1. ICD codes

Diagnoses, surgical procedures, and pharmacotherapy used for defining the study population, comorbidity, and outcomes

Study population		
Atrial fibrillation	Defined from diagnosis	ICD8: 42793, 42794 ICD10: I48
Myocardial infarction	Defined from diagnosis	ICD8: 41009, 14099 ICD10: I21, I22
Percutaneous coronary intervention	Defined from procedure performed	NCSP: KFNG (KFNG05, stent implantation)

Comorbidity		
Thromboembolism	Defined from diagnosis including ischemic stroke, transient ischemic attack, systemic thromboembolism	ICD10: I63, I64, I26, I74 G458, G459 ICD8: 433-8, 444, 450
Vascular disease	Defined from diagnosis including myocardial infarction, aortic plaque and peripheral arterial disease.	ICD10: I21-22, I700, I702-I709 ICD8: 410, 440
Alcohol abuse	Defined from diagnosis and adverse alcohol consumption reported during hospitalization	ICD10: E244, E52, F1, G312, G621, G721, I426, K292, K70, K860, L278A, O354, T51, Z714, Z721
Liver disease	Defined from diagnoses of liver cancer, chronic liver disease, liver surgery, cirrhosis, and hepatitis	ICD10: B15-B19, C22, D684C, I982B, K70-K77, DQ618A, Z944
Ischemic stroke	Defined from diagnosis	ICD10: I64, I64, G458, G459 ICD8: 433-8
Arterial embolism	Defined from diagnosis	ICD10:I74 ICD8: 444
Diabetes mellitus	Defined from treatment	Treatment: Glucose-lowering medication
Hypertension	Defined from combination treatment with a least two classes of antihypertensive drugs. This definition of hypertension has a positive predictive value of 80.0% and a specificity 94.7%[1]	Treatment: Adrenergic α-antagonist, non-loop-diuretics, vasodilators, beta- blockers, calcium channel blockers, and renin-angiotensin system inhibitors.
Peripheral arterial disease	Defined from diagnosis	ICD10:I702-I709

		ICD8: 440
Malignancy	Defined from diagnosis	ICD10:
Congestive heart failure	Defined from diagnosis plus treatment[2]	ICD10: I110, I42, I50, J819 ICD8: 425, 4270-1 Treatment: Loop-diuretics
Chronic renal failure	Defined from diagnosis of chronic glomerulonephritis, chronic tubulointestinal nephropathy, non-end-stage chronic kidney disease, and diabetic and hypertensive nephropathy.[3]	ICD10: E102, E112, E132, E142, I120, M200, M313, M319, M321B, N02-N08, N11-N12, N14, N18-N19, N26, N158-N160, N162-N164, N168, Q612-Q613, Q615, Q619 ICD8: 403, 404, 580-4, 590, 223, 25002, 40039, 59009, 59320, 75310-1, 75319
Bleeding	Defined from diagnosis of gastrointestinal, intracranial, respiratory, and urinary tract bleedings; and anemia caused by bleeding.	ICD10: I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066 ICD8: 430-432

Outcomes

Myocardial infarction / Coronary death	Diagnosis of myocardial infarction or coronary death	ICD10: I21-I22 (I20-I25 Coronary death)
Thromboembolism	Death from or diagnosis of ischemic stroke, transient ischemic attack and systemic arterial embolism	ICD10: I63-I64, G458-G459, I74
Serious bleeding	Death from or diagnosis of gastrointestinal, intracranial, respiratory, and urinary tract bleedings; and anemia caused by bleeding.	ICD10: I60-I62, I690-I692, J942, K250, K254, K260, K264, K270, K280, K920-K922, N02, R04, R31, S064-S066,

ICD8: 8th revision of the International Classification of Diseases system
ICD10: 10th revision of the International Classification of Diseases system
NCSP: The Nordic Medical Statistics Committees Classification of Surgical Procedures

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Supplemental Table 2. ATC codes

Treatment		
Oral anticoagulants	ATC: BO11AA03-4	Vitamin K antagonists including warfarin and phenprocoumon
Aspirin	ATC: BO1AC06, NO2BA01	Acetylsalicylic acid
Clopidogrel	ATC: BO1AC04	
Non-steroidal anti-inflammatory drugs	ATC: M01A	
Statins	ATC: C10A	
Beta-blockers	ATC: C07	
Renin angiotensin system inhibitors	ATC: C09	Including: angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers
Loop-diuretics	ATC: C03C	
Thiazides	ATC: C03A	
Spironolactone	ATC: C03DA01	
Digoxin	ATC: C01AA05	
Proton-pump inhibitors	ATC: A02BC	
Oral glucose-lowering drugs	ATC: A10	Defines diabetes mellitus
Glucocorticoids	ATC: H02AB	Including: prednisolon

ATC: Anatomical Therapeutic Chemical (ATC) system

Supplemental Table 3. Unadjusted and adjusted analysis of primary outcomes

	MI/Coronary death		Thromboembolism		Serious bleeding	
Treatment	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**	**Unadjusted HR**	**Adjusted HR**
VKA plus aspirin plus clopidogrel	1.43 [0.86-2.39]	1.76 [1.04-2.94]	1.05 [0.53-2.07]	1.31 [0.66-2.59]	2.47 [1.61-3.79]	2.81 [1.82-4.33]
VKA plus clopidogrel	1.41 [0.86-2.32]	1.53 [0.93-2.52]	1.70 [0.75-2.61]	1.56 [0.83-2.90]	1.74 [1.05-2.88]	1.84 [1.11-3.06]
VKA plus aspirin	0.99 [0.83-1.17]	1.12 [0.94-1.34]	0.77 [0.61-0.98]	0.86 [0.67-1.09]	1.36 [1.12-1.64]	1.50 [1.23-1.82]
VKA	Reference	Reference	Reference	Reference	Reference	Reference
Aspirin plus clopidogrel	2.14 [1.69-2.70]	2.24 [1.76-2.84]	1.98 [1.48-2.64]	1.77 [1.32-2.38]	1.09 [0.80-1.49]	1.04 [0.76-1.42]
Clopidogrel	1.83 [1.35-2.47]	1.73 [1.27-2.34]	1.82 [1.24-2.65]	1.73 [1.18-2.53]	1.25 [0.85-1.84]	1.12 [0.72-1.65]
Aspirin	1.74 [1.49-2.04]	1.73 [1.48-2.02]	1.39 [1.14-1.70]	1.39 [1.13-1.70]	0.73 [0.61-0.89]	0.72 [0.59-0.87]

Unadjusted and adjusted hazard ratios (HR) with 95% confidence intervals (CI) of primary outcomes. Adjusted analyses were controlled for gender, age, inclusion year, PCI status, pharmacotherapy and comorbidity (including factors comprising the CHA_2DS_2-VASc and HAS-BLED scores. Abbreviations: VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval, PCI, percutanous coronary intervention. CHA2DS2-VASc and HAS-BLED, please see text.

Supplemental Table 4. Risk of effectiveness and safety outcomes in AF patients with and without previous PCI

	MI/Coronary death (total 512 events)		Thromboembolism (total 291 events)		Serious bleeding (total 370 events)	
Treatment with previous PCI	**Rate [95% CI]**	**HR [95% CI]**	**Rate [95% CI]**	**HR [95% CI]**	**Rate [95% CI]**	**HR [95% CI]**
VKA plus aspirin plus clopidogrel	4.2 [1.9-9.3]	1.02 [0.43-2.42]	3.1 [1.3-7.5]	1.43 [0.54-3.78]	6.8 [3.8-12.3]	2.09 [1.06-4.14]
VKA plus clopidogrel	3.9 [1.7-8.6]	0.89 [0.38-2.08]	4.5 [2.1-9.4]	1.92 [0.83-4.47]	6.8 [3.8-12.3]	1.84 [0.94-3.60]
VKA plus aspirin	3.3 [2.7-3.9]	0.92 [0.66-1.29]	1.8 [1.4-2.3]	0.91 [0.58-1.42]	4.5 [3.9-5.3]	1.34 [0.96-1.88]
VKA	3.8 [2.9-5.0]	Reference	2.2 [1.5-3.2]	Reference	3.5 [2.6-4.8]	Reference
Aspirin plus clopidogrel	8.8 [6.5-11.8]	2.18 [1.42-3.35]	4.6 [3.2-6.8]	1.79 [1.02-3.14]	3.1 [2.0-4.9]	0.91 [0.51-1.60]
Clopidogrel	4.9 [2.9-8.2]	1.34 [0.74-2.44]	3.9 [2.1-7.0]	2.03 [0.99-4.12]	3.8 [2.1-6.8]	1.00 [0.52-1.98]
Aspirin	4.7 [4.1-5.4]	1.46 [1.06-2.00]	2.8 [2.3-3.3]	1.51 [0.99-2.30]	2.3 [1.9-2.7]	0.70 [0.49-1.02]
	MI/Coronary death (total 1,466 events)		**Thromboembolism (total 749 events)**		**Serious bleeding (total 691 events)**	
Treatment without previous PCI	**Rate [95% CI]**	**HR [95% CI]**	**Rate [95% CI]**	**HR [95% CI]**	**Rate [95% CI]**	**HR [95% CI]**
VKA plus aspirin plus clopidogrel	16.1 [8.7-29.9]	2.78 [1.46-5.32]	4.4 [1.7-11.7]	1.26 [0.46-3.45]	16.2 [9.6-27.3]	4.11 [2.33-7.23]
VKA plus clopidogrel	14.1 [7.8-25.4]	2.42 [1.30-4.49]	4.9 [1.8-13.0]	1.25 [0.46-3.41]	7.4 [3.3-16.5]	1.88 [0.82-4.31]
VKA plus aspirin	6.2 [5.4-7.1]	1.22 [0.98-1.51]	2.9 [2.4-3.5]	0.85 [0.64-1.13]	6.0 [5.2-6.9]	1.59 [1.25-2.02]
VKA	5.1 [4.4-6.1]	Reference	3.5 [2.8-4.3]	Reference	4.0 [3.3-4.9]	Reference
Aspirin plus clopidogrel	14.0 [11.2-17.6]	2.25 [1.68-3.02]	8.4 [6.4-11.0]	1.80 [1.27-2.56]	5.5 [4.0-7.6]	1.14 [0.77-1.67]
Clopidogrel	12.6 [9.3-17.1]	1.94 [1.36-2.76]	7.4 [5.0-11.1]	1.71 [1.08-2.70]	5.9 [3.8-9.2]	1.18 [0.73-1.93]
Aspirin	10.5 [9.8-11.2]	1.83 [1.52-2.20]	5.2 [4.7-5.7]	1.40 [1.11-1.77]	3.2 [2.8-3.6]	0.73 [0.58-0.93]

Effectiveness and safety outcomes in 3,393 atrial fibrillation patients with previous PCI treatment, and 5,307 without previous PCI treatment. All rates are crude incidence rates (events per 100 person-years). HRs reported are adjusted estimates. Abbreviations: VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval, PCI, percutanous coronary intervention.

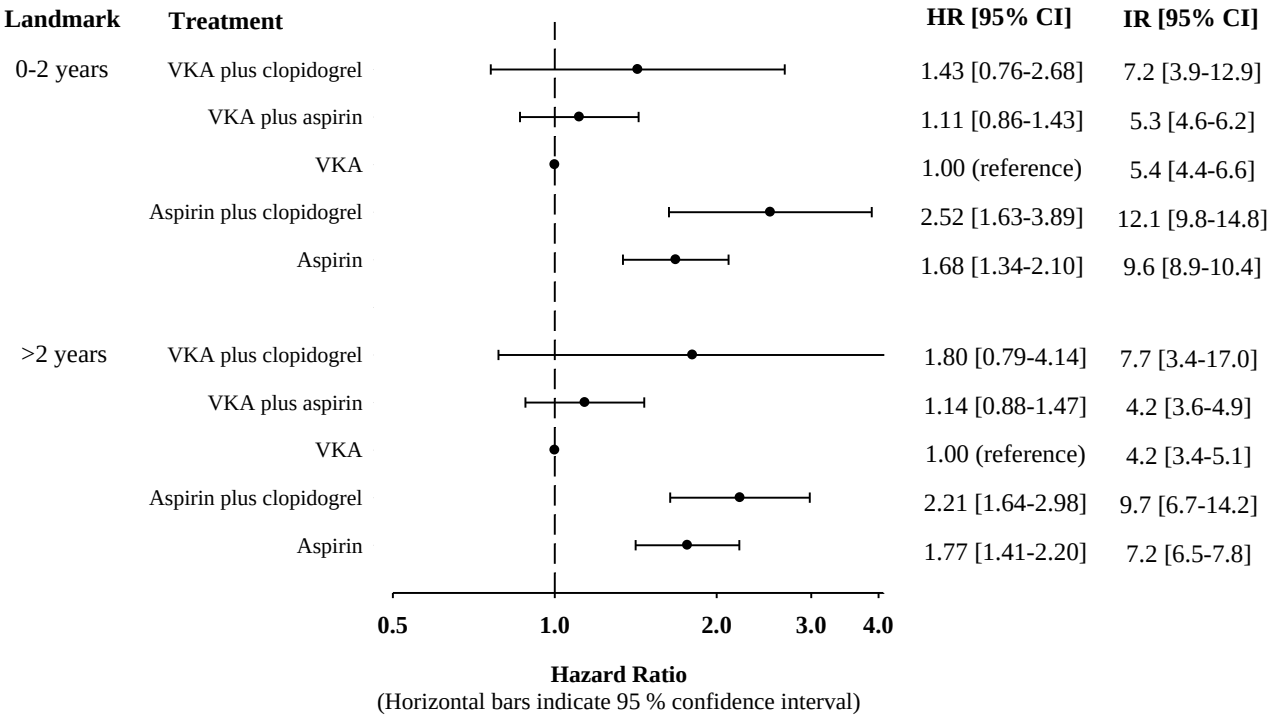
Supplemental Table 5. Risk of death from bleeding

	Fatal bleeding only			Fatal bleeding and death within 30 day from nonfatal bleeding		
Treatment	**Number**	**Rate [95% CI]**	**HR [95% CI]**	**Number**	**Rate [95% CI]**	**HR [95% CI]**
VKA plus aspirin plus clopidogrel	4	1.5 [0.6-4.0]	3.67 [1.23-10.95]	6	2.3 [1.0-5.1]	3.69 [1.52-8.99]
VKA plus clopidogrel	2	0.8 [0.2-3.1]	1.78 [0.41-7.72]	3	1.1 [0.4-3.6]	1.75 [0.53-5.79]
VKA plus aspirin	53	0.8 [0.5-0.9]	1.67 [0.99-2.83]	68	0.9 [0.7-1.1]	1.37 [0.89-2.11]
VKA	19	0.5]0.3-0.7]	1.00 (reference)	15	0.7 [0.5-1.0]	1.00 (reference)
Aspirin plus clopidogrel	12	0.9 [0.5-1.6]	1.58 [0.75-3.31]	30	1.1 [0.7-1.9]	1.27 [0.67-2.40]
Clopidogrel	1	0.1 [0.0-1.1]	0.28 [0.04-2.08]	3	0.4 [0.1-1.4]	0.53 [0.16-1.73]
Aspirin	63	0.5 [0.4-0.6]	0.91 [0.54-1.52]	92	0.7 [0.6-0.9]	0.83 [0.55-1.26]

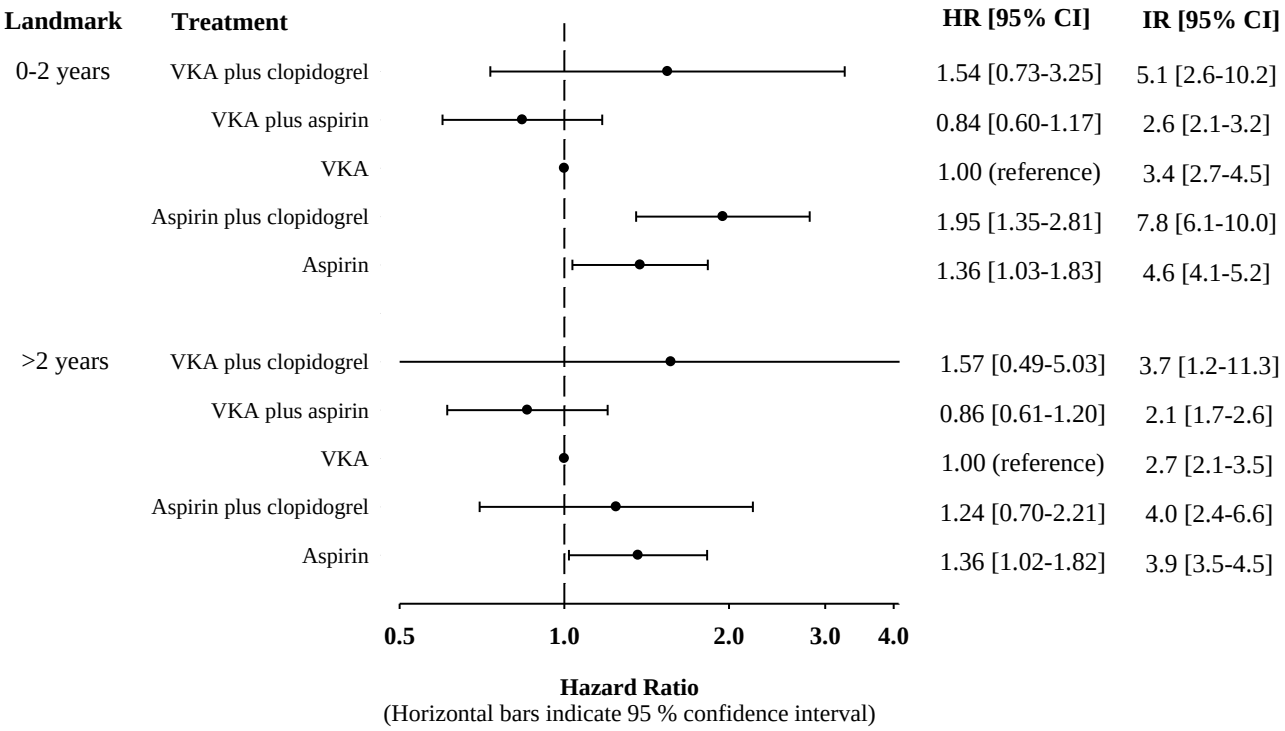
All rates are crude incidence rates (events per 100 person-years). HRs reported are adjusted estimates. Due to low number of events the models were controlled for age, gender, inclusion year and PCI status. Abbreviations: VKA, vitamin K antagonist; HR, hazard ratio; CI, confidence interval

Supplemental Figure 1 A-C – Landmark analyses: Risk of MI/coronary death, thromboembolism and serious bleeding

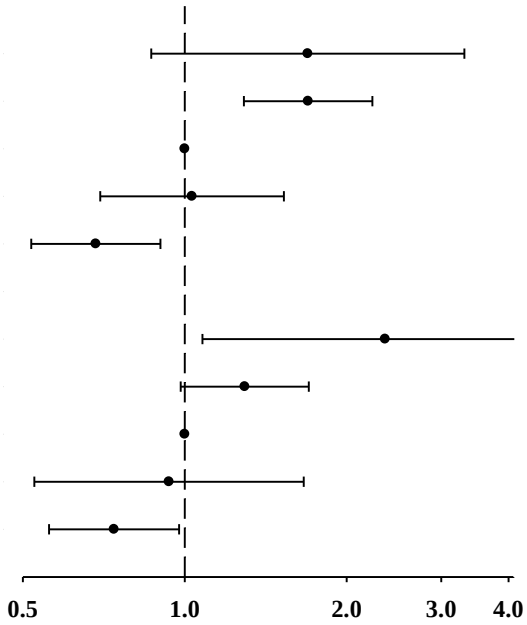
A: Risk of myocardial infarction/coronary death



B: Risk of thromboembolism



C: Risk of serious bleeding



Landmark	Treatment	HR [95% CI]	IR [95% CI]
0-2 years	VKA plus clopidogrel	1.69 [0.87-3.31]	7.2 [3.9-12.9]
	VKA plus aspirin	1.70 [1.29-2.23]	5.3 [4.6-6.2]
	VKA	1.00 (reference)	5.4 [4.4-6.6]
	Aspirin plus clopidogrel	1.03 [0.70-1.53]	12.1 [9.8-14.8]
	Aspirin	0.68 [0.52-0.90]	9.6 [8.9-10.4]
>2 years	VKA plus clopidogrel	2.36 [1.08-5.16]	8.5 [4.0-17.8]
	VKA plus aspirin	1.29 [0.98-1.70]	4.4 [3.8-5.2]
	VKA	1.00 (reference)	3.6 [2.9-4.5]
	Aspirin plus clopidogrel	0.94 [0.53-1.66]	3.3 [2.0-5.6]
	Aspirin	0.74 [0.56-0.98]	2.6 [2.2-3.0]

Hazard Ratio
(Horizontal bars indicate 95 % confidence interval)