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ORIGINAL ARTICLE

Venous thrombosis risk during and after medical and surgical hospitalizations: The medical inpatient thrombosis and hemostasis (MITH) study

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Abstract

Background: Thirty to seventy percent of all venous thromboembolism (VTE) events are associated with hospitalization. The absolute and relative risks during and after hospitalization are poorly characterized.

Objectives: Quantify the absolute rate and relative risk of VTE during and up to 3 months after medical and surgical hospitalizations.

Patients/Methods: We conducted an observational cohort study between 2010 and 2016 of patients cared for by the University of Vermont (UVM) Health Network's primary care population. Cox proportional hazard models with hospitalization modeled as a time-varying covariate were used to estimate VTE risk.

Results: Over 4.3 years of follow-up, 55 220 hospitalizations (156 per 1000 person-years) and 713 first venous thromboembolism events (2.0 per 1000 person-years) occurred. Among individuals not recently hospitalized, the rate of venous thromboembolism was 1.4 per 1000 person-years and 71.8 per 1000 person-years during hospitalization. During the first, second, and third months after discharge, the rates

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of venous thromboembolism were 35.1, 11.3, and 5.2 per 1000 person-years, respectively. Relative to those not recently hospitalized, the age- and sex-adjusted HRs of venous thromboembolism were 38.0 (95% CI 28.0, 51.5) during hospitalization, and 18.4 (95% CI 15.0, 22.6), 6.3 (95% CI 4.3, 9.0), and 3.0 (95% CI 1.7, 5.4) during the first, second, and third months after discharge, respectively. Stratified by medical versus surgical services the rates were similar.

Conclusion: Hospitalization and up to 3 months after discharge were strongly associated with increased venous thromboembolism risk. These data quantify this risk for use in future studies.

KEYWORDS
cohort studies, epidemiology, hospitalization, patient discharge, venous thromboembolism

1 | INTRODUCTION

Venous thromboembolism (VTE) consists of deep venous thrombosis (DVT) and pulmonary embolism (PE) and affects approximately 1 million individuals in the United States annually resulting in 100 000 deaths.[1-4] Unique among vascular diseases, VTE has effective pharmacologic prevention strategies (albeit at the cost of increased bleeding) and risk is often concentrated around identifiable and sometimes transient risk factors.[5] Provoked VTE are those events in which one or more clear temporally associated risk factors are identified, for example surgery, fracture, or hospitalization.[6]

Thirty to seventy percent of all VTE events are associated with hospitalization and the time periods after hospitalization.[7,8] Efforts to prevent VTE in hospitalized patients include administration of low-dose anticoagulants, but the benefit of this strategy in the post-discharge period is less clear.[9] According to recently published randomized clinical trials, extending thromboprophylaxis after hospital discharge does not provide clinical benefit and may result in excessive bleeding.[10] This could be in part due to not selecting the patients at highest risk of VTE and lowest risk of bleeding.

To address the gap in contemporary knowledge of the relative and absolute contribution of hospitalization on VTE risk, we followed a cohort of individuals receiving primary care at sites affiliated with an academic medical center in Vermont. We sought to (1) determine the relative and absolute risk of VTE during and up to 3 months after hospitalization and (2) assess VTE risk by medical and surgical hospitalizations.

Essentials

- Hospitalization is a key risk factor for Venous Thrombosis but little is known about the absolute and relative risk in a contemporary population.
- We assessed hospitalization as a risk factor for VTE in a primary care population in northwest Vermont, United States.
- Hospitalization resulted in a 38-fold increased hazard of VTE, with risk remaining 3-fold higher up to 3-months after discharge.
- We characterized the relative and absolute risk of VTE during and up to 3-months after hospitalization which can be used to design further intervention studies.

2 | METHODS

2.1 | Population

Individuals 18 years old and older who received at least one primary care visit at the UVM Health Network were included in the cohort. UVM Medical Center is a tertiary care hospital in northwestern Vermont that serves as the primary (and only) hospital and imaging center for Chittenden County, VT with a population of 164 572 (Figure 1).[11] UVM Medical Center deployed the fully integrated Epic electronic medical record across its inpatient and ambulatory services in October 2010 (Epic Systems Corporation, Verona, WI). Thus, individuals receiving primary care with UVM providers have near complete capture of their healthcare utilization. Individuals with a past history of VTE defined per International Classification of Diseases, Ninth or Tenth Edition, Clinical Modification (ICD-9/10-CM) diagnosis codes occurring within the first 3 months of entry to the cohort were excluded from all analyses (codes listed in Tables S1 and S2).[12]

2.2 | Follow-up time

Patients entered the cohort at the time of their first encounter with a UVM primary care provider, on or after October 1, 2010, to the time of change to a non-UVM primary care provider, death, a VTE event, or December 31, 2016 (whichever occurred first). Admission

to the hospital included both 'observation' and inpatient admissions and follow-up continued after people were discharged from the hospital. Observation status corresponded to those patients who spent only one night at the hospital (Figure 2). Follow-up time in the hospital was defined as days between admission and discharge inclusive of the admission and discharge day. Subsequent 1-month (30-day) periods after discharge and up to 3 months were assessed as risk factors for VTE. If an individual was readmitted within the 3 months after discharge from the hospital, the follow-up accrued with the most recent hospitalization (Figures 2 and 3). All other time was considered "no recent hospitalization" time.

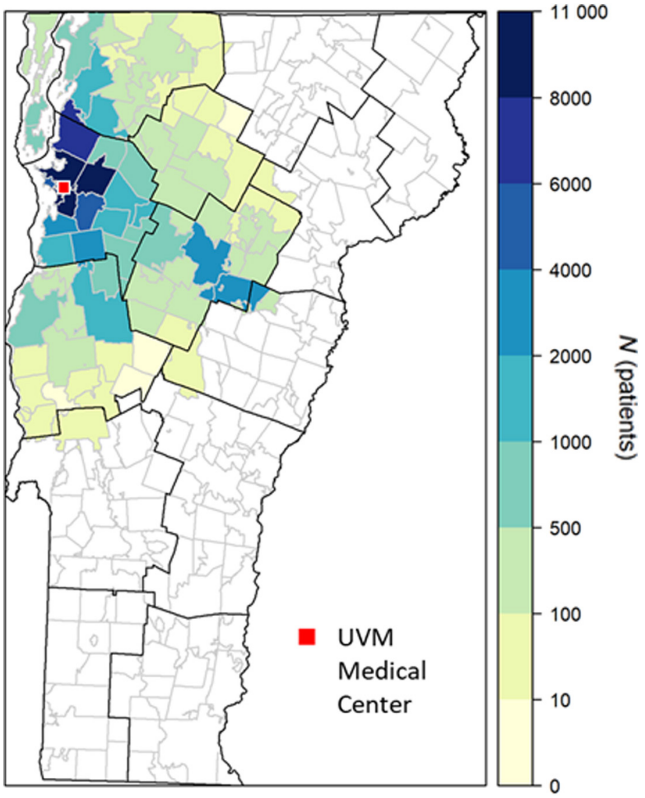


FIGURE 1 Geographic distribution of the cohort within the state of Vermont

2.3 | Outcome and risk factor ascertainment

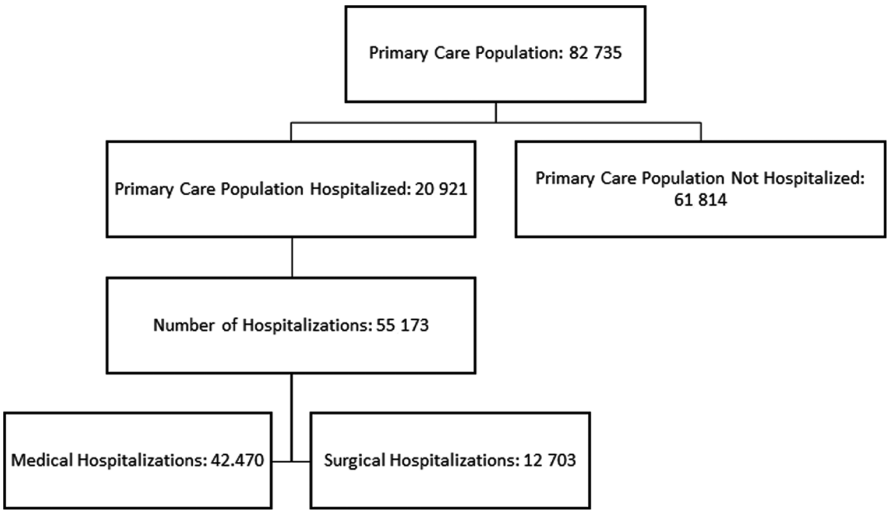
Incident VTE was defined as having one inpatient or two outpatient VTE ICD-9/10-CM codes 7–185 days apart, and with an anticoagulation prescription occurring within 30 days of the index report.[12] The event date was the first date of a positive code.[12] This definition was previously shown to increase the positive predictive value for VTE to >90%.[13] VTE were classified into mutually exclusive groups as (1) those occurring during hospitalization when VTE was identified more than 24 h after admission to the hospital; (2) those occurring during time periods after hospitalization, defined as successive 1 month intervals for the total of 3 months post discharge; and (3) those occurring with no hospitalization in the prior 3 months (Figure 2).

Hospitalization and the dates of hospitalization were identified from the electronic medical record, as were age at the time of cohort entry and biologic sex. Surgical and medical hospitalizations were defined by the discharge service regardless of whether procedures were performed during the hospitalization. Surgical services consisted of cardiothoracic surgery, orthopedic surgery, urologic surgery, vascular surgery, general surgery, trauma surgery, or surgical intensive care unit and medical services consisted of cardiology, hematology, oncology, internal medicine/family medicine, medical intensive care, or neurology).

2.4 | Statistical analyses

We compared age, sex, follow-up time, and the type of hospitalization by VTE status using univariate analysis (χ^2 tests for categorical risk factors and two-tailed *t*-tests for continuous risk factors). Hazard ratios and 95% confidence intervals for the association between hospitalization and VTE incidence were estimated using age- and sex-adjusted Cox proportional hazards models. The main exposure

FIGURE 2 Population flow chart



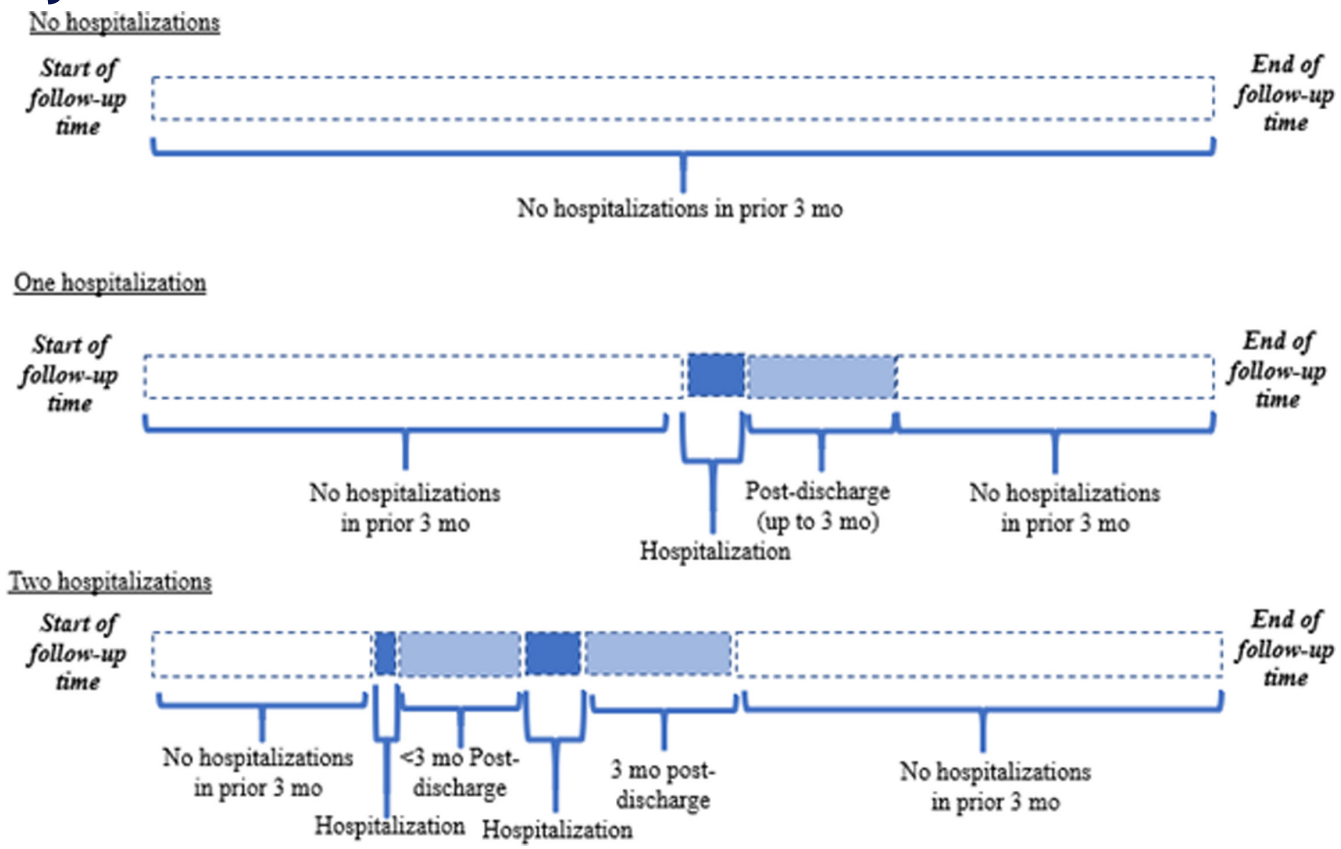


FIGURE 3 Graphical explanation of follow-up time under various scenarios

TABLE 1 Characteristics of the 82 735 participants by VTE case status and Hospitalization: University of Vermont Medical Center, 2010–2016

	Outcome		Exposure	
	VTE free	VTE[a]	Not hospitalized	Hospitalized
Number	82 022	713	59 813	22 922
Baseline Mean Age (SD)	46 (18.1)	58 (16.5)	44 (16.6)	54 (20.0)
Female	46 284 (56.4%)	378 (53.0%)	32 457 (54.3%)	14 205 (62.0%)
Male	35 738 (43.6%)	335 (47.0%)	27 356 (45.7%)	8717 (38.0%)
Median Years Follow-up (IQR)	4.2 (2.2, 6.3)	2.7 (1.0, 4.3)	4.6 (1.9, 6.2)	6.0 (3.6, 6.5)
Total number of hospitalizations	55 173	47	0	55 220
Non-surgical Hospitalizations (*N*)	42 470	34	0	42 504
Surgical Hospitalizations (*N*)	12 703	13	0	12 716

[a]Note, follow-up censored at the first VTE-event among VTE cases.

windows of interest (time in the hospital and each of the successive 1-month periods after discharge [up to 3 months]) were modeled as time-varying covariates. Separate analyses were also conducted by hospitalization type (surgical or medical). If a person was readmitted to the hospital within 3-months of discharge, the risk reset to the appropriate variable (surgical or medical hospitalization and time periods after hospitalization). Three months after discharge, the exposure reset to no recent hospitalization (Figure 3). There was no missingness for age, sex, dates of hospitalization, discharge services, or discharge ICD codes. Statistical analyses were performed using R 3.5.1 (R Foundation for Statistical Computing).

3 | RESULTS

3.1 | Population

From October 2010 through December 2016, 82 735 individuals 18 and older were followed for a median of 4.2 years. Among those, 46 284 were women (56%) and the median age was 46. All individuals were residents of the state of Vermont and 72.6% were resident of Chittenden County, Vermont (Figures 1 and 2). Table 1 presents the baseline characteristics of the population stratified by those who had

and did not have VTE over follow-up as well as those who were hospitalized versus those who were not hospitalized during follow-up.

3.2 | Follow-up time, VTE events and hospitalizations

Over 354 022 person-years of follow-up there were 713 first VTE events among 82 735 individuals and 55 173 hospitalizations among 20 921 individuals (some individuals were hospitalized more than once). There were 42 470 hospitalizations with a medical discharge service and 12 703 with a surgical discharge service.

3.3 | VTE rate and incidence

The overall rate of VTE in the cohort was two events per 1000 person-years (Table 2). Among the 214 VTE events occurring during or 3 months after hospitalization, 47 (22%) occurred during hospitalization and 167 (78%) within 3 months after discharge. While 97% of the follow-up time occurred when individuals were not hospitalized (344 793 of 354 022 person-years), only 69% (499 of 713) of VTE events occurred outside of the context of hospitalization and the 3 months post-discharge.

3.4 | VTE rate and incidence by hospitalization status

In individuals who were not hospitalized and did not have a hospital discharge within the prior 3 months, there were 499 VTE events over 344 793 person-years of follow-up (1.4 VTE events per 1000 patient-years) (Table 2). The absolute rate of VTE was 71.8 per 1000 patient-years during hospitalization (47 events among 655 person-years). Over the successive 1-month periods after discharge, the rates of VTE were: 35.1 per 1000 person-years (124 events over 3530 person-years) in month 1, 11.3 per 1000 person-years (31 events over 2746 person-years) in month 2, and 5.2 per 1000 patient-years (12 events over 2298 person-years) in month 3. The cumulative incidence of VTE during hospitalization and for 3 months afterwards was 0.39% (214 events among 55 173 hospitalizations). For medical hospitalizations the corresponding rates were 73.9 per 1000 patient-years during hospitalization and 36.6, 12.5 and 5.3 per 1000 patient-years for the successive 1-month periods after discharge. The cumulative incidence of VTE during and for 3-months after hospitalization was 0.38% (162 VTE among 42 470 medical hospitalizations) For surgical hospitalizations, these rates were 66.7 per 1000 patient-years during hospitalization and 30.8, 8.5, and 5.1 per 1000 patient-years for the successive 1-month periods after discharge (Table 2). The cumulative incidence of VTE for surgical hospitalization and the 3 months after discharge was 0.41% (52 VTE among 12 702 hospitalizations).

Using age- and sex-adjusted Cox proportional hazards models with hospitalization modeled as a time-varying covariate, and with those not hospitalized in the prior 3 months as the reference group, the hazard ratio of VTE for hospitalization was 38.0 (95% CI 28.0, 51.5). The hazard ratios of VTE were 18.4 (95% CI 15.0, 22.6) for the first month, 6.33 (95% CI 4.3, 9.0) for the second month, and 3.0 (95% CI 1.7, 5.4) for the third month post-discharge. For non-surgical hospitalizations, compared to those not hospitalized in this prior 3 months, the hazard ratio for VTE was 36.5 (95% CI 25.6, 51.9). For the subsequent 1-month periods after discharge versus those

TABLE 2 Relative and absolute risk of VTE for hospitalization and surgical and medical

Timeframe	Person-years follow-up	N of VTE	VTE per 1000 person-years	Age- and Sex-adjusted HR (95% CI)
No recent hospitalization	344 793	499	1.4	1.0 (Reference)
All hospitalizations				
During hospitalization	655	47	71.8	38.0 (28.0, 51.5)
Month 1 after discharge	3530	124	35.1	18.4 (15.0, 22.6)
Month 2 after discharge	2746	31	11.3	6.3 (4.3, 9.0)
Month 3 after discharge	2298	12	5.2	3.0 (1.7, 5.4)
Non-surgical hospitalizations				
During hospitalization	460	34	73.9	36.5 (25.6, 51.9)
Month 1 after discharge	2622	96	36.6	17.4 (13.8, 21.9)
Month 2 after discharge	1920	24	12.5	6.2 (4.1, 9.4)
Month 3 after discharge	1518	8	5.3	2.7 (1.4, 5.5)
Surgical hospitalizations				
During hospitalization	195	13	66.7	41.6 (24.0, 72.3)
Month 1 after discharge	908	28	30.8	22.2 (15.2, 32.6)
Month 2 after discharge	826	7	8.5	6.2 (3.0, 13.2)
Month 3 after discharge	780	4	5.1	3.8 (1.4, 10.1)

not within 3 months of a hospitalization, the respective hazard ratios were 17.4 (95% 13.8, 21.9), 6.2 (95% CI 4.1, 9.4), and 2.7 (95% CI 1.4, 5.5). The corresponding hazard ratios for surgical hospitalizations were 41.6 (95% CI 24.0, 72.3) during the hospitalization and 22.2 (95% CI 15.2, 32.6), 6.2 (95% CI 3.0, 13.2), and 3.8 (95% CI 1.4, 10.1) for subsequent 1-month periods after discharge.

4 | DISCUSSION

In a cohort of adults receiving primary care through the University of Vermont Health Network, hospitalization and the 3 months after hospitalization accounted for 31% of all VTE events, while only accounting for 3% of the total follow-up time. Hospitalization was associated with a dramatically increased risk of VTE, with a hazard ratio of 38.0, as compared with non-hospitalized time periods, and this risk remained elevated for at least 3 months after discharge, gradually diminishing over time.

These findings confirm and extend previous observations about risk for VTE in hospitalized patients and the persistence of risk after discharge.[14] Our results revealed that hospitalized, patients had an absolute rate of 71.8 VTE events per 1000 person-years, as compared to 1.4 VTE events per 1000 person-years with no recent hospitalization, corresponding to a 38.0-fold increased hazard of VTE while in the hospital. Similar to the current study, in a study based in Olmstead County, Minnesota in the 1980s, the absolute rate of VTE in hospitalized patients was 96 per 1000 person-years, which was approximately 100-fold greater than in those not hospitalized.[15] In the prospective, IMPROVE study, the cumulative incidence of VTE occurring during a medical hospitalization or in the 3 months after discharge was 1%, with ~45% of these after discharge.[16] This cumulative incidence in IMPROVE was higher than that reported in the current study (0.39%), likely because the IMPROVE study selected medical patients deemed at 'higher' VTE risk.

The current study differs from prior studies in that the proportion of hospital-associated VTE events occurring post-discharge is higher. However, the IMPROVE study selected sicker hospitalized patients by requiring a minimum length of hospital stay and so should not be used to estimate the risk for all hospitalizations. Secular trends in the average length of hospitalization would also be expected to impact VTE rates and incidence patterns; the current average length of stay for medical admissions is 4–5 days (similar to that observed here) in comparison to 5–8 days 10 years ago.[17] Length of stay is nowadays considered a quality measurement and there has been significant efforts nationwide to decrease this number[18] however in terms of thrombosis risk this trend may result in shifting the risk of VTE to the immediate post-discharge period.[19] In prior studies, half of hospital-acquired VTE events occurred by hospital-day 5.[20] Mirroring the current study, a similar proportion of hospital-associated VTE events (70%) occurring after discharge was reported in a contemporary study of unselected hospitalizations from public hospitals in New South Wales, Australia.[8] This suggests that shorter hospital stays have moved the risk of hospital-associated VTE from the inpatient to the post-discharge setting. The risk of post-discharge VTE was the justification for trials assessing the efficacy of post-discharge VTE prophylaxis with apixaban, betrixaban, rivaroxaban, and enoxaparin in medical patients.[21-25] These trials revealed that bleeding is a real concern in this population[22] and that post-discharge prophylaxis does not reduce VTE in everyone[21,25] but may benefit some patient populations.[23] Overall, given the unclear benefit and inability to define a population who may benefit, American Society of Hematology's guidelines currently advise to not continue thromboprophylaxis in the post-discharge period.[9,26]

Our analysis has strengths and limitations. The strengths of our study are the size of the cohort, the number of VTE events, and appropriate statistical methods to capture the time-varying nature of hospitalization as a risk factor for VTE. We may have missed some VTE events diagnosed outside the UVM Health Network. However, given that the overall rate of VTE is consistent with the general population and the consistency of our results with the prior literature, this unlikely biased our results to a significant degree.[4] Another source of potential bias is that we followed a population engaged with health care that may be sicker (and have a higher baseline rate of VTE) than the general population; however, we would expect that this would bias our results for the association of hospitalization versus no hospitalization towards the null. Further, given we did not adjudicate VTE events, some VTE events are likely misclassified. However, prior studies have demonstrated a high positive predictive value for the definition we used.[12] We did not perform extensive risk factor adjustment because our goal was to determine the impact of hospitalization as a risk factor for VTE and not the reasons underlying the association. As the population included people who were hospitalized and those not hospitalized, there is likely underascertainment of co-morbid conditions in those not hospitalized making this study design less than ideal for determining the reasons behind hospitalization as a risk factor for HA-VTE. Similarly, repeated hospitalization over short periods of time is likely a risk factor for hospital-associated VTE but the current study is underpowered to address this. Further research will determine higher or lower risk groups for hospital-associated VTE.

In conclusion, risk of VTE is dramatically higher during hospitalization and in the 3 months after hospitalization, with risk gradually decreasing over time. In contrast to prior studies, this contemporary study demonstrates a greater proportion of VTE events occurring after discharge than during hospital stay, highlighting the importance of further research into risk assessment and preventive interventions as a means of reducing the incidence of potentially preventable VTE. As reflected by the American Society of Hematology's guidelines on VTE prophylaxis, post-discharge prophylaxis is not currently the standard of care. However, the current findings provide a strong rationale and foundation for future studies to refine post-discharge VTE risk assessment and design possible interventions to reduce VTE risk.

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CONFLICT OF INTEREST

Ximena Jordan Bruno, Insu Koh, Pamela L. Lutsey, Robert F. Walker, Nicholas S. Roetker, Katherine Wilkinson, Nicholas L. Smith, Timothy B. Plante, Allen B. Repp, Chris E. Holmes, Mary Cushman, and Neil A. Zakai report no conflicts of interest.

INFORMED CONSENT

The research reported here conformed to the tenants of the Declaration of Helsinki and was determined exempt by the University of Vermont Institutional Review Board based on exemption category 4 under the 2018 Common rule.

AUTHOR CONTRIBUTIONS

Secured Funding: N.A. Zakai, P.L. Lutsey. Concept and Design: X. Jordan Bruno, I Koh, N.S. Roetker, A.B. Repp, N.A. Zakai. Statistical Analysis: I. Koh, P.L. Lutsey, R.F. Walker, N.S. Roetker, K Wilkinson. Manuscript Drafting and Revision: X. Jordan Bruno, N.A. Zakai. Critical Revision: I. Koh, P.L. Lutsey, R.F. Walker, N.S. Roetker, N.L. Smith, T. B. Plante, A.B. Repp, C. E. Holmes, M. Cushman.

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SUPPORTING INFORMATION

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