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ORIGINAL ARTICLE

Effectiveness and safety of direct oral anticoagulants with antiplatelet agents in patients with venous thromboembolism: A multi-database cohort study

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Abstract

Background: Patients with venous thromboembolism (VTE) often have comorbidities that require use of antiplatelets. However, evidence on the effects of concomitant use of direct oral anticoagulants (DOACs) and antiplatelets in this high-risk population is scarce. Our international, multi-database cohort study assessed the real-world effectiveness and safety of concomitant use of DOACs and antiplatelets among patients with VTE.

Methods: We assembled two population-based cohorts using administrative health care databases from Québec and Germany. We included patients with incident VTE who initiated treatment with a DOAC or a vitamin K antagonist (VKA), while being exposed to antiplatelets (acetylsalicylic acid, clopidogrel, ticagrelor, prasugrel, dipyridamole). The study period spanned from 2012 to 2016 (Québec) or 2019 (Germany). Concomitant use of DOACs and antiplatelets was compared with concomitant use of VKAs and antiplatelets, using inverse probability of treatment weighting to balance exposure groups. Cox proportional hazards models estimated site-specific hazard ratios (HRs) and 95% confidence intervals (CIs) of major bleeding, all-cause mortality (primary outcomes), and recurrent VTE (secondary outcome). Site-specific estimates were meta-analyzed using random-effects models.

Results: Overall, 4971 patients with VTE initiated concomitant use of a DOAC (n = 2289) or a VKA (n = 2682) and antiplatelets. Compared with concomitant use of VKAs and antiplatelets, concomitant use of DOACs and antiplatelets was associated with similar risks of major bleeding (HR, 0.81; 95% CI, 0.46-1.45), all-cause mortality (HR, 1.25; 95% CI, 0.87-1.79), and recurrent VTE (HR, 0.96; 95% CI, 0.40-2.27).

Conclusions: Among patients with VTE using antiplatelets, there were no major differences in effectiveness and safety between DOACs and VKAs.

KEYWORDS
antithrombotics, drug interactions, pharmacoepidemiology, real-world evidence, retrospective study, thrombosis

Essentials

- Evidence on the effects of concomitant use of direct oral anticoagulants (DOACs) and antiplatelets in patients with venous thromboembolism (VTE) is scarce.
- We conducted an international, multi-database cohort study to address this knowledge gap.
- In patients with VTE using antiplatelets, the effectiveness and safety of DOACs was similar to vitamin K antagonists.
- Our results support the use of DOACs in patients with VTE who require dual antithrombotic treatment.

1 | INTRODUCTION

Venous thromboembolism (VTE) is one of the most common cardiovascular adverse outcomes, with an incidence of roughly 1 per 1000 person-years.[1] VTE is associated with reduced survival, substantial health care costs, and high rates of recurrence.[1] To improve survival and to decrease the risk of recurrent VTE, current guidelines recommend direct oral anticoagulants (DOACs) as first-line treatment over vitamin K antagonists (VKAs) for a minimum duration of 3 to 6 months.[2]

Patients with VTE often have cardiovascular comorbidities, including peripheral artery disease, coronary artery disease, and history of stroke.[3] Consequently, up to 10% of patients with VTE are treated with antiplatelet agents upon VTE occurrence.[3,4] However, the available clinical evidence on the effects of DOACs among patients with VTE who concomitantly use antiplatelet agents is scarce and limited, which is reflected in current guidelines.[2,5,6]

To date, two post hoc analyses of randomized controlled trials (RCTs) have assessed the efficacy and safety of concomitant use of DOACs and antiplatelet agents among patients with VTE.[7,8] However, both studies were based on few events and generated largely inconclusive results. In addition, they had methodological limitations including their post hoc nature,[7,8] misclassification of exposure,[7] and residual confounding.[7-9] Moreover, there is a need to evaluate the effects of concomitant use of DOACs and antiplatelet agents among patients with VTE in routine clinical practice. Thus, the objective of our international, multi-database cohort study was to assess the effectiveness and safety of concomitant use of DOACs and antiplatelet agents compared with concomitant use of VKAs and antiplatelet agents among patients with VTE.

2 | METHODS

2.1 | Data sources

This was a retrospective cohort study with an active-comparator, new-user design.[10] We used the linked electronic health care databases from the Canadian province of Québec and the research database of the Institute for Applied Health Research Berlin (InGef) in Germany. The electronic health care databases in Québec include the Régie de l'assurance maladie du Québec (RAMQ), Maintenance et exploitation des données pour l'étude de la clientèle hospitalière (MEDÉCHO), and Institut de la statistique du Québec (ISQ). The RAMQ database contains demographics, outpatient diagnoses (coded using the International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] or enhanced version of ICD-10 for Canada [ICD-10-CA]), procedures, and dispensed prescriptions. In Québec, medical services are covered for all residents, while the Public Prescription Drug Insurance Plan covers all residents aged ≥65 years, residents without private drug insurance plans, and recipients of financial assistance.[11] The quality of RAMQ data has been shown to be high.[12,13] The MEDÉCHO database includes records of all hospitalizations in Québec with date and type of admission and discharge, inpatient diagnoses (coded using ICD-10-CA), and inpatient procedures. Finally, the ISQ database contains vital statistics data with date and underlying cause of death.

The InGef research database is an electronic health care database with claims from 57 German statutory health insurances and roughly 9 million individuals. It includes demographics, outpatient data (eg, diagnoses, procedures, dispensed prescriptions), and inpatient data (eg, data of admission and discharge, discharge diagnoses, procedures). All diagnoses are coded using ICD-10, German modification. The database is representative of the German general population.[14] In Québec, the study protocol was approved by the Research Ethics Committee of the Jewish General Hospital, Montreal, Canada. In Germany, institutional review board approval was not required (eMethods 1 in Appendix S1). All data were anonymized, and patient informed consent was waived.

2.2 | Study population

Our source population comprised all patients with an incident inpatient or outpatient VTE (the definition of VTE can be found in eMethods 2 in Appendix S1). The study period spanned from January 1, 2012 (when rivaroxaban was approved as the first DOAC for the treatment of VTE in Québec and in Germany) to the latest date of data availability (RAMQ: December 31, 201,5 with follow-up up to December 31, 2016; InGef: December 31, 2019). Patients were

required to be aged ≥18 years and have ≥1 year of insurance coverage with the Public Prescription Drug Insurance Plan of the RAMQ or with the respective statutory health insurance in the InGef database before the incident VTE diagnosis.

From this source population, we identified all patients who initiated treatment with an oral anticoagulant, that is, a DOAC (RAMQ: apixaban, dabigatran, or rivaroxaban; InGef: apixaban, dabigatran, edoxaban, or rivaroxaban) or a VKA (RAMQ: primarily warfarin; InGef: primarily phenprocoumon), within 15 days of the incident VTE, while being exposed to an antiplatelet agent (acetylsalicylic acid [ASA], clopidogrel, ticagrelor, prasugrel, or dipyridamole). To identify new users of oral anticoagulants, we excluded patients with a dispensed prescription for an oral anticoagulant in the year before the incident VTE. Since the question of interest was whether the underlying use of antiplatelet agents can impact the clinical outcomes of patients with VTE initiating treatment with oral anticoagulants, prevalent use of antiplatelet agents was allowed. The date of cohort entry was day 15 after the incident VTE. To eliminate selection bias, we excluded patients diagnosed with major bleeding in the first 14 days after the incident VTE and also those who switched exposure group (from DOACs and antiplatelet agents to VKAs and antiplatelet agents or vice versa) or stopped concomitant use in the same time period. Patients diagnosed with VTE in the first 14 days after the incident VTE were not excluded since early diagnoses are probably related to prevalent disease and not to recurrent VTE. All patients were followed from cohort entry until the earliest of the following: discontinuation or switching of concomitant use (described below), occurrence of one of the study outcomes (described below), end of the registration with the Public Prescription Drug Insurance Plan of the RAMQ or with the statutory health insurance in the InGef database, or end of the study period (RAMQ: December 31, 2016; InGef: December 31, 2019).

2.3 | Exposure definition

Patients were classified into one of the following two exposure groups: (i) concomitant use of DOACs with antiplatelet agents and (ii) concomitant use of VKAs with antiplatelet agents. The latter exposure group was the reference category to control for confounding by indication, since VKAs are a therapeutic alternative to DOACs for the treatment of VTE. We used an *as-treated* exposure definition, where patients were considered continuously exposed to the drug combination if the prescription durations of the drugs of interest are overlapping each other, allowing for a 30-day grace period in the event of nonoverlapping prescriptions.

2.4 | Outcome definition

The primary outcomes were major bleeding and all-cause mortality. Major bleeding was defined as an inpatient diagnostic code for bleeding (anywhere in the hospitalization record; complete list of diagnostic codes in eTable 1 in Appendix S1). Regarding all-cause mortality, the ISQ database contains month and year of death but not the exact date due to data protection regulations. Thus, all death events in the RAMQ were assigned the 15th of the respective month as the date of death. The secondary outcome was recurrent VTE. Recurrent VTE was defined as a combination of an inpatient diagnostic code for deep vein thrombosis or pulmonary embolism combined with a relevant procedure code (eg, Doppler ultrasound, computed tomography angiography of the chest, or ventilation/perfusion scan) in the same hospitalization (complete list of diagnostic and procedure codes in eTable 2 in Appendix S1). Recurrent VTE was a secondary outcome given the expected low incidence rate under dual antithrombotic treatment.

2.5 | Covariates

We assessed the following potential confounders at cohort entry: age (modeled flexibly as a continuous variable using restricted cubic splines to account for potential nonlinear associations with the study outcomes[15]), sex, obesity, varicose veins/postthrombotic syndrome, arterial hypertension, congestive heart failure, myocardial infarction, stroke, diabetes mellitus, chronic kidney disease, moderate to severe liver disease, inflammatory bowel disease, cancer (excluding nonmelanoma skin cancer), bleeding, fracture, and major surgery (all comorbidities diagnosed in the year before cohort entry). We also assessed the duration of prior continuous use of antiplatelet agents in the year before cohort entry (modeled flexibly). Moreover, we assessed the use of nonantithrombotic outpatient prescription drugs that have been associated with the risk of thrombosis or bleeding such as oral contraceptives, tamoxifen, hormone replacement therapy, systemic corticosteroids, selective serotonin reuptake inhibitors, proton pump inhibitors, and nonsteroidal anti-inflammatory drugs in the year before cohort entry. Finally, we assessed the overall number of hospitalizations and non-antithrombotic outpatient prescription drugs in the year before cohort entry as proxies of overall health. Covariates were defined using relevant diagnostic and procedure codes as in previously published studies on VTE from our group.[16]

2.6 | Statistical analyses

We calculated crude incidence rates for the study outcomes with 95% confidence intervals (CIs) for each exposure group assuming a Poisson distribution. Cox proportional hazards models estimated hazard ratios (HRs) and 95% CIs of the study outcomes associated with concomitant use of DOACs and antiplatelet agents compared with concomitant use of VKAs and antiplatelet agents. For confounding control, we used inverse probability of treatment weighting.[17] Multivariable logistic regression models estimated the probability (propensity) of receiving a DOAC and antiplatelet agents versus a VKA and antiplatelet agents, conditional on all previously

listed covariates with a prevalence of >1%, in all patients in the cohort. We then assigned weights to patients based on the inverse of their propensity score and ran the outcome model in the weighted cohort. Potential imbalances in covariates pre- and postweighting were assessed using the standardized difference (values ≥0.1 were considered important). Finally, we performed a meta-analysis of the RAMQ- and InGef-specific estimates using DerSimonian and Laird random-effects models and Mantel-Haenszel weighting for the study outcomes.[18] Meta-analytic results were presented as pooled weighted HRs with 95% CIs. Heterogeneity was estimated using the I^2 statistic.

2.7 | Additional analyses

We conducted three exploratory secondary analyses, stratifying by age (<80 years vs ≥80 years), sex, and subtype of major bleeding (ie, intracranial hemorrhage, gastrointestinal bleeding, other major bleeding). We also conducted three sensitivity analyses to test the robustness of our findings. First, to assess possible exposure misclassification, we used a 15-day grace period between nonoverlapping successive prescriptions. Second, to assess possible outcome misclassification due to the use of the 15th day of the month as date of death in the ISQ database, we repeated the RAMQ analysis with the first day of the month as date of death. Finally, to assess the potential impact of informative censoring due to the as-treated exposure definition, we used an *intention-to-treat* approach to define exposure censoring patients 3 months after cohort entry given the expected short median follow-up. All analyses were conducted with SAS statistical software (SAS Institute, Cary, NC, USA) and R (R Foundation for Statistical Computing, Vienna, Austria).

3 | RESULTS

We identified 4971 patients with incident VTE who initiated treatment with a DOAC (n = 2289) or a VKA (n = 2682) while being exposed to antiplatelet agents (Figure 1). Among patients taking a DOAC, 25% received apixaban, 2% dabigatran, 4% edoxaban, and 69% rivaroxaban. Tables 1-2 show that baseline patient characteristics were similar between the two exposure groups before weighting in both databases, with weighting further improving covariate balance.

The mean follow-up was 2.9 months for the outcome major bleeding (almost identical mean follow-up for all-cause mortality and recurrent VTE). During follow-up, 159 patients developed major bleeding (incidence rate, 13.3,100 person-years) and 146 patients died from any cause (incidence rate, 11.9/100 person-years). Table 3 shows that compared with concomitant use of VKAs and antiplatelet agents, concomitant use of DOACs and antiplatelet agents was not associated with the risk of major bleeding (incidence rates, 11.6 vs 14.4/100 person-years; weighted HR, 0.81; 95% CI, 0.46-1.45; I^2, 0.51) or all-cause mortality (incidence rates, 13.6 vs 10.8/100 person-years; weighted HR, 1.25; 95% CI, 0.87-1.79; I^2, 0.00). The site-specific analyses for major bleeding and all-cause mortality are presented in eTables 3 and

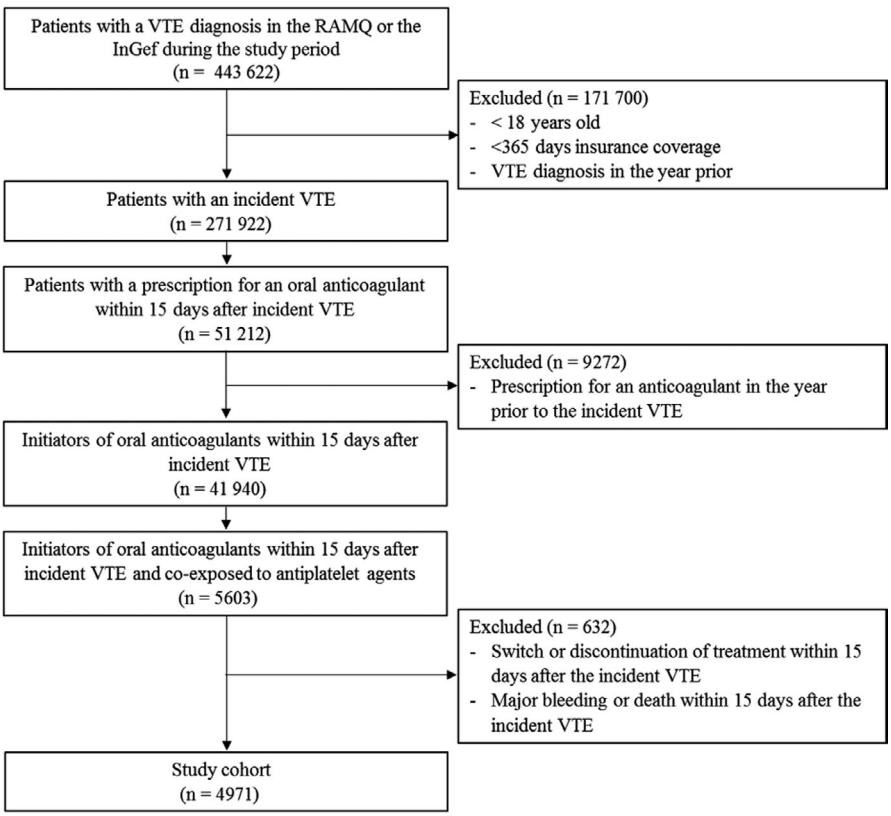

FIGURE 1 Flowchart of the study. RAMQ, Régie de l'assurance maladie du Québec; InGef, Institute for Applied Health Research Berlin; VTE, venous thromboembolism

TABLE 1 Baseline characteristics of patients with VTE initiating concomitant use of oral anticoagulants and antiplatelet agents before and after propensity score weighting (RAMQ database)

	Before weighting					After weighting				
Characteristic[a]	DOACs + APs (n = 1055)		VKAs + APs (n = 2189)		SMD	DOACs + APs (n = 1061)		VKAs + APs (n = 2189)		SMD
Age, y, mean (SD)	73.8	9.8	75.7	11.0	−0.175	75.1	10.5	75.1	10.7	0.003
Female sex	521	49.4	1121	51.2	−0.037	524	49.4	1102	50.34	−0.019
Comorbidities										
Obesity	92	8.7	181	8.3	−0.016	93	8.7	185	8.5	−0.010
Varicose veins/PTS	S	S	6	0.3	NA	…	…	…	…	NA
Arterial hypertension	650	61.6	1503	68.7	0.148	706	66.5	1454	66.4	−0.002
Congestive heart failure	151	14.3	403	18.4	0.111	195	18.4	376	17.2	−0.032
Myocardial infarction	98	9.3	320	14.6	0.165	139	13.1	282	12.9	−0.006
Stroke	50	4.7	142	6.5	0.076	64	6.0	130	5.9	−0.003
Diabetes mellitus	331	31.4	740	33.8	0.052	355	33.4	721	33.0	−0.010
Chronic kidney disease	18	1.7	190	8.7	0.318	75	7.1	140	6.4	−0.029
Moderate to severe liver disease	6	0.6	12	0.6	NA	…	…	…	…	NA
Inflammatory bowel disease	14	1.3	29	1.3	0.000	14	1.4	29	1.3	−0.002
Cancer	162	15.4	365	16.7	0.036	175	16.5	357	16.3	−0.004
Bleeding	115	10.9	338	15.4	0.135	150	14.1	305	13.9	−0.005
Fracture	66	6.3	104	4.8	−0.066	51	4.8	113	5.2	0.015
Major surgery	370	35.1	772	35.3	0.004	365	34.4	770	35.2	0.016
Comedications										
APs, duration in days, mean (SD)	307.6	109.8	297.8	118.6	0.086	297.7	119.3	300.9	115.9	−0.028
Oral contraceptives	16	1.5	45	2.1	0.041	22	2.0	41	1.9	−0.011
Hormone replacement therapy	0	0.0	S	S	NA	…	…	…	…	NA
Tamoxifen	13	1.2	12	0.6	NA	…	…	…	…	NA
Systemic corticosteroids	232	22.0	498	22.8	0.018	233	22.0	492	22.5	0.012
SSRIs	156	14.8	292	13.3	−0.042	148	14.0	302	13.8	−0.006
Proton pump inhibitors	661	62.7	1452	66.3	0.077	681	64.2	1422	65.0	0.016
NSAIDs	274	26.0	427	19.5	−0.155	223	21.0	472	21.6	0.013
Proxies of overall health										
Number of hospitalizations										
0	317	30.1	507	23.2	−0.130	268	25.3	556	25.4	0.003
1	426	40.4	924	42.2	0.037	430	40.5	909	41.5	0.020
≥2	312	29.6	758	34.6	0.108	363	34.2	724	33.1	−0.024
Number of non-antithrombotic drugs										
0-10	391	37.1	647	29.6	−0.132	330	31.1	699	31.9	0.014
11-15	314	29.8	662	30.2	0.010	321	30.2	659	30.1	−0.002
≥16	350	33.2	880	40.2	0.146	410	38.7	831	38.0	−0.014

Abbreviations: APs, antiplatelet agents; DOACs, direct oral anticoagulants; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; PTS, postthrombotic syndrome; RAMQ, Régie de l'assurance maladie du Québec; S, suppressed due to small numbers (<5) as per confidentiality agreement with the RAMQ; SD, standard deviation; SMD, standardized mean difference; SSRIs, selective serotonin reuptake inhibitors; VKAs, vitamin K antagonists.

[a]Values are numbers (percentages) unless stated otherwise.

4 in Appendix S1. As expected, recurrent VTE was not common under dual antithrombotic treatment (incidence rate, 2.7/100 person-years), which limited study power. Risk assessment was feasible only in the RAMQ (Table 3) and was based on few events (incidence rates 3.1 vs 3.0/100 person-years; weighted HR, 0.96; 95% CI, 0.40-2.27).

Secondary analyses for the primary outcomes major bleeding and all-cause mortality (not feasible for recurrent VTE) suggested

TABLE 2 Baseline characteristics of patients with VTE initiating concomitant use of oral anticoagulants and antiplatelet agents before and after propensity score weighting (InGef database)

	Before weighting					After weighting				
Characteristic[a]	DOACs + APs (n = 1234)		VKAs + APs (n = 493)		SMD	DOACs + APs (n = 1235)		VKAs + APs (n = 489)		SMD
Age, y, mean (SD)	74.8	11.8	72.7	11.1	0.181	74.2	11.6	74.0	11.5	0.016
Female sex	685	55.5	292	59.2	−0.075	699	56.7	281	57.4	−0.014
Comorbidities										
Obesity	S	S	0	0.0	NA	…	…	…	…	NA
Varicose veins/PTS	36	2.9	12	2.4	0.029	35	2.9	15	3.1	−0.016
Arterial hypertension	1,140	92.4	449	91.1	0.048	1,135	91.9	448	91.6	0.011
Congestive heart failure	479	38.8	189	38.3	0.010	477	38.6	182	37.3	0.028
Myocardial infarction	174	14.1	63	12.8	0.038	170	13.8	65	13.3	0.013
Stroke	293	23.7	91	18.5	0.127	275	22.3	112	22.8	−0.013
Diabetes mellitus	513	41.6	210	42.6	−0.021	519	42.1	210	43.0	−0.018
Chronic kidney disease	320	25.9	179	36.3	−0.230	357	28.9	141	28.9	0.000
Moderate to severe liver disease	11	0.9	5	1.0	NA	…	…	…	…	NA
Inflammatory bowel disease	20	1.6	16	3.3	−0.114	26	2.1	10	2.1	0.002
Cancer	298	24.2	109	22.1	0.048	291	23.6	113	23.1	0.011
Bleeding	234	19.0	91	18.5	0.013	233	18.9	90	18.4	0.012
Fracture	81	6.6	18	3.7	0.126	71	5.7	27	5.4	0.013
Major surgery	472	38.3	209	42.4	−0.085	486	39.4	189	38.6	0.017
Comedications										
APs, duration in days, mean (SD)	195.8	125.7	179.6	127.0	0.128	190.6	126.3	188.6	126.5	0.015
Oral contraceptives	9	0.7	6	1.2	NA	…	…	…	…	NA
Hormone replacement therapy	0	0.0	0	0.0	NA	…	…	…	…	NA
Tamoxifen	7	0.6	7	1.4	NA	…	…	…	…	NA
Systemic corticosteroids	248	20.1	96	19.5	0.016	244	19.8	95	19.4	0.010
SSRIs	133	10.8	45	9.1	0.054	127	10.3	49	10.1	0.007
Proton pump inhibitors	756	61.3	277	56.2	0.104	739	59.8	293	59.9	−0.002
NSAIDs	470	38.1	191	38.7	−0.013	474	38.4	193	39.5	−0.021
Proxies of overall health										
Number of hospitalizations										
0	417.00	33.79	158.00	32.05	0.037	411.31	33.32	164.10	33.53	−0.005
1	356.00	28.85	146.00	29.61	−0.017	359.76	29.14	142.18	29.05	0.002
2	195.00	15.80	96.00	19.47	−0.098	208.73	16.91	82.40	16.84	0.002
>2	266.00	21.56	93.00	18.86	0.066	254.71	20.63	100.69	20.58	0.001
Number of non-antithrombotic drugs										
0–10	561.00	45.46	235.00	47.67	−0.044	568.90	46.08	225.64	46.11	−0.001
11–15	386.00	31.28	129.00	26.17	0.112	366.87	29.72	142.12	29.04	0.015
≥16	287.00	23.26	129.00	26.17	−0.068	298.73	24.20	121.60	24.85	−0.015

Abbreviations: APs, antiplatelet agents; DOACs, direct oral anticoagulants; InGef, Institute for Applied Health Research Berlin; S, suppressed due to small numbers (<5) as per confidentiality agreement with the health insurances contributing data to the InGef database; NA, not applicable; NSAIDs, nonsteroidal anti-inflammatory drugs; PTS, postthrombotic syndrome; SD, standard deviation; SMD, standardized mean difference; SSRIs, selective serotonin reuptake inhibitors; VKAs, vitamin K antagonists.

[a]Values are numbers (percentages) unless stated otherwise.

an effect modification by sex. Concomitant use of DOACs and antiplatelet agents was associated with a decreased risk of major bleeding among male patients (weighted HR, 0.54; 95% CI, 0.30–0.96; I^2, 0.00) but not among female patients (weighted HR, 1.05; 95% CI, 0.62-1.77; I^2, 0.00). Moreover, while there was no association between concomitant use of DOACs and antiplatelet agents and the

TABLE 3 Crude and adjusted HRs of the study outcomes associated with concomitant use of DOACs and antiplatelet agents compared with concomitant use of VKAs and antiplatelet agents among patients with VTE

	N patients	N events	N person-years	IR[a]	Unweighted HR (95% CI)	Weighted[b] HR (95% CI)	I^2
Major bleeding							
DOACs + antiplatelet agents	2289	56	483	11.6	0.80 (0.39–1.66)	0.81 (0.46–1.45)	0.51
VKAs + antiplatelet agents	2682	103	715	14.4	1.00 (reference)	1.00 (reference)	
All-cause mortality							
DOACs + antiplatelet agents	2289	67	493	13.6	0.97 (0.51–1.82)	1.25 (0.87–1.79)	0.00
VKAs + antiplatelet agents	2682	79	733	10.8	1.00 (reference)	1.00 (reference)	
Recurrent VTE[c]							
DOACs + antiplatelet agents	1055	7	227	3.1	0.85 (0.36–2.04)	0.96 (0.40–2.27)	NA
VKAs + antiplatelet agents	2189	19	636	3.0	1.00 (reference)	1.00 (reference)	

Abbreviations: CI, confidence interval; DOACs, direct oral anticoagulants; HR, hazard ratio; IR, incidence rate; NA, not applicable; RAMQ, Régie de l'assurance maladie du Québec; VKAs, vitamin K antagonists; VTE, venous thromboembolism.

[a]Per 100 person-years. Calculated on the basis of the weighted cohort.

[b]After propensity score based inverse probability of treatment weighting.

[c]Based only on the analysis in the RAMQ database.

risk of all-cause mortality among male patients (weighted HR, 0.95; 95% CI, 0.56-1.60; I^2, 0.00), there was a nonsignificant trend toward an increased risk among female patients (weighted HR, 1.64; 95% CI, 0.98-2.72; I^2, 0.00). However, secondary analyses were based on few events and should be interpreted with caution (results presented in eTables 5 and 6 in Appendix S1). Sensitivity analyses yielded findings that were generally consistent with those of the primary analyses (results presented in eTable 7 in Appendix S1).

4 | DISCUSSION

Our international, multi-database cohort study included roughly 5000 patients with incident VTE who initiated treatment with oral anticoagulants while on antiplatelet agents. Compared with concomitant use of VKAs and antiplatelet agents, concomitant use of DOACs and antiplatelet agents was not associated with the risk of major bleeding or all-cause mortality. The risk of recurrent VTE was also comparable between groups, but the analysis was based on few events.

Concomitant use of oral anticoagulants and antiplatelet agents among patients with VTE is relatively common.[3,4] To date, the effects of DOACs in this setting were assessed by two post hoc analyses of RCTs.[7,8] The first study, a prospective analysis of observational data from the EINSTEIN trials, reported that compared with concomitant use of VKAs and ASA, concomitant use of rivaroxaban and ASA was not associated with the risk of major bleeding (HR, 0.54; 95% CI, 0.19-1.51).[8] However, the number of events was low (6 in the rivaroxaban/ASA arm vs 9 in the VKAs/ASA arm), not allowing the generation of precise risk estimates. The second study, a subgroup analysis of the AMPLIFY trial, reported that compared with concomitant use of warfarin and antiplatelet agents, concomitant use of apixaban and antiplatelet agents was not associated with the risk of recurrent VTE (rate ratio, 1.23; 95% CI, 0.58-2.62) but with a decreased risk of major bleeding (rate ratio, 0.30; 95% CI, 0.11-0.81).[7] This study was also based on few events (14 in the apixaban/antiplatelet agents arm vs 12 in the warfarin/antiplatelet agents arm for recurrent VTE; 5 vs 17 for major bleeding). Except for the low statistical power, both studies also had methodological limitations including their post hoc nature,[7,8] important misclassification of exposure,[7] and residual confounding.[7-9] Finally, the generalizability to real-world settings is not clear, since in the EINSTEIN trials concomitant use of antiplatelet agents was discouraged,[8] while AMPLIFY excluded patients on dual antiplatelet therapy or on daily doses of ASA over 165 mg.[7]

In our study, concomitant use of DOACs and antiplatelet agents was not associated with the risk of major bleeding compared with concomitant use of VKAs and antiplatelet agents. These results are opposed to the previously shown decreased risk of major bleeding with DOACs in monotherapy compared with VKAs in monotherapy among patients with VTE.[19] Potential explanations could be related to the distribution of oral anticoagulants in our study cohort. For example, roughly 70% of our patients taking a DOAC were on rivaroxaban, which has a less favorable bleeding profile than other DOACs.[20,21] Moreover, phenprocoumon, the predominant VKA in the InGef database, can lead to higher levels of time in therapeutic range and possibly to improved anticoagulation control compared with other VKAs.[22-24] Thus, using phenprocoumon as comparator could attenuate the protective effects of DOACs that were shown in comparison with warfarin. Congruently, the risk of major bleeding with concomitant use of DOACs and antiplatelet agents was borderline decreased in the warfarin-dominated RAMQ database (weighted HR, 0.63; 95% CI, 0.39-1.02), but not in the phenprocoumon-dominated InGef database (weighted HR, 1.14; 95% CI, 0.59-2.21).

Our results also showed no association between concomitant use of DOACs and antiplatelet agents and the risk of all-cause mortality. This is concordant with the RCTs that compared DOACs with VKAs in monotherapy.[19] Finally, our secondary analyses suggested more favorable effects for male patients. However, given that these analyses were based on few events, and considering the absence of an effect modification by sex in the RCTs,[25-27] the results should be interpreted with caution and require confirmation in future studies.

Our study has some strengths. First, this is the first observational study to assess the effectiveness and safety of DOACs among patients with VTE concomitantly using antiplatelet agents, a high-risk but yet understudied population. Second, the application of a population-based design, the few exclusion criteria, and the inclusion of patients from two different countries make the study findings highly generalizable to patients with VTE seen in routine clinical practice. Finally, the precise assessment of concomitant use of oral anticoagulants and antiplatelet agents minimized the risk of exposure misclassification, which was an important limitation of one of the two published post hoc analyses.[7]

Our study also has some potential limitations. First, residual confounding is possible given the observational nature of the study. Moreover, some of the covariates included in our analyses such as obesity may be poorly recorded in administrative health care data.[28] To minimize this bias, we used an active comparator (ie, concomitant use of VKAs and antiplatelet agents), which is a well-established approach in pharmacoepidemiologic studies.[10] Moreover, propensity score–based inverse probability of treatment weighting led to two well-balanced groups. Second, outcome misclassification is possible. While major bleeding has been validated in administrative health care databases showing very high sensitivity (94%) and high specificity (83%),[29,30] and all-cause mortality can be captured with good accuracy,[31] the assessment of recurrent VTE in such data sources is challenging.[32] Therefore, we defined recurrent VTE using only inpatient diagnostic codes accompanied by relevant procedure codes during the same hospitalization episode to increase specificity and minimize outcome misclassification. The downside of this decision was reduced sensitivity and decreased statistical power. Third, our study was able to only detect relatively large changes in the relative risk of the outcomes due to lower statistical power. For example, our study had 80% power to identify a 36% decrease in the risk of major bleeding, the outcome with the highest incidence rate, associated with the concomitant use of DOACs and antiplatelet agents (HR, 0.64). Fourth, the last available date of follow-up in the RAMQ was December 31, 2016. Thus, recent prescribing patterns could not be considered in that database. Finally, our results on major bleeding showed moderate-to-substantial statistical heterogeneity with an I^2 of 51%. We decided to meta-analyze the site-specific estimates acknowledging that some degree of heterogeneity is inevitable due to differences in populations and health care system–related factors such as formulary restrictions. To account for the heterogeneity at the analytical level, we meta-analyzed the site-specific estimates using random-effects models.

Overall, our study showed no major differences in effectiveness and safety between DOACs and VKAs among patients with VTE who concomitantly use antiplatelet agents. Considering the known advantages of DOACs over VKAs such as more rapid onset of pharmacologic action and decreased need for monitoring,[33] our results support the use of DOACs in patients with VTE who require dual antithrombotic treatment.

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RELATIONSHIP DISCLOSURE

All authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

All authors have directly participated in the planning, execution, or analysis of the study.

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SUPPORTING INFORMATION

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