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Antithrombotic Therapy and First Myocardial Infarction in Patients With Atrial Fibrillation

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CME/MOC Objective for This Article: After reading this article, the reader should be able to: 1) describe the association between atrial fibrillation and first-time myocardial infarction; and 2) compare the antithrombotic regimens in the primary prevention of myocardial infarction.

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Antithrombotic Therapy and First Myocardial Infarction in Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Patients with atrial fibrillation (AF) have increased risk of thromboembolic events such as stroke and myocardial infarction (MI). Although it has been established that the efficacy of anticoagulation is superior to that of antiplatelet agents for stroke prophylaxis in AF, the optimal antithrombotic treatment remains uncertain for primary protection against MI.

OBJECTIVES The authors investigated the incidence of first-time MI in patients with AF according to antithrombotic treatment and estimated the risk of stroke and bleeding.

METHODS Subjects with first-time AF diagnosed from 1997 to 2012 without history of coronary artery disease were identified using Danish nationwide administrative registries. Subjects were divided into time varying exposure groups according to antithrombotic treatment. The relative risks of outcomes were estimated by Poisson regression models.

RESULTS A total of 71,959 patients (median 75 years of age; females: 47%). At baseline, 37,539 patients (52%) were treated with vitamin K antagonist (VKA) monotherapy, 25,458 (35%) with acetylsalicylic acid (ASA) monotherapy and 8,962 (13%) with dual-therapy (VKA + ASA). The incidence of MI was 3% (n = 2,275). Relative to the VKA-treated group, the associated risk of MI was significantly higher for ASA (incidence rate ratio [IRR]: 1.54; 95% confidence interval [CI]: 1.40 to 1.68) and dual-therapy (IRR: 1.22; 95% CI: 1.06 to 1.40). The bleeding risk was significantly higher for dual-therapy (IRR: 1.93; 95% CI: 1.81 to 2.07). The risk of stroke relative to that of VKA therapy was significantly higher for both ASA (IRR: 2.00; 95% CI: 1.88 to 2.12) and dual-therapy (IRR: 1.30; 95% CI: 1.18 to 1.43).

CONCLUSIONS VKA monotherapy in patients with AF was associated with a lower risk of first-time MI and stroke than ASA monotherapy. Combination of ASA and VKA therapy was not associated with a lower risk of MI but was associated with increased bleeding risk. (J Am Coll Cardiol 2017;69:2901–9) © 2017 by the American College of Cardiology Foundation.

Thromboprophylaxis is the primary treatment focus in patients with atrial fibrillation (AF) due to the 5-fold increased risk of ischemic stroke compared with that in the general population. The potential benefit of antithrombotic treatment in AF patients is based on the expected difference between the decreased risk of ischemic stroke and the increased risk of bleeding (1). In addition to the increased risk of stroke, patients with AF are also at increased risk of developing coronary artery disease (CAD), including myocardial infarction (MI) (2). Atherothrombosis and AF often coexist and share similar pathogenic mechanisms (3). The overlap of risk factors leading to the development of both atherothrombosis and AF adds to the complexity of determining the optimal antithrombotic treatment strategy for the primary prevention of both stroke and atherothrombotic events in AF patients. For the prevention of CAD, acetylsalicylic acid (ASA) therapy is standard of care, but in patients with AF, anticoagulation with vitamin K antagonists (VKA) has been shown to be more beneficial than ASA in preventing ischemic stroke (4–6). Most of the previous studies of MI risk in patients with AF have investigated the risk of recurrent MI, whereas data for the effectiveness of ASA and VKA in primary prevention of MI is lacking (7,8). In this nationwide study, we investigated the incidence of first-time MI in a real-world

cohort of patients with AF and the risk of MI according to type of antithrombotic treatment regimen.

METHODS

DATA REGISTRIES. For all Danish residents, the health care system, both primary and secondary care, is tax-financed and free of charge, and drug prescriptions are partially reimbursed. Through the Civil Registration System all residents in Denmark are given a unique and permanent identification number at the date of birth or immigration. The personal identification number enables cross-linkage among all the Danish administrative registries on a personal level (9). The Danish National Patient Registry has held information for 99.4% of all discharges from nonpsychiatric hospitals in Denmark since 1978 (10).

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In this registry, operational classification codes also have been maintained by the Nordic Medical Statistics Committees Classification of Surgical Procedures since 1996. At discharge, each hospitalization is coded by the treating physician with 1 primary and 1 or more secondary diagnoses according to the International Classification of Diseases (ICD-8th revision [ICD-8]) until 1994 and then according to the ICD-10 from 1994 on. The Danish Registry of Medicinal Product Statistics (national prescription registry) has kept records on all drug prescriptions dispensed from Danish pharmacies since 1995 (11). Each dispensed drug is registered according to the Anatomical Therapeutic Chemical Classification (ATC), including the date, quantity, strength, and formulation of the redeemed prescription. Vital status and cause of death were identified from the Civil Registration System and the Danish Registry of Causes of Death (Online Table 1 shows all ICD and ATC codes used in this study) (12).

POPULATION. All Danish residents hospitalized with first-time AF and without a history of CAD between January 1, 1997, and December 31, 2012, were included in the study (**Figure 1**). The specification of the population of AF without CAD was done to ensure the antithrombotic treatment exposures were chosen for the treatment of AF. The diagnosis of AF has been validated in the Danish National Patient Registry with a positive predictive value of 99% (13). Valvular AF was defined as in previous studies (14) as no previous hospitalizations for mitral or aortic valve disease and no prior mitral or aortic valve surgery. Only patients treated with ASA and/or VKA at index were included. Exclusion criteria were younger than 18 or older than 100 years of age, prior stroke, ablation therapy, cardioversion, vascular disease, treatment with clopidogrel, coronary artery bypass grafting, and percutaneous coronary intervention. Patients were followed until the end of study, time of death, emigration, or date of an outcome of interest.

ANTITHROMBOTIC TREATMENT REGIMENS. Baseline treatment was identified as a prescription of VKA as monotherapy, ASA as monotherapy, or VKA + ASA as dual-therapy. A 30-day quarantine period after index date was introduced to ensure adequate time for redemption of prescriptions and to exclude patients dying shortly after AF discharge. Patients were able to change treatment group during follow-up based on subsequent prescription claims. The definition of exposure took into account the date of prescription and the number and strength of tablets. For ASA, the daily dosage was fixed, whereas for VKA, the estimated daily dosage could change. All definitions of exposure were based on prior prescriptions without conditions on future prescriptions. Therefore patients were considered exposed only if they received a prescription of antithrombotic therapy and were able to change therapy groups. Their exposure status was continually updated under the follow-up period. This method of change of dosage and exposure status during follow-up has previously been described (15).

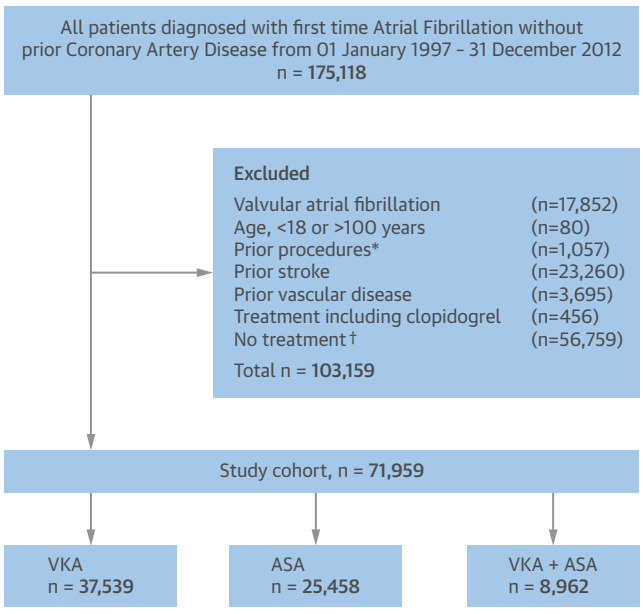
OUTCOMES. The primary outcome was first-time MI. The diagnosis of MI in the Danish registries has previously been validated with a positive predictive value of 92 to 100% (9,16). Secondary outcomes were stroke and bleeding. Stroke was defined as cerebral infarction, unspecified stroke, and transient cerebral ischemia. The characterization of bleeding requiring hospitalization was diagnosis of gastrointestinal, intracranial, respiratory, and urinary tract bleeding and anemia caused by bleeding. Stroke and bleeding have been previously defined (Online Table 1) (14,17,18).

CONCOMITANT TREATMENT AND COMORBIDITY. Outpatient medication at baseline was identified based on prescriptions dispensed within 180 days prior to inclusion. Prescriptions of statins, renin-angiotensin system inhibitors, beta-blockers; and antiarrhythmic drugs consisting of digoxin, amiodarone, dronedarone, and Class 1C antiarrhythmic drugs were identified based on ATC codes. Prior diagnosis of heart failure, chronic obstructive pulmonary disease, chronic renal failure, liver disease, and malignancy were identified using ICD codes. Hypertension was defined as the redemption of at

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
ASA = acetylsalicylic acid
ATC = Anatomical Therapeutic Chemical Classification
CAD = coronary artery disease
INR = international normalized ratio
IRR = incidence rate ratio
MI = myocardial infarction
PY = person-years
VKA = vitamin k antagonist

FIGURE 1 Overview of Study Population



*Procedures included coronary artery bypass grafting, percutaneous coronary intervention, ablation therapy, and direct current conversion. †No treatment indicates not treated with VKA or ASA. ASA = acetylsalicylic acid; VKA = vitamin K antagonist.

least 2 antihypertensive drugs concomitantly, as previously validated (14). Diabetes was defined as prescription of antidiabetic medication. All pharmacotherapies and comorbidities were defined at baseline but also updated during follow-up examination based on subsequent hospital admissions and prescription claims (Online Table 1).

Thromboembolic and bleeding risk factors were assessed by the CHA_2DS_2-VASc (Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, previous Stroke, Vascular disease, Age 65-74 years, Sex category) score and the HAS-BLED (hypertension, abnormal renal/liver function, stroke or thromboembolism, bleeding history, labile international normalized ratio [INR], age >65 years, and drug and/or alcohol abuse) score. The HAS-BLED score was modified, as data for labile INR and direct alcohol consumption were unavailable.

STATISTICAL ANALYSES. Baseline characteristics are median values with first and third interquartile range (IQR) limits or frequencies and percentages. All events were first events only, and recurrent events were not included in the analyses. Crude incidence rates (IR) were calculated as percentages of events per 1,000 person-years (PY) with 95% confidence intervals (CIs). Adjusted incidence rate ratios (IRR) with 95% CI were calculated in a multiple Poisson regression model with time-dependent treatment exposure. Vitamin K antagonist monotherapy was used as reference. This method allowed patients to switch from 1 exposure group to another. Regression models were adjusted for age, sex, calendar year, chronic heart failure, chronic kidney disease, diabetes, hypertension, peripheral arterial disease, alcohol-related diseases, liver diseases, stroke, and bleeding; models based on the secondary outcomes of stroke and bleeding, however, were not adjusted for the stroke and bleeding. Intention-to-treat analyses were performed as sensitivity analyses (using multiple Cox proportional hazard models estimating risk of outcomes based on exposure to antithrombotic treatment at baseline) to exclude possible selection bias issues related to treatment susceptibility. Cox models were adjusted for the same factors as the Poisson regression models. Subgroups stratified by sex, age, ASA dosage, and VKA type were analyzed. Validity of model assumptions were tested, fulfillment of the proportional hazards assumption, significant interaction between sex and age, goodness-of-fit chi-square test, and found to be valid. Statistical calculations were performed using SAS version 9.4 software (SAS Institute, Cary, North Carolina) and R version 3.2.4 software (R Foundation for Statistical Computing, Vienna, Austria) (19).

ETHICS. Registry studies do not require prior approval from the ethics committees in Denmark, and data were anonymized. The Danish Data Protection Agency approved this study (ref. no. 2007-58-0015 and international reference GEH-2014-013 I-Suite no.2731).

RESULTS

POPULATION. During a study period of 16 years, 71,959 patients with AF and without diagnosis of CAD or other vascular diseases were included in the study (median 75 years of age; 47% female). At baseline, 37,539 patients (52%) were treated with VKA monotherapy, 25,485 (35%) with ASA monotherapy, and 8,962 (13%) with VKA + ASA dual-therapy (**Figure 1**). At baseline, 4% were treated with phenprocoumon and 96% with warfarin. For ASA monotherapy or dual-therapy of VKA + ASA, the median dose of ASA during follow-up was 75 mg (IQR: 75 to 100 mg). The characteristics of the patients differed among the treatment groups: the ASA monotherapy group was older, proportionately more female, and characterized by higher CHA_2DS_2-VASc score rate than other groups. The ASA plus VKA dual-therapy groups were

characterized by greater prevalence of heart failure, hypertension, and diabetes. Baseline characteristics of the 3 treatment groups are shown in Table 1. Median follow-up time was 4.1 years, and 32,962 patients (46%) died during follow-up.

MYOCARDIAL INFARCTION. A total of 2,275 patients (3%) developed MI during follow-up with a median time from AF diagnosis to MI of 4.0 years (IQR: 1.7 to 5.0 years). The incidence rate of MI for the total population was 8.0 per 1,000 PY (95% CI: 7.7 to 8.3). Crude incidence rates of MI were 5.8 per 1,000 PY (95% CI: 5.4 to 6.2) for VKA, 11.2 per 1,000 PY (95% CI: 10.6 to 11.8) for ASA, and 7.8 per 1,000 PY (95% CI: 6.9 to 8.8) for VKA + ASA dual-therapy. Compared to VKA monotherapy, the risk of MI was increased in the ASA monotherapy group (IRR: 1.54; 95% CI: 1.40 to 1.68) and in the VKA + ASA dual-therapy group (IRR: 1.22; 95% CI: 1.06 to 1.40) (Figure 2).

STROKE AND BLEEDING. During follow-up, 5,575 patients (8%) experienced stroke and 6,069 (8%) developed bleeding that required hospitalization. Incidence rates and IRR for the secondary outcomes are shown in Figure 2. The risk of stroke was greatest in the ASA monotherapy group (IR: 3.21; 95% CI: 3.10 to 3.32). Both ASA monotherapy (IRR: 2.00; 95% CI: 1.88 to 2.12) and VKA + ASA dual-therapy (IRR: 1.30; 95% CI: 1.18 to 1.43) were associated with a greater risk of stroke than VKA monotherapy. Vitamin K antagonist plus ASA dual-therapy was associated with the greatest risk of bleeding (IR: 4.52; 95% CI: 4.28 to 4.78; and IRR: 1.93; 95% CI: 1.81 to 2.07, respectively); the risk was double that of VKA monotherapy alone. No significant differences between bleeding risk for the ASA monotherapy group (IRR: 0.95; 95% CI: 0.90 to 1.01) and that of the VKA monotherapy group were observed.

SENSITIVITY ANALYSES. The risks associated with baseline antithrombotic therapy, consisting of VKA monotherapy, ASA monotherapy, and VKA + ASA dual-therapy, were analyzed in an intention-to-treat design. Results were similar to the main analyses for both the primary and secondary outcomes (Online Figure 1). Results remained unchanged when elective percutaneous coronary intervention, coronary artery bypass graft, and MI were used as a combined endpoint. For MI, similar results were found when the population was stratified by ASA dosage or VKA type (Online Figures 2 and 3). For the main Poisson analyses, interactions were significant for age and MI ($p = 0.028$), and the interaction between sex and treatment as exposure were significant for bleeding ($p = 0.001$). Subgroup analyses of the primary endpoint MI stratified by age and sex, respectively, were performed (Online Figures 4 and 5). In the subgroup analysis stratified for sex, VKA + ASA dual-therapy was not associated with a significantly increased risk of MI compared that of VKA monotherapy in men; however, VKA + ASA dual-therapy in women was associated with a significantly increased risk of MI compared to that of VKA monotherapy in women.

TABLE 1 Patient Characteristics at Inclusion

	VKA (n = 37,539)	ASA (n = 25,458)	ASA + VKA (n = 8,962)
Male	22,302 (59.4)	10,951 (43.0)	4,979 (55.6)
Age, yrs	71 (63–78)	80 (70–86)	74 (66–80)
Comorbidities			
Malignancy	2,917 (7.8)	2,748 (10.8)	657 (7.3)
Chronic obstructive pulmonary disease	3,250 (8.7)	2,873 (11.3)	858 (9.6)
Chronic heart failure	6,937 (18.5)	5,192 (20.4)	2,147 (24.0)
Chronic kidney disease	651 (1.7)	669 (2.6)	222 (2.5)
Liver disease	386 (1.0)	395 (1.6)	120 (1.3)
Bleeding	1,730 (4.6)	1,872 (7.4)	498 (5.6)
Hypertension	18,897 (50.3)	10,601 (41.6)	5,851 (65.3)
Diabetes	6,418 (17.1)	3,752 (14.7)	1,923 (21.5)
Concomitant medication			
Beta-blockers	28,778 (76.7)	15,099 (59.3)	7,234 (80.7)
Amiodarone	5,191 (13.8)	1,522 (6.0)	1,333 (14.9)
Dronedarone	405 (1.1)	126 (0.5)	70 (0.8)
Class IC antiarrhythmics	2,891 (7.7)	1,161 (4.6)	455 (5.1)
Diuretics	33,595 (89.5)	20,526 (80.6)	8,254 (92.1)
Loop diuretics	21,345 (56.9)	15,295 (60.1)	5,734 (64.0)
RAS inhibitors	22,293 (59.4)	11,588 (45.5)	6,082 (67.9)
Statins	13,107 (34.9)	5953 (23.4)	3,951 (44.1)
NSAID	17,225 (45.9)	11,914 (46.8)	4,033 (45.0)
Digoxin	24,206 (64.5)	15,120 (59.4)	5,759 (64.3)
CHA_2DS_2-VASc score			
0 low	5,611 (14.9)	2,342 (9.2)	621 (6.9)
1 intermediate	6,350 (16.9)	2,270 (8.9)	1,141 (12.7)
≥2 high	25,578 (68.2)	20,846 (81.8)	7,200 (80.3)
HAS-BLED score			
0-1 low	14,766 (39.3)	2,244 (8.8)	646 (7.2)
2 intermediate	15,914 (42.4)	13,301 (52.2)	3,427 (38.2)
≥3 high	6,859 (18.3)	9,913 (38.9)	4,889 (54.6)

Values are n (%) or median (interquartile range).

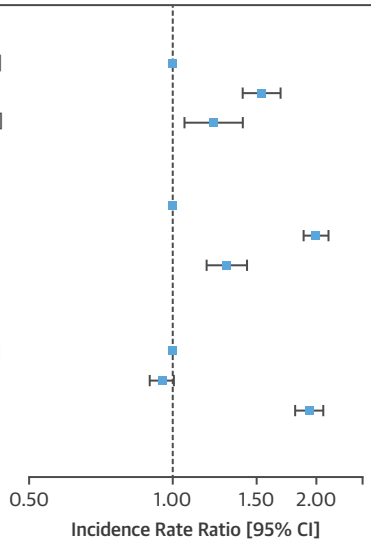
ASA = acetylsalicylic acid; CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes, previous stroke, vascular disease, age 65–74 years, sex category; HAS-BLED = hypertension, abnormal renal or liver function, stroke, bleeding, labile international normalized ratio, elderly, drugs or alcohol; NSAID = non-steroidal anti-inflammatory drug; RAS = renin-angiotensin; VKA = vitamin K antagonist.

DISCUSSION

In this nationwide study of patients with AF without prevalent CAD, we found an overall incidence rate of MI of 8.0 per 1,000 PY (95% CI: 7.7 to 8.3) during a median follow-up of 4.0 years. As primary prophylaxis of MI, we found VKA monotherapy was associated with a lower risk compared to ASA monotherapy.

FIGURE 2 Incidence Rate and Incidence Rate Ratios by Antithrombotic Treatment for Myocardial Infarction, Stroke, and Bleeding

Outcome	Events	Risk time (years)	Incidence Rate	IRR, ref.= VKA
Myocardial Infarction				
VKA	870	150188	0.58 [0.54 - 0.62]	1.00
ASA	1152	103017	1.12 [1.06 - 1.18]	1.54 [1.40 - 1.68]
ASA + VKA	253	32479	0.78 [0.69 - 0.88]	1.22 [1.06 - 1.40]
Stroke				
VKA	1768	144775	1.22 [1.17 - 1.28]	1.00
ASA	3180	99158	3.21 [3.10 - 3.32]	2.00 [1.88 - 2.12]
ASA + VKA	527	31617	1.67 [1.53 - 1.82]	1.30 [1.18 - 1.43]
Bleeding				
VKA	2684	133906	2.00 [1.93 - 2.08]	1.00
ASA	2141	87975	2.43 [2.33 - 2.54]	0.95 [0.90 - 1.01]
ASA + VKA	1244	27492	4.52 [4.28 - 4.78]	1.93 [1.81 - 2.07]



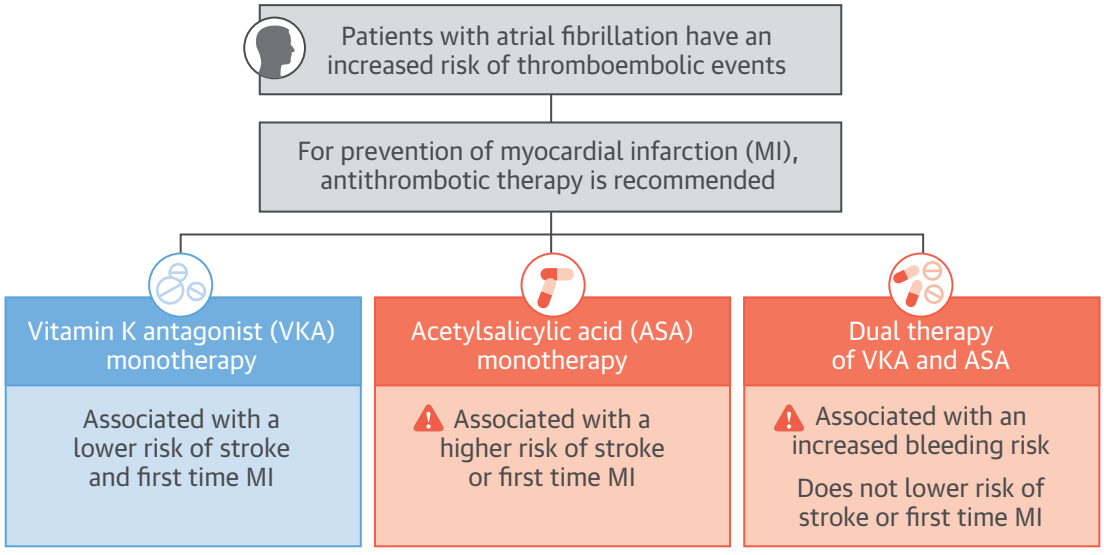
VKA was used as a reference. Incidence rate ratio (IRR) = 1.00. CI = confidence interval; Ref = reference; other abbreviations as in Figure 1.

Importantly, combination therapy was not associated with better prevention, but the bleeding risk was increased (Central Illustration).

INCIDENCE OF MI. The overall annual rate of MI in our study is similar to that reported in other observational studies of AF patients, where the annual rates of MI ranged from 0.4% to 2.5% (20). In a recent study by Soliman et al. (2), the incidence rate of MI was 12 per 1,000 PY (95% CI: 9.6 to 14.9). That study showed that the risk of developing MI was almost twice as high for AF patients than for patients without AF. Higher incidence rates of MI have been found in patients with concomitant stable ischemic heart disease and in patients undergoing coronary intervention. Those patients were excluded in our cohort, where the main objective was to investigate the primary prophylactic effect of antithrombotic treatment. The annual incidence rate of 5.8 per 1,000 PY in patients treated with VKA is similar to that in reports from clinical randomized trials. Those trials showed that the rate of MI in patients treated with non-vitamin K oral anticoagulants (NOACs) was similar to that in patients treated with VKAs.

PROPHYLACTIC EFFECT OF ANTITHROMBOTIC THERAPY ON MI. Although the role of VKA treatment in secondary MI protection has been demonstrated in clinical trials (20), few other studies have examined the primary prophylactic effect of VKA compared to that of ASA. TPT (Thrombosis Prevention Trial), consisting of 5,499 patients with mean 57.5 years of age, concluded that, in high-risk patients, low-intensity VKA therapy provided greater protection against coronary events than ASA (6). However, the study population included in the TPT consisted of patients with and without AF, and inclusion was restricted to men and high-risk patients only. The risk of MI was investigated in the ACTIVE-W (Atrial Fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events) trial (n = 6,706; mean 70.2 years of age), demonstrating that dual antiplatelet therapy consisting of ASA in combination with clopidogrel was inferior to VKA for prevention of vascular events (reinfarction) in an AF population (4). Our findings support an increased protection against coronary events with anticoagulant therapy compared to antiplatelet therapy. For reinfarction, the Warfarin, Aspirin, Reinfarction Study (n = 3,630; mean 60 years of age) found an overall significant risk reduction of 29% with dual-therapy and 19% with VKA monotherapy compared to ASA monotherapy for a composite outcome of death, nonfatal stroke, or nonfatal reinfarction (21). An exploratory analysis of the Stroke Prevention using an Oral Thrombin Inhibitor in atrial fibrillation Trial (n = 7,304; mean 71.1 years of age) found no significant reduction of MI with ASA plus VKA dual-therapy compared to VKA

CENTRAL ILLUSTRATION **Atrial Fibrillation and Myocardial Infarction**



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The optimal antithrombotic treatment for the primary prevention of myocardial infarction in patients with atrial fibrillation. ASA = acetylsalicylic acid; MI = myocardial infarction; VKA = vitamin K antagonist.

monotherapy (22). Two major randomized controlled studies, the Coumadin Aspirin Reinfarction Study (n = 8,803; mean 59 years of age) (8) and the Combination Hemotherapy and Mortality Prevention study (n = 5,059; mean 64 years of age) (23) found no reduction in mortality, reinfarction, or stroke with VKA + ASA dual-therapy compared with ASA monotherapy. Acetylsalicylic acid monotherapy used as primary prevention of cardiovascular outcomes has been debatable, with different recommendations (24).

Previous studies have focused mainly on the efficacy and safety of VKA or ASA, or both, after MI. In addition to the TPT, the endpoints of the other trials were prevention of recurrent MI or combined endpoints of stroke, recurrent MI, and mortality or had a broader population. Neither the therapeutic level of international normalized ratio (INR) or the population demographics selected for the trials were equivalent. As INR was unknown in our study, we were not able to ascertain whether patients were in therapeutic range when the MI occurred. This may explain why we found dual-therapy to be associated with a greater risk of MI than VKA monotherapy. To further investigate the lack of effect of ASA-based therapy, we investigated whether it was dependent on the dosage of ASA. We found that ASA-based therapy had no beneficial effect, regardless of dose. This lack of efficacy of ASA may be that the underlying pathophysiology for MI in patients with AF may be less due to plaque rupture. The bleeding risk was significantly increased in the dual-therapy group compared to that in the VKA group, which is also supported by several studies (15,18,25). The greater risk of MI of the dual-therapy group could also possibly be attributed to confounding by indication and those receiving dual-therapy be at greater risk of MI, although other clinical studies with reinfarction support our findings with increased or same risk with dual antithrombotic therapy.

In the era of NOACs, the new anticoagulants that inhibit thrombin or factor Xa are increasingly used in patients with AF. The Randomized Evaluation of Long-term anticoagulation therapy study found VKA therapy associated with a nonsignificant lower incidence of MI than dabigatran etexilate (26). In a recent meta-analysis, Capodanno et al. (27) found no differences between rates of MI in NOAC treatment group and those in warfarin treatment group, whereas other meta-analyses supported a higher risk of MI with NOACs than with VKA (28,29). Further research in prevention of coronary atherothrombotic events is warranted in high-risk patients with AF treated with NOACs compared with VKA treatment.

STUDY LIMITATIONS. The main strengths of this study are the unique possibility of linkage between nationwide registries on the individual level of a large sample size. The positive predictive value of AF is very high in the Danish National Patient Registry, and the completeness of data ensures minimal risk of loss to follow-up. Our study population follows real-world patients, and we were able to follow subgroups at high risk, which are often excluded in randomized controlled trials. In Denmark, expenses related to prescription medication are partially reimbursed. As such, all pharmacies are required to register all redeemed prescriptions to ensure complete and accurate registration. The reimbursement ensures high consistency in chronic users, although ASA is also available as an over-the-counter drug. Additionally, Schmidt et al. (30) previously studied use of aspirin in Denmark and found 92% of all low-dose ASA sold in Denmark was registered by prescription (30).

Several limitations are relevant due to the observational design of the study. First, residual confounding was not avoidable, where we lacked clinical information such as body mass index, blood pressure, and INR. Second, the method of identifying AF with ICD codes does not identify patients with undiagnosed AF or patients outside of the primary health care setting, hence there is a risk of misclassification. The adherence of prescribed antithrombotics was also unknown, but in Denmark, the percentage of adherence of guidelines are high (31). Third, confounding by indication is most likely because the reasons for or factors of determining prescriptions were unknown.

CONCLUSIONS

In patients with AF, VKA monotherapy was associated with lower risk of first-time MI compared with ASA monotherapy and ASA plus VKA dual-therapy. However, dual-therapy was also associated with greater risk of bleeding.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with AF, anticoagulation using a VKA is associated with a lower risk of first myocardial infarction than either antiplatelet therapy with aspirin alone or the combination of aspirin plus VKA, and the combination is associated with a higher risk of bleeding.

TRANSLATIONAL OUTLOOK: Randomized trials that include target-specific oral anticoagulants are needed to define optimum antithrombotic strategies for prevention of stroke, systemic embolism, and MI in patients with AF and to clarify the relative roles of platelets and the coagulation system in the pathogenesis of ischemic events.

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APPENDIX For a supplemental table and figures, please see the online version of this article.

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