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Risk of Myocardial Infarction in Anticoagulated Patients With Atrial Fibrillation

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ABSTRACT

BACKGROUND Evidence is conflicting as to the efficacy of direct oral anticoagulation (DOAC) and vitamin K antagonist (VKA) for prevention of myocardial infarction (MI).

OBJECTIVES This study aimed to investigate the risk of MI associated with the use of apixaban, dabigatran, rivaroxaban, and VKA in patients with atrial fibrillation.

METHODS Patients with atrial fibrillation were identified using Danish health care registers and stratified by initial oral anticoagulant treatment. Standardized absolute 1-year risks were estimated based on Cox regression for hazard rates of MI hospitalizations and mortality. Reported were absolute risks separately for the oral anticoagulation treatments and standardized to the characteristics of the study population.

RESULTS Of the 31,739 patients included (median age, 74 years; 47% females), the standardized 1-year risk of MI for VKA was 1.6% (95% confidence interval [CI]: 1.3 to 1.8), apixaban was 1.2% (95% CI: 0.9 to 1.4), dabigatran was 1.2% (95% CI: 1.0 to 1.5), and rivaroxaban was 1.1% (95% CI: 0.8 to 1.3). No significant risk differences were observed in the standardized 1-year risks of MI among the DOACs: dabigatran versus apixaban (0.04%; 95% CI: −0.3 to 0.4), rivaroxaban versus apixaban (0.1%; 95% CI: −0.4 to 0.3), and rivaroxaban versus dabigatran (−0.1%; 95% CI: −0.5 to 0.2). The risk differences for DOACs versus VKA were all significant: −0.4% (95% CI: −0.7 to −0.1) for apixaban, −0.4% (95% CI: −0.7 to −0.03) for dabigatran, and −0.5% (95% CI: −0.8 to −0.2) for rivaroxaban.

CONCLUSIONS No significant risk differences of MI were found in the direct comparisons of DOACs, and DOACs were all associated with a significant risk reduction of MI compared with VKA. (J Am Coll Cardiol 2018;72:17–26)
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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation

CI = confidence interval

DOAC = direct oral anticoagulant

HR = hazard ratio

MI = myocardial infarction

VKA = vitamin K antagonist

For decades, vitamin K antagonists (VKA) have been used for prevention of stroke in patients with atrial fibrillation (AF). Currently, direct oral anticoagulants (DOACs) are recommended in stroke prevention guidelines, and they have been shown to be noninferior to VKA treatment in both efficacy (stroke risk) and safety (bleeding risk) (1,2). Additionally, studies have observed a prevalence of myocardial infarction (MI) in up to one-third of patients with AF, and patients with AF are at increased risk of developing MI (3–6). The randomized clinical trial RE-LY (Randomized Evaluation of Long-Term Anticoagulant Therapy) observed an increased risk of MI with dabigatran compared with VKA in patients with AF (7). However, the retrospective substudy of RE-LY found the increased rate of MI in patients treated with dabigatran nonsignificant (8). In the ARISTOTLE trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), a nonsignificant reduced risk of MI was observed for apixaban compared with VKA (9). Similarly, a nonsignificant reduction in annual risk of MI was also observed in the ROCKET-AF trial comparing rivaroxaban with VKA (10).

SEE PAGE 27

The randomized clinical trials have not definitively demonstrated a significantly reduced/increased risk of MI associated with DOACs compared with VKA; however, elderly and frail patients at particular high risk are generally excluded from clinical trials. Questions remain as to the efficacy of the DOACs and VKA for mitigation of MI risk. Furthermore, data are lacking on the effect of the various DOACs and direct comparisons among the DOACs. Accordingly, we investigated the treatment-specific 1-year risk of MI in oral-anticoagulative-naive patients with nonvalvular AF initiating oral anticoagulation therapy with apixaban, dabigatran, rivaroxaban, or VKA.

METHODS

DATA REGISTERS. In Denmark, all residents are given a unique and permanent identification number through the Civil Registration System; this enables cross-linkage among all the Danish administrative registers on an individual level (11,12). The Danish National Patient Register holds information regarding hospitalizations, which are coded with 1 primary and 1 or more secondary diagnoses according to the International Classification of Diseases (13). All drug prescriptions dispensed from Danish pharmacies are recorded by The Danish register of Medicinal Product Statistics (the national prescription register), where each dispensed drug is registered according to the Anatomical Therapeutic Chemical Classification system (14). Vital status and cause of death was identified from the Civil Registration System and the Danish Register of Causes of Death (12). See Online Table 1 for all International Classification of Diseases and Anatomical Therapeutic Chemical Classification system codes used in this study.

STUDY POPULATION. Patients with a first-time hospitalization or outpatient clinic visit with a diagnosis of AF and first-time users of oral anticoagulants were identified in the study period of January 1, 2013, to June 30, 2016 (**Figure 1**). The diagnosis of AF has been validated with a positive predictive value of 92% in the Danish National Patient Register (15). Only patients treated with oral anticoagulation were included. We excluded patients with valvular AF as previously done (11). Other exclusion criteria were age younger than 30 or older than 100 years, and total hip or knee arthroplasties within 5 weeks. Patients with chronic kidney disease were also excluded because glomerular filtration rate <15 ml/min (dabigatran glomerular filtration rate <30 ml/min) is a contraindication for initiating treatment with DOACs; this ensured that all treatments were possible for each group.

ORAL ANTICOAGULANT TREATMENT REGIMENS. Dabigatran has been available in Denmark from August 22, 2011, rivaroxaban from February 6, 2012, and apixaban from December 10, 2012. Baseline treatment was identified as the first prescription of oral anticoagulation therapy in the study period. Discontinuation of oral anticoagulation treatment was defined by failure to redeem a new prescription within 30 days of the expiration of the preceding prescription.

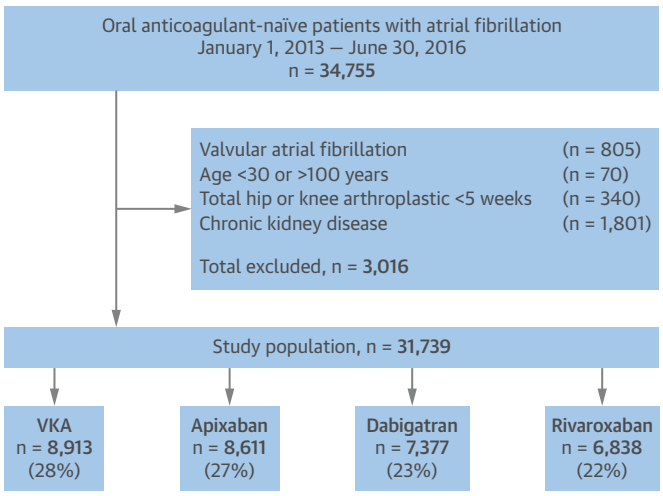
STUDY OUTCOMES. The primary outcome was first event of hospitalization with MI during the first year after start of oral anticoagulative treatment. The diagnosis of MI has been validated with a positive predictive value of 92% to 100% in the Danish registers (11,16). Secondary outcome was a composite outcome of MI or all-cause mortality.

CONCOMITANT TREATMENT AND COMORBIDITY. Concomitant treatment was identified based on prescriptions redeemed within 180 days before index using Anatomical Therapeutic Chemical Classification system codes. Comorbidities were defined as prior diagnoses 10 years before date of inclusion. Hypertension was defined when the patient records include at least 2 antihypertensive prescriptions as previously

done (17) or a diagnosis of hypertension. Diabetes was defined by the any prescription of antidiabetic medication. Thromboembolic risk factors were those of the CHA_2DS_2-VASc score (congestive heart failure, hypertension, age ≥75 years or 65 to 74 years, diabetes, previous stroke, vascular disease, sex category female) (17).

STATISTICAL ANALYSES. Baseline characteristics were presented as frequencies and percentages or as medians with first and third interquartile ranges (Q1 and Q3). Patients were followed from the date of initial oral anticoagulation treatment (study entry) until whichever came first: date 1 year after the study entry; June 30, 2017; date of MI; date of death; or date of emigration. Crude nonadjusted risks of MI after 1 year on oral anticoagulation therapy were computed with the Aalen-Johansen method and supplied by crude hazard ratios (HRs) obtained with simple Cox regression (oral anticoagulation therapy as the only variable) for the hazard rate of MI. Crude nonadjusted MI-free survival probabilities after 1 year on oral anticoagulation therapy were computed with the Kaplan-Meier method and supplied by crude HRs obtained with simple Cox regression (oral anticoagulation therapy as the only variable) for the hazard rate of the combined endpoint MI or all-cause death. Multiple Cox regression models for the hazard rate of MI and the hazard rate of the competing risk (all-cause death without MI) had an age-stratified baseline hazard (30 to 50, from 50 to 90 by 5 years, and 90 to 100 years) and were adjusted for oral anticoagulation treatment, sex, heart failure, diabetes, hypertension, vascular disease, liver disease, stroke, and bleeding. Reported are HRs for MI or combined endpoint MI or mortality with 95% confidence intervals (CI). Based on the 2 Cox regression models (1 for MI, 1 for all-cause death without MI) we predicted the patient-specific absolute 1-year risks of MI using the formula of Benichou and Gail (18) (for details, see Online Figure 1A). Second, we predicted the patient-specific MI-free survival probability based on a Cox regression for the hazard of the combined endpoint MI or all-cause death (Online Figure 1B). For each oral anticoagulation treatment separately, reported are average 1-year absolute risks of MI both standardized to the patient characteristics of the full study population obtained as follows. Based on the Cox regression models and the formula of Benichou and Gail, for each patient, we calculated x versions of the predicted 1-year risk of MI. For each version we used the patients' observed risk factors and set the treatment to one of the x anticoagulants for all patients. For each oral anticoagulant, the standardized 1-year absolute risk of MI (MI-free survival) is the average of the patient-specific 1-year risks (g-formula).

FIGURE 1 Selection of Study Cohort



VKA = vitamin K antagonists.

Similarly, standardized absolute risks of the combined endpoint (MI or all-cause death) were obtained based on the Cox regression model by predicting the risk as 100% minus the predicted MI-free survival probability using the patient's factual risk factors and setting possibly counter to the fact the treatment to 1 of the oral anticoagulants. The differences between the standardized average 1-year risks of MI (g-formula) can, within the limitations of the observational data and our models, be interpreted as what we would have observed had we randomized the patients to 1 of the oral anticoagulation treatment options (19). For all absolute 1-year risks we show 95% CI based on 1,000 bootstrap samples.

Sensitivity analyses were performed by extending the follow-up period to 3 years, and in subgroups defined by DOAC dose, use of acetylsalicylic acid therapy; low and high risk by presence of prior ischemic heart disease, percutaneous coronary intervention, and use of dual antiplatelet therapy or acetylsalicylic acid therapy. Furthermore, an on-treatment analysis was computed with censoring of patients discontinuing oral anticoagulative treatment. Finally, a combined endpoint analysis of cardiovascular mortality and MI was done in the period 2013 to 2015, because data of cause of death were not available after 2015. The level of statistical significance was set at 5%. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina), and R 3.4.1 (20).

ETHICS. Register studies do not require prior approval from the ethics committees in Denmark, and

TABLE 1 Patient Characteristics by Oral Anticoagulant Treatment at Baseline

	VKA (n = 8,913)	Apixaban (n = 8,611)	Dabigatran (n = 7,377)	Rivaroxaban (n = 6,838)	p Value
Male	5,232 (58.7)	4,226 (49.1)	4,102 (55.6)	3,490 (51.0)	<0.001
Age, yrs	73 (66-81)	76 (68-84)	72 (65-80)	74 (67-83)	<0.001
Comorbidities					
Bleeding	1,031 (11.6)	1,118 (13.0)	765 (10.4)	746 (10.9)	<0.001
Stroke	1,151 (12.9)	1,753 (20.4)	1,051 (14.2)	1,141 (16.7)	<0.001
Heart failure	1,555 (17.4)	1,397 (16.2)	1,036 (14.0)	997 (14.6)	<0.001
Liver disease	140 (1.6)	123 (1.4)	78 (1.1)	74 (1.1)	0.007
Hypertension	5,359 (60.1)	5,413 (62.9)	4,336 (58.8)	4,234 (61.9)	<0.001
Diabetes	1,080 (12.1)	1,042 (12.1)	806 (10.9)	753 (11.0)	0.019
Malignancy	1,383 (15.5)	1,345 (15.6)	961 (13.0)	974 (14.2)	<0.001
Chronic obstructive pulmonary disease	1,002 (11.2)	1,055 (12.3)	723 (9.8)	788 (11.5)	<0.001
Myocardial infarction	928 (10.4)	635 (7.4)	523 (7.1)	407 (6.0)	<0.001
Ischemic heart disease	2,234 (25.1)	1,783 (20.7)	1,438 (19.5)	1,293 (18.9)	<0.001
PCI	310 (3.5)	80 (0.9)	91 (1.2)	57 (0.8)	<0.001
Concomitant medication					
Acetylsalicylic acid	3,410 (38.3)	2,962 (34.4)	2,537 (34.4)	2,414 (35.3)	<0.001
ADP receptor inhibitors	908 (10.2)	1,013 (11.8)	648 (8.8)	714 (10.4)	<0.001
Dual antiplatelet inhibition	420 (4.7)	285 (3.3)	228 (3.1)	213 (3.1)	<0.001
Diuretics	2,773 (31.1)	2,707 (31.4)	2,323 (31.5)	2,199 (32.2)	0.570
Beta-blockers	3,816 (42.8)	2,994 (34.8)	2,639 (35.8)	2,497 (36.5)	<0.001
Calcium-channel blockers	2,305 (25.9)	2,252 (26.2)	1,885 (25.6)	1,770 (25.9)	0.862
Digoxin	564 (6.3)	505 (5.9)	419 (5.7)	452 (6.6)	0.072
Renin angiotensin system inhibitors	3,695 (41.5)	3,640 (42.3)	3,041 (41.2)	2,771 (40.5)	0.175
Loop diuretics	1,760 (19.7)	1,511 (17.5)	1,052 (14.3)	1,151 (16.8)	<0.001
Statins	3,205 (36.0)	2,873 (33.4)	2,455 (33.3)	2,196 (32.1)	<0.001
Nonsteroidal anti-inflammatory drug	1,203 (13.5)	1,175 (13.6)	1,059 (14.4)	982 (14.4)	0.246
CHA_2DS_2-VASc score					
0	858 (9.6)	427 (5.0)	624 (8.5)	372 (5.4)	
1	966 (10.8)	733 (8.5)	911 (12.3)	728 (10.6)	
2	1,827 (20.5)	1,582 (18.4)	1,717 (23.3)	1,406 (20.6)	
3	5,262 (59.0)	5,869 (68.2)	4,125 (55.9)	4,332 (63.4)	

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

ADP = adenosine diphosphate receptor; CHA_2DS_2-VASc score = congestive heart failure, hypertension, age ≥75 years or 65 to 74 years, diabetes, previous stroke, vascular disease, sex category female; PCI = percutaneous coronary intervention; VKA = vitamin k antagonist.

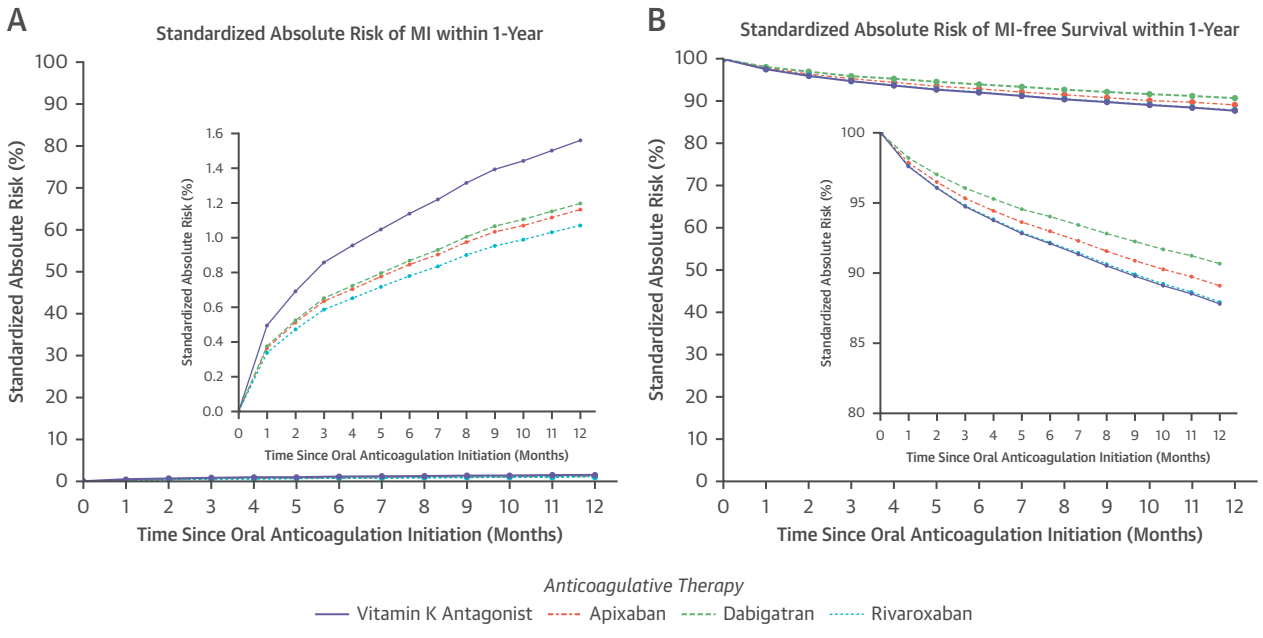
data were anonymized. The Danish Data Protection Agency approved use of data for this study (reference: 2007-58-0015; internal reference: GEH-2014-012; I-Suite number: 02720).

RESULTS

STUDY COHORT. In the study period from January 2013 to June 2016, a total of 31,339 patients with nonvalvular AF were included in the study (median age, 74 years; 47% females). At inclusion, 8,913 (28%) patients were treated with VKA, 8,611 (27%) with apixaban, 7,377 (23%) with dabigatran, and 6,838 (22%) with rivaroxaban (**Figure 1**). The VKA group included the highest proportion of men (59%), whereas the apixaban group was oldest (median age, 76 years; Q1, Q3 = 68, 84 years). The apixaban and rivaroxaban group had the highest proportion of CHA_2DS_2-VASc score ≥3 (**Table 1**). At baseline, 2,059 (7%) were treated with acetylsalicylic acid; 70% received a 75-mg dose, 12% a 100-mg dose, and 18% a 150-mg dose. During the 1-year follow-up, 8,905 (28%) discontinued their oral anticoagulation treatment.

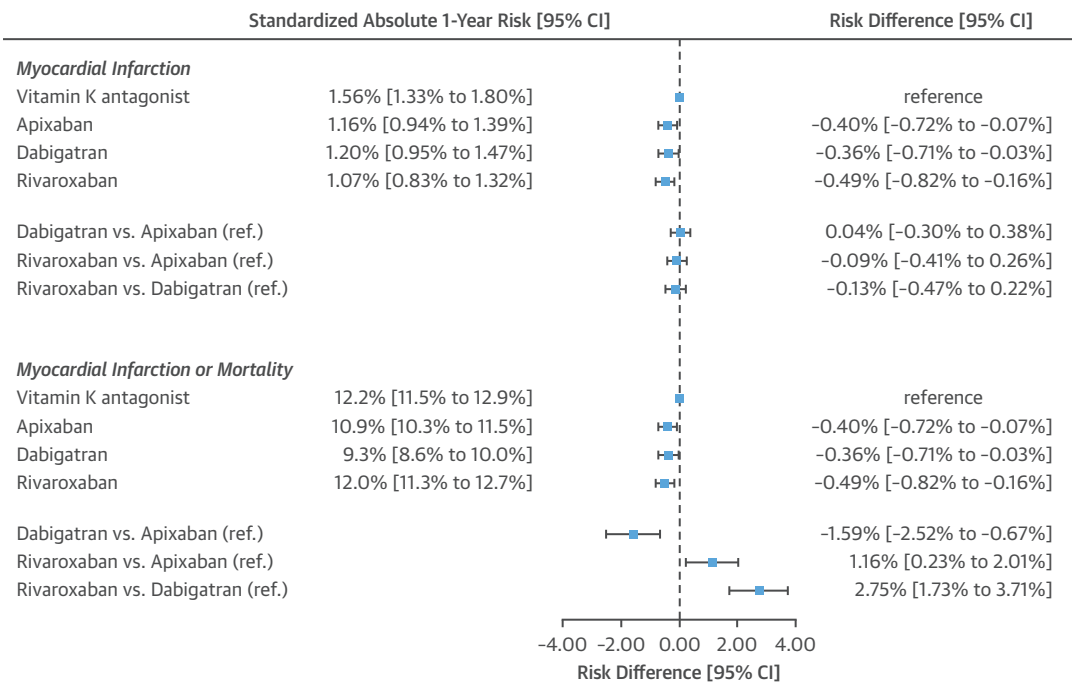
MYOCARDIAL INFARCTION. The crude 1-year risks of MI and the 1-year MI-free survival probabilities are shown in the Online Table 2. **Figure 2** shows the standardized absolute risk of MI and the standardized absolute MI-free survival during the 1-year follow-up. VKA had the highest standardized absolute risk, and rivaroxaban the lowest standardized absolute risk of MI, whereas the standardized absolute MI-free survival was highest for dabigatran and lowest for VKA and rivaroxaban (**Figure 2**). The standardized absolute 1-year risk of MI was highest for VKA (1.56%; 95% CI: 1.33% to 1.80%) and lowest for the DOACs: apixaban,

FIGURE 2 **Standardized Absolute Risk of MI and Standardized Absolute MI-Free Survival Probability Within 1 Year**



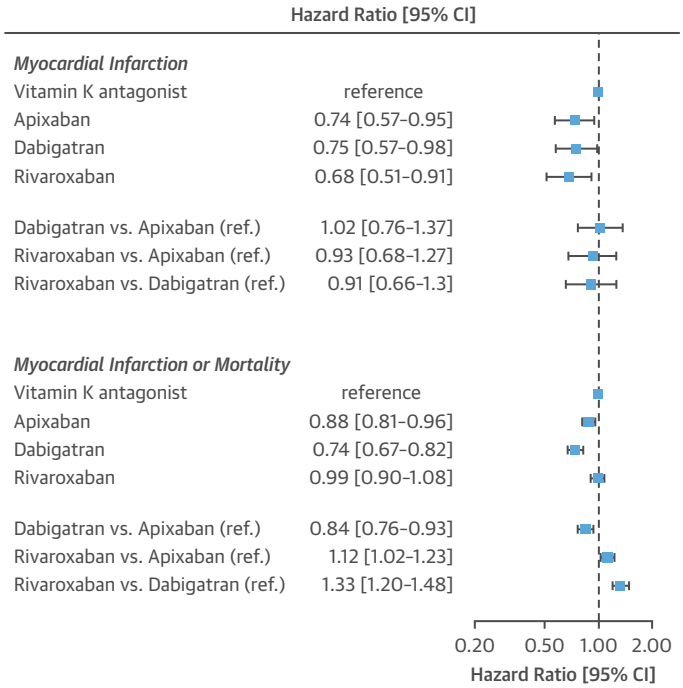
(A) Standardized absolute risk of MI within 1 year. **(B)** Standardized absolute risk of MI-free survival within 1 year. MI = myocardial infarction.

FIGURE 3 **Standardized 1-Year Absolute Risk**



CI = confidence interval.

FIGURE 4 Cox Regression for 1-Year Risk of Myocardial Infarction and the Combined Endpoint of Myocardial Infarction or All-Cause Mortality



CI = confidence interval.

1.16% (95% CI: 0.94% to 1.39%); dabigatran, 1.20% (95% CI: 0.95% to 1.47%), and rivaroxaban, 1.07% (95% CI: 0.83% to 1.32%) (**Figure 3**). The comparison of the DOACs apixaban, dabigatran, and rivaroxaban revealed no significant differences in the standardized absolute risks of MI (**Figure 3**). The highest absolute risk difference was found between VKA and rivaroxaban (−0.49%), and the lowest difference was found between VKA and dabigatran (−0.36%). The crude and adjusted HRs of MI and the combined endpoint of MI or all-cause mortality for the DOAC comparisons and DOACs compared with VKA are shown in the Online Figure 2 and in **Figure 4**, respectively.

SENSITIVITY ANALYSES. The on-treatment analysis showed similar results as our primary analysis (Online Table 3). During the 3 years of follow-up, 654 (2.1%) patients had an MI with 234 (36%) in VKA therapy, 153 (23%) in apixaban therapy, 157 (24%) in dabigatran therapy, and 110 (17%) in rivaroxaban therapy. The HR of the MI risk in the 3-year follow-up was similar to the primary analysis (Online Figure 3). When stratified by dose of DOACs, all doses were associated with a lower standardized absolute risk of 1-year MI compared with VKA, although only significant for 5-mg twice daily apixaban, 20 mg twice daily rivaroxaban, and 150 mg twice daily dabigatran (Online Table 4). In subgroups stratified by low and high risk defined by prior ischemic heart disease and concomitant antiplatelet therapy, the results were similar to the primary analysis (Online Table 5). The standardized 1-year absolute risk for MI varied from 1.81% to 2.52% in the high-risk group, and 0.40% to 0.66% in the low-risk group. Subgroup analyses with or without acetylsalicylic acid therapy also showed similar results as our primary.

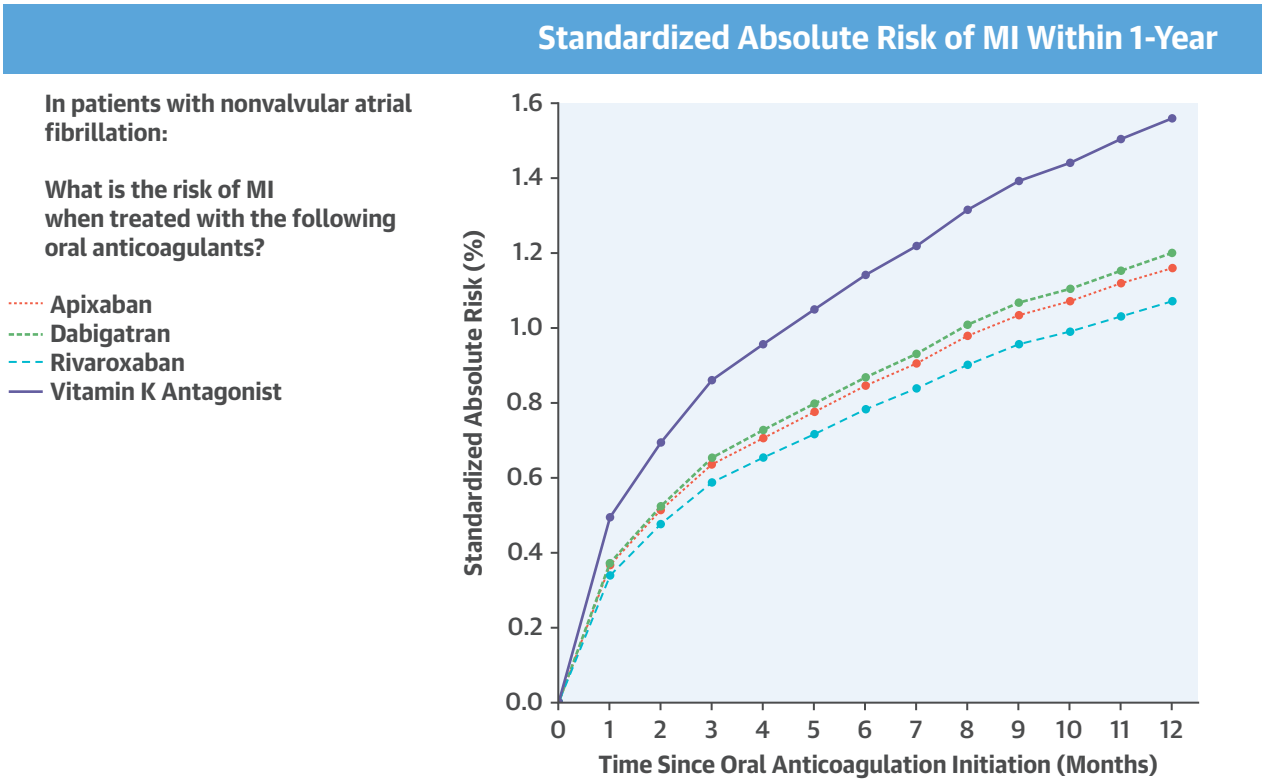
For the combined endpoint of cardiovascular mortality and MI from 2013 to 2015, the unadjusted 1-year cumulative incidence was 8.69% (95% CI: 7.82% to 9.26%) for VKA, 7.54% (95% CI: 6.52% to 8.55%) for apixaban, 4.91% (95% CI: 4.36% to 5.46%) for dabigatran, and 10.6% (95% CI: 9.39% to 11.7%) for rivaroxaban. The absolute standardized 1-year risk of the combined endpoint cardiovascular mortality and MI was 8.61% (95% CI: 7.90% to 9.35%) for VKA, 6.25% (95% CI: 5.43% to 7.11%) for apixaban, 5.75% (95% CI: 5.18% to 6.42%) for dabigatran, and 9.04% (95% CI: 8.04% to 10.08%) for rivaroxaban. The absolute standardized 1-year risk of the combined endpoint cardiovascular mortality and MI was associated with a nonsignificantly higher absolute risk for rivaroxaban compared with VKA (absolute risk difference of 0.44%; $p = 0.512$), and rivaroxaban was associated with a significantly higher risk than apixaban (absolute risk difference of 2.79%; $p < 0.001$) and dabigatran (absolute risk difference of 3.29%; $p < 0.001$).

DISCUSSION

In this nationwide retrospective cohort study, the standardized absolute 1-year risk of MI ranged from 1.1% to 1.2% for the DOACs and 1.6% for VKA for oral-anticoagulation-naive patients with AF (**Central Illustration**). No significant differences were found in the direct comparisons of the DOACs apixaban, dabigatran, and rivaroxaban in the risk of MI. All the DOACs were associated with a significant risk reduction of MI compared with VKA. Furthermore, the results were consistent for patients with and without prior ischemic heart disease and concomitant antiplatelet therapy.

Since the RE-LY trial, MI risk and use of dabigatran have been debated, although clinical trials have not shown a significant increase or reduction in MI with the respective DOACs compared with VKA (8-10). Nevertheless, MI was not a primary endpoint for any of the trials, and the results pertaining to the risk of

CENTRAL ILLUSTRATION **Oral Anticoagulation Therapy and Risk of MI in Patients With Atrial Fibrillation**



Lee, C.J.-Y. et al. J Am Coll Cardiol. 2018;72(1):17–26.

Patients with atrial fibrillation have a higher risk of myocardial infarction (MI), and the optimal prevention of MI with oral anticoagulative therapy is unknown. Our study finds no significant difference in the standardized absolute 1-year risk for MI in the direct comparison of the direct oral anticoagulants. Furthermore, all the direct oral anticoagulants were associated with a significantly lower standardized absolute risk of MI than vitamin K antagonists.

MI associated with DOAC use could reflect differences in comorbidity burden and selection bias. The trials did not include the elderly or individuals with multiple comorbidities, which are those at high risk of MI; furthermore, the overall incidence of MI remains low, leading to challenges related to MI as a primary outcome in scientific settings. Although randomized clinical trials can evaluate the efficacy of the DOACs, our findings support the effectiveness of DOACs and the risk of MI in a real-life cohort setting.

Several meta-analyses have found a significantly increased risk of MI with the use of dabigatran compared with VKA (18-21). However, not all of the studies included in the meta-analyses were limited to AF-specific patients, some of the included study durations were <1 year, and MI as an outcome was only pre-specified in 3 out of 10 trials. In addition, many of the meta-analyses included the same randomized clinical trials. Another meta-analysis did not detect any difference in the risk of MI for DOACs compared with VKA (22). For the factor Xa inhibitors apixaban, edoxaban, and rivaroxaban, no significant difference of MI risk was found in a pooled meta-analysis of 4 double-blinded randomized clinical trials (19). In a systematic review and meta-analysis of observational studies, nonsignificantly lower rates of MI for dabigatran and higher risk for rivaroxaban compared with VKA were reported (23). Notably, a study observed an increased rate of MI associated with VKA compared with DOACs with an adjusted HR of 2.11 (95% CI: 1.08 to 4.12) (24). Their study cohort was similar in terms of age distribution and comorbidity burden compared with our cohort. However, the study only included 1,266 patients (mean age, 72 years) treated with either dabigatran or rivaroxaban and 13,098 patients treated with VKAs leading to a paucity of MI endpoints; only 81 and 10 MIs were identified in patients treated with

dabigatran and rivaroxaban versus VKA, respectively.

VKA treatment has been shown to protect against recurrent MI (25,26). It has been proposed that dabigatran does not increase the risk of MI, but dabigatran might be the less effective than VKA. Although dabigatran has been shown to enhance platelet reactivity via increased thrombin receptor expression (27,28), our results observed a decrease in risk of MI associated with dabigatran compared with VKA. However, our study is an observational study and the results remain nonrandomized, and thus prone to confounding-by-indication (i.e., a perceived benefit or risk may lead to conscious avoidance in use of dabigatran in specific patient subsets). Mortality was also decreased in patients treated with dabigatran compared with VKA, whereas for rivaroxaban and apixaban no differences were observed compared with VKA. Another hypothesis for our lower risk might be that we investigated MI in oral-anticoagulative-naive patients with AF, whereas for shifters (patients who had changed oral anticoagulant therapy) the risk of MI has been shown to be higher (29,30). Furthermore, VKA inhibits the carboxylation Matrix Gla protein, an inhibitor of calcification, and VKA has been associated with an increase in vascular calcification and atherosclerosis (31–33), which could also support our findings of an increased risk of MI in patients in VKA therapy.

Of note, no significant differences in the standardized absolute 1-year risks of MI were observed among apixaban, dabigatran, and rivaroxaban. Similarly, an observational study comparing the benefit and safety of the DOACs for prevention of stroke, systemic embolism, and major bleeding did not report any difference in direct comparison of apixaban, dabigatran, and rivaroxaban (34). Likewise, rivaroxaban was associated with similar risk of stroke, but greater mortality compared with dabigatran (35).

Besides the efficacy of DOACs compared with VKA, the addition of antiplatelet therapy to DOACs also needs further investigation. Recently, the COMPASS study showed that in patients with stable atherosclerotic vascular disease, the use of rivaroxaban with or without addition of acetylsalicylic acid had an insignificantly lower HR of MI than acetylsalicylic acid alone, but a significantly increased HR of major bleedings (36). Previous studies of VKA and acetylsalicylic acid therapy compared with acetylsalicylic acid alone have shown similar results (6,26,37,38). Dual therapy with dabigatran has also shown noninferiority in the risk of the combined endpoint of thromboembolic events, death, or unplanned revascularization in patients with AF who had undergone a percutaneous coronary intervention with the addition of clopidogrel or ticagrelor compared with triple therapy of VKA, clopidogrel, or ticagrelor with acetylsalicylic acid (39). Further studies of DOAC and additional antiplatelet therapy in the risk of MI and bleeding are warranted.

To summarize, the evidence of an association of DOACs and increased MI risk remains ambiguous. Compared with VKA, DOACs are not associated with an increased risk of MI. Presently, there are no results from randomized clinical trials directly comparing the DOACs head-to-head, although current evidence has not shown superiority of 1 DOAC over the other. Present evidence from supporting biological studies remains insufficient, and studies in sizeable cohorts comparing the effects of DOACs and VKAs on platelet function and reactivity continue to be wanted.

STUDY STRENGTHS AND LIMITATIONS. Major strengths of the study are the large sample size used and the use of validated national health care registers. Our study is one of the largest retrospective observational study cohorts investigating the risk of MI in patients with AF, permitting sensitivity analyses in relevant subgroups traditionally excluded from randomized clinical trials. The health care system in Denmark is tax financed and therefore free of charge. Importantly, the Danish registers have been shown to be accurate, and our definition of population, exposure, and outcome are well validated (11).

Unmeasured confounders are always a limitation in observational studies; we did not have access to clinical data, such as body mass index, smoking status, type of AF, and international normalized ratio. Because data of international normalized ratio were unavailable, it was unknown whether patients were at therapeutic level at the time of MI. Furthermore, our results are only valid under the assumption of positivity (that any patient has a positive probability of receiving all values of the treatment variable), consistency (if a patient has a specific treatment, then we observe the counter-factual variable of this patient), and conditional exchangeability (no unmeasured confounders and no informative censoring based on the measured covariates). Drug prescriptions are partially reimbursed, although data on over-the-counter use of acetylsalicylic acid were

unavailable, but in Denmark only 8% of low-dose acetylsalicylic acid was not registered by prescription (40). Additionally, the indication governing the choice of specific oral anticoagulation remains unknown; of note, information pertaining to renal function remained unavailable, and therefore possible selection bias cannot be excluded. As such, we cannot exclude the possibility that confounding-by-indication influenced our results; however, results were robust in our sensitivity analyses.

CONCLUSIONS

In oral-anticoagulative-naive patients with nonvalvular AF initiating oral anticoagulation, no significant differences were found in the direct comparisons of apixaban, dabigatran, and rivaroxaban in the standardized absolute risk of MI. Importantly, the DOACs were all associated with a significant standardized absolute risk reduction of MI compared with VKA.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: In a large nationwide cohort of patients with AF, there were no significant differences in the risk of MI related to treatment with one DOAC compared with another, and the risk of MI was lower with DOACs than with VKA therapy.

TRANSLATIONAL OUTLOOK: Direct comparative studies of the DOACs with and without concurrent antiplatelet therapy are needed to determine optimum antithrombotic therapy for patients with AF who are at elevated risk of MI.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.