Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Full Length Article

The association between anticoagulation and adverse outcomes after a positive SARS-CoV-2 test among older outpatients: A population-based cohort study

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ABSTRACT

Introduction: Anticoagulation may improve outcomes in patients with COVID-19 when started early in the course of illness.

Materials and methods: This was a population-based cohort study using linked administrative datasets of outpatients aged ≥65 years old testing positive for SARS-CoV-2 between January 1 and December 31, 2020 in Ontario, Canada. The key exposure was anticoagulation with warfarin or direct oral anticoagulants before COVID-19 diagnosis. We calculated propensity scores and used matching weights (MWs) to reduce baseline differences between anticoagulated and non-anticoagulated patients. The primary outcome was a composite of death or hospitalization within 60 days of a positive SARS-CoV-2 test. We used the Kaplan-Meier method and cumulative incidence functions to estimate risk of the primary and component outcomes at 60 days.

Results: We studied 23,159 outpatients (mean age 78.5 years; 13,474 [58.2%] female), among whom 3200 (13.8%) deaths and 3183 (13.7%) hospitalizations occurred within 60 days of the SARS-CoV-2 test. After application of MWs, the 60-day risk of death or hospitalization was 29.2% (95% CI 27.4%–31.2%) for anticoagulated individuals and 32.1% (95% CI 30.7%–33.5%) without anticoagulation (absolute risk difference [ARD], −2.9%; $p = 0.005$). Anticoagulation was also associated with a lower risk of death: 18.6% (95% CI 17.0%–20.2%) with anticoagulation and 20.9% (95% CI 19.7%–22.2%) in non-anticoagulated patients (ARD -2.3%; p = 0.005).

Conclusions: Among outpatients aged ≥65 years, oral anticoagulation at the time of a positive SARS-CoV-2 test was associated with a lower risk of a composite of death or hospitalization within 60 days.

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1. Introduction

The coronavirus disease of 2019 (COVID-19) has defied conventional treatments for viral pneumonias and the acute respiratory distress syndrome, prompting intense scrutiny of its underlying pathological processes in order to identify novel therapeutic approaches. Patients with COVID-19 have a high risk of thrombosis, prompting the hypothesis that anticipating and counteracting this risk with therapeutic anticoagulation could improve patient outcomes [1–9]. Several randomized controlled trials (RCTs) have evaluated a strategy of higher-dose versus prophylactic anticoagulation in patients hospitalized with COVID-19 [10–16]. These studies have yielded conflicting results with regards to efficacy. The benefit of anticoagulation was more likely observed in patients who were not critically ill at time of randomization [10,11,13], suggesting that early initiation of anticoagulation may be integral to deriving benefit from this therapeutic strategy [17,18]. Indeed, the predisposition to thrombosis among patients with COVID-19 begins before admission to hospital, and early markers of thrombosis at time of hospitalization are predictive of poor downstream outcomes [19–23]. The ACTIV-4b RCT studied the impact of antithrombotic therapy in symptomatic but stable outpatients with COVID-19 [24]. In this trial, treatment with aspirin or apixaban did not reduce the risk of major adverse cardiopulmonary outcomes. However, this trial studied a relatively low-risk group, and most events occurred before patients began the intervention they were randomized to. Thus, the ideal window of opportunity for anticoagulation in COVID-19 may precede the period studied by the published RCTs.

Since older age is one of the strongest predictors of adverse outcomes following a diagnosis of COVID-19 [22,25–27], we hypothesized that older patients with COVID-19 are the most likely to benefit from early anticoagulation, i.e., before hospitalization. Accordingly, we conducted a population-based cohort study of outpatients aged ≥65 years to examine the association between anticoagulation at time of testing positive for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the subsequent risk of death or hospitalization. We hypothesized that patients who were anticoagulated would have a lower risk of death and hospitalization following a positive SARS-CoV-2 test. Secondly, we hypothesized that anticoagulation would have a larger protective effect in men than women, as men generally experience acute cardiovascular events at a younger age than women [28] and have worse outcomes following COVID-19 infection [20,22,23].

2. Methods

2.1. Cohort creation

Ontario is Canada's most populous province; its residents receive universal coverage for physician services and hospital-based care through the Ontario Health Insurance Plan (OHIP). This facilitates the conduct of population-based cohort studies using administrative health datasets that use unique encoded identifiers and are analyzed at ICES (formerly the Institute for Clinical Evaluative Sciences). The Canadian Institute for Health Information (CIHI) Discharge Abstract Database records data on hospitalized patients, while the National Ambulatory Care Reporting System collects data on emergency department visits; collection of these data is mandatory for all Ontario hospitals. Outpatient prescription medication coverage is provided for patients aged ≥65 years using the Ontario Drug Benefit (ODB) program [29]. Physician billing claims are recorded in the OHIP physician claims database. Residence in long-term care (LTC) can be identified based on physician billings in the OHIP database and ODB drug dispensation records. The Registered Persons Database maintains vital statistics data, including deaths in and out of hospital. Multiple algorithms have been validated to ascertain medical diagnoses using these databases [30–45]. The Immigration, Refugees and Citizenship Canada Permanent Resident database was used to identify individuals who immigrated to Canada after 1984 (henceforth referred to as recent immigrants). We also used the Johns Hopkins Adjusted Clinical Groups System, Version 10, to determine collapsed Aggregated Diagnosis Groups based on these datasets [46,47].

The Ontario Laboratories Information System contains data on laboratory tests, including polymerase chain reaction (PCR) results for SARS-CoV-2. This was used to identify individuals with a positive SARS-CoV-2 PCR test in Ontario between January 1 and December 31, 2020. For people with more than one positive test, we retained the first test. Next, we applied the following exclusion criteria: missing or invalid key data (age, sex, OHIP number), Ontario non-residents or OHIP coverage <1 year before the SARS-CoV-2 test (to allow ascertainment of medical history), age < 65 years plus 100 days (to allow ascertainment of prescription medication exposure), exposure to low molecular weight heparin (which is used for venous thromboembolism [VTE] prophylaxis and cancer-associated thrombosis), or surgery within 6 weeks before the index date (i.e., increased risk of VTE independent of SARS-CoV-2 infection). We also excluded individuals whose index positive SARS-CoV-2 test was collected on a date when the individual was admitted in hospital (i.e., if the testing date was between the admission and discharge dates from hospital, inclusive). The remaining patients constituted the cohort of outpatients with diagnosed COVID-19, whose index date was that of collection of the qualifying SARS-CoV-2 test.

2.2. Exposures and outcomes

The primary exposure was anticoagulation with warfarin or direct oral anticoagulant (DOAC: apixaban, rivaroxaban, dabigatran, or edoxaban). Patients were defined as anticoagulated if they were dispensed a prescription for warfarin or DOAC in the 100 days preceding the index date (maximum number of days for prescriptions covered by the ODB is 100) with a sufficient supply to include the index date. Patients who were not dispensed a prescription for anticoagulation within 100 days of the index date were classified as non-anticoagulated. We excluded patients who were dispensed prescriptions for anticoagulation within 100 days of the SARS-CoV-2 test if their dispensed supply was insufficient for complete medication adherence through the test date, as their anticoagulation status at the time of the test was uncertain.

Given the broad range of adverse effects potentially mediated by anticoagulation in COVID-19 and fluctuations in clinical practice of hospital transfers for LTC residents during the study period [48], the primary outcome was chosen to be a composite of death or hospitalization within 60 days of the index date in order to provide a comprehensive estimate of net clinical benefit in outpatients within the health system. We also studied death and hospitalization separately. Furthermore, we assessed the following secondary outcomes: ICU admission, mechanical ventilation, ischemic stroke, acute myocardial infarction, VTE, pneumonia, bleeding events diagnosed in-hospital (which may or may not have been the most responsible diagnosis), and hemorrhagic stroke (see diagnostic codes in Supplementary Table 1).

2.3. Statistical analysis

Baseline characteristics were summarized using the mean (with standard deviation [SD]) for continuous variables and frequencies for categorical variables. Standardized differences were used to assess for potentially meaningful differences between anticoagulated and non-anticoagulated individuals [49].

We calculated propensity scores (PS) for being anticoagulated at the index date conditional on the baseline characteristics listed in Table 1. Using the estimated PS, we calculated matching weights (MWs) for each subject in the cohort [50–52]. Unlike conventional PS weighting approaches, the use of MWs targets inferences at a population with equipoise about the exposure. Once weights were estimated, baseline characteristics were compared between anticoagulated and non-anticoagulated patients using weighted standardized differences, with values <0.1 considered indicative of good balance [53]. Outcomes were

Table 1
Baseline characteristics of 23,159 outpatients with COVID-19 infection, stratified by anticoagulation status before and after application of matching weights. Std diff: standardized difference; SD: standard deviation.

Variable	Before marginal weights				After marginal weights		
	Anticoagulated	Not anticoagulated	p-value	Std diff	Anticoagulated	Not anticoagulated	Std diff
	$n = 2871$	$n = 20{,}288$	–	–	–	–	–
Age, mean ± SD	83.5 ± 8.6	77.8 ± 9.7	<0.001	0.63	82.6	82.8	0.02
Male sex	1187 (41.3%)	8498 (41.9%)	0.58	0.01	42.7%	42.8%	0.001
Week of pandemic, mean ± SD	34.6 ± 15.5	37.5 ± 14.5	<0.001	0.19	35.1	35.0	0.01
Median neighborhood income quintile							
Quintile 1 (lowest income)	742 (25.8%)	5030 (24.8%)		0.02	25.7%	25.9%	0.003
Quintile 2	689 (24.0%)	4847 (23.9%)		<0.01	23.7%	23.7%	0.001
Quintile 3	541 (18.8%)	4188 (20.6%)	<0.001	0.05	19.9%	19.7%	0.003
Quintile 4	407 (14.2%)	3244 (16.0%)		0.05	14.3%	14.6%	0.01
Quintile 5 (highest income)	464 (16.2%)	2888 (14.2%)		0.05	15.6%	15.5%	0.003
Neighborhood residential instability quintile							
Quintile 1 (least unstable)	366 (12.7%)	4054 (20.0%)		0.20	13.6%	13.9%	0.01
Quintile 2	350 (12.2%)	2989 (14.7%)		0.07	12.9%	12.8%	0.001
Quintile 3	520 (18.1%)	3326 (16.4%)	<0.001	0.05	17.8%	17.7%	0.003
Quintile 4	593 (20.7%)	3814 (18.8%)		0.05	20.8%	21.3%	0.01
Quintile 5 (most unstable)	984 (34.3%)	5911 (29.1%)		0.11	33.0%	32.9%	0.003
Neighborhood material deprivation quintile							
Quintile 1 (least deprived)	548 (19.1%)	3570 (17.6%)		0.04	18.2%	18.4%	0.00
Quintile 2	535 (18.6%)	3665 (18.1%)		0.01	19.0%	18.9%	0.002
Quintile 3	572 (19.9%)	4189 (20.6%)	<0.001	0.02	20.0%	19.9%	0.004
Quintile 4	554 (19.3%)	4052 (20.0%)		0.02	19.6%	20.0%	0.01
Quintile 5 (most deprived)	604 (21.0%)	4618 (22.8%)		0.04	21.2%	21.4%	0.004
Neighborhood economic dependency quintile							
Quintile 1 (least dependent)	402 (14.0%)	4198 (20.7%)		0.18	14.8%	15.0%	0.01
Quintile 2	428 (14.9%)	3640 (17.9%)		0.08	15.3%	15.1%	0.01
Quintile 3	476 (16.6%)	3426 (16.9%)	<0.001	0.01	16.7%	16.7%	0.001
Quintile 4	430 (15.0%)	3071 (15.1%)		0.00	15.2%	15.4%	0.003
Quintile 5 (most dependent)	1077 (37.5%)	5759 (28.4%)		0.20	36.0%	36.4%	0.007
Neighborhood ethnic concentration quintile							
Quintile 1 (least ethnicity)	299 (10.4%)	1848 (9.1%)		0.04	10.3%	10.8%	0.02
Quintile 2	348 (12.1%)	2285 (11.3%)		0.03	12.5%	12.7%	0.01
Quintile 3	588 (20.5%)	3151 (15.5%)	<0.001	0.13	19.9%	19.9%	0.000
Quintile 4	716 (24.9%)	4651 (22.9%)		0.05	24.3%	24.5%	0.003
Quintile 5 (most ethnicity)	862 (30.0%)	8159 (40.2%)		0.21	31.1%	30.7%	0.01
Rural residence	102 (3.6%)	849 (4.2%)	<0.001	0.03	3.8%	3.7%	0.003
Recent immigrant (landed in Ontario after 1984)	303 (10.6%)	4884 (24.1%)	<0.001	0.36	12.0%	11.6%	0.01
Acute myocardial infarction	143 (5.0%)	602 (3.0%)	<0.001	0.10	4.8%	4.9%	0.005
Percutaneous coronary intervention	77 (2.7%)	425 (2.1%)	0.04	0.04	2.8%	3.0%	0.01
Coronary artery bypass graft surgery	29 (1.0%)	137 (0.7%)	0.05	0.04	1.2%	1.3%	0.01
Heart failure	1289 (44.9%)	2215 (10.9%)	<0.001	0.82	33.8%	34.8%	0.02
Atrial fibrillation	1752 (61.0%)	987 (4.9%)	<0.001	1.49	41.1%	40.7%	0.01
Ischemic stroke	529 (18.4%)	1446 (7.1%)	<0.001	0.34	14.5%	14.8%	0.01
Hemorrhagic stroke	76 (2.6%)	369 (1.8%)	0.00	0.06	2.8%	2.9%	0.005
Venous thromboembolism	1085 (37.8%)	4223 (20.8%)	<0.001	0.38	34.5%	35.6%	0.02
Hypertension	2583 (90.0%)	15,206 (75.0%)	<0.001	0.40	87.3%	87.4%	0.00
Diabetes	1244 (43.3%)	8079 (39.8%)	<0.001	0.07	42.7%	42.5%	0.003
Cancer	176 (6.1%)	926 (4.6%)	<0.001	0.07	6.2%	6.5%	0.01
Chronic obstructive pulmonary disease	501 (17.5%)	1945 (9.6%)	<0.001	0.23	16.4%	16.5%	0.005
Asthma	382 (13.3%)	2363 (11.6%)	0.01	0.05	12.8%	12.6%	0.005
Dementia	1499 (52.2%)	7091 (35.0%)	<0.001	0.35	49.9%	50.7%	0.02
Long term care residence	1600 (55.7%)	6941 (34.2%)	<0.001	0.44	52.1%	52.9%	0.02
Bleeding event	332 (11.6%)	981 (4.8%)	<0.001	0.25	10.3%	10.4%	0.001
Pneumonia	1056 (36.8%)	4139 (20.4%)	<0.001	0.37	32.6%	32.8%	0.01
2019–2020 influenza vaccination	923 (32.1%)	7188 (35.4%)	<0.001	0.07	33.1%	32.4%	0.01
Number of hospitalizations in 2019, mean ± SD	1.57 ± 1.03	1.39 ± 0.83	<0.001	0.39	0.4	0.4	0.00
Hospital frailty score category			<0.001				
Missing (not hospitalized)	705 (24.6%)	11,325 (55.8%)		0.67	32.7%	28.8%	0.08
Quartile 1 (lowest)	388 (13.5%)	2595 (12.8%)		0.02	14.0%	14.0%	0.000
Quartile 2	507 (17.7%)	2079 (10.2%)		0.22	16.3%	16.5%	0.01
Quartile 3	576 (20.1%)	2179 (10.7%)		0.26	18.1%	18.6%	0.01
Quartile 4 (highest)	695 (24.2%)	2110 (10.4%)		0.37	18.9%	22.1%	0.08
John Hopkins Collapsed Aggregated Diagnosis Groups							
Acute Minor	2409 (83.9%)	15,886 (78.3%)	<0.001	0.14	81.8%	81.6%	0.003
Acute Major	2527 (88.0%)	16,492 (81.3%)	<0.001	0.19	86.3%	86.5%	0.01
Likely to Recur	1997 (69.6%)	12,683 (62.5%)	<0.001	0.15	67.4%	67.1%	0.01
Asthma	159 (5.5%)	1141 (5.6%)	0.85	0.00	5.4%	5.4%	0.001
Chronic Medical: Unstable	2430 (84.6%)	10,744 (53.0%)	<0.001	0.73	80.0%	80.4%	0.01
Chronic Medical: Stable	2198 (76.6%)	14,862 (73.3%)	<0.001	0.08	74.5%	74.4%	0.002
Chronic Specialty: Stable	239 (8.3%)	1472 (7.3%)	0.04	0.04	7.9%	8.0%	0.00
Eye/Dental	420 (14.6%)	2757 (13.6%)	0.13	0.03	14.2%	14.1%	0.003
Chronic Specialty Unstable	557 (19.4%)	3690 (18.2%)	0.12	0.03	18.4%	17.8%	0.02
Psychosocial	1925 (67.0%)	10,570 (52.1%)	<0.001	0.31	64.4%	65.2%	0.02

(*continued on next page*)

Table 1 (*continued*)

Variable	Before marginal weights				After marginal weights		
	Anticoagulated	Not anticoagulated	p-value	Std diff	Anticoagulated	Not anticoagulated	Std diff
Preventive/ Administrative	1297 (45.2%)	6588 (32.5%)	<0.001	0.26	41.0%	40.7%	0.01
Estimated glomerular filtration rate category							
<15 mL/min per 1.73 m2	16 (0.6%)	207 (1.0%)		0.05	0.8%	0.9%	0.01
15 to 30 mL/min per 1.73 m2	150 (5.2%)	575 (2.8%)		0.12	4.9%	5.2%	0.01
>30 to 60 mL/min per 1.73 m2	1232 (42.9%)	5392 (26.6%)		0.35	39.4%	39.6%	0.004
>60 to 90 mL/min per 1.73 m2	1349 (47.0%)	11,749 (57.9%)		0.22	49.5%	48.8%	0.01
> 90 mL/min per 1.73 m2	124 (4.3%)	2365 (11.7%)	<0.001	0.27	5.4%	5.5%	0.003
Total cholesterol category							
Missing	318 (11.1%)	2538 (12.5%)		0.04	12.1%	12.5%	0.01
<4.14 mmol/L	1738 (60.5%)	8721 (43.0%)		0.36	56.5%	56.5%	0.001
4.14–5.15 mmol/L	560 (19.5%)	5153 (25.4%)		0.14	21.3%	21.3%	0.002
5.16–6.19 mmol/L	200 (7.0%)	2948 (14.5%)		0.25	7.9%	7.6%	0.009
6.20–7.24 mmol/L	45 (1.6%)	753 (3.7%)		0.13	1.7%	1.8%	0.003
≥ 7.25 mmol/L	10 (0.3%)	175 (0.9%)	<0.001	0.07	0.4%	0.4%	0.01
Low density lipoprotein category							
Missing	336 (11.7%)	2715 (13.4%)		0.05	12.8%	13.3%	0.01
<2.0 mmol/L	1576 (54.9%)	7926 (39.1%)		0.32	51.4%	51.4%	0.001
2.0–3.5 mmol/L	839 (29.2%)	7758 (38.2%)		0.19	31.0%	30.8%	0.005
>3.5–5.0 mmol/L	111 (3.9%)	1765 (8.7%)		0.20	4.4%	4.2%	0.01
>5.0 mmol/L	9 (0.3%)	124 (0.6%)	<0.001	0.04	0.4%	0.4%	0.01
High density lipoprotein category							
Missing	322 (11.2%)	2567 (12.7%)		0.04	12.2%	12.6%	0.01
<0.9 mmol/L	406 (14.1%)	1919 (9.5%)		0.15	12.9%	13.1%	0.01
0.9–1.16 mmol/L	782 (27.2%)	4704 (23.2%)		0.09	26.0%	25.6%	0.01
1.17–1.29 mmol/L	332 (11.6%)	2532 (12.5%)		0.03	12.5%	12.6%	0.004
1.30–1.55 mmol/L	509 (17.7%)	4043 (19.9%)		0.06	17.8%	17.5%	0.01
>1.55 mmol/L	520 (18.1%)	4523 (22.3%)	<0.001	0.10	18.7%	18.6%	0.002
Baseline medications							
Angiotensin antagonists	1271 (44.3%)	8402 (41.4%)	0.004	0.06	44.6%	44.3%	0.007
Beta blockers	1592 (55.5%)	3768 (18.6%)	<0.001	0.83	44.4%	44.6%	0.004
Statins	1596 (55.6%)	9110 (44.9%)	<0.001	0.21	53.0%	52.8%	0.004
Steroids	193 (6.7%)	983 (4.8%)	<0.001	0.08	6.3%	6.6%	0.01
P2Y12 antagonists	53 (1.8%)	1281 (6.3%)	<0.001	0.23	2.8%	2.9%	0.01

then compared between exposed and unexposed subjects in the weighted sample, after which the absolute risk difference (ARD) and numbers needed to treat or harm (NNT/NNH) associated with anticoagulation at 60 days was calculated.

We used the Kaplan-Meier (KM) method to compare differences in risk of the composite of death or hospitalization between treatment group, as well as the risk of death (in separate analyses). The cumulative incidence function (CIF) was used to study the risk of hospitalization and other secondary outcomes, while treating death without hospitalization as a competing risk [54]. Patients were censored if they were event-free at the end of the 60-day follow-up window. Statistical significance of differences between groups was determined using the weighted log rank test for the primary outcome and for all-cause mortality. We used a weighted univariable Fine-Gray model with a robust, sandwich-type estimator to determine statistical significance for the remaining outcomes [53].

Based on clinical considerations, we decided a priori to perform two subgroup analyses. Since we hypothesized that anticoagulation may be more protective in men as a result of their higher baseline cardiovascular risk, we conducted stratified analyses by sex. We also conducted stratified analyses by LTC residency, as the first wave of COVID-19 in Ontario disproportionately affected long-term care (LTC) residents, who tend to be older and frail, with multiple comorbidities and limited life expectancy. They are more likely to have do-not-resuscitate orders, and they were less likely to be transferred to hospital during the pandemic than previously (which is expected to alter hospitalization outcomes in this group) or receive aggressive treatment for severe COVID-19 [48,55–57]. Furthermore, we conducted a post hoc analysis wherein DOACS and warfarin were studied separately. The PS was derived, and MW applied separately for each subgroup of interest (men/women, LTC residents/community-dwelling individuals).

Statistical significance was defined as a two-tailed p-value <0.05. All analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute Inc., Cary, NC).

3. Results

3.1. Baseline characteristics

As illustrated in the Supplementary Fig. 1, we identified 23,159 individuals with a positive SARS-CoV-2 PCR test who were aged ≥65 years plus 100 days and who met study inclusion criteria. The mean age was 78.5 (SD 9.8) years, 13,474 (58.2%) were female, and 8541 (36.9%) were LTC residents. We identified 2871 (12.3%) who were receiving anticoagulation at the time of their SARS-CoV-2 test, with 320 (11.1%) dispensed warfarin, 1550 (54.0%) apixaban, 816 (28.4%) rivaroxaban, 122 (4.2%) dabigatran, and 91 (3.2%) edoxaban (28 were dispensed more than one anticoagulant within the 100-day period). The baseline characteristics of the cohort, after stratification by prior anticoagulation status, are described in the left-sided columns of Table 1. As expected, anticoagulation was associated with older age and greater prevalence of cardiovascular disease, cardiovascular risk factors, and LTC residence. The baseline characteristics after application of MW are summarized in the right-sided columns of Table 1. The standardized differences were < 0.1 for all measured variables, indicating that they were not meaningfully different between anticoagulated and non-anticoagulated individuals in the weighted sample [49,53].

3.2. Outcomes

A total of 5400 (23.3%) individuals died or were hospitalized within 60 days after testing positive for SARS-CoV-2. Separately, there were 3200 (13.8%) deaths and 3183 (13.7%) hospitalizations. The crude risk of the composite outcome of death or hospitalization at 60 days was higher for SARS-CoV-2-positive outpatients who were prescribed anticoagulants at time of their positive test: 31.0% (95% CI 29.3%–32.7%)

in anticoagulated individuals versus 22.2% (95% CI 21.7%–22.8%) in non-anticoagulated individuals (please see Table 2). However, the association between outpatient anticoagulation and the composite outcome reversed following application of MWs, so that anticoagulation was associated with a lower risk of death or hospitalization at 60 days in the weighted sample (29.2%; 95% CI 27.4%–31.2%) compared to no anticoagulation (32.1%; 95% CI 30.7%–33.5%; p = 0.005). The results in the weighted sample are illustrated in Fig. 1.

Analyses of death revealed a similar pattern. The crude 60-day mortality was higher in anticoagulated patients (19.7%; 95% CI 18.3%–21.3%) than in the non-anticoagulated group (13.0%; 95% CI 12.5%–13.4%). After application of MWs, however, the mortality risk at 60 days was lower in anticoagulated patients (18.6%; 95% CI 17.0%–20.2%) than in non-anticoagulated patients (20.9%; 95% CI 19.7%–22.2%; p = 0.005). These results are summarized in Fig. 2.

The crude risk of hospitalization was 18.0% (95% CI 16.6%–19.4%) in anticoagulated individuals and 13.1% (95% CI 12.7%–13.6%) without anticoagulation. There was no difference in risk in the weighted sample at 60 days: 17.0% (95% CI 15.4%–18.6%) of anticoagulated individuals were hospitalized, compared to 17.2% (95% CI 16.0%–18.4%) of non-anticoagulated individuals (Supplementary Fig. 2). Anticoagulation was not associated with significant differences in the 60-day risk of most secondary outcomes (Supplementary Table 2). However, there was a significantly higher risk of bleeding in anticoagulated individuals: 1.1% (95% CI 0.7%–1.6%) with anticoagulation vs. 0.7% (95% CI 0.4%–0.9%) without anticoagulation ($p = 0.046$). Haemorrhagic strokes were rare but occurred more frequently in anticoagulated patients (0.2%, 95% CI 0.1%–0.5%) than non-anticoagulated patients (0.1%,95% CI 0.04%–0.1%, $p = 0.02$).

Subgroup analyses (Table 3) showed that anticoagulation was associated with comparable reductions in the risk of mortality (RRD of −10% to −15%) but variable directions of associations with regards to hospitalization, leading to some heterogeneity across subgroups in the composite outcome of death or hospitalization. Anticoagulation was associated with a significant reduction in the risk of the composite outcome in men but not in women, and for community-dwelling individuals but not LTC residents. However, anticoagulation was associated with a significant reduction in mortality among LTC residents. DOACs, but not warfarin, were associated with a significant reduction in the composite outcome. Warfarin was associated with a comparable reduction in the risk of mortality, but warfarin-treated people had higher hospitalization risk relative to non-anticoagulated individuals.

4. Discussion

This population-based cohort study examined the association of oral anticoagulation at the time of positive SARS-CoV-2 test with death or hospitalization among outpatients aged ≥65 years. As expected, people who were anticoagulated at the time of testing positive for SARS-CoV-2 were older and had a greater burden of comorbidity than non-anticoagulated patients, and had greater risk of adverse outcomes in

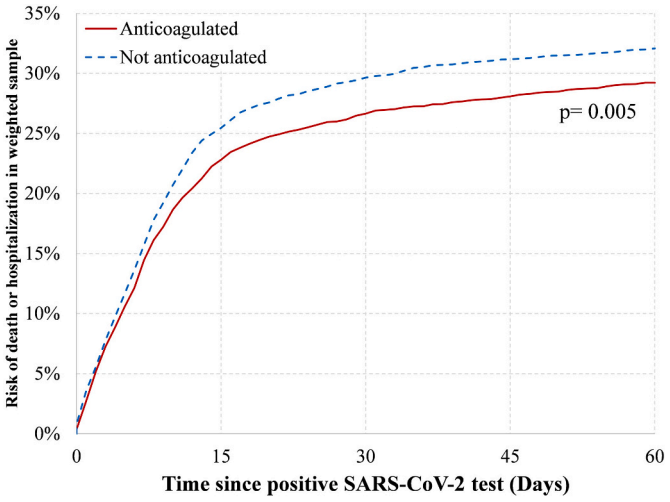

Fig. 1. Risk of death or hospitalization among outpatients aged ≥65 years old with a positive SARS-CoV-2 test for anticoagulated (red line) and non-anticoagulated (dotted blue line), after application of matching weights (estimated using Kaplan-Meier method). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

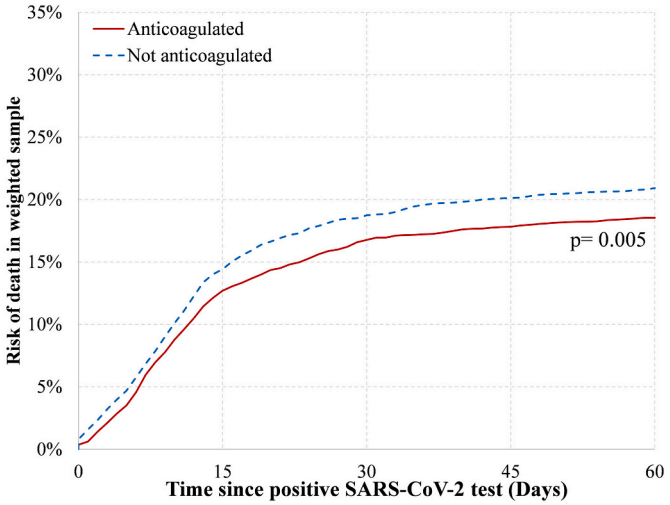

Fig. 2. Risk of all-cause death among outpatients aged ≥65 years old with a positive SARS-CoV-2 test for anticoagulated (red line) and non-anticoagulated (dotted blue line), after application of matching weights (estimated using Kaplan-Meier method). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Risk of composite and component outcomes at 60 days following a positive SARS-CoV-2 test by anticoagulation status before and after application of matching weights.

	Anticoagulated	Non-anticoagulated	p-value	RRD	ARD	NNT
		Risk of death or hospitalization within 60 days				
Crude	31.0% (95%CI 29.3%–32.7%)	22.2% (95%CI 21.7%–22.8%)	<0.001	+39.6%	+8.8%	–
After weighting	29.2% (95%CI 27.4%–31.2%)	32.1% (95%CI 30.7%–33.5%)	0.005	−9.0%	−2.9%	35
		Risk of death within 60 days				
Crude	19.7% (95%CI 18.3%–21.3%)	13.0% (95%CI 12.5%–13.4%)	<0.001	+51.5%	+6.7%	–
After weighting	18.6% (95%CI 17.0%–20.2%)	20.9% (95%CI 19.7%–22.2%)	0.005	−11.0%	−2.3%	44
		Risk of hospitalization within 60 days				
Crude	18.0% (95%CI 16.6%–19.4%)	13.1% (95% CI 12.7%–13.6%)	<0.001	+36.7%	+4.8%	–
After weighting	17.0% (95%CI 15.4%–18.6%)	17.2% (95%CI 16.0%–18.4%)	0.86	−1.2%	−0.2%	500

RRD = relative risk difference associated with anticoagulation. ARD = Absolute risk difference.

Table 3
Risk of adverse outcomes at 60 days following a positive SARS-CoV-2 test relative to anticoagulation status in prespecified subgroups of interest after application of matching weights.

Subgroup	Anticoagulated	Non-anticoagulated	p-value	RRD	ARD
Risk of death or hospitalization within 60 days in the weighted sample					
Men	31.2% (95%CI 28.4%–34.3%)	36.0% (95%CI 33.9%–38.3%)	0.003	−13.3%	−4.8%
Women	27.2% (95%CI 24.8%–29.7%)	29.2% (95%CI 27.4%–31.1%)	0.12	−7.1%	−2.1%
Non-LTC	23.5% (95%CI 21.0%–26.3%)	27.0% (95%CI 25.1%–29.0%)	0.01	−12.9%	−3.5%
LTC	34.2% (95%CI 31.6%–36.9%)	36.8% (95%CI 34.8%–38.9%)	0.1	−7.1%	−2.6%
DOACs	28.8% (95%CI 26.8%–30.8%)	32.1% (95%CI 30.7%–33.7%)	0.002	−10.4%	−3.3%
Warfarin	33.9% (95%CI 28.9%–39.6%)	34.1% (95%CI 31.6%–36.7%)	0.95	−0.4%	−0.1%
Risk of death within 60 days in the weighted sample					
Men	19.9% (95%CI 17.5%–22.6%)	23.4% (95%CI 21.5%–25.5%)	0.008	−15.1%	−3.5%
Women	17.1% (95%CI 15.1%–19.4%)	19.0% (95%CI 17.5%–20.7%)	0.08	−10.1%	−1.9%
Non-LTC	9.1% (95%CI 7.5%–11.1%)	10.2% (95%CI 9.0%–11.7%)	0.17	−10.7%	−1.1%
LTC	27.1% (95%CI 24.6%–29.7%)	30.3% (95%CI 28.3%–32.3%)	0.047	−10.6%	−3.2%
DOACs	18.6% (95%CI 16.9%–20.4%)	21.0% (95%CI 19.7%–22.4%)	0.005	−11.6%	−2.4%
Warfarin	19.5% (95%CI 15.4%–24.5%)	22.0% (95%CI 19.8%–24.3%)	0.23	−11.2%	−2.5%
Risk of hospitalization within 60 days in the weighted sample					
Men	18.3% (95%CI 15.9%–20.8%)	20.3% (95%CI 18.4%–22.2%)	0.23	−9.7%	−2.0%
Women	15.7% (95%CI 13.7%–17.6%)	15.0% (95%CI 13.4%–16.7%)	0.61	+4.1%	+0.6%
Non-LTC	20.5% (95%CI 17.8%–23.1%)	23.1% (95%CI 21.0%–25.3%)	0.12	−11.4%	−2.6%
LTC	13.4% (95%CI 11.5%–15.3%)	12.6% (95%CI 11.3%–13.9%)	0.52	+6.5%	+0.8%
DOACs	16.2% (95%CI 14.7%–17.8%)	17.1% (95%CI 15.8%–18.3%)	0.44	−5.0%	−0.9%
Warfarin	24.7% (95%CI 20.0%–29.3%)	18.6% (95%CI 16.0%–21.1%)	0.02	+32.8%	+6.1%

LTC: Long-Term Care. RRD = relative risk difference associated with anticoagulation in given stratum. ARD = Absolute risk difference associated with anticoagulation in given stratum.

crude comparisons. After application of MWs to account for baseline differences in health status and risk factors, however, outpatient anticoagulation was associated with a significantly lower risk of a composite of death or hospitalization. This difference was driven by a lower risk of death among anticoagulated patients; there was no significant difference in hospitalizations overall.

Consistent with our a priori hypothesis, outpatient anticoagulation had a larger protective effect against the composite outcome among men 65 years of age or older, with 4.8% absolute risk reduction at 60 days. At a population level, this absolute risk reduction is clinically meaningful, albeit with a p-value (0.047) at the traditional border of statistical significance. In subgroup analyses, anticoagulation was not associated with a significantly lower risk of primary or secondary outcomes in women. Anticoagulation was associated with lower risk of the composite outcome in community-dwelling patients (3.5% absolute risk reduction at 60 days), but not among LTC residents. However, anticoagulation was associated with a 3.2% absolute reduction in the risk of death at 60 days in LTC residents. This difference may reflect practice patterns in Ontario during the pandemic, wherein LTC patients with COVID-19 were typically not transferred to hospital if perceived to be at high risk of death [48].

There have been conflicting results from published RCTs of higher-dose vs. prophylactic anticoagulation in hospitalized COVID-19 patients about benefit of this strategy, although most studies reported higher bleeding risk in anticoagulated patients. The ACTION study randomized 615 patients hospitalized for COVID-19 with elevated D-dimers to therapeutic versus prophylactic anticoagulation at a median of 10 days following symptom onset. The primary outcome (a hierarchical analysis of time to death, duration of hospitalization, and duration of oxygen use through 30 days) was not statistically significant between groups (win ratio 0.86, 95% CI 0.59–1.22, $p = 0.40$) [16]. The INSPIRATION trial [15] randomized critically ill COVID-19 patients to intermediate-dose (enoxaparin, 1 mg/kg daily) vs standard-dose prophylactic anticoagulation at an average of 11 days after symptom onset. In this trial, therapeutic anticoagulation did not reduce the risk of a composite outcome of venous/ arterial thrombosis, extracorporeal membrane oxygenation, or death within 30 days (odds ratio 1.06 95% CI, 0.76–1.48; $p = 0.7$). A collaborative analysis of ATTACC, ACTIV-4a, and REMAP-CAP was terminated early because of futility and increased bleeding risk in patients who were critically ill at time of randomization [14], but was terminated early in non-critically ill patients given high likelihood of superiority of therapeutic anticoagulation [10]. Therapeutic-dose anticoagulation in non-critically ill patients increased organ support–free days and improved survival to hospital discharge without organ support, translating to a 97.3% probability of superiority of therapeutic-dose anticoagulation over usual-care in patients with high d-dimer levels, 92.9% in patients with low d-dimer levels, and 97.3% in the unknown d-dimer group. The HEP-COVID [11] trial randomized 249 hospitalized adults with COVID-19 and elevated D-dimer levels to therapeutic-dose low-molecular weight heparin or prophylactic-dose anticoagulation. Therapeutic anticoagulation significantly reduced a composite outcome of venous or arterial thromboembolism, or death from any cause, but the benefit was limited to non-critically ill patients (relative risk 0.46; 95%CI, 0.27–0.81; $p = 0.004$). The RAPID [13] trial randomized 465 adults hospitalized with COVID-19 and increased D-dimer levels to therapeutic or prophylactic dose heparin. Patients were symptomatic for an average of 7.1 days pre-randomization. Therapeutic anticoagulation did not significantly reduce risk of a composite of death, mechanical ventilation, or ICU admission (OR 0.69, 95%CI 0.43–1.10; $p = 0.12$) but significantly reduced the risk of death (HR 0.22, 95% CI 0.07 to 0.65; $p = 0.006$).

The ACTIV-4b RCT tested the hypothesis that antithrombotic therapy would improve outcomes in stable, symptomatic outpatients with COVID-19 [24]. However, the 657 patients in that trial were at lower risk of adverse outcomes than the ones we studied, with 75% of patients aged ≤59 years. Furthermore, patients started anticoagulation at a median of 10 days after symptom onset (7 days to randomization, plus 3 days from randomization to anticoagulation). There were 22 (3.3%) hospitalizations (of which 2 were fatal) after randomization but before treatment initiation, but only 5 hospitalization and no deaths after treatment initiation. Our study complements these RCTs by examining the potential impact of anticoagulation at an earlier stage of COVID-19 in an older outpatient cohort.

Our data suggest that exposure to anticoagulation very early in the course of COVID-19 infection warrants further investigation in the high-risk population of older patients who constituted our study cohort. Our analysis overcomes several limitations of prior small studies. A single-site Italian study of 70 patients with chronic heart disease who were diagnosed with COVID-19 and interstitial pneumonia reported that DOAC use at time of COVID-19 diagnosis was associated with lower mortality [59]. Another case-control study reported no significant differences in mortality when comparing 31 anticoagulated patients with 62 non-anticoagulated patients [60]. These two studies could only adjust their analyses for age and sex, given their small sample size. A single-centre observational study from New York used a PS derived from a model that included age, sex, race, Charlson Comorbidity Index, and obesity to match 139 anticoagulated to 417 non-anticoagulated patients [61]. They observed no differences in survival or time-to-mechanical

ventilation. Another study of 2878 patients hospitalized with COVID-19 in 24 French hospitals (382 [13.2%] anticoagulated before hospitalization) demonstrated a lower risk of ICU admission or in-hospital mortality for patients anticoagulated before hospital admission. Finally, an analysis of 6195 patients with COVID-19 (5597 initially treated as outpatients, of whom 160 were on anticoagulation) concluded that outpatient anticoagulation was associated with a 43% reduction in risk for hospital admission but was not associated with mortality. Interestingly, the point estimate of the HR for mortality (0.88, 95% CI 0.50–1.52) was comparable to the relative risk estimate for mortality in our higher-risk patient group.

Since the sample size and number of events in our study is far larger than all 3 studies combined, we were better powered to detect a potential impact of anticoagulation. We also included a larger number of potential confounders in our PS model and studied a broader range of outcomes. Importantly, we studied a higher-risk patient population where the risk-benefit balance is more likely to favour initiation of outpatient anticoagulation. We identified one other population-based study [62], which assessed the association of DOAC use with severe COVID-19 between February and May 2020 using all adults aged 45–84 years in Sweden (rather than restricting the study sample to individuals diagnosed with COVID-19). Since there were < 25,000 COVID-19 diagnoses before May 2020 [63] in a population of >10,000,000, this study design cannot be used to make conclusions about the efficacy of OAC use in patients diagnosed with COVID-19. It is also important to highlight that this study did not focus on older patients are at highest risk for severe COVID-19 [22,25–27].

4.1. Limitations

A limitation of our study is its observational design, meaning that we cannot preclude residual confounding. If anticoagulation was more readily offered to healthier eligible patients and avoided in eligible patients at poor health, this treatment bias may have led to better outcomes in anticoagulated patients if adjustment was not complete using our approach. Our reliance on administrative datasets means that we cannot report on some variables of clinical relevance (e.g., oxygen use out of hospital or long-term disability). We cannot account for "crossover" due to initiation, interruption, or non-adherence to anticoagulation after testing positive for SARS-CoV-2; this would potentially bias our results towards the null hypothesis. The ODB program eligibility criteria meant that we could not study the impact of anticoagulation in patients aged <65 years; however, these patients are at lower risk for severe COVID-19, so are unlikely to be considered for anticoagulation before hospitalization if diagnosed with COVID-19. We defined our exposure based on anticoagulation with warfarin or DOAC; though we accounted for prescription antiplatelet use in the PS, we could not determine exposure to aspirin. This limited our ability to assess the impact of antiplatelet use and biases our results towards the null hypothesis (i.e., we would be underestimating the effect of anticoagulation). Finally, our study was conducted before widespread COVID-19 vaccination, so our results do not apply to vaccinated patients.

5. Conclusions

In this population-based observational study of outpatients diagnosed with COVID-19 aged ≥65 years, oral anticoagulation at the time of a positive SARS-CoV-2 PCR test was associated with a lower risk of death or hospitalization. These results lend support to the hypothesis that initiating oral anticoagulation for high-risk outpatients at the time of a positive SARS-CoV-2 PCR test may yield benefit. However, this observational study does not establish causation; and there was a higher bleeding risk (including haemorrhagic stroke) in anticoagulated patients. Thus, our findings should not prompt the initiation of anticoagulation in patients with COVID-19 who do not have another indication for anticoagulation. Rather, the main implication of our analysis is that early use of anticoagulation in higher-risk patients with COVID-19 merits further study in RCTs.

CRediT authorship contribution statement

Study concept and design: All.
Acquisition of data: Abdel-Qadir, Austin, Pang, Atzema.
Analysis and interpretation of data: All.
Drafting of the manuscript: Abdel-Qadir.
Critical revision of the manuscript for important intellectual content: All.
Statistical Analysis: Abdel-Qadir, Austin, Pang, Fang, Atzema.
Obtained funding: Atzema.

Declaration of competing interest

Dr. Atzema had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors declare that they have no conflicts of interests.

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of the author(s), and not necessarily those of IRCC

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.thromres.2021.12.010.

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