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

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\textbf{Abstract}

\textbf{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.

\textbf{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.

\textbf{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).

\textbf{Conclusions:} Among patients with VTE using antiplatelets, there were no major differences in effectiveness and safety between DOACs and VKAs.
1 | INTRODUCTION

Venous thromboembolism (VTE) is one of the most common cardiovascular adverse outcomes, with an incidence of roughly 1 per 1000 person-years. VTE is associated with reduced survival, substantial health care costs, and high rates of recurrence. 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.

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

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. However, both studies were based on few events and generated largely inconclusive results. In addition, they had methodological limitations including their post hoc nature, misclassification of exposure, and residual confounding. 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. 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. The quality of RAMQ data has been shown to be high. 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. 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, 2015 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. Meta-analytic results were presented as pooled weighted HRs with 95% CIs. Heterogeneity was estimated using the I² 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; I², 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; I², 0.00). The site-specific analyses for major bleeding and all-cause mortality are presented in eTables 3 and
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 1** Baseline characteristics of patients with VTE initiating concomitant use of oral anticoagulants and antiplatelet agents before and after propensity score weighting (RAMQ database)

| Characteristica | Before weighting | After weighting |
|-----------------|------------------|-----------------|
|                 | 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 (50.3%) | -0.019 |
| Comorbidities |
| Obesity | 92 (8.7%) | 181 (8.3%) | -0.016 | 93 (8.7%) | 185 (8.5%) | -0.010 |
| Varicose veins/PTS | 5 | 6 | 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 |
| 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 | 5 | NA | ... | ... | ... |
| Tamoxifen | 13 (1.2%) | 12 (0.6%) | 0.000 | 14 (1.4%) | 29 (1.3%) | -0.002 |
| 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.

aValues 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; I², 0.00) but not among female patients (weighted HR, 1.05; 95% CI, 0.62–1.77; I², 0.00). Moreover, while there was no association between concomitant use of DOACs and antiplatelet agents and the

### 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)

| Characteristic | Before weighting | VKAs + APs (n = 493) | SMD | After weighting | 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 | 41.6 | 0.018 | 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 | 0.127 | 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 |

| Characteristic | Before weighting | VKAs + APs (n = 493) | SMD | After weighting | VKAs + APs (n = 489) | SMD |
|---------------|------------------|----------------------|-----|----------------|----------------------|-----|
| Comedications | | | | | | | |
| APs, duration in days, mean (SD) | 195.8 | 125.7 | 179.6 | 127.0 | 0.018 | 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

| Number of hospitalizations | Before weighting | VKAs + APs (n = 493) | SMD | After weighting | VKAs + APs (n = 489) | SMD |
|---------------------------|------------------|----------------------|-----|----------------|----------------------|-----|
| 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

| Number of non-antithrombotic drugs | Before weighting | VKAs + APs (n = 493) | SMD | After weighting | VKAs + APs (n = 489) | SMD |
|------------------------------------|------------------|----------------------|-----|----------------|----------------------|-----|
| 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 insurance 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.

aValues are numbers (percentages) unless stated otherwise.
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 | IRa | Unweighted HR (95% CI) | Weightedb HR (95% CI) | I² |
|----------------------|------------|----------|----------------|-----|------------------------|-----------------------|----|
| **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.

| N patients | N events | N person-years | IRa | Unweighted HR (95% CI) | Weightedb HR (95% CI) | I² |
|------------|----------|----------------|-----|------------------------|-----------------------|----|
| 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 VTEc |            |          |                |     |                        |                       |    |
| 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)      |    |

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

aAfter propensity score based inverse probability of treatment weighting.
bBased on only the analysis in the RAMQ database.

We found a risk of all-cause mortality among male patients (weighted HR, 0.95; 95% CI, 0.56–1.60; I², 0.00), there was a nonsignificant trend toward an increased risk among female patients (weighted HR, 1.64; 95% CI, 0.98–2.72; I², 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. To date, the effects of DOACs in this setting were assessed by two post hoc analyses of RCTs. 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). 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). 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, important misclassification of exposure, and residual confounding. Finally, the generalizability to real-world settings is not clear, since in the EINSTEIN trials concomitant use of antiplatelet agents was discouraged, while AMPLIFY excluded patients on dual antiplatelet therapy or on daily doses of ASA over 165 mg.

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. 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. 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. 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.\textsuperscript{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,\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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%),\textsuperscript{29,30} and all-cause mortality can be captured with good accuracy,\textsuperscript{31} the assessment of recurrent VTE in such data sources is challenging.\textsuperscript{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,\textsuperscript{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

Additional supporting information may be found in the online version of the article at the publisher’s website.

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