DR. PRAHLAD HO (Orcid ID : 0000-0002-1373-7437)

Received Date : 15-Mar-2017
Accepted Date : 16-Mar-2017
Article type : Original Article

Retrospective evaluation of Venous Thromboembolism (VTE): are all transient provoking events the same?

Running title: *Are all provoked VTE the same?*

***Chong Chyn Chua[1], *Hui Yin Lim[1,2], Mark Tacey[2,3], Harshal Nandurkar[4,5], Prahlad Ho[1,2,3,4]**

*joint first authors with equal contribution

1. Austin Health, Heidelberg, Melbourne, VIC, Australia
2. Northern Health, Epping, Melbourne, VIC, Australia
3. University of Melbourne, Parkville, VIC, Australia
4. Florey Institute of Neurosciences and Mental Health, Parkville, VIC, Australia
5. Monash University, Clayton, VIC, Australia

Corresponding author
Dr Prahlad Ho
Department of Haematology
Northern Health
185 Cooper Street
Epping, VIC 3076
Australia

Telephone: +613-84058000

Fax: +613-84058683

Email: Prahlad.Ho@nh.org.au

Abstract word count: 200 words

Manuscript word count: 3632 words

Number of references: 24

Number of figures and tables: 2 figures and 4 tables

Number of supplemental illustrations/tables: 0

Funding: The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

ABSTRACT

Objectives: Venous thromboembolism (VTE) provoked by transient risk factors has traditionally been classified as a single entity with lower risk of recurrence. We evaluated the association between different categories of transient provoking factors and the relative risk of recurrence.

Methods: Retrospective evaluation of VTE events in non-cancer patients from July 2011 to December 2012 at two tertiary institutions in Australia with a minimum follow up of 24 months.

Results: 747 VTE cases were identified and following exclusion of cases with mortality within 30 days of presentation (n=26), unprovoked cases (40.2%) had a higher risk of recurrence (4.6 versus 2.3/100 event-years, p=0.01). Provoking factors included surgery (40.4%), injury (16.7%), medical-related factors including non-surgical hospitalisation or active infection (22.0%), travel (13.2%) and oestrogen-related (6.5%). Air travel had the highest recurrence rate of 5.9/100 event-years, comparable to unprovoked VTE. VTE provoked by surgery showed lower recurrence rate at 1.8/100 event-years (p=0.03). 62.5% of patients with provoked VTE recurred with an unprovoked event.

Conclusion: Transient provoking factors for VTE are heterogeneous with varying potency and should not be considered a single entity. The high recurrence rate after travel-provoked VTE suggests that it is a "minor", if not negligible provoking factor with higher thrombotic predisposition.

Key words: Venous thromboembolism, provoking factors, travel, clot recurrence, epidemiological studies

INTRODUCTION

Venous thromboembolism (VTE) is a common condition affecting 1 to 2 per 1000 persons per year in developed countries with an overall risk of recurrence of up to 30% over 10 years.(1, 2) It is well recognised that the risk of VTE recurrence after an unprovoked event is highest within the first 12 months and the presence of a transient provoking factor is associated with a lower risk of recurrence.(3)

Traditionally, provoking factors have been reported in up to 75% of all VTE, and have been classified as a single unifying entity.(2, 4) However, in reality, a provoked VTE can be due to multiple different factors such as surgery, injury, medical-related factors (including non-surgical hospitalisation, active infection or other significant active medical illnesses), long-distance travel, oestrogen therapy, pregnancy and malignancy.(5) Each risk factor has varying magnitude and reversibility, and may influence the risk of VTE recurrence in different ways.(5) For instance, a systematic

review have shown that recent surgery is a major reversible provoking factor with a very low estimated risk of recurrence of 0.7% per patient-year after anticoagulation cessation, as compared to 4.2% per patient-year in those with non-surgically related provoking factors.(6) Furthermore, different studies have reported varying time periods between exposures and the associated VTE event, and international recommendations often do not specify the proposed lead-time as well. (5-7)

Despite the heterogeneity in provoking factors, international VTE recommendations do not specify the type of provoking factor but rather, group them as a single category. In 2016, the American College of Chest Physicians recommends treatment of all provoked VTE with therapeutic anticoagulation for 3 months over extended therapy.(7) Moreover, many patients are reassured that the risk of VTE recurrence in provoked VTE is low after cessation of anticoagulation unless they are re-exposed to a similar reversible provoking factor.

To further our understanding of the relative significance of each provoking factor and specifically, their subsequent relative risk of VTE recurrence, we performed a retrospective review of patients with lower limb deep vein thrombosis (DVT) and/or pulmonary embolus (PE) in a "real-world" hospital setting.

METHODS

This was a retrospective observational study of all consecutive patients presenting with VTE between 1 July 2011 and 31 December 2012 across two tertiary teaching hospitals (Austin Health and Northern Health) in Northeast Melbourne, Victoria, Australia. Both institutions are the only tertiary hospitals and major referral centres serving Northeast Melbourne with an estimated population of 1.5 million. All patients were followed up to 31 December 2015, with a minimum of 24 months from initial diagnosis.

Potential cases were identified and retrieved from hospital medical records using the relevant ICD-10 codes (International Classification of Diseases, 10th Revision): I26 (pulmonary embolism) and I80 (phlebitis and thrombophlebitis).(8) The use of ICD-10 codes for case identification was a reliable method in both institutions, as it was

mandatory for every patient to have a discharge summary that was reviewed and coded using ICD-10 codes to enable assignment of appropriate Diagnosis Related Groups, which impacted on funding allocation to the hospitals. Computerised medical record of each case was assessed for demographics, provoking factors, thrombosis risk factors, family and personal medical history, thrombophilia testing, anticoagulation management, bleeding complications, thrombosis recurrence, subsequent development of malignancy and mortality.

Isolated distal deep vein thrombosis (IDDVT) was defined as isolated DVT below the level of the popliteal vein including isolated muscular vein thrombosis. Major VTE was defined as above-knee DVT, including DVT involving the popliteal vein, and/or PE with or without concomitant DVT. All VTE cases were confirmed on radiological imaging and it was standard of care for both institutions to perform routine whole leg ultrasound for all patients with suspected DVT. No routine radiological testing for PE was performed for patients with symptomatic DVT and no clinical features of PE. For the purpose of this analysis, only lower limb DVT and PE were included due to the differences in the natural history of thrombosis involving other unusual sites. Patients with known active malignancy or myeloproliferative neoplasm (MPN) were excluded, as these conditions were not deemed to be reversible in the short term. The duration of anticoagulation was subject to the treating physician's discretion.

Provoking factors

The VTE cases were stratified according to the presence of an identifiable transient provoking factor. Each provoking factor was defined as follow:

(i) Surgery within eight weeks of VTE presentation including associated factors such as immobility or injury.
(ii) Lower limb or spinal injury unrelated to surgery, occurring within eight weeks of VTE presentation.
(iii) Medical-related provoking factors including non-surgical hospitalisation, active infection or other significant active medical illnesses, occurring within eight weeks of VTE presentation.

(iv) Travel as determined by treating physician; however only continuous air travel of more than 3 hours, occurring within eight weeks of VTE presentation were included in our sub-analysis.(9) Information regarding travel destinations were documented for all travel-related cases, thus they were further stratified according to the estimated travel duration based on a one-way trip.
(v) Oestrogen-related factors including concomitant administration of oral contraceptive pills or hormone replacement therapy within eight weeks of presentation, active pregnancy, or up to six weeks post partum.

The remaining cases with no identifiable provoking factors were classified as "unprovoked" events.

Recurrent thrombosis was defined as a clinically significant recurrence of the thrombosis in the same area that has previously been documented to have resolved or in a new site following an index event. Bleeding complications were assessed based on the International Society on Thrombosis and Haemostasis – Scientific and Standardisation Committee bleeding assessment tool, with events scoring 3 or more points being considered clinically significant.(10) Subsequent malignancy was classified as the detection of a new malignancy within 12 months following the index VTE, without evidence of malignancy at the time of VTE diagnosis. Patients who did not re-present to either hospital, or have subsequent documentation of a new VTE in our medical records were further tracked through medical records of two major private haematology medical practices in the same catchment area. If no further data were identified, these patients were deemed not to have had a recurrent VTE event, bleeding complication or subsequent malignancy. Given that most patients in the warfarin era would require administration of subcutaneous low molecular weight heparin either as inpatient or through a hospital-based outpatient program, it is likely that hospital presentation was required. Cause-specific mortality data was updated as per hospital records at the last date of follow-up.

Statistical analysis

Descriptive statistics (counts and percentage frequencies, mean or median, range, 95% confidence interval [CI]) are provided as appropriate to summarise patient

characteristics and outcomes. Differences in categorical variables were evaluated using the Chi-squared test, or Fisher's Exact test on occasions when frequencies were less than 5. For the continuous variables, which were non-normally distributed, the Mann-Whitney (rank-sum) test was applied.

Time to event analysis was conducted with two end points: recurrent thrombosis and clinically significant bleeding, with mortality treated as a competing risk, by the method of Fine and Gray. (11) Cumulative incident curves for recurrent thrombosis and clinically significant bleeding were prepared to compare groups, with univariate and multivariate proportional hazards competing risk regression analyses used to identify and quantify associations between recurrent thrombosis and patient or clinical variables. Variables were selected for the multivariate analysis if the p-values were <0.2 on univariate analysis, with manual backward stepwise regression techniques employed and provoked status treated as the primary exposure variable. Results were presented as Hazard Ratios with associated 95% confidence intervals. An analysis of time to VTE recurrence was also conducted in a sub-group where duration of anti-coagulation therapy was known, with duration on anti-coagulation treated as a time-dependent covariate.

A two-tailed P-value of less than 0.05 was considered to indicate statistical significance. STATA statistical analysis software (version 12.1) was used (StataCorp, College Station, TX, USA).

Ethics approval was obtained from the Austin and Northern Human Research Ethics Committee (Numbers LHR/14/Austin/660 and ALR 10.2015).

RESULTS

Case identification

A total of 1024 consecutive VTE events were identified (Figure 1), involving 1002 patients with 22 recurrent hospital presentations. Of these, 747 (72.9%) events (total of 737 patients) met the specified inclusion criteria: 449 VTE events were classified as provoked (total of 443 patients) and 298 VTE events were unprovoked (total of 294

patients). Patients with active malignancy, MPN and/or non-lower limb DVT or non-PE VTE were excluded (26.3%). All patients were followed-up for a minimum of 24 months, with a median of 27 months post cessation of anticoagulation (range 1-48 months).

Patient characteristics

Baseline characteristics comparing provoked and unprovoked VTE patient cohorts are shown in Table 1. The median age was 64 years with a lower median age in the provoked group (62 years vs 65 years, p=0.04), and a female predominance (56.0% vs 43.0%, p<0.01). The proportion of patients presenting with major VTE was also significantly lower in the provoked versus unprovoked cohorts (336/449 (74.8%) vs 246/298 (82.6%), p=0.013). The majority (97.0%) of patients were symptomatic at VTE diagnosis.

VTE Risk factors

Prior VTE history was less common in provoked cases (11.3% vs 35.7%, p<0.01) but notably, provoked patients that had a prior VTE history were more likely to report subsequent recurrence (6/50 (12.0%) vs 18/393 (4.6%); p=0.03). No difference in recurrence in the unprovoked cohort was identified based on prior history of VTE (9.5% vs 10.6%, p=0.77). There were no statistical significant differences in family or smoking history.

Thrombophilia screen was performed in 27.6% of the provoked cases and 59.4% of unprovoked cases (p<0.01), with no significant differences in the proportion of cases with any positive result (p=0.62). Of note, greater than 95% of patients had Protein C, S and Antithrombin tests performed whilst on anticoagulation and hence these results were not interpretable.

Provoking factors

The various type of provoking factors (as attributable to by the treating physicians) in our cohort is identified in Table 2, with the majority of patients having surgery-related

events. Interestingly, there were 57 patients identified as having travel-related VTE, including 13 patients with air travel between 3 and 8 hours, 36 patients with air travel of more than 8 hours and 8 with land-only travel. There were no sea travels reported.

Management

Most patients (423/449, 94.2%) with provoked VTE received therapeutic anticoagulation, though this was lower than the unprovoked group (294/298, 98.7% $p<0.01$). Of the 26 provoked cases that did not receive therapeutic anticoagulation, 5 had prophylactic anticoagulation, 3 had antiplatelet therapy and 18 did not receive anticoagulation.

Information regarding cases with a finite duration of anticoagulation was available in 282 (62.8%) of the provoked and 146 (49.0%) of the unprovoked group (Figure 1). While there was no difference in the median duration of anticoagulation in either group, provoked patients were less likely to have more than 6 months of anticoagulation (67/282 (23.8%) vs 48/146 (32.9%), $p=0.02$), or proceed to long-term anticoagulation (39/434 (9%) vs 94/293 (32%), $p<0.01$),

No statistical significant differences in the acute interventions implemented were identified between the provoked and unprovoked population, including IVC filters (14, (3.1%) vs 9 (3.3%)), thrombolysis (3 (0.7%) vs 3 (1.0%)), both IVC filter plus thrombolysis (4 (0.9%) vs 3 (1.0%)), and one extracorporeal membrane oxygenation use in each cohort.

VTE Recurrence

Following exclusion of cases with mortality at presentation or within 30 days of index event, 721 cases (involving 711 patients) were included in the assessment of VTE recurrence. There were 24 cases of VTE recurrence (5.6%) in the provoked group of 431 cases (involving 425 patients) representing a rate of 2.3 recurrences per 100 event-years, compared to 32 cases (involving 286 patients including 2 patients with 2 cases of recurrences each) of VTE recurrence (11.0%) and a recurrence rate of 4.6 per

100 event-years in the unprovoked group. The breakdown of the type of provoking factors and the respective rate of VTE recurrence are shown in Table 2.

Overall, patients with provoking events at baseline were found to have a lower hazard ratio of VTE recurrence (HR 0.50, 95% CI: 0.29-0.85) (Table 2 and Figure 2). When considering types of provoking events, surgery had the lowest risk of VTE recurrence (HR 0.41, 95% CI: 0.19-0.90). Travel-related VTE, on the other hand, was associated with the highest rate of VTE recurrence (5.8 events per 100 event-years) comparable to unprovoked VTE (HR: 1.30, 95% CI: 0.61-2.79). No other factors were associated with VTE recurrence upon multivariate analysis, and as shown in Table 2 there was no association between types of VTE at baseline with VTE recurrence (IDDVT vs Major VTE: HR 1.38, 95% CI: 0.78-2.47).(12)

Of the 24 patients in the provoked cohort who developed recurrence, 15 (62.5%) had an unprovoked VTE recurrence. Of the nine provoked recurrence, 1 was on therapeutic anticoagulation, 1 had subtherapeutic anticoagulation, 3 were post surgery on prophylactic anticoagulation and 4 were not anticoagulated. There was no significant difference in VTE recurrence rate regardless of whether patients were on long-term anticoagulation (Table 3). After excluding patients on long-term anticoagulation or had an unknown duration of anticoagulation, the median time to VTE recurrence was 7 months after anticoagulation cessation in both the provoked and unprovoked patients (p=0.68).

VTE-related bleeding

No differences in clinically significant bleeding events between the 2 groups were identified (24 (5.3%) vs 17 (5.7%), p=0.83), including time to bleeding event.

Mortality rates

There were no differences in mortality between the provoked and unprovoked cohort (65/443 (14.6%) vs 43/294 (14.6%); p=1.00) including similar proportion of thrombosis-related mortality (16 (3.6%) vs 9 (3.1%); p=0.69).

Subsequent malignancy

The incidence of subsequent malignancy was lower in the provoked group compared to the unprovoked patients (6 (1.4%) vs 8 (2.7%); RR 0.50, 95% CI 0.17-1.42, p=0.19). Metastatic cancer was also more common in the unprovoked population (6/8 vs 2/6, p=0.19). Of those with provoked VTE, 3 (4.6%) were secondary to medical-related factors, 2 (1.3%) had surgery-related factors and 1 (1.4%) had injury-related immobility.

DISCUSSION

This study provides a "real-world" analysis of VTE with a specific focus on the impact of provoking factors on clinical outcomes and VTE recurrence. Importantly, we confirm that provoked VTE has a lower rate of recurrence compared to unprovoked VTE (2.3 recurrences per 100 event-years vs 4.6 recurrences per 100 event-years, p=0.01). However, the cumulative recurrence rate of 5.6% in the 24-month follow-up period in our provoked cohort, although lower than that of the unprovoked group, is nonetheless much higher than the baseline VTE risk of a normal population, which is estimated to have an incidence of 0.1 to 0.2 per 100 patients per year.(13) Our findings are consistent with results from prior published studies, with a systematic review reporting a recurrence rate of 3.3% per patient-year for patients with a transient provoking factor, and a recent population study reporting a cumulative VTE recurrence of 13% in 3 years in a similar cohort. (14, 15) This suggests that the risk of VTE recurrence after a provoked VTE may not return to the population baseline, and highlights the importance of individualised evaluation of patients and risk stratification of the initial provoking event.

Interestingly, while provoked VTE has traditionally been classified as a single entity, our sub-analysis of traditionally well-recognised provoking factors suggests that the overall risk of thrombosis is a sum of the strength of provoking stimuli and the individual's intrinsic thrombotic tendency. For example, the risk of VTE recurrence was substantially lower when the VTE was provoked by major transient risk factors such as surgery (HR 0.41, p=0.03) or injury (HR 0.12, p=0.04), and no instances of VTE recurrence were observed for hormone-related factors. (6, 16) On the contrary,

travel-related VTE, which is viewed as one of the most common VTE risk factors by our community, conferred the highest risk of recurrence, with a recurrence rate comparable to that of the unprovoked cohort (HR 1.30, p=0.50). Furthermore, we also note that 50% of individuals with travel-related thrombosis had a prior history of VTE, suggesting that these individuals have a stronger inherent thrombotic tendency. This is consistent with two systematic reviews, which reported long duration travel to be a minor risk factor for the development of VTE. (17, 18)

Similarly, VTE provoked by medical-related factors (mainly comprising of patients with recent hospitalisation and/or multiple co-morbid medical illnesses) had a moderate risk of recurrence – 2-fold higher than that of the surgical group (VTE recurrence rate of 3.4 per 100 event-years compared to 1.8 per 100 event-years). The retrospective nature of our data rendered it difficult to accurately characterise the exact nature of each immobility episode and patients with trivial immobilisation may have been included in our cohort. Nevertheless, despite the heterogeneity, this finding suggests that medical illness and hospitalisation may not be as strong a provoking factor as traditionally thought and may carry a substantial risk of recurrence.

Previous studies have suggested that there is a travel dose-response curve with an association between air travel of more than 8 hours and an increased risk of VTE (9, 18) although VTE prophylaxis has been suggested for individuals who are travelling on continuous flights greater than 3 hours.(9) While there has been substantial community interest in the incidence of travel-related VTE, there remains a paucity of data regarding its risk of VTE recurrence. With the comparable recurrence between travel-related VTE and unprovoked patients, our study suggests that rather than merely viewing travel as a ‘minor provocateur’, greater emphasis should be placed on recognising that travel-related VTE is minimally provoked and may unmask patients with a stronger existing predisposition for thrombosis and should be targeted for more extensive risk assessment.

Overall, our findings suggest that stratifying a patient’s VTE recurrent risk purely based on whether an event was unprovoked, or provoked by a transient risk factor is insufficient. It also highlights the importance of evaluating the magnitude of each provoking factor as this may be predictive of the risk of future thrombosis recurrence.

Based on the hazard ratio with unprovoked VTE as the reference group, we propose categorising these factors accordingly (Table 4 and Figure 2) – "strong" provoking factors to include surgery, injury and oestrogen; hospitalisation and medical illnesses as "intermediate" risks; and travel as a "minor" provoking factor. We note that there were no recurrences in the 32 oestrogen-related events and as such oestrogen exposure was classified as a strong factor. However, we also recognise that the lower VTE recurrence may be confounded by the fact that oestrogen exposure is more common in younger women who inherently have a lower risk of VTE. (19) Classifying patients with provoking factors into these risk groups will aid clinicians in their clinical assessment of future thrombosis recurrence risk, which may impact on the management of the VTE episode. In addition, consideration of intrinsic factors such as male sex, hereditary or acquired thrombophilia as well as advanced age is important.(5)

While multiple scoring systems have been developed in attempts to predict the recurrent VTE risk in the unprovoked cohort, none have focused on assessing VTE risk in the provoked population, despite a substantial recurrence risk in certain subgroups, including the majority (62.5%) recurring as unprovoked events.(20, 21) Hence, we propose the need for prospective clinical studies to further evaluate the appropriate management of provoked VTE, which form the majority of VTE presentations, taking into account the varying magnitude of importance of the provoking factors. On the other hand, studies in unprovoked VTE have also shown that it is equally important to accurately identify the subset of patients who have a very low risk of VTE recurrence and thus can safely discontinue anticoagulation.(21) Recent studies have utilised D-dimer testing for further risk stratification, especially the level one-month post anticoagulation cessation, in combination with other factors such as gender. This additional marker may help to predict the risk of VTE recurrence and the need for extended anticoagulation in VTE provoked by a "minor" factor.(7, 23) This is particularly relevant in the modern anticoagulation era, where the availability of the direct oral anticoagulants have enabled convenient administration with a relatively lower bleeding risk when compared to the traditional vitamin K antagonists, resulting in increase acceptance of extended anticoagulation and decreased tolerance of the risk of VTE recurrence.(24)

This is a retrospective study of tertiary hospital-only presentations, which may reflect a higher risk population compared to community presentations. However during our study period in the warfarin era, most patients with a newly diagnosed VTE require presentation to hospital, as the administration of bridging subcutaneous low molecular heparin would usually be done through the hospital-based outpatient program. There are multiple potential biases, including patients and treatment selection biases, reliance on ICD-10 coding for case identification and quality of medical record documentation. Some patients were lost to follow up and may not have re-presented to our hospitals with complications, hence the rate of VTE recurrence and subsequent malignancy may be underreported in this study. The duration and mode of treatment of each VTE event were up to individual physician discretion, thus factors affecting decision-making may not be fully captured from medical record documentation. The retrospective nature of the data also resulted in inadequate information regarding the duration of anticoagulation in one-third of the patients in the time-to-VTE recurrence analysis, hence detailed analysis of the impact of anticoagulation status was unable to be adequately performed. Patients who were on long-term anticoagulation were also included in our VTE recurrence rate analysis, which may result in a lower overall VTE recurrence rate in both cohorts. Nevertheless, the patient cohort shown in this study is more reflective of "real-world" VTE practice.

CONCLUSION

Transient provoking factors for VTE are heterogeneous with different provoking strengths resulting in inversely proportional rates of VTE recurrence. Despite an overall lower risk of recurrence, the type and magnitude of each provoking factor should be carefully evaluated in the management and determination of recurrent VTE risk given that provoking factors such as travel may confer a comparable recurrence risk to unprovoked VTE. Further prospective studies are needed to confirm these findings.

ACKNOWLEDGEMENT

Not applicable

REFERENCES

1. Naess IA, Christiansen SC, Romundstad P, et al. Incidence and mortality of venous thrombosis: a population-based study. Journal of thrombosis and haemostasis : J Thromb Haemost 2007;5:692-9.

2. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol 2015;12:464-74.

3. Prandoni P, Noventa F, Ghirarduzzi A, et al. The risk of recurrent venous thromboembolism after discontinuing anticoagulation in patients with acute proximal deep vein thrombosis or pulmonary embolism. A prospective cohort study in 1,626 patients. Haematologica 2007;92:199-205.

4. Heit JA, Lahr BD, Ashrani AA, et al. Predictors of venous thromboembolism recurrence, adjusted for treatments and interim exposures: a population-based case-cohort study. Thromb Res 2015;136:298-307.

5. Kearon C, Ageno W, Cannegieter SC, et al. Categorization of patients as having provoked or unprovoked VTE: guidance from the SSC of ISTH. J Thromb Haemost 2016;14:1480-3.

6. Iorio A, Kearon C, Filippucci E, et al. Risk of recurrence after a first episode of symptomatic venous thromboembolism provoked by a transient risk factor: a systematic review. Arch Intern Med 2010;170:1710-6.

7. Kearon C, Akl EA, Ornelas J, et al. Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. Chest 2016;149:315-52.

8. World Health Organization. International statistical classification of diseases and related health problems, 10th revision. Available at: http://apps.who.int/classifications/icd10/browse/2010. Accessed October 7, 2013.

9. Watson HG, Baglin TP. Guidelines on travel-related venous thrombosis. BrJ Haematol 2011;152:31-4.
10. ISTH-SSC Bleeding Assessment Tool. Available at: https://http://www.isth.org/resource/resmgr/ssc/isth-ssc_bleeding_assessment.pdf. Accessed October 10, 2013.
11. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. J Am Stat Assoc 1999;94:496-509.
12. Ho P, Lim HY, Chua CC, et al. Retrospective review on isolated distal deep vein thrombosis (IDDVT) - A benign entity or not? Thromb Res 2016;142:11-6.
13. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. Arch Intern Med 1998;158:585-93.
14. Spencer FA, Emery C, Joffe SW, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. J Thromb Thrombolysis 2009;28:401-9.
15. Huang W, Goldberg RJ, Anderson FA, et al. Occurrence and predictors of recurrence after a first episode of acute venous thromboembolism: population-based Worcester Venous Thromboembolism Study. J Thromb Thrombolysis 2016;41:525-38.
16. Baglin T, Luddington R, Brown K, et al. Incidence of recurrent venous thromboembolism in relation to clinical and thrombophilic risk factors: prospective cohort study. Lancet 2003;362:523-6.
17. Trujillo-Santos AJ, Jimenez-Puente A, Perea-Milla E. Association between long travel and venous thromboembolic disease: a systematic review and meta-analysis of case-control studies. Ann Hematol 2008;87:79-86.
18. Philbrick JT, Shumate R, Siadaty MS, et al. Air travel and venous thromboembolism: a systematic review. J Gen Intern Med 2007;22:107-14.
19. Le Gal G, Kovacs MJ, Carrier M, et al. Risk of recurrent venous thromboembolism after a first oestrogen-associated episode. Data from the REVERSE cohort study. Thromb Haemost 2010;104:498-503.
20. Tritschler T, Mean M, Limacher A, et al. Predicting recurrence after unprovoked venous thromboembolism: prospective validation of the updated Vienna Prediction Model. Blood 2015;126:1949-51.

21. Tosetto A, Iorio A, Marcucci M, et al. Predicting disease recurrence in patients with previous unprovoked venous thromboembolism: a proposed prediction score (DASH). J Thromb Haemost 2012;10:1019-25.
22. Rodger MA, Kahn SR, Wells PS, et al. Identifying unprovoked thromboembolism patients at low risk for recurrence who can discontinue anticoagulant therapy. CMAJ 2008;179:417-26.
23. Palareti G, Cosmi B, Legnani C, et al. D-dimer to guide the duration of anticoagulation in patients with venous thromboembolism: a management study. Blood 2014;124:196-203.
24. van der Hulle T, Kooiman J, den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost 2014;12:320-8.

LEGENDS TO FIGURES AND TABLES

Table 1. Patient demographics and characteristics of VTE events

Table 2. Provoking factors and univariate association with rate of VTE recurrence

Table 3. VTE recurrence rate (per 100 event-years) based on long-term vs finite duration of anticoagulation by provoked status

Table 4. Possible categorisation of strength of provoking factors

Figure 1. Schematic diagram showing breakdown of venous thromboembolism (VTE) events and cohorts included in VTE recurrence analysis

Figure 2. Cumulative Incidence of VTE recurrence stratified by (A) provoked vs unprovoked VTE; (B) different strengths of provoking factors (strong: surgery, injury, oestrogen related; intermediate: hospitalisation, medical illnesses; low: travel)

Table 1. Patient demographics and characteristics of VTE events

	Unprovoked n (%)	Provoked n (%)	p-value
Patient demographics			
Number of Patients	294 (39.9)	443 (60.1)	
Male	167 (56.8)	197 (44.5)	<0.01
Age, median (range)	65 (48 - 82)	62 (43- 81)	0.04
Prior history of VTE	105 (35.7)	50 (11.3)	<0.01
First-degree relative with VTE	26 (8.8)	30 (6.8)	0.30
Active Smoker	53 (18.0)	67 (15.1)	0.59
Characteristics of VTE events			
Number of Episodes	298	449	
VTE sub-type			0.01
Major VTE	246 (82.5)	336 (74.8)	
Isolated distal deep vein thrombosis	52 (17.5)	113 (25.1)	
Symptomatic at presentation	288 (96.6)	428 (95.3)	0.38

Table 2. Provoking factors and univariate association with rate of VTE recurrence

Provoking Factor	Total (n)	VTE Recurrence (n)	VTE Recurrence rate (100 event-years)	HR	95% CI	p-value
Unprovoked VTE	290	32	4.6	1	-	-
All Provoked VTE	431	24	2.3	0.50	0.29 - 0.85	0.01
Provoking factor						
Surgery and other related factors	174	8	1.8	0.41	0.19 - 0.90	0.03
Orthopaedic	84	4	1.9	0.43	0.02 - 0.91	0.11
Non-Orthopaedic	90	4	1.8	0.40	0.14 - 1.14	0.09
Injury (non surgery)	72	1	0.5	0.12	0.02 - 0.91	0.04
Medical-related provoking factors including non-surgical hospitalisation, active infection or other significant active medical illnesses	95	7	3.4	0.67	0.29 - 1.51	0.33
Travel	57	8	5.8	1.30	0.61 - 2.79	0.50
Air	49	7	5.9	1.34	0.60 -	0.47

					3.02	
3 - 8 hours	13	1	3.0	0.70	0.10 - 5.02	0.72
>8 hours	36	6	7.0	1.59	0.67 - 3.77	0.29
Land	8	1	4.9	1.06	0.17 - 6.75	0.95
Hormone-related	32	0	-	-	-	-
Two or more non-surgical factors	1	0	-	-	-	-
Other variables						
Gender						
Female	363	22	2.5	1	-	-
Male	358	34	3.9	1.59	0.93 - 2.72	0.09
Age						
<65	377	30	3.1	1	-	-
≥65	344	26	3.3	0.96	0.57 - 1.61	0.87
Prior history of VTE						
No	559	38	2.8	1	-	-
Yes	162	18	4.6	1.67	0.95 - 2.91	0.07
First-degree relative with VTE						
No	615	43	2.9	1	-	-
Yes	56	7	4.9	1.81	0.83 - 3.95	0.14
Smoking Status[$]						
Non-Active Smoker	445	33	3.0	1	-	-
Active Smoker	121	11	3.9	1.25	0.63 - 2.47	0.52
VTE sub-type						

Major VTE	557	40	3.0	1	-	-
IDDVT	164	16	4.0	1.38	0.78 - 2.47	0.27
Thrombophilia Screen*						
Performed and negative	245	26	4.2	1	-	-
Thrombophilia screen positive	54	4	2.8	0.69	0.24 - 1.96	0.48

[$] n=155 episodes with unknown smoking status

* n=422 with no thrombophilia screen performed

Table 3. VTE recurrence rate (per 100 event-years) based on long-term vs finite duration of anticoagulation by provoked status

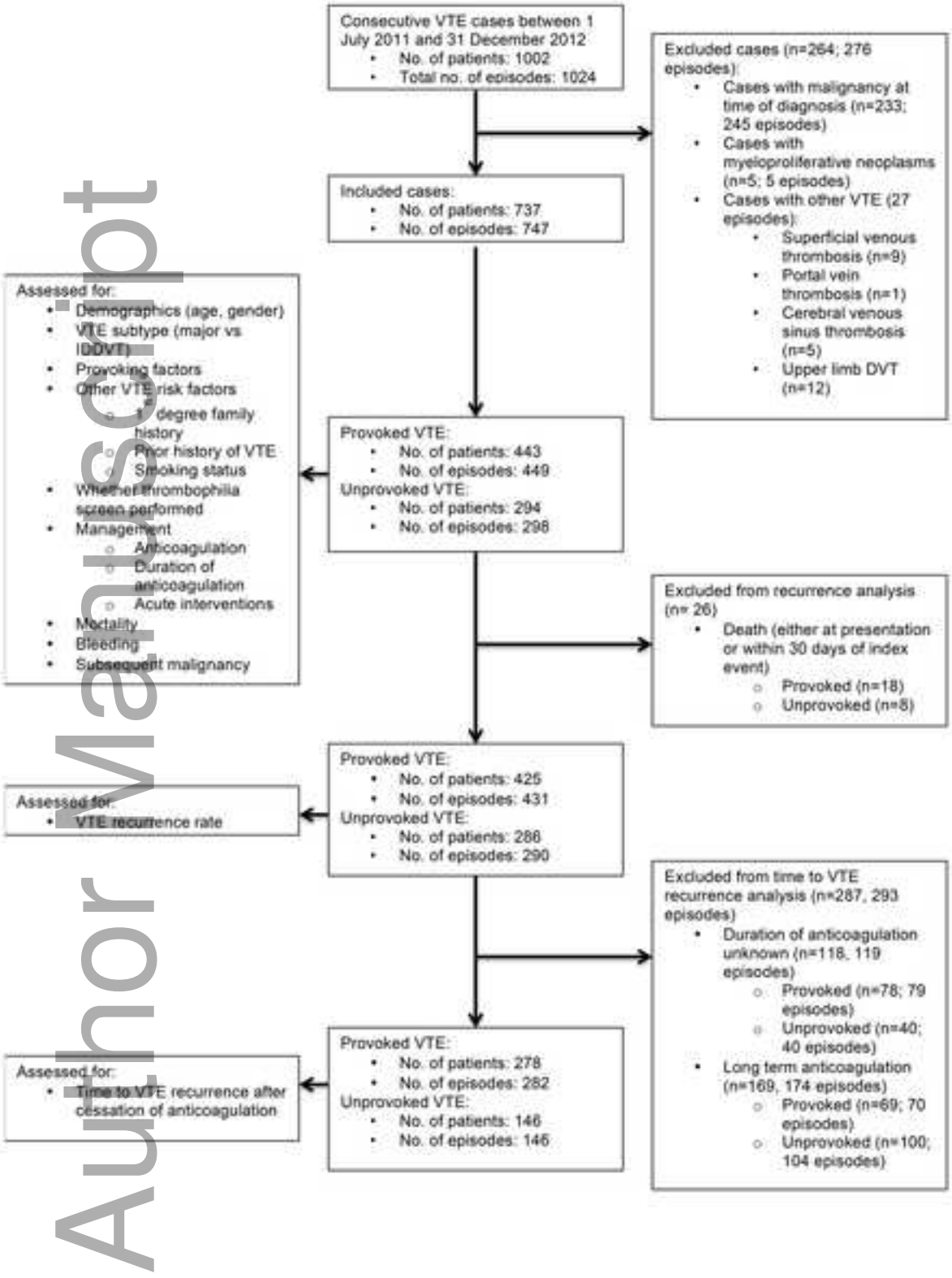
	Total VTE events	VTE recurrence	VTE Recurrence rate (100 event-years)	p-value
Provoked cases				0.913

• Long-term anticoagulation • Finite duration of anticoagulation	39 392	2 22	1.93 2.30	
Unprovoked cases • Long-term anticoagulation • Finite duration of anticoagulation	94 196	8 24	3.34 5.25	0.349

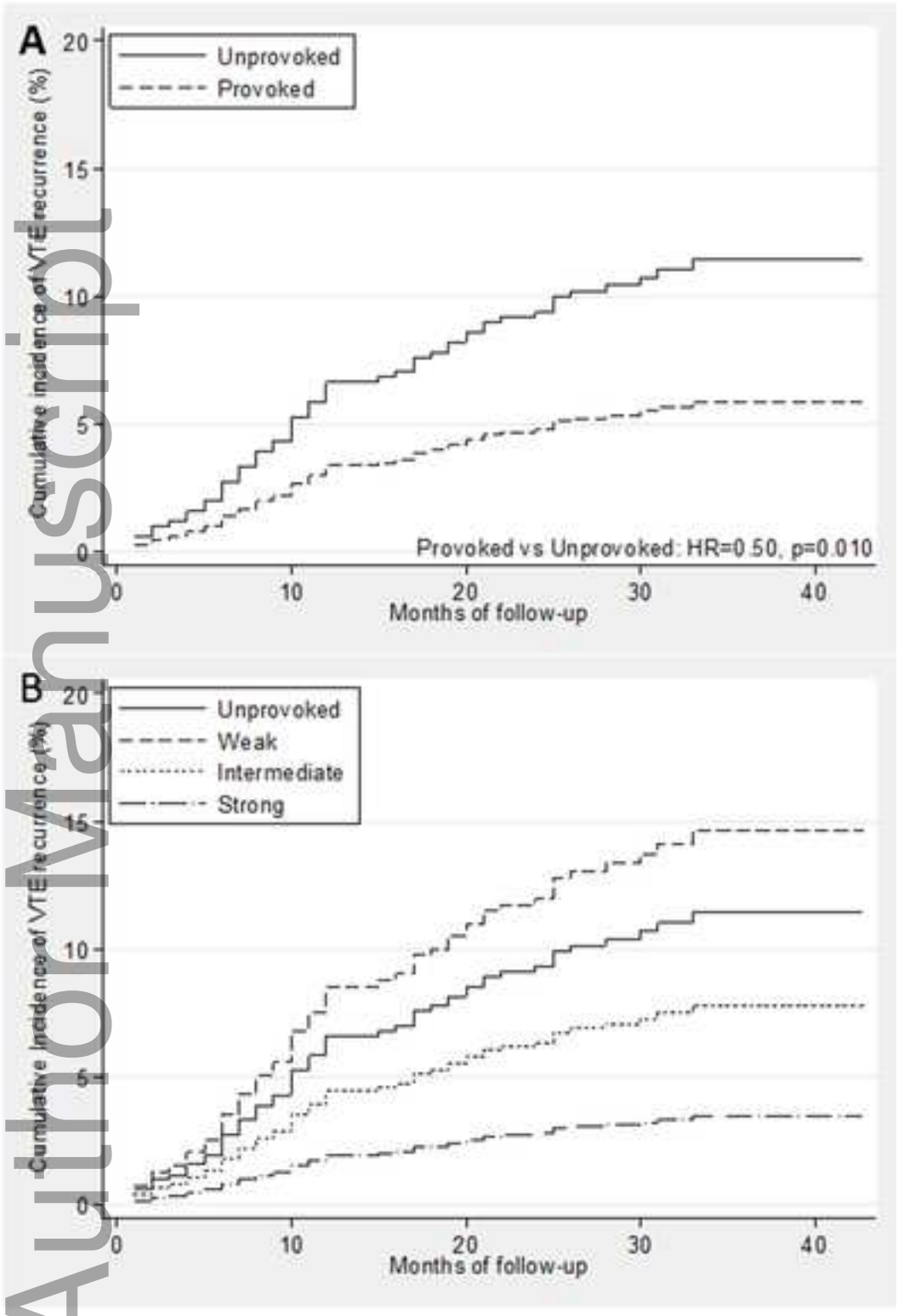
Table 4. Proposed categorisation of strength of provoking factors

Strength of provoking factor	VTE absolute recurrence rate (100 event-years)	Relative risk of VTE recurrence compared to unprovoked VTE	HR (95% CI)	Predominant risk factor types
Unprovoked	4.6	1.0 (reference group)	1.00	Not applicable
Strong	1.3	<0.3	0.29 (0.14 – 0.61)	Surgery, injury, oestrogen
Intermediate	3.8	0.3-0.8	0.67 (0.30 – 1.51)	Medical-related

				provoking factors including non-surgical hospitalisation, active infection or other significant active medical illnesses
Low	5.8	>0.8	1.30 (0.61 – 2.80)	Travel



ejh_12884_f1.jpg



ejh_12884_f2.jpg