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Combining Oral Anticoagulants With Platelet Inhibitors in Patients With Atrial Fibrillation and Coronary Disease

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ABSTRACT

BACKGROUND The optimal treatment strategy when combining antiplatelets with oral anticoagulants in patients with atrial fibrillation (AF) and myocardial infarction (MI) or undergoing percutaneous coronary intervention (PCI) is unknown.

OBJECTIVES The authors investigated the risk of bleeding, ischemic stroke, MI, and all-cause mortality associated with direct oral anticoagulants (DOACs) compared with vitamin K antagonists (VKAs) in combination with aspirin, clopidogrel, or both in patients with AF following MI and/or PCI.

METHODS Danish nationwide registries were used to identify patients with AF who were admitted with a MI and/or underwent PCI, between August 2011 and June 2017, treated with OAC in combination with antiplatelet(s). Patients were followed for 12 months or until an outcome, study end, or death. Standardized absolute risks were estimated on the basis of outcome-specific Cox regression models adjusted for potential confounders. Average treatment effects were obtained as standardized absolute risk differences (ARD) in risks at 3 and 12 months using the g-formula.

RESULTS Overall, 3,222 patients were included in the study population, of which 875 (27%) were treated with VKA+single antiplatelet therapy (SAPT), 595 (18%) were treated with DOAC+SAPT, 1,074 (33%) were treated with VKA+dual antiplatelet therapy (DAPT), and 678 (22%) were treated with DOAC+DAPT. At 3 months, there was a significant difference in the absolute risk of MI associated with DOAC+SAPT compared with VKA+SAPT (3-month ARD −1.53% (95% confidence interval: −3.08% to −0.11%), with no significant differences found regarding bleeding, ischemic stroke, and all-cause mortality. Compared with VKA+DAPT, DOAC+DAPT was associated with a significantly reduced risk of bleeding (3-month ARD −1.96%, 95% confidence interval: −3.46% to −0.88%), with no significant difference in the absolute risk of all-cause mortality, stroke, or MI.

CONCLUSIONS In a real-world population of AF patients with MI and/or after PCI, the authors found that DOAC in combination with DAPT was associated with a significantly decreased risk of bleeding and similar thromboembolic protection compared with VKA in combination with DAPT. (J Am Coll Cardiol 2018;72:1790–800) © 2018 by the American College of Cardiology Foundation.

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Patients with atrial fibrillation (AF) and at moderate-to-high risk of stroke have indication for lifelong anticoagulation therapy with either vitamin K antagonists (VKAs) or direct oral anticoagulants (DOACs), for example, rivaroxaban, dabigatran, apixaban, or edoxaban (1,2). AF patients experiencing a myocardial infarction (MI) and/or undergoing a percutaneous coronary intervention (PCI) are concomitantly treated with an antiplatelet, such as aspirin, clopidogrel, or both, because of an increased risk of coronary vascular events (1,2). Dual or triple antithrombotic therapy may be effective in reducing the risk of thromboembolic events, but the risk of bleeding inherent to treatment has been shown to increase with combinations of antiplatelets and oral anticoagulants (OACs) (3,4).

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An increase in the use of DOACs in combination with antiplatelets, has been shown (5). However, knowledge on the comparative safety and effectiveness of DOACs and VKAs has for many years mainly been derived from either post hoc analyses from pivotal randomized clinical trials assessing individual DOACs compared with warfarin (6–8) or from trials examining DOACs in combination with antiplatelets in patients with MI/PCI, not limited to patients with AF (9–13). Recently, 2 randomized clinical trials have investigated the safety and efficacy of rivaroxaban and dabigatran versus VKAs in patients with AF undergoing PCI (14,15). The REDUAL-PCI (Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting) trial, compared dabigatran (110 mg or 150 mg) in combination with either clopidogrel or ticagrelor with VKA in combination with triple therapy, and found that patients receiving dabigatran, in combination with a $P2Y_{12}$ inhibitor had significantly less major bleeding than those patients receiving triple therapy with VKAs (15). In the PIONEER AF-PCI study (A Study Exploring Two Strategies of Rivaroxaban [JNJ39039039; BAY-59-7939] and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention), where low-dose rivaroxaban (2.5 mg b.i.d.) in combination with dual antiplatelet therapy (DAPT), found that patients receiving rivaroxaban had significantly less bleeding than those receiving triple therapy with standard dosage VKAs. The study was limited by using dosages that are not approved for stroke prophylaxis in AF, and the risk of bleeding when using recommended dosages remains therefore unknown (14). The aim of our study was to investigate the comparative risk of bleeding, ischemic stroke, MI, and all-cause mortality during treatment with DOACs or VKAs, and concomitant use of aspirin, clopidogrel, or both, in patients with AF following MI and/or PCI.

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
ARD = absolute risk difference
b.i.d. = twice daily
CI = confidence interval
DAPT = dual antiplatelet therapy
DOAC = direct oral anticoagulants
HR = hazard ratio
INR = international normalized ratio
MI = myocardial infarction
OAC = oral anticoagulant
o.d. = once daily
PCI = percutaneous coronary intervention
PPI = proton pump inhibitor
SAPT = single antiplatelet therapy
VKA = vitamin K antagonist

METHODS

DATASETS. Danish nationwide administrative registries were used (16–18). A personal identification number is given to every Danish resident at either birth or immigration. The number is unique to the individual, which makes it possible to link different administrative registries on an individual level (16). The Danish National Patient Registry holds information on hospital contacts from 1978 and onward, including both in-patient and outpatient data (17). All diagnoses are registered according to the International Classification of Diseases and are classified as a primary diagnosis, and if appropriate, also as secondary diagnoses (17). From 1995, information on all prescribed dispensed drugs has been available through the Danish National Prescription Registry (18). Information on date of birth, date of death, and sex is available through the Danish Civil Registration system.

STUDY POPULATION. Patients hospitalized with MI, PCI, or both in the period August 22, 2011 to June 30, 2017 were identified. Patients were eligible for inclusion if they had AF and were in treatment with an OAC (VKA [phenprocoumon and warfarin], rivaroxaban, dabigatran, or apixaban) and an antiplatelet

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(aspirin and/or clopidogrel) 7 days after a hospital discharge with an MI, PCI, or both. Patients below 30 years of age or above 100 years were excluded, as were patients with valvular AF. The inclusion date was defined as 7 days after discharge with an MI, PCI, or both, thus providing a quarantine period of 7 days. A quarantine period was introduced to allow patients to collect a prescription from a pharmacy and also to minimize the risk of registering complications that were related to the hospitalization. Patients who died or experienced 1 of the pre-defined outcomes (bleeding, ischemic stroke, or MI) during the quarantine period were also excluded.

EXPOSURE TO VKAs, DOACs, ASPIRIN, AND CLOPIDOGREL. Treatment regimens were classified into 4 categories based on filled prescriptions from the pharmacies. These included: OAC+single antiplatelet therapy (SAPT): VKA+SAPT (VKA+aspirin or clopidogrel), DOAC+SAPT (DOAC+aspirin or clopidogrel), and OAC+ DAPT: VKA+DAPT (VKA+aspirin+clopidogrel) and DOAC+DAPT (DOAC+aspirin+clopidogrel). Exposure to any of the treatment regimens was calculated using an algorithm based on filled prescriptions, whereby it was possible to estimate exposure at any given point in time using date of filled prescriptions, number of tablets, and strength (19). Standard dosages of DOACs and antiplatelets were defined as rivaroxaban 20 mg once daily (o.d.), dabigatran 150 mg b.i.d., apixaban 5 mg b.i.d., aspirin 75 mg o.d., clopidogrel 75 mg o.d. Reduced dosages of DOACs were defined as rivaroxaban 15 mg o.d., dabigatran 110 mg b.i.d., apixaban 2.5 mg b.i.d. Allocation of treatment regimens was defined as drug exposure at day 7 after discharge from a MI, PCI, or both, and we refer to this date as the date of inclusion (i.e., baseline).

COMORBIDITIES AND CONCOMITANT MEDICATION. From the Danish National Patient Registry, comorbidities registered within 10 years before date of inclusion were identified using the International Classification of Diseases-10 diagnosis codes (Online Table 1). From the Danish National Prescription Registry, concomitant medication was identified from claimed prescriptions up to 180 days before the inclusion date, using ATC codes (Online Table 1). The CHA_2DS_2-VASc score was used to assess the risk of stroke, and a modified HAS-BLED score was used to assess the risk of bleeding, Labile international normalized ratio (INR) was not available in our data and use of antiplatelets was the exposure variable in our study, hence, these were not included in the calculation of the modified HAS-BLED score.

OUTCOMES. The outcomes investigated were ischemic stroke (positive predictive value 97% to 100% [20]), MI (positive predictive value 91% to 99% [21]), all-cause mortality, and bleeding. Bleeding was defined as a bleed leading to a hospitalization, with gastrointestinal bleeding, intracranial bleeding, urinary tract bleeding, retroperitoneal bleeding, intraspinal bleeding, or pericardial bleeding. This definition has been shown in similar databases to have a positive predictive value of 89% to 99% (22).

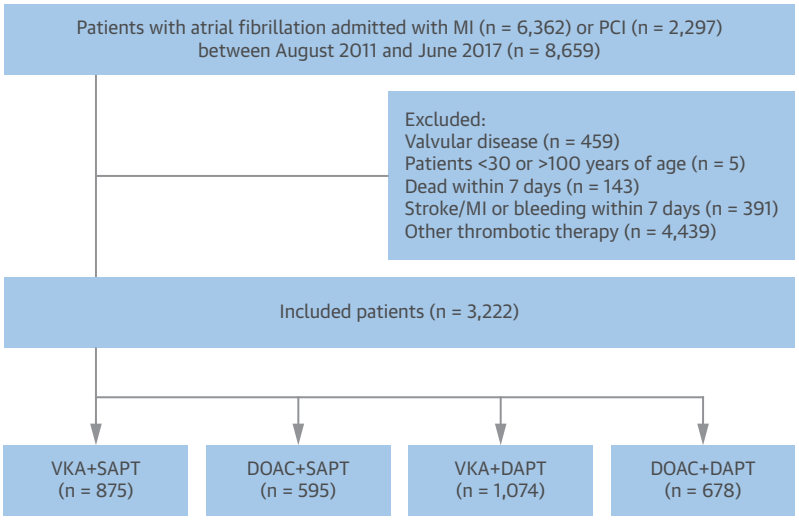
STATISTICAL ANALYSIS. Baseline characteristics are presented on the basis of each of the antithrombotic treatment regimens at baseline. Differences between the groups were examined using the Kruskal-Wallis or Student's *t*-test for continuous variables, where appropriate. Differences in categorical variables were examined using the chi-square test.

To investigate the comparative risk of bleeding, ischemic stroke, MI, or all-cause mortality between patients treated with VKA versus DOACs and concomitantly treated with antiplatelet(s), outcome-specific Cox regression models were used. For comparison, VKA+SAPT was compared with DOAC+SAPT, and VKA+DAPT was compared with DOAC+DAPT. All analyses were performed on an intention-to-treat basis. Groups containing VKA were used as a reference. Death was considered a competing risk for the outcomes of MI, stroke, and bleeding (23). All models were adjusted for inclusion event (MI and/or PCI), age, sex, calendar year. Variables in the modified HAS-BLED for the bleeding outcomes were used for the models for bleeding because the score has been found valid to predict the risk of bleeding in atrial fibrillation patients (24,25). The models for ischemic stroke, MI, and all-cause mortality were adjusted for risk factors incorporated in the CHA_2DS_2-VASc score, because stroke and MI share many of the same risk factors (26,27). In addition, the CHA_2DS_2-VASc score has been found to also correlate well with mortality (26,27).

Absolute risk of each of the outcomes was calculated on the basis of multiple outcome-specific Cox regression models, whereby average treatment effects between the groups could be obtained as standardized differences in absolute risks at 3 and 12 months. This was done using the g-formula, and 95% confidence intervals (CIs) based on 1,000 bootstrap samples were obtained (28). Patients were followed for 12 months or until an event, death, immigration, or 30th June 2017.

All models were tested for significant interactions with age, sex, DOAC dosage, and proton pump

FIGURE 1 Flow Chart



Flow chart on the selection process. Patients with atrial fibrillation included between 2011 and 2016 with myocardial infarction, percutaneous coronary intervention or both. DAPT = dual antiplatelet therapy; DOAC = direct oral anticoagulants; MI = myocardial infarction; PCI = percutaneous coronary intervention; SAPT = single antiplatelet therapy; VKA = vitamin K antagonist.

inhibitors (PPIs). No significant interactions were found. Furthermore, the models were tested for deviations from linearity for continuous variables and for violations of the proportionality of the Cox proportional hazards. A 2-sided significance level of 0.05 was used. Handling of data and statistical analysis were performed using SAS (Statistical Analytical System, version 9.4, SAS Institute, Gary, North Carolina) and R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) software.

SENSITIVITY ANALYSES. Sensitivity analyses were performed where the drug exposure was defined as a time-dependent variable, meaning that patients only were deemed at risk in the different exposure groups while on the antithrombotic regimen (3). In order to investigate this, data on individuals were split at every change in treatment and then used time dependently in Cox regression models. Several supplementary analyses were performed: 1) risk of MI in patients treated with dabigatran+antiplatelet(s) compared with VKA+antiplatelet(s); 2) risk of any of the outcomes associated with DOAC dosages (reduced/standard); 3) risk of any of the outcomes in patients >79 years of age with and without chronic kidney disease treated with reduced dosage DOAC compared with similar VKA population; and 4) a comparison with VKA+SAPT versus VKA+DAPT, and DOAC+SAPT versus DOAC+DAPT.

RESULTS

BASELINE CHARACTERISTICS. A total of 3,222 patients were included into the study (Figure 1). Baseline characteristics according to the different treatment regimens are shown in Table 1. Overall, patients had a median age of 76 (interquartile range: 69 to 82) years, and 2,201 (68.3%) were men. Mean CHA_2DS_2-VASc score was 4.15 ± 1.63, and mean modified HAS-BLED score was 2.13 ± 0.94. The lowest mean modified HAS-BLED score was found in the DOAC+DAPT group (1.97 ± 0.91), which was also the group with the lowest mean CHA_2DS_2-VASc score (3.88 ± 1.67). A total of 1,514 (47.0%) patients were treated with PPIs, and the percentage of patients treated with PPIs was higher in patients treated with an OAC+DAPT (VKA+DAPT [49.5%], DOAC+DAPT [48.8%]), compared with an OAC+SAPT (VKA+SAPT [43.1%], DOAC+SAPT [46.1%]).

BLEEDING. A total of 210 bleeding events (6.5%) were registered during 12 months of follow-up, and Online Table 2 summarizes the number of bleeding events according to treatment groups and according to sites of bleeding. The 3-months absolute risk of bleeding was highest in the VKA+DAPT group (3.93%), followed by VKA+SAPT (3.16%), DOAC+SAPT (3.12%), and DOAC+DAPT (1.98%). Compared with VKA+DAPT, DOAC+DAPT was

TABLE 1 Baseline Characteristics

	Total (N = 3,222)	VKA+ SAPT (n = 875)	DOAC+SAPT (n = 595)	VKA+DAPT (n = 1,074)	DOAC+DAPT (n = 678)
DOAC					
Rivaroxaban	–	–	181 (30.4)	–	211 (31.1)
Dabigatran	–	–	190 (31.9)	–	209 (30.8)
Apixaban	–	–	224 (37.6)	–	258 (38.1)
Dosages					
Reduced dosage	–	–	370 (62.2)	–	460 (67.8)
Patient characteristics					
Men	2,201 (68.3)	571 (65.3)	364 (61.2)	786 (73.2)	480 (70.8)
Age, yrs	76 (69-82)	77 (70-83)	77 (70-84)	75 (69-81)	73 (67-80)
Inclusion event					
MI as inclusion event	2,092 (64.9)	637 (72.8)	448 (75.3)	589 (54.8)	418 (61.7)
PCI within 1 day	626 (19.4)	92 (10.5)	71 (11.9)	258 (24.0)	205 (30.2)
PCI within 2-7 days	192 (6.0)	42 (4.8)	13 (2.2)	89 (8.3)	48 (7.1)
PCI as inclusion event	1,130 (35.1)	238 (27.2)	147 (24.7)	485 (45.2)	260 (38.3)
With stent	999 (31.0)	192 (21.9)	121 (20.3)	449 (41.8)	237 (34.9)
CHA_2DS_2VASC					
Intermediate (n = 2)	146 (4.5)	30 (3.4)	19 (3.2)	51 (4.7)	46 (6.8)
High (n = >2)	3,076 (95.5)	845 (96.6)	576 (96.8)	1023 (95.3)	632 (93.2)
Mean $CHADS_2VASC$	4.15 (1.63)	4.39 (1.60)	4.38 (1.66)	3.99 (1.57)	3.88 (1.67)
Modified HAS-BLED					
Low	92 (2.9)	19 (2.2)	16 (2.7)	34 (3.2)	23 (3.4)
Intermediate	2,137 (66.3)	553 (63.2)	399 (67.1)	697 (64.9)	488 (72.0)
High	993 (30.8)	303 (34.6)	180 (30.3)	343 (31.9)	167 (24.6)
Mean modified HAS-BLED	2.13 (0.94)	2.22 (0.91)	2.16 (0.96)	2.14 (0.95)	1.97 (0.91)
Comorbidity					
Previous bleeding	702 (21.8)	226 (25.8)	130 (21.8)	236 (22.0)	110 (16.2)
Stroke	553 (17.2)	159 (18.2)	121 (20.3)	154 (14.3)	119 (17.6)
Heart failure	1,288 (40.0)	395 (45.1)	219 (36.8)	442 (41.2)	232 (34.2)
Chronic kidney disease	319 (9.9)	102 (11.7)	43 (7.2)	131 (12.2)	43 (6.3)
Liver disease	47 (1.5)	14 (1.6)	13 (2.2)	12 (1.1)	8 (1.2)
Hypertension	2408 (74.7)	655 (74.9)	425 (71.4)	835 (77.7)	493 (72.7)
Diabetes	732 (22.7)	202 (23.1)	137 (23.0)	245 (22.8)	148 (21.8)
Cancer	503 (15.6)	148 (16.9)	102 (17.1)	172 (16.0)	81 (11.9)
COPD	490 (15.2)	152 (17.4)	83 (13.9)	164 (15.3)	91 (13.4)
Concomitant medication					
Beta-blockers	2,685 (83.3)	726 (83.0)	486 (81.7)	906 (84.4)	567 (83.6)
Calcium channel blockers	1,092 (33.9)	320 (36.6)	182 (30.6)	381 (35.5)	209 (30.8)
RAS	2,162 (67.1)	578 (66.1)	377 (63.4)	762 (70.9)	445 (65.6)
Loop diuretics	1,611 (50.0)	512 (58.5)	285 (47.9)	527 (49.1)	287 (42.3)
PPI	1,514 (47.0)	377 (43.1)	274 (46.1)	532 (49.5)	331 (48.8)
Digoxin	873 (27.1)	267 (30.5)	159 (26.7)	303 (28.2)	144 (21.2)
Statins	2,624 (81.4)	679 (77.6)	437 (73.4)	926 (86.2)	582 (85.8)
NSAID	278 (8.6)	69 (7.9)	61 (10.3)	72 (6.7)	76 (11.2)

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

COPD = chronic obstructive pulmonary disease; DAPT = dual antiplatelet therapy (aspirin+clopidogrel); DOAC = direct oral anticoagulant; MI = Myocardial infarction; NSAID = non-steroidal anti-inflammatory drug; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; RAS = renin angiotensin system blocker; SAPT = single antiplatelet therapy (aspirin or clopidogrel); VKA = vitamin K antagonist.

associated with a significantly decreased risk of bleeding (absolute risk difference [ARD] −1.94%, 95% CI: −3.46% to −0.88%) (Table 2, Figure 2). There was no significant difference in the risk of bleeding between patients treated with VKA+SAPT and DOAC+SAPT (ARD −0.04%, 95% CI: −1.17% to 1.53%) (Table 2, Figure 3). Similar associations were found for the 12-months absolute risks.

ISCHEMIC STROKE. Overall, 83 ischemic stroke events (2.6%) were registered during 12-months follow-up. No significant difference in the 3-month risk of ischemic stroke was found between patients treated with VKA+DAPT and DOAC+DAPT (ARD: 0.38%, 95% CI: −0.22% to 0.97%) (Table 2, Figure 2). Likewise, no significant difference was found between VKA+SAPT and DOAC+SAPT (ARD: −0.51%, 95% CI: −1.50% to 0.33%) (Table 2, Figure 3). Similar associations were found for the 12-month absolute risks.

MYOCARDIAL INFARCTION. A total of 193 MI events (6.0%) were observed during 12-months follow-up. No significant difference in the 3-months risk of MI was found between patients treated with VKA+DAPT and DOAC+DAPT (ARD: −0.23% [−1.38% to 1.31%]) (Table 2, Figure 2). A significant difference was found between VKA+SAPT and DOAC+SAPT (ARD: −1.53% [−3.08% to −0.11%]). Similar associations were found for the 12-months absolute risks. No significant difference in the risk of MI was found in patients treated with dabigatran+antiplatelet(s) compared with VKA+antiplatelet(s) (hazard ratio [HR]: 0.85; 95% CI: 0.57 to 1.28).

ALL-CAUSE MORTALITY. A total of 365 patients (11.3%) died during 12-months follow-up. Compared with VKA+DAPT, there was no significant decrease in the 3-months absolute risk of all-cause mortality in patients treated with DOAC+DAPT (ARD: −0.70%, CI: −1.73% to 0.53%) (Table 2, Figure 2, Online Figure 1). However, no significant difference was found between VKA+SAPT and DOAC+SAPT (ARD: 0.47%, CI: −0.74% to 2.08%) (Table 2, Figure 3). Similar associations were found for the 12-months absolute risks.

SENSITIVITY AND SUBGROUP ANALYSES. The analyses using the exposure to any of the antithrombotic regimens as a time dependent variable showed similar results as the main results with regard to all-cause mortality, bleeding, ischemic stroke, and MI (Table 3). Furthermore, baseline characteristics (Online Table 3) when stratifying on the basis of DOAC dosage (reduced or standard dosage) showed that patients initiated on reduced dosage DOAC were older, less often had PCI, had more heart failure, and had chronic kidney disease, which resulted in these patients having a higher HAS-BLED score. In all subgroup analyses regarding dosages, results were comparable to the main analyses (Online Tables 4 and 5). In addition, we compared VKA+SAPT with VKA+DAPT, and likewise for the DOAC groups, where it was found

TABLE 2 Standardized Absolute Risks of Outcomes at 3 and 12 Months

	3 Months			12 Months		
	Events, n	Standardized Absolute Risk	Absolute Risk Difference	Events, n	Standardized Absolute Risk	Absolute Risk Difference
Bleeding, %*						
VKA+DAPT	45	3.93 (2.93 to 5.33)	Ref.	98	9.39 (7.75 to 11.31)	Ref.
DOAC+DAPT	10	1.98 (1.30 to 2.84)	**−1.94 (−3.46 to −0.88)**	27	4.89 (3.34 to 6.59)	**−4.50 (−7.16 to −2.24)**
VKA+SAPT	25	3.16 (2.14 to 4.09)	Ref.	54	6.16 (4.42 to 7.77)	Ref.
DOAC+SAPT	20	3.12 (2.04 to 4.65)	−0.04 (−1.17 to 1.53)	31	6.05 (4.35 to 8.52)	−0.11 (−2.33 to 2.56)
Stroke, %†						
VKA+DAPT	9	0.79 (0.39 to 1.26)	Ref.	24	2.38 (1.37 to 3.27)	Ref.
DOAC+DAPT	7	1.17 (0.60 to 1.80)	0.38 (−0.22 to 0.97)	21	3.51 (2.06 to 4.93)	1.13 (−0.57 to 3.04)
VKA+SAPT	13	1.44 (0.82 to 2.29)	Ref.	28	3.14 (2.21 to 4.19)	Ref.
DOAC+SAPT	5	0.94 (0.33 to 1.66)	−0.51 (−1.50 to 0.33)	10	2.03 (0.78 to 3.46)	−1.11 (−2.88 to 0.65)
MI, %†						
VKA+DAPT	31	2.96 (2.15 to 3.90)	Ref.	62	5.75 (4.49 to 7.32)	Ref.
DOAC+DAPT	18	2.73 (1.76 to 4.11)	−0.23 (−1.38 to 1.31)	31	5.35 (3.63 to 7.56)	−0.40 (−2.63 to 2.48)
VKA+SAPT	37	4.19 (2.91 to 5.47)	Ref.	72	8.35 (6.32 to 10.23)	Ref.
DOAC+SAPT	15	2.66 (1.60 to 3.66)	**−1.53 (−3.08 to −0.11)**	28	5.36 (3.35 to 6.92)	**−2.99 (−5.90 to −0.19)**
All-cause mortality, %†						
VKA+DAPT	41	4.14 (3.20 to 5.01)	Ref.	108	10.48 (8.64 to 12.38)	Ref.
DOAC+DAPT	26	3.44 (2.50 to 4.67)	−0.70 (−1.73 to 0.53)	52	8.79 (6.92 to 11.00)	−1.69 (−4.25 to 1.30)
VKA+SAPT	41	4.82 (3.65 to 6.04)	Ref.	125	14.56 (12.37 to 17.06)	Ref.
DOAC+SAPT	31	5.29 (3.94 to 6.76)	0.47 (−0.74 to 2.08)	80	15.82 (13.03 to 19.10)	1.26 (−1.95 to 5.60)

Statistical significance is reached, when the 95% confidence interval for the absolute risk difference does not include 0. **Bold** indicates that the absolute risk difference is significant. *Adjusted for sex, age, calendar year, inclusion event, heart failure, hypertension, diabetes, prior stroke, vascular disease, prior bleeding, liver disease, chronic kidney disease, alcohol abuse, and non-steroidal anti-inflammatory drugs. †Adjusted for sex, age, calendar year, inclusion event, heart failure, hypertension, diabetes, prior stroke, and vascular disease.

CI = confidence interval; other abbreviations as in Table 1.

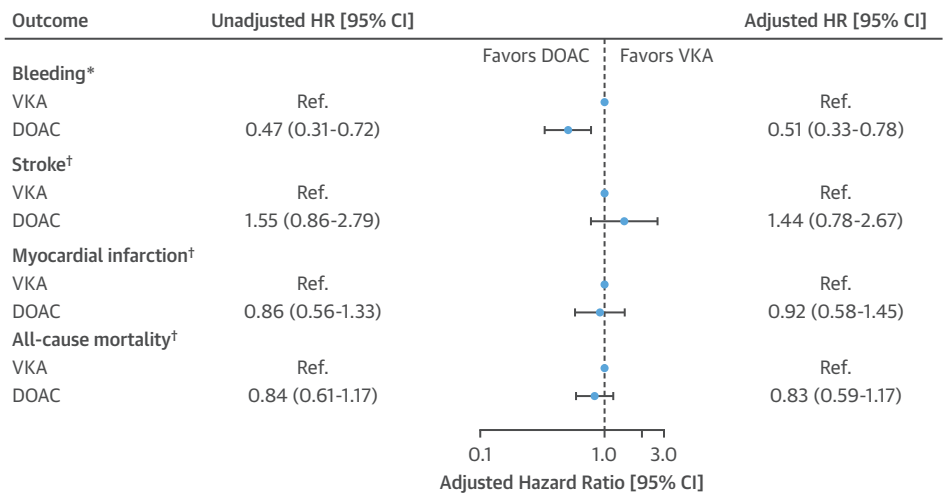
that VKA+DAPT was associated with a 2-fold increased risk of bleeding compared with VKA+SAPT (Online Table 6).

DISCUSSION

The main results of this study were: 1) compared with VKA+DAPT, DOAC+DAPT was associated with a significantly decreased risk of bleeding; 2) no significant differences in the risk of ischemic stroke, MI, or all-cause mortality was found between VKA+DAPT and DOAC+DAPT; and 3) no significant differences in the risk of bleeding, ischemic stroke, or all-cause mortality were found between VKA+SAPT versus DOAC+SAPT, but a significantly decreased risk of MI was found to be associated with DOAC+SAPT (**Central Illustration**).

The comparative safety and efficacy of DOACs for stroke prophylaxis in patients with AF have been established through randomized controlled trials. Post hoc analyses of the trials have shown that the use of concomitant antiplatelet therapy did not influence the comparative risk of stroke or bleeding between DOACs and VKA (6-8). In addition, a recent meta-analysis based on these randomized trials suggests that the use of concomitant aspirin significantly lowered the risk of bleeding and stroke in patients treated with a DOAC compared with VKA (29). The PIONEER AF-PCI study found that rivaroxaban in very low dose (2.5 mg b.i.d.) in combination with DAPT was associated with a significantly lower risk of bleeding compared with VKA+DAPT (HR: 0.63; 95% CI: 0.50 to 0.80) and an insignificantly higher risk of stroke (HR: 1.44; 95% CI: 0.40 to 5.09) (14). Results from this real-world study both complement the post hoc analyses and the recent PIONEER AF-PCI trial, because we found that DOAC+DAPT was associated with a significantly decreased risk of bleeding when compared with VKA+DAPT. Noteworthy, it was observed that the risk of stroke was insignificantly higher in patients treated with DOAC+DAPT compared with VKA+DAPT. We found that two-thirds of patients treated with a DOAC were initiated on a reduced dosage. Previous consensus from the European Society of Cardiology (2014) has been that when DOAC is combined with antiplatelet(s), the lower dose tested for stroke prophylaxis should be used; however, this statement was later updated to the European Society of Cardiology recommending the use of the lowest DOAC dosage approved for stroke prophylaxis (1,2). It has been questioned whether the reduced dosage of DOAC is as effective

FIGURE 2 Outcome-Specific HRs for Oral Anticoagulation Therapy in Combination With Dual Antiplatelet Therapy



Outcome-specific hazard ratios in patients treated with DOAC or VKA in combination with aspirin and clopidogrel. *Adjusted for sex, age, calendar year, inclusion event, and factors incorporated the CHA_2DS_2-VASc score. †Adjusted for sex, age, calendar year, inclusion event, and factors incorporated in the HAS-BLED score. CI = confidence interval; HR = hazard ratio; other abbreviations as in Figure 1.

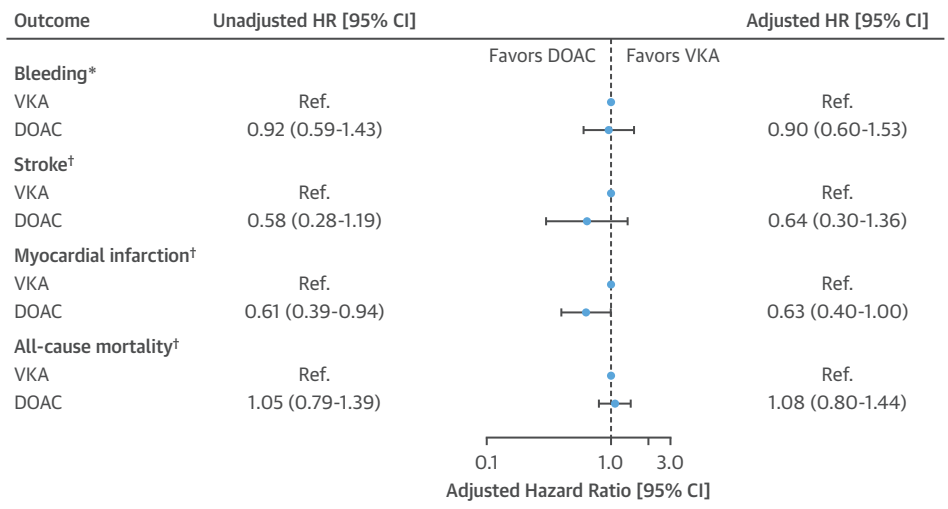
in preventing stroke, even in combination with antiplatelets (1,2). Our sensitivity analyses showed comparable results regarding the associated risk of bleeding, stroke, MI, and all-cause mortality when stratifying patients according to reduced/standard dose.

The absolute risk of MI was insignificantly lower in the DOAC+DAPT and was significantly lower in the DOAC+SAPT group compared with the respective VKA groups. Results from the RE-LY (Randomized Evaluation of Long Term Anticoagulant Therapy) trial gave rise to a potential association between dabigatran and the risk of MI, because a small difference in the number of MIs was observed between the dabigatran and VKA groups. In addition, a meta-analysis found a significantly increased risk of MI with dabigatran compared with warfarin (HR: 1.33; 95% CI: 1.03 to 1.71) (30). However, recent observational studies and meta-analyses have shown conflicting results (31,32). When performing a sensitivity analyses only including patients treated with dabigatran or VKA in combination with clopidogrel and/or aspirin, there were no suggestion toward dabigatran increasing the risk of MI (HR: 0.85; 95% CI: 0.57 to 1.28).

Despite our study having a small study population (N = 3,222), the results complement the recent trials well, and provides an insight into the risk of bleeding, MI, stroke, and all-cause mortality in real-world patients with good generalizability. Especially all-cause mortality is a good measure for the health of a study population, and all-cause mortality was rather high in our study, ranging from 8% to 16%, whereas this number was in the range of 5% to 6% in the PIONEER AF-PCI and REDUAL-PCI trials. Absolute risk regarding stroke, MI, and bleeding in this study were comparable to estimates obtained in the PIONEER AF-PCI, REDUAL-PCI, and WOEST (What Is the Optimal Antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) trials (14,15,33).

The optimal treatment in AF patients following MI, PCI, or both has been discussed for many years because the risk of thromboembolic events might be reduced with the combination of antiplatelets and OACs at the expense of an increased bleeding risk (1,2). The recent (2017) European Society of Cardiology guideline recommends the use of triple therapy in patients with AF and MI, PCI, or both for the shortest period of time. However, we found that only 54% of our study population was initiated on an OAC+DAPT (1,2). Similarly, other studies have reported an underuse of triple therapy in patients with AF and MI, PCI, or both, and these studies have shown that the choice of treatment is not necessarily influenced by the patients' risk of stroke or bleeding (3,5,34-36). This strongly suggests that the physicians' choice of treatment regimen is

FIGURE 3 Outcome-Specific HRs for Oral Anticoagulation Therapy in Combination With Single Antiplatelet Therapy



Outcome-specific hazard ratios in patients treated with DOAC or VKA in combination with aspirin and clopidogrel. *Adjusted for sex, age, calendar year, inclusion event, and factors incorporated the CHA_2DS_2-VASc score. †Adjusted for sex, age, calendar year, inclusion event, and factors incorporated in the HAS-BLED score. Abbreviations as in Figures 1 and 2.

complex and that it is based on multiple factors that need to be explored. We found that patients treated with VKA+DAPT had the highest absolute risk of bleeding with the risk decreasing when VKA was combined with SAPT. Interestingly, the DOAC+DAPT group had the lowest absolute risk of bleeding, which is likely explained by this group having the lowest mean modified HAS-BLED score and possibly confounding by indication (i.e., because physicians may be more prone to prescribe the DOACs to less sick patients). The WOEST trial questioned the risk benefit of triple therapy, because it was found that using SAPT with OAC was associated with a significantly decreased risk of bleeding (HR: 0.36; 95% CI: 0.26 to 0.50) when compared with triple therapy, with no significant differences in the risk of thromboembolic events (33). In addition, the recent REDUAL-PCI study found that patients treated with dabigatran (110 or 150 mg b.i.d.) in combination with a single $P2Y_{12}$ inhibitor had significantly less bleeding compared with triple therapy with VKA, and this therapy was noninferior with regard to thromboembolic events. Comparable to the WOEST and REDUAL-PCI trials, our study found VKA+SAPT to be associated with a significantly reduced risk of bleeding compared with VKA+DAPT. It was noteworthy that the absolute risks of MI, stroke, and all-cause mortality were higher for patients treated with VKA+SAPT compared with VKA+DAPT in our study. This may be explained by differences in age and comorbidities between the groups, and thus, after adjustments in the models, the results did not reach statistical significance.

TABLE 3 Sensitivity Analyses, Time-Dependent Analysis Based on Multiple-Adjusted Cox Regression Models

	OAC+DAPT	OAC + SAPT
	Time Dependent	Time Dependent
Bleeding*		
VKA	Ref.	Ref.
DOAC	0.39 (0.20–0.76)	0.93 (0.59–1.47)
Stroke†		
VKA	Ref.	Ref.
DOAC	1.19 (0.38–3.64)	1.09 (0.58–2.06)
MI†		
VKA	Ref.	Ref.
DOAC	0.85 (0.49–1.50)	0.75 (0.48–1.16)
All-cause mortality†		
VKA	Ref.	Ref.
DOAC	1.19 (0.75–1.88)	1.35 (0.96–1.93)

Values are hazard ratio (95% CI). *Adjusted for sex, age, calendar year, inclusion event, heart failure, hypertension, diabetes, prior stroke, vascular disease, prior bleeding, liver disease, chronic kidney disease, alcohol abuse, and non-steroidal anti-inflammatory drugs. †Adjusted for sex, age, calendar year, inclusion event, heart failure, hypertension, diabetes, prior stroke, and vascular disease.

HR = hazard ratio; OAC = oral anticoagulant; other abbreviations as in Table 1.

STUDY STRENGTHS AND LIMITATIONS. Several strengths regarding our study should be mentioned.

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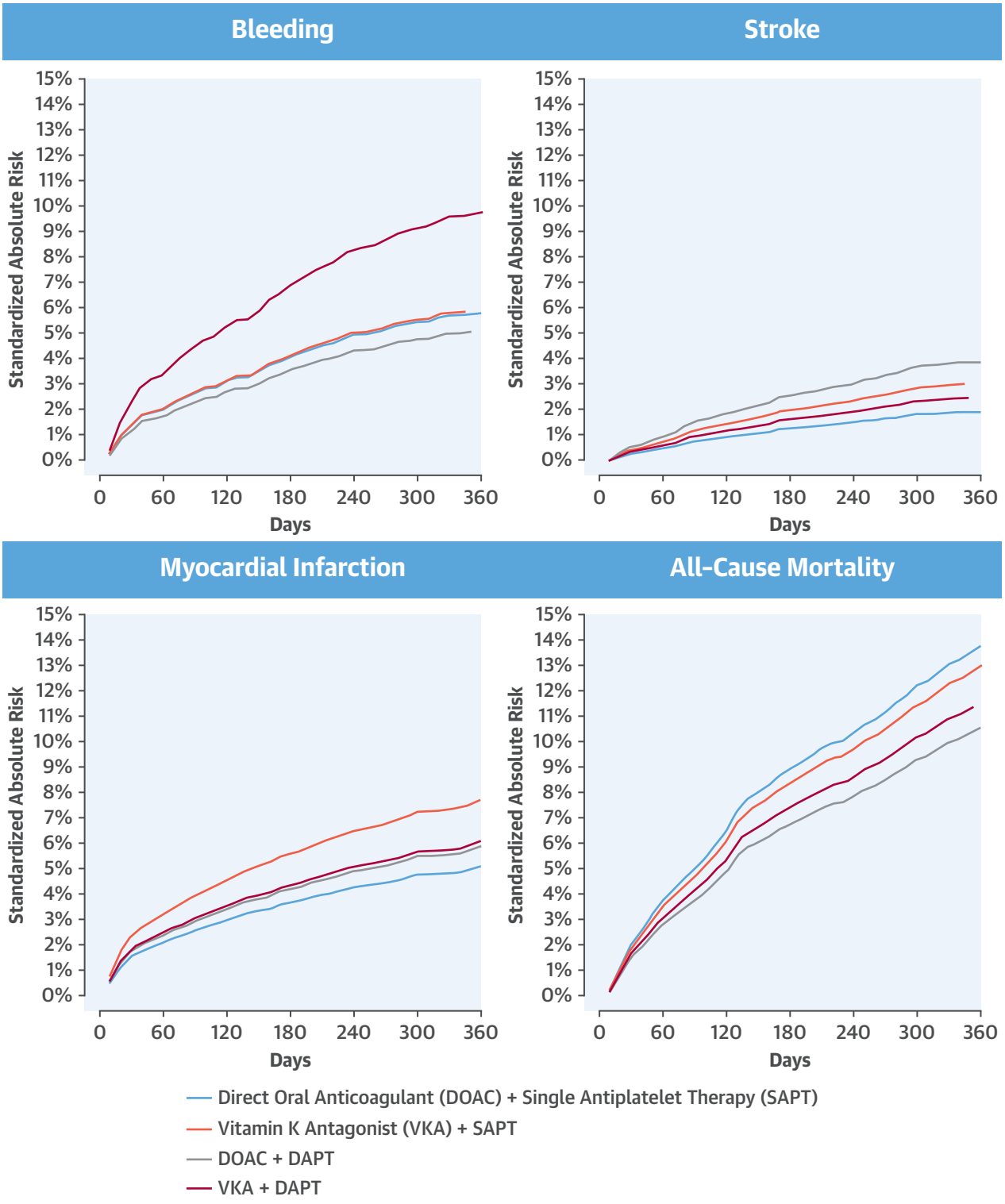
CENTRAL ILLUSTRATION **Anticoagulants and Antiplatelets in AF: Standardized Absolute Risks**



Sindet-Pedersen, C. et al. J Am Coll Cardiol. 2018;72(15):1790–800.

Standardized absolute risk of bleeding, stroke, myocardial infarction and all-cause mortality in patients treated with vitamin K antagonists or direct oral anticoagulants. AF = atrial fibrillation; DAPT = dual antiplatelet therapy (aspirin+clopidogrel); DOAC = direct oral anticoagulant; SAPT = single antiplatelet therapy (aspirin or clopidogrel); VKA = vitamin K antagonist.

First, it was possible to describe the associated risk of bleeding, MI, stroke, and all-cause mortality of DOAC and VKA in combination with antiplatelet(s) in real-world patients, regardless of geography, socioeconomic status, or participation in a health care insurance program (37). Second, the diagnoses of AF, bleeding, MI, and stroke have been validated in the registries. Third, it was possible to investigate the antithrombotic regimens in both intention-to-treat analyses and in time-dependent analyses. Fourth, estimating the standardized absolute risks and average treatment effects provided a more causal interpretation of the data (28). Finally, the patient population included in this present study was 6 years older than the population included in the randomized trials, which emphasizes the generalizability of this present study.

A number of limitations exist; despite efforts to adjust for potential confounders, it is possible that the adjustments were not enough to even out the significant differences between the groups, because confounding by indication might be a major issue in our study. Furthermore, it is possible to buy aspirin over the counter at Danish pharmacies, thus introducing the possibility of misclassification bias. However, the reimbursement system on prescription drugs in Denmark is likely to diminish the misclassification bias. A major limitation in this study was the lack of clinical parameters, such as INR, blood pressure, estimated glomerular fraction, creatinine clearance, and alanine amino transferase, which are all important clinical parameters for the risk of bleeding. Importantly, treatment preference for VKA versus DOAC might be influenced by renal function, which was not available for our cohort, due to the lack of estimated glomerular fraction. In addition, because of the lack of important clinical variables such as labile INR, body mass index, smoking, and alcohol consumption, this could have influenced the patients' predicted bleeding and stroke risk assessed by the HAS-BLED and CHA2DS2-VASc scores. Because of the limited number of patients, it was not possible to investigate the comparative safety and effectiveness associated with the individual DOACs. This is especially relevant to investigate, because apixaban has not yet been investigated in this setting, and it is unknown whether results are generalizable to other countries or ethnicities.

CONCLUSIONS

In a nationwide cohort of AF patients following MI, PCI, or both, we found that DOAC+DAPT was associated with a significantly decreased risk of bleeding compared with VKA+DAPT. No significant differences in the risk of ischemic stroke, MI, or all-cause mortality were found between VKA+DAPT and DOAC+DAPT. Our data suggest that despite lack of trial evidence on the safety and effectiveness of DOAC versus VKA in combination with antiplatelets(s), DOACs seem safe and effective in real-world AF patients following MI or PCI.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In a nationwide registry of patients with AF experiencing MI or undergoing PCI, the combination of a DOAC plus DAPT was associated with a lower risk of bleeding and similar protection against thromboembolism compared with the combination of a VKA plus DAPT.

TRANSLATIONAL OUTLOOK: Adequately powered prospective studies are needed to compare the safety and efficacy of individual DOACs when combined with antiplatelet agents.

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KEY WORDS antiplatelets, atrial fibrillation, direct oral anticoagulants, myocardial infarction, percutaneous intervention, vitamin K antagonists

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