Received: 28 December 2022 | Revised: 30 March 2023 | Accepted: 16 April 2023

https://doi.org/10.1016/j.rpth.2023.100167

ORIGINAL ARTICLE

Venous thromboembolism secondary to hospitalization for COVID-19: patient management and long-term outcomes

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Abstract

Background: Venous thromboembolism (VTE) is a complication of COVID-19 in hospitalized patients. Little information is available on long-term outcomes of VTE in this population.

Objectives: We aimed to compare the characteristics, management strategies, and long-term clinical outcomes between patients with COVID-19–associated VTE and patients with VTE provoked by hospitalization for other acute medical illnesses.

Methods: This is an observational cohort study, with a prospective cohort of 278

patients with COVID-19–associated VTE enrolled between 2020 and 2021 and a comparison cohort of 300 patients without COVID-19 enrolled in the ongoing START2-Register between 2018 and 2020. Exclusion criteria included age <18 years, other indications to anticoagulant treatment, active cancer, recent (<3 months) major surgery, trauma, pregnancy, and participation in interventional studies. All patients were followed up for a minimum of 12 months after treatment discontinuation. Primary end point was the occurrence of venous and arterial thrombotic events.

Results: Patients with VTE secondary to COVID-19 had more frequent pulmonary embolism without deep vein thrombosis than controls (83.1% vs 46.2%, P <.001), lower prevalence of chronic inflammatory disease (1.4% and 16.3%, P <.001), and history of VTE (5.0% and 19.0%, P <.001). The median duration of anticoagulant treatment (194 and 225 days, P = 0.9) and the proportion of patients who discontinued anticoagulation (78.0% and 75.0%, P = 0.4) were similar between the 2 groups. Thrombotic event rates after discontinuation were 1.5 and 2.6 per 100 patient-years, respectively (P = 0.4).

Conclusion: The risk of recurrent thrombotic events in patients with COVID-19–associated VTE is low and similar to the risk observed in patients with VTE secondary to hospitalization for other medical diseases.

KEYWORDS
anticoagulant treatment, COVID-19, pulmonary embolism, recurrence, venous thromboembolism

Essentials

- Little information is available on long-term outcomes of venous thromboembolism (VTE) in patients with COVID-19.
- A cohort of patients with COVID-19–associated VTE was enrolled and followed for at least 12 months after discontinuation of anticoagulant treatment.
- A control cohort of acutely ill hospitalized medical patients with VTE and no COVID-19 was included.
- The risk of recurrent thrombotic events in patients with COVID-19–associated VTE is low and similar to the risk in medical patients without COVID 19.

1 | INTRODUCTION

Several studies have reported a high incidence of venous thromboembolic (VTE) events in patients hospitalized because of COVID-19. The pooled rate of VTE was estimated to range from 15% in patients admitted to medical wards to 23% in patients admitted to intensive care units [1]. This incidence appears to be considerably higher compared to the incidence reported in medical patients with non-SARS-CoV-2–related infection, sepsis, or septic shock [2]. The increased risk of thromboembolic complications is attributed to SARS-CoV-2–related pulmonary endothelial dysfunction and systemic activation of coagulation as a result of a thromboinflammatory process [3,4].

Different therapeutic strategies are available for the treatment of VTE in hospitalized patients, including unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) followed by a direct oral anticoagulant (DOAC), warfarin, or monotherapy with a DOAC. LMWH has been proposed for patients with COVID-19–associated VTE during hospitalization due to the absence of known drug-drug interactions with antiviral agents or other therapies used to treat COVID-19, while DOACs have been proposed in the post–hospital discharge setting [5]. Little evidence is available on the long-term clinical history of COVID-19–associated VTE, in particular on the risk of recurrence after treatment is discontinued and, therefore, the optimal duration of anticoagulant treatment remains uncertain.

We aimed to compare baseline characteristics, management strategies, and long-term clinical outcomes between patients with COVID-19–associated VTE and patients with VTE secondary to hospitalization for acute medical illness without COVID-19.

2 | METHODS

In a multicenter observational study, the START-COVID VTE, we prospectively enrolled a cohort of patients with COVID-19–

associated VTE diagnosed between June 2020 and December 2021. These patients were followed up for a minimum of 12 months after treatment discontinuation. We then identified a control cohort using the database of an ongoing registry, the START2-Register. We selected patients without COVID-19 who developed VTE secondary to hospitalization before February 2020 and had a minimum follow-up of 12 months after treatment discontinuation.

The present study was carried out in the frame of the START2-Register, and approval was obtained from the institutional review board or ethics committee at each participating center. The START2-Register (NCT02219984) is an inception, prospective, observational, multicenter, dynamic, independent study that enrolls adult patients who start anticoagulant therapy, regardless of the drug and dosage used [6]. Patients are included only after providing signed informed consent. All participating centers have professional personnel qualified by education, training, and experience to perform the required tasks. All collected clinical material is property of the Arianna Anticoagulazione Foundation.

All data were gathered using an electronic clinical report form (e-CRF) developed for the START2-Register. Each participating center had access to the e-CRF by a specific account and password. All centers were invited to include patients consecutively in order to avoid a selection bias as much as possible. The e-CRF included all demographic patient data in anonymous form; only the enrolling center was able to connect the anonymous information with the name of each patient. The accuracy and completeness of data entry in the central database were monitored by dedicated study personnel at the Arianna Foundation. Information on baseline characteristics, comorbidities, and the site and extension of VTE was collected. Renal failure was defined using the Cockroft-Gault formula. Information on the type, dosage, and duration of anticoagulant treatment was collected at study entry and during follow-up. Information on study outcomes occurring during follow-up was collected. At each participating center, patients with VTE were regularly followed, with at least 1 in-person visit at 6 and 12 months. A final visit, in-person or by telephone contact, was requested at the end of follow-up.

All therapeutic decisions were entirely left to the discretion of the treating physicians.

2.1 | Study population

Patients were eligible for inclusion in the prospective cohort if they had objectively diagnosed proximal or distal deep vein thrombosis (DVT) of the lower limbs or DVT of the upper limbs and/or pulmonary embolism (PE) diagnosed during hospitalization for COVID-19. Diagnosis of SARS-CoV-2 infection in these patients had to be confirmed by reverse-transcriptase polymerase chain reaction method on nasopharyngeal and oropharyngeal swabs. Patients were eligible for inclusion in the control cohort if they had objectively diagnosed proximal or distal DVT of the lower or DVT of the upper limbs and/or PE diagnosed during hospitalization for an acute medical illness without COVID-19. For both cohorts, the following exclusion criteria were applied: failure to provide written informed consent, other indications to anticoagulant treatment, active cancer, recent (<3 months) major surgery, trauma, pregnancy, and participation in interventional studies.

2.2 | Study outcomes

The primary end points of the study included the occurrence of symptomatic venous or arterial thrombotic events during follow-up, both on treatment and after treatment discontinuation; overall mortality; and major bleeding during anticoagulant treatment. The occurrence of recurrent DVT or PE had to be objectively confirmed by appropriate imaging tests (compression ultrasonography and/or angio-computed tomography scan). Information on all outcome events was centrally reviewed, and discrepancies in the interpretation of the outcomes were resolved by contacting local investigators. Major bleeding was defined using the International Society on Thrombosis and Haemostasis (ISTH) definition [7]. Long-term outcome events were measured and collected prospectively for all patients with COVID-19–associated VTE. For the control cohort, information on long-term outcome events was ascertained from the START2-VTE register database.

Secondary end points included the occurrence of the individual components of the primary end point, DVT at any site, PE, acute myocardial infarction, acute ischemic stroke, and acute peripheral artery disease, as well as clinically relevant nonmajor bleeding, using the ISTH definition [8].

2.3 | Statistical analysis

Data are described as the median value and IQR or mean value ± SD for continuous variables and as proportions for categorical variables. Differences between continuous values were assessed using the unpaired *t*-test, and categorical variables were compared by the chi-squared test or Fisher exact test, as appropriate. The median and IQR follow-up times were calculated, and the median test applied to test difference between groups is reported. The incidence of recurrence, death, and bleeding events was calculated by dividing the number of events by person time at risk. The incidence rate ratios (IRRs) together with the 95% CI were calculated. *P* values <.05 were considered statistically significant. The data were analyzed using SPSS software for Windows, V.26 (SPSS), and Stata V.14 statistical software package (StataCorp).

3 | RESULTS

From June 2020 to December 2021, 290 patients who developed VTE events during hospitalization for COVID-19 were included in 16 centers in Italy. Twelve patients were excluded from the analysis, as 9 were lost to follow-up and 3 withdrew informed consent. We identified 300 patients with VTE secondary to hospitalization for an

TABLE 1 Baseline characteristics.

	COVID-19	Controls
Patients, *n*	278	300
Male sex, *n* (%)	193 (69.4)	164 (54.7)
Age (y), mean (SD)	64 (14)	66 (15)
Body mass index, mean (SD)	27 (5)	28 (5)
Hypertension, *n* (%)	128 (46.0)	128 (42.7)
Diabetes mellitus, *n* (%)	51 (18.3)	33 (11.0)
Coronary artery disease, *n* (%)	16 (5.7)	19 (6.3)
Congestive heart failure, *n* (%)	8 (2.9)	15 (5.0)
Peripheral arterial disease, *n* (%)	6 (2.2)	9 (3.0)
Chronic obstructive pulmonary disease, *n* (%)	25 (9.0)	30 (10.0)
Chronic inflammatory disease, *n* (%)	4 (1.4)	49 (16.3)
Severe renal failure (eGFR < 30 mL/min), *n* (%)	6 (2.2)	8 (2.7)
eGFR 30-59 mL/min, *n* (%)	48 (17.3)	71 (23.7)
History of major bleeding events, *n* (%)	5 (1.8)	15 (5.0)
Previous ischemic cerebrovascular disease, *n* (%)	6 (2.2)	14 (4.7)
Previous VTE, *n* (%)	14 (5.0)	57 (19.0)

eGFR, estimated glomerular filtration rate; VTE, venous thromboembolism.

acute medical illness, but not related to COVID-19, who were included in the START2-Register between January 2019 and January 2021. The baseline characteristics of the study population are described in Table 1. Briefly, male sex (69.4% and 54.7%, P <.001) and diabetes (18.3% and 11.0%, P <.01) were more prevalent in patients with VTE related to COVID-19, whereas the prevalence of chronic inflammatory disease (1.4% and 16.3%, P <.001), history of cerebrovascular events (2.2% and 4.7%, P <.001), history of VTE (5.0% and 19.0%, P <.001), and history of major bleeding events (1.8% and 5.0%, P <.001) were significantly lower in patients with COVID-19 than in controls. No difference was found between the 2 groups with regard to other variables. The characteristics of VTE events are described in Table 2. PE without concomitant DVT occurred more frequently in patients with VTE secondary to COVID-19 than in controls (P <.0001).

During the acute phase treatment, significantly more patients with COVID-19–associated VTE received parenteral anticoagulant treatment than controls (86.3% and 42.6%, P <.001). LMWH was the most frequently prescribed drug in patients with COVID-19 (75.5% and 27.3%, P <.001), whereas significantly fewer patients

TABLE 2 Characteristics of the index VTE event and type and duration of anticoagulant treatment.

	COVID-19 *N* = 278	Controls *N* = 300
Deep vein thrombosis of the lower limbs, *n* (%)	68 (24.4)	248 (82.7)
Proximal deep vein thrombosis, *n* (%)	37 (54.4)	170 (68.5)
Distal deep vein thrombosis, *n* (%)	31 (45.6)	78 (31.4)
Upper extremity venous thrombosis, *n* (%)	8 (2.9)	16 (5.3)
Pulmonary embolism, *n* (%)	243 (87.4)	78 (26.0)
Isolated pulmonary embolism	202 (83.1)	36 (46.2)
Site of pulmonary embolism,[a] *n* (%)		
Main artery	49 (20.2)	Not available
Segmentary artery	144 (59.2)	Not available
Subsegmentary artery	50 (20.6)	Not available
Incidentally detected pulmonary embolism, *n* (%)	16 (6.5)	6 (7.7)
Anticoagulants, acute phase treatment, *n* (%)		
LMWH	210 (75.5)	82 (27.3)
UFH	17 (6.1)	-
Fondaparinux	13 (4.7)	46 (15.3)
DOACs	38 (13.7)	172 (57.3)
Anticoagulants, secondary prevention, *n* (%)		
Vitamin K antagonists	6 (2.2)	35 (11.7)
Fondaparinux	2 (0.7)	7 (2.3)
Low-molecular-weight heparin	22 (7.9)	21 (7.0)
Direct oral anticoagulants, *n* (%)	248 (89.2)	233 (77.7)
Apixaban	111	82
Dabigatran	31	22
Edoxaban	65	48
Rivaroxaban	41	81
Duration of anticoagulant treatment (d), median (IQR)	194 (106; 335)	225 (138; 413)
Duration of treatment (d), *n* (%)		
≤90 d	37 (13.3)	34 (11.3)
91-180 d	88 (31.6)	72 (24.0)
181-365 d	99 (35.6)	86 (28.7)
>365 d	54 (19.4)	108 (36.0)

DOAC, direct oral anticoagulant; LMWH, low-molecular-weight heparin; UFH, unfractionated heparin; VTE, venous thromboembolism.
[a]Information available for 243 patients.

TABLE 3 Events during the follow-up.

	COVID-19 *N* = 278	Controls *N* = 300	IRR (95% CI)
Events during anticoagulation			
Duration of follow-up on treatment (patient-y)	180.4	194.0	
Thrombotic events, *n* (rate/100 patient-y)	4 (2.2)	5 (2.6)	0.8 (0.2-3.9)
Deep vein thrombosis, *n*	1	1	
Acute myocardial infarction, *n*	3[a]	1	
Pulmonary embolism recurrence, *n*		1[a]	
Peripheral artery disease, *n*		1	
Stroke, *n*		1	
Major bleeding, *n* (rate/100 patient-y)	3 (1.6)	3 (1.5)	1.0 (0.1-7.8)
Hematuria, *n*	1		
Muscular hematoma, *n*	1		
Intracranial bleeding, *n*		1	
Gastrointestinal bleeding, *n*	1	2	
Overall mortality, *n* (%) [rate/100 patient/y]	11 (3.8) [6.1]	16 (4.8) [8.2]	1.3 (0.5-3.2)
Anticoagulant treatment discontinuation			
Patients, *n* (%)	217 (78.0)	225 (75.0)	
Duration of follow-up after discontinuation (d), median (IQR)	312 (300; 365)	341 (313; 365)	
Duration of follow-up (patient-y)	201	264	
Reasons for discontinuation			
End of the planned treatment period, *n*	212	215	
Major bleeding, *n*	2	1	
Contraindications, *n*		4	
General practitioner decision, *n*	1	3	
Patient decision, *n*	2	2	
Outcome events after treatment discontinuation			
Thrombotic events, *n* (rate/100 patient-y)	3 (1.5)	7 (2.6)	1.6 (0.4-10.6)
Deep vein thrombosis, *n*		6	
Deep vein thrombosis and pulmonary embolism, *n*	1		
Cerebral vein thrombosis, *n*	1		
Stroke, *n*	1	1	
Overall mortality, *n*		3	

IRR, incidence rate ratio.
[a]One fatal.

with COVID-19 received fondaparinux (4.7% and 15.3%, P <.001) or DOACs (13.7% and 57.3%, P <.001) than controls. Following the acute phase treatment, DOACs were more frequently prescribed to patients with COVID-19 than to controls (89.2% and 77.7%, P =.03). The median duration of anticoagulant treatment was similar between the 2 groups, but the proportion of patients treated for >365 days was lower in patients with VTE secondary to COVID-19 than in the control group (19.4% and 36.0%, P <.001). The reasons for treatment discontinuation are described in Table 3.

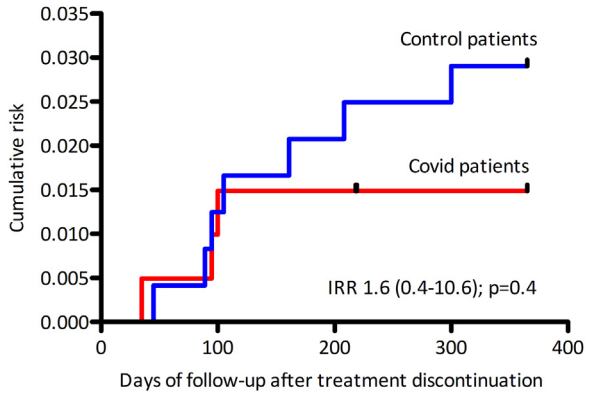

FIGURE Kaplan-Meier curves for cumulative thrombotic event rates after treatment discontinuation in patients with COVID-19 and controls. IRR, incidence rate ratio.

3.1 | Follow-up

The median duration of follow-up was 180.4 patient-years for patients with COVID-19–associated VTE and 194.0 patient-years for controls (Table 3). While on treatment, a total of 9 thrombotic events and 6 major bleeding events occurred, with no difference between patients with COVID-19–associated VTE and controls. One thrombotic event in each group was fatal.

During treatment, 27 deaths were recorded: 11 in the COVID-19 group and 16 in the control group. Seven patients with COVID-19 died during hospitalization, and none died in the control group. Mortality rates were similar between the 2 groups. Causes of death in the COVID-19 group included acute myocardial infarction (n = 1), acute respiratory failure (n = 7), and sepsis (n = 1); in 2 patients the cause of death remained unknown. In the control group, information on causes of death was available for 4 patients: PE (n = 1) and heart failure (n = 3). The remaining fatalities (n = 12) were all reported to be of unknown cause.

The proportion of patients who discontinued anticoagulation was similar between the 2 groups (78.0% and 75.0%, respectively); the duration of follow-up after discontinuation of anticoagulant treatment was similar between the 2 groups (Table 3). After treatment discontinuation, there were 3 thrombotic events in the COVID-19–related VTE group and 7 in the control group (P = n.s.; Figure). Three additional patients died in the control group: 2 due to heart failure and 1 of unknown cause. No more patients died in the COVID-19–related VTE group.

4 | DISCUSSION

In this observational cohort study, we compared baseline characteristics, anticoagulant treatment strategies, and long-term outcomes of patients with COVID-19–associated VTE and patients with VTE secondary to hospitalization for other medical reasons. Patients with COVID-19–associated VTE had fewer comorbidities and a significantly higher proportion of isolated PE events than controls. Patients with COVID-19–associated VTE more frequently received parenteral treatment with LMWH during hospitalization and DOACs after discharge than controls. The duration of anticoagulant treatment was similar between the 2 groups. The rates of thrombotic events during follow-up were low and similar between the 2 groups, also after discontinuation of anticoagulant treatment. Bleeding rates occurring during anticoagulant treatment and mortality rates during follow-up were also comparable between the 2 groups.

There is currently no guidance in the literature on the duration of secondary prevention of VTE with anticoagulant drugs in patients who developed VTE during hospitalization for COVID-19, and uncertainty exists on the optimal duration of treatment in these patients. Previous studies have shown a potential for late cardiovascular complications due to subclinical cardiovascular inflammation in patients with COVID-19, with an increased 12-month burden of incident thromboembolic events, in particular PE, regardless of the severity of disease [9,10]. These findings may suggest the need for a more extended secondary prophylaxis, in particular in patients with PE as the index event and in those with residual respiratory symptoms. By contrast, the low event rates found in our study after treatment discontinuation support the use of a definite duration of anticoagulation (ie, 3-6 months) also in this setting, as it is currently recommended for all patients with VTE secondary to a transient risk factor, including hospitalization for an acute medical illness [11].

Our findings are in keeping with the results of a single-center, prospective cohort study that reported no recurrent events after 12 months of follow-up in 48 patients who developed COVID-19–associated VTE developed during hospitalization, 83% of whom had PE [12]. In this study, treatment was stopped at 6 months in the majority of patients, while 16% continued indefinitely. Our results are also consistent with the findings of a recently published subgroup analysis of the RIETE registry, which reported on 1372 patients with COVID-19–associated VTE [13]. In 51.6% of patients who had discontinued treatment after a median of 4.6 months, the recurrence rate of VTE was 4.8 per 100 patient-years. As compared to these 2 studies, our study had a longer duration of follow-up after treatment discontinuation and a carefully selected control group of patients that further strengthen our conclusions. In the present study, we have also included arterial thrombotic events in the primary outcome given the long-term increased risk of cardiovascular disease reported in patients with COVID-19 in previous studies [10]. Few episodes of acute myocardial infarction, ischemic stroke, or peripheral artery disease were documented during follow-up, and no difference was detected between the 2 groups.

Treatment duration in the present study was heterogeneous, exceeding the 3- to 6-month duration suggested in the presence of transient risk factors in as many as 53% of patients with COVID-19–associated VTE and 61% of patients in the control group, suggesting that the decision to extend treatment duration was unrelated to the previous SARS-CoV-2 infection. Heterogeneous duration of anticoagulant treatment for the secondary prevention of VTE associated with removable risk factors has been previously reported. In a subgroup analysis of the RIETE study, 42% of patients with VTE secondary to transient risk factors were treated for more than 12 months

[14]. Probably, underlying risk factors are not the only drivers for treatment duration in clinical practice, but the decision is based on a more general risk stratification in an individual patient that takes into account the site of VTE, presence of additional risk factors for recurrence and bleeding, even when minor, and patient preferences.

Some limitations of this study need to be acknowledged. First, the study requested a minimum number of visits during follow-up, but the total number of in-person visits or telephone contacts during follow-up was left to the discretion of the treating clinician. We cannot exclude that differences in the number of visits performed at each center may have influenced event rates. However, all outcome events reported by the study center were centrally assessed and investigators were contacted in case of unclear adjudications. We consider unlikely that major clinical events were missed. Second, data for the control group were collected retrospectively, and some information may have been missed. However, the START2-Register is conducted prospectively and includes all variables of interest also for this study, and the quality of information is routinely assessed at the coordinating center. Third, patients with upper limb DVT and distal DVT were included in the study. Although we acknowledge that long-term outcome rates of recurrence are likely lower in these patients, patients with upper limb DVT were few and equally distributed between the 2 groups, and most patients with distal DVT had concomitant PE, in particular in the COVID-19 group. Thus, the number of patients with isolated distal DVT was small and not different between the 2 groups. For these reasons, we consider unlikely that the presence of these patients may have influenced the overall event rates reported in this study. Fourth, given the low number of events, we did not adjust for differences in baseline characteristics or treatment strategies between the 2 groups, as we consider highly unlikely that such imbalances result in different results. Finally, although centers were invited to enroll eligible patients consecutively, a screening log was not available at most of these centers, and the number of patients excluded because of participation in interventional trials was not reported. However, only 5 of the 28 centers also participated in interventional studies, and the number of patients enrolled in these studies was extremely low, suggesting a low risk of selection bias.

In conclusion, the risk of recurrent thrombotic events in patients with COVID-19–associated VTE is low and similar to the risk observed in patients with VTE secondary to hospitalization for other medical diseases. A definite duration of anticoagulant treatment for 3 to 6 months seems reasonable for the majority of these patients.

APPENDICES

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FUNDING

The Arianna Anticoagulation Foundation promotes and supports the START-Register, including the present study. The authors do not disclose receipt of the financial support for the research, authorship, and/or publication of this article.

ETHICS STATEMENT

The present study was conducted in the frame of the START2-Register, and approval was obtained from the institutional review board or ethics committee at each participating center.

AUTHOR CONTRIBUTIONS

W.A.: study design, interpretation of data, manuscript preparation; E.A.: patient identification, interpretation and analysis of data, manuscript approval; E.B.: acquisition and interpretation of data, manuscript approval; A.C.: acquisition and interpretation of data, manuscript approval; V.F.: acquisition and interpretation of data, manuscript approval; R.P.: acquisition and interpretation of data, manuscript approval; S.P.: acquisition and interpretation of data, manuscript approval; F.P.: acquisition and interpretation of data, manuscript approval; P.P.: acquisition and interpretation of data, manuscript approval; A.M.P., G.M.P.: acquisition and interpretation of data, manuscript approval; N.P.: acquisition and interpretation of data, manuscript approval; L.S.: acquisition and interpretation of data, manuscript approval; S.T.: acquisition and interpretation of data,

manuscript approval; A.V.: acquisition and interpretation of data, manuscript approval; G.P., D.P.: study design, manuscript revision and approval.

RELATIONSHIP DISCLOSURE

W.A. has received payment or honoraria for lectures from Aspen, Bayer, BMS, Leo Pharma, Norgine, Pfizer, Sanofi, and Werfen and participated on Advisory Boards for Bayer, Leo Pharma, Norgine, Sanofi, and Viatris. G.P. has received consulting fees from Alfa Sigma. All other authors have no competing financial or other interests or activities to disclose.

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