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Safety and efficacy of pharmacological thromboprophylaxis for hospitalized patients with cirrhosis: a single-center retrospective cohort study

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Summary.

Background: Hospitalized patients with cirrhosis are at increased risk for venous thromboembolism (VTE). The benefits and risks of pharmacological thromboprophylaxis in these patients have not been well studied.

Objectives: To examine the safety and efficacy of pharmacological VTE prophylaxis in hospitalized cirrhotic patients.

Patients/Methods: Retrospective cohort study of patients with cirrhosis hospitalized at an academic tertiary care referral center over a 5-year period.

Results: Six hundred hospital admissions accounting for 402 patients were included. VTE prophylaxis was administered during 296 (49%) admissions. Patients receiving VTE prophylaxis were older (59 years vs. 55 years, $P < 0.001$), had longer lengths of stay (9.6 days vs. 6.8 days, $P = 0.002$), and lower Model for End-Stage Liver Disease scores (13.2 vs. 16.1, $P < 0.001$). In-hospital bleeding events (8.1% vs. 5.5%, $P = 0.258$), gastrointestinal bleeding events (3.0% vs. 3.2% $P = 0.52$), new VTE events (2.37% vs. 1.65%, $P = 0.537$), and mortality (8.4% vs. 7.3%, $P = 0.599$) were similar in the two groups. VTE prophylaxis did not reduce the risk of VTE (odds ratio 0.94, 95% confidence interval 0.23–3.71), and patients receiving unfractionated heparin, but not low molecular weight heparin, were at increased risk for in-hospital bleeding events (odds ratio 2.38, 95% confidence interval 1.15–4.94 vs. 0.87, 0.37–2.05, respectively).

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Addendum

J. Shatzel was responsible for project design, organization, data collection and analysis, and manuscript drafting. P. S. Dulai was responsible for interpretation of data, manuscript drafting, and critical revisions. D. Harbin was responsible for data collection and analysis and manuscript drafting. H. Cheung was responsible for manuscript drafting and statistical analysis. T. N. Reid was responsible for data collection and analysis and manuscript drafting. J. Kim was responsible for data collection and analysis and manuscript drafting. S. James was responsible for statistical analysis and manuscript drafting. H. Khine was responsible for data collection and analysis and manuscript drafting. S. Batman was responsible for data collection and analysis and manuscript drafting. J. Whyman was responsible for manuscript drafting. R. C. Dickson was responsible for manuscript drafting. D. L. Ornstein was responsible for project design, manuscript drafting, and critical revisions.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Conclusion: The rate of VTE in this cohort of hospitalized cirrhotic patients was low and was unaffected by pharmacological thromboprophylaxis. Unfractionated heparin was associated with an increased risk for in-hospital bleeding, suggesting that if thromboprophylaxis is indicated, low molecular weight heparin may be favored

Keywords

cirrhosis; low molecular weight heparin; prophylaxis; unfractionated heparin; venous thromboembolism

Introduction

Hospitalized patients are at increased risk for venous thromboembolism (VTE) [1,2], and the use of pharmacological VTE prophylaxis reduces this risk in moderate- and high-risk cohorts [3]. Although the coagulopathy associated with advanced liver disease is frequently thought to be protective, recent data suggest that cirrhotic patients have a substantial risk for developing VTE during hospitalization [4,5]. Moreover, the occurrence of VTE in this group is associated with increased morbidity and mortality [5-9]. Previous studies demonstrating a benefit for thromboprophylaxis in hospitalized patients routinely excluded patients with cirrhosis; thus, the benefit of VTE prophylaxis in this group is unclear [10-14].

Patients with advanced liver disease are at increased risk for bleeding due to complex coagulation derangements. The use of anticoagulants for VTE prevention may therefore be perceived as risky [15] and lead to wide variability in the use of VTE prophylaxis [16,17]. Given the impact of VTE on morbidity and mortality in cirrhotic patients, it is important to characterize the risks and benefits of pharmacological prophylaxis.

The purpose of our study was to assess the safety and efficacy of pharmacological thromboprophylaxis in hospitalized patients with cirrhosis. Specifically, we aimed to measure the rate of in-hospital bleeding in patients receiving anticoagulants and to identify characteristics associated with increased risk for bleeding complications. Finally, we aimed to assess the impact of thromboprophylaxis on reducing VTE risk.

Methods

This study was designed as a retrospective cohort analysis conducted at a single tertiary care academic medical center and received institutional review board approval from the Dartmouth Committee for the Protection of Human Subjects (CPHS Study number 00023916). Using hospital billing codes, we identified patients diagnosed with cirrhosis who were hospitalized at the Dartmouth Hitchcock Medical Center between 2007 and 2012. Only patients admitted to a general internal medicine service were included in this study. Medical records were reviewed to confirm the diagnosis of cirrhosis by using problem lists, laboratory values, radiological imaging, or pathology reports of liver biopsies. Patients were included if they were ≥ 18 years of age and admitted to the inpatient medicine service for at least 24 h. There are no internal guidelines at our institution directing how admitting physicians administer VTE prophylaxis. All providers are prompted by our electronic medical records to consider VTE prophylaxis with either unfractionated heparin (UFH) or

low molecular weight heparin (LMWH) when admitting a patient, without specific direction on type or dosage. The use of UFH or LMWH for VTE prophylaxis was determined by review of pharmacy billing records. Administration of the medication was confirmed by review of the electronic medical record and the medication administration record. New bleeding and thrombosis events were identified by review of the medical record. Bleeding episodes were adjudicated as either gastrointestinal (GI) or non-GI events. All documented episodes of hematochezia, melena, or hematemesis or endoscopic findings suggestive of a GI bleeding event were recorded, as well as any invasive procedure-associated or spontaneous bleeding events. Details about VTE events were abstracted from the medical record, and only in-hospital VTE events were included in this study. Any newly documented lower extremity, upper extremity, visceral vein, or pulmonary artery thrombosis not considered to be present at the time of admission was adjudicated as an in-hospital VTE event. Unequivocal radiographic demonstration of a new thrombosis by compression ultrasonography, venography, computed tomography angiography, or ventilation-perfusion scanning was required for inclusion as a qualifying event. VTE risk in each patient cohort was calculated by using the Padua predictive score, a previously validated VTE risk prediction model [18]. Analysis of current and previous admission *International Classification of Diseases, Ninth Revision* (ICD-9) codes along with relevant patient characteristics were reviewed for Padua score calculation.

Patients with insufficient evidence to support a diagnosis of cirrhosis were excluded. Patients were also excluded if clinical bleeding or VTE was present at the time of admission, including GI or non-GI bleeding, pulmonary embolism, or deep vein thrombosis. Additional exclusion criteria included treatment with full-dose anticoagulation prior to admission, transfer to or from another hospital service other than internal medicine, direct transfer to or from another facility, or insufficient records for analysis.

Statistical analysis

The primary outcome assessed was in-hospital bleeding in patients receiving or not receiving VTE prophylaxis during hospitalization. Secondary outcomes included new VTE events, blood product transfusions, and in-hospital mortality. Categorical data for both groups were analyzed by using a two-tailed Fisher exact test. A Student *t* test was used for continuous data, unless a difference was noted in means and medians, in which case a Wilcoxon Mann–Whitney test was used. Logistic regression analysis was applied to identify predictors of in-hospital bleeding. As exposure variables, we considered (i) any UFH treatment, (ii) any LMWH treatment, (iii) only UFH treatment, (iv) only LMWH treatment, (v) UFH plus LMWH treatment, (vi) number of doses of UFH, and (vii) number of doses of LMWH. Because we analyzed all seven of our exposures as predictors and used five different outcomes, this analysis included a total of 35 tests. We defined the null hypothesis such that antithrombotic prophylaxis had no effect on each of these individual outcomes. Because we used seven measures of prophylaxis as an exposure, we essentially conducted seven tests per outcome. Given our null hypothesis, we applied a Bonferroni correction of seven to reduce the possibility of inflated type I error. Thus, our threshold for significance for each outcome was $0.05/7 = 0.007$. We further examined factors that might be associated with in-hospital bleeding or VTE events with logistic regression analysis including baseline

patient characteristics: age, length of stay, and indicators of cirrhosis severity (Model for End-stage Liver Disease [MELD] score, INR, total bilirubin, serum creatinine, platelet count). All analyses were performed by using STATA 12.0 (StataCorp LP, College Station, TX, USA).

Results

A total of 996 hospital admissions (711 unique patients) were screened, of which 600 admissions (402 patients) were included in the final analysis, with an even distribution into the VTE prophylaxis and no-VTE prophylaxis groups (Fig. 1). Baseline patient characteristics according to prophylaxis status are summarized in Table 1. Compared with patients not receiving anticoagulants for VTE prophylaxis, those receiving prophylaxis were older (mean age 59 years vs. 55 years, $P < 0.001$), had lower admission MELD scores (13.6 vs. 16.1, $P < 0.001$), lower INRs (1.4 vs. 1.7, $P < 0.001$), and higher Padua predictive scores (4.3 ± 2.17 vs. 3.5 ± 2.25 , $P < 0.001$), but similar prothrombin times (19.3 s vs. 20.5 s, $P = 0.463$). Patients receiving VTE prophylaxis were more likely to have alcoholic or virus-associated cirrhosis, while patients who did not receive thromboprophylaxis were more likely to have non-alcoholic steatohepatitis as the cause of cirrhosis. During the 296 admissions in which pharmacologic VTE prophylaxis was administered, LMWH was administered in 134 (45%), while UFH was administered in 141 (48%). Both LMWH and UFH were given during 21 admissions (7%). UFH was administered at a dose of 5000 units subcutaneously every 8 or 12 h, and LMWH consisted exclusively of enoxaparin administered at a dose of 40 mg subcutaneously every 24 h. On average, patients received 5.3 doses of LMWH (range 1–34) and 11.9 doses of UFH (range 1–74). Patients receiving LMWH had a mean serum creatinine level of 1.36 ± 0.827 mg dL⁻¹, while those receiving UFH had a mean serum creatinine level of 2.12 ± 1.56 mg dL⁻¹. Patients who received UFH had significantly higher serum creatinine levels compared with all other patients in the dataset (i.e., patients who received LMWH and patients who did not receive VTE prophylaxis; $P < 0.001$), while those who received LMWH did not ($P = 0.144$).

There was a trend toward an increased rate of in-hospital bleeding events in the prophylaxis group, but this difference did not reach statistical significance (8.1% vs. 5.5%, for the prophylaxis and non-prophylaxis group, respectively; $P = 0.258$). There were 19 episodes of GI hemorrhage with virtually the same incidence of hemorrhage in the group that received or did not receive prophylaxis (3.0% vs. 3.2%, respectively; $P = 0.52$). By comparison, there were 22 non-GI hemorrhages with more events occurring in the VTE prophylaxis group compared with the no-prophylaxis group (15 vs. 7, respectively). This difference approached, but did not reach, statistical significance ($P = 0.074$). Non-GI bleeds were mostly associated with invasive procedures (64%) and included post-paracentesis procedure site ($n = 6$), post-transjugular intrahepatic portosystemic shunt ($n = 3$), injection site ($n = 2$), postoperative incision site ($n = 2$), and central line site bleeding ($n = 1$). Non-procedural, non-GI bleeds included one episode each of spontaneous intra-abdominal varix rupture, anterior abdominal bleed, retroperitoneal bleed, and hemoptysis and two episodes each of perianal bleeding and hematuria. Characteristics of patients in the VTE prophylaxis group with ($n = 24$) and without ($n = 272$) bleeding complications are summarized in Table 2. Patients who bled had a higher average baseline MELD score and INR compared with those

who did not bleed. Within the prophylaxis group, patients receiving any UFH were more likely to have an in-hospital bleeding event than were those not receiving thromboprophylaxis, while thromboprophylaxis with LMWH was not associated with an increased risk for in-hospital bleeding events compared with no prophylaxis (Table 3).

There were no differences in the rate of major outcomes between the prophylaxis and no-prophylaxis groups (Table 4). There was a trend toward a higher proportion of patients receiving red blood cell transfusions and a higher number of red blood cell units transfused in the prophylaxis group compared with the no-prophylaxis group, but neither of these parameters reached statistical significance (Table 4). New VTE were documented in 12 patients; seven patients had received pharmacological VTE prophylaxis and five had not ($P = 0.537$). Within the group that received VTE prophylaxis, logistic regression was performed to evaluate for correlations between the proportion of the hospitalization during which anticoagulation was administered and occurrence of VTE, compared with those who did not received prophylaxis. We did not detect a difference in VTE risk among those who received prophylactic LMWH for < 50% of their hospital stay (odds ratio [OR] 1.56, 95% confidence interval [CI] 0.26–9.38, $P = 0.47$), nor was a difference found among those who received prophylactic UFH for < 50% of their stay (OR 1.83, 95% CI 0.20–11.35, $P = 0.51$). Forty-seven in-hospital deaths occurred, accounting for 7.8% of study patients (25 in the prophylaxis group and 22 in the no-prophylaxis group, $P = 0.599$). Five deaths in the prophylaxis group (three LMWH and two UFH) and one death in the no-prophylaxis group were attributed to hemorrhage. We evaluated predictors of in-hospital VTE and bleeding. Length of hospital stay was a weak predictor of VTE, and type of VTE prophylaxis was the only predictor of in-hospital bleeding after controlling for the variables listed in Tables 5 and 6, respectively. We found an increased bleeding risk with UFH (OR 2.381, 95% CI 1.147–4.945, $P = 0.020$) but not LMWH (OR 0.866, 95% CI 0.366–2.047, $P = 0.743$) after controlling for the same variables.

Discussion

The liver synthesizes both coagulant and anticoagulant factors, and severe liver dysfunction results in an unstable balance between procoagulation and anticoagulation [16,19]. This and the acquired platelet dysfunction and fibrinolytic system derangements associated with cirrhosis make it difficult to quantify the competing bleeding and clotting risks in these patients [16,19–25]. The frequently cited notion that patients with cirrhosis are ‘autoanticoagulated,’ on the basis of prolongation of the prothrombin time (PT) and consequent INR elevation, is a gross mis-representation, as these patients have levels of thrombin generation similar to or greater than those of non-cirrhotic controls [23,24]. In fact, recent studies of thrombin generation suggest that cirrhosis may be a hypercoagulable state. This is further supported by observational studies in which these patients have a clinically significant incidence of VTE. Indeed, large population studies have found the relative risk of VTE in patients with cirrhosis to be approximately double that of healthy controls [7], with studies of inpatients reporting a VTE incidence of up to 6.4% [4,5,7,26,27]. Clearly, screening coagulation tests can be misleading, and a prolonged PT/INR does not correlate with and is not protective against VTE in hospitalized patients with advanced liver disease [26]. The inability to practically assess baseline risk of bleeding and clotting, together with

provider uncertainty regarding risks and benefits of therapy, has led to great variability in the use of pharmacological thromboprophylaxis in cirrhotic patients during hospitalization [11].

The major aim of our study was to assess bleeding risk associated with pharmacologic thromboprophylaxis in patients with cirrhosis. Current recommendations for thromboprophylaxis in this population are extrapolated from prophylaxis studies in general hospitalized patients, which routinely excluded patients with hepatic insufficiency and a resultant laboratory coagulopathy [10-14]. In this retrospective study, we found that, overall, the use of pharmacological thromboprophylaxis was associated with an increased risk for in-hospital bleeding, but this increase was attributable to the use of UFH but not of LMWH (Table 6). More than half of the non-GI bleeding episodes in our study were associated with invasive procedures, with a trend toward an increase in non-GI bleeding in those receiving prophylactic therapy. Although this difference did not reach statistical significance in our single-institution analysis, this effect may be clinically significant and would suggest a role for withholding prophylaxis for a suitable period of time before elective procedures. Further evaluation is needed in larger studies that are appropriately powered to detect a difference.

Somewhat surprisingly, the overall rate of in-hospital VTE in our study was low in patients with cirrhosis and unaffected by pharmacological prophylaxis. Thus, while generally safe, thromboprophylaxis in hospitalized cirrhotic patients does not seem to prevent VTE in other-wise unselected patients. However, this finding should be interpreted with caution. We found that the mean Padua score of those who received VTE prophylaxis was significantly higher than those who did not receive prophylaxis (4.3 vs. 3.5, respectively, $P < 0.001$). The Padua risk assessment model suggests that patients with a score > 4 have a significantly increased risk for hospital-associated VTE. While this model was not developed in patients with liver disease and correlation of risk is mostly inferred [18], a recent retrospective study suggested that the Padua score is effective in predicting VTE in hospitalized cirrhotic patients [28]. It is also noteworthy that a lower proportion of patients who receive VTE prophylaxis had non-alcoholic steatohepatitis. While it is unclear whether this is due to chance or is a true selection bias, these patients often have a high number of prothrombotic comorbidities and may have an increased inherent thrombotic risk, independent of other diagnoses, [29,30] again suggesting that the intrinsic VTE risk was not uniform between those receiving and those not receiving VTE prophylaxis. Nevertheless, the difference in Padua scores suggests that clinicians in our institution are considering thrombotic risk when selecting patients for prophylaxis. In addition, this finding may imply that the group who received VTE prophylaxis was at higher risk for VTE, and may have benefited from prophylaxis. Our failure to find a significant difference in VTE events between the groups that did or did not receive VTE prophylaxis must be considered with caution, as it is possible that risk reduction in the prophylaxis group effectively prevented VTE in the higher-risk group, thus removing any significant difference in incidence. It is worthwhile to note that within the group of patients who received VTE prophylaxis, we were unable to detect a change in VTE incidence in the patients who received anticoagulation for a shorter fraction of their hospitalization, suggesting that the overall observation of decreased efficacy of prophylaxis in this population may hold some credence. It is quite possible, however, that our study was simply underpowered to detect a difference in VTE occurrence, if one exists.

Our findings are consistent, however, with the results of previous studies, including a meta-analysis of seven trials that included both inpatients and outpatients. In this review, neither an increase in bleeding episodes nor a decrease in VTE events in patients with cirrhosis who received prophylactic anticoagulation was documented [31]. One large retrospective study of inpatients with cirrhosis receiving VTE prophylaxis similarly found a low rate (2.5%) of in-hospital GI bleeding [32], and one prospective trial concluded that prophylactic-dose LMWH was safe in inpatients with cirrhosis [33]. Our trial was limited to the inpatient population, but small trials have evaluated the use of outpatient anticoagulation for portal vein thrombosis prophylaxis in patients with cirrhosis and have shown a low risk of bleeding similar to our results [34-38]. We identified no difference in the risk for GI bleeding or death from all causes in patients who received VTE prophylaxis compared with those who did not.

A novel and somewhat unexpected finding in our study was that UFH, but not LMWH, was associated with an increased risk for in-hospital bleeding events. While provocative, and consistent with studies in patients without cirrhosis [39], this finding requires confirmation by additional investigation and should be interpreted with caution, as there is a clear bias to use UFH over LMWH in patients with decreased renal function. Our subgroup analysis showed the patients who received UFH had significantly higher serum creatinine levels than all others, while those who received LMWH did not. While we did not find creatinine level itself to be predictive of bleeding or thrombosis in our study, the hemostatic alterations and platelet dysfunction present in patients with renal disease have been shown to lead to an increased rate of both thrombotic and bleeding events [40]. It is unknown how the complex interplay of concurrent renal and liver disease behaves clinically and, as such, this can only be theorized. It is possible there was an inherent increased bleeding risk in the group who received UFH that contributed to our finding. It is nevertheless plausible to hypothesize that LMWH might be safer in this population given the predictability of response. LMWH has been studied previously in patients with chronic liver dysfunction and appears to display an acceptable safety profile [32-37], leading some to propose as the anticoagulant of choice for VTE treatment and prevention in patients with cirrhosis [41]. Our study is the first to document a potential advantage over UFH in this patient population. Results of laboratory studies performed by others may help to explain our findings. Although the level of thrombin generation in patients with cirrhosis is similar or increased compared with that of non-cirrhotic controls [25,26], the level of thrombin inhibition by various anticoagulants may not be the same and may vary with the level of liver dysfunction [42]. Recently, Potze and colleagues investigated the effect of various anticoagulants on endogenous thrombin potential in patients with cirrhosis. The investigators found that both UFH and LMWH had a greater effect on thrombin generation in cirrhotic patients than in non-cirrhotic controls. While both LMWH and UFH exhibited a greater effect on thrombin generation in patients with cirrhosis than in controls, UFH produced a more significant change. This suggests a more potent anticoagulant effect for UFH than for LMWH in cirrhotic patients, which may in part explain our finding of an increased bleeding risk with UFH. Senzolo and colleagues performed a similar analysis with higher doses of LMWH and found higher levels of thrombin inhibition as well as greater variation in response based on the level of liver dysfunction [43]. While monitoring of anticoagulants in the general patient population is well established, there is a lack of data in patients with cirrhosis. Several studies have shown

an inverse relationship between anti-factor Xa level and the degree of liver disease in patients exposed to LMWH [33,43,44], and UFH [44], suggesting the anti-FXa level underestimates drug levels of LMWH and UFH in patients with cirrhosis [41]. While UFH may be monitored with standard measurements of coagulation such as the activated partial thromboplastin time, these parameters may be abnormal in patients with cirrhosis, making standard titration protocols ineffective.

While our study failed to find useful clinical predictors of VTE, this is consistent with previous studies in which PT/INR, platelet count, MELD score, and multiple other laboratory variables did not correlate with VTE risk [5,6]. Low serum albumin levels appear to correlate with VTE risk [5,6], a finding we did not analyze in our study. Northrup and colleagues suggested that a low serum albumin implies impaired hepatic synthetic function and thus low levels of the endogenous anticoagulant factors [6]. This was explored by Tripodi and colleagues, who discovered that as the degree of liver dysfunction increases and albumin levels decrease, FVIII levels increase while protein C decreases [45]. This imbalance between procoagulant and anticoagulant factors may in part explain the VTE risk seen in this population. Larger prospective studies will be required to confirm this, and the effect of classical clinical risk factors for VTE in cirrhotic patients (e.g., age, sex, smoking, obesity) remains to be investigated.

Our study has important limitations. First, the retrospective design and single-institution nature of the study may limit the generalizability of the results. The two patient populations analyzed (i.e., those who did and those who did not receive VTE prophylaxis) were not homogeneous and may have somewhat different risks for both VTE and bleeding. There was a clear bias on the part of treating clinicians to defer thromboprophylaxis in patients with elevated INRs or thrombocytopenia, although our prophylaxis use rate of 49% was higher than that reported in previous studies [26]. The group that received thromboprophylaxis in our study included fewer men and fewer baseline laboratory abnormalities (Table 1) than the group that did not receive thromboprophylaxis. Interestingly, while the mean baseline INR of the non-prophylaxis group was higher than the prophylaxis group, there was no statistical difference in the prothrombin time between the two populations. Patients who received pharmacological prophylaxis in our study had a longer average length of hospital stay than those who did not receive prophylaxis. We believe this may be due to the tendency of physicians to prescribe thromboprophylaxis for patients with longer lengths of hospital stays, who are typically sicker and are perceived to be at higher risk for VTE than patients with shorter anticipated stays, and less likely a direct effect of prophylaxis.

Another potential confounder is the use of antiplatelet agents. Clopidogrel was administered in only two admissions during the study period; thus, its effect was deemed negligible and not considered in this study. Data on the administration of aspirin could not be obtained, as this was not routinely billed during the study period, although, based on our clinical experience, we think aspirin use was likely low. Nevertheless, these unmeasured variables could conceivably influence bleeding rates. Due to the complexity of the medical record, we could not accurately assess classic risk factors for VTE, including body mass index, smoking history, and malignancy, and such confounders were not compared between intervention groups. Last, sequential compression devices were variably used during the

study period; however, the utilization rate and patient compliance were not readily available for analysis. The use of sequential compression devices may well have contributed to the lack of apparent benefit of thromboprophylaxis.

Despite the limitations, our finding that pharmacological thromboprophylaxis is generally safe in patients with cirrhosis is similar to findings from previous studies. Our finding that LMWH appears safer than UFH in this patient population is novel but plausible based on the results of laboratory studies performed by others. Reassuringly, the rates of bleeding and death were not significantly different for those who received pharmacological prophylaxis of any type compared with those who did not. However, it is worth noting that our study, like previous studies, failed to show a reduction in the incidence of in-hospital symptomatic VTE, making further study of VTE risk factors in these patients imperative. Our study also highlights physician hesitancy to prescribe VTE prophylaxis for patients with a laboratory coagulopathy, and highlights a general lack of understanding of the complex coagulation derangements associated with chronic liver disease. Although further studies are required to understand the role of classic risk factors on VTE rates in this patient population and tools for VTE risk stratification are needed, for now our data support the use of LMWH over UFH thromboprophylaxis for selected hospitalized patients with cirrhosis at increased risk for VTE.

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Fig. 1.

Inclusion/exclusion schema. Nine hundred ninety-six hospital admissions were identified for potential inclusion in the study, and 600 admissions involving 402 unique patients qualified for entry. *The unique patient number includes 66 patients with multiple admissions who received VTE prophylaxis during some admissions but not during others. These patients are therefore included in both the prophylaxis and no-prophylaxis groups, accounting for 235 and 233 patients, respectively.

Baseline patient characteristics*

Table 1

	VTE prophylaxis (n = 296 admissions)	No VTE prophylaxis (n = 304 admissions)	P value
Age, yrs, mean (median, p25, p75, IQR)	59 (59, 52, 68, 16)	55 (56, 48, 64, 16)	< 0.001
Male, n (%)	145 (49.3)	198 (65.5)	< 0.001
Platelets $9 \times 10^3 \text{ IL}^{-1}$, mean (median, p25, p75, IQR)	169 (144, 101, 206, 105)	126 (100.5, 60, 164, 104)	< 0.001
MELD score, mean (median, p25, p75, IQR)	13.2 (12.4, 5.7, 18.7, 12.9)	16.1 (15.8, 10, 21, 4, 11.4)	< 0.001
Total bilirubin, mg dL^{-1} , mean (median, p25, p75 IQR)	2.8 (1.2, 0.6, 2.8, 2.2)	5.2 (2.6, 1.1, 5.3, 4.2)	< 0.001
Serum creatinine, mg dL^{-1} , mean (median, p25, p75 IQR)	1.64 (1.1, 0.7, 1.8, 1.1)	1.35 (0.96, 0.7, 1.5, 0.8)	0.022
INR, mean (median, p25, p75 IQR)	1.43 (1.3, 1.2, 1.6, 0.4)	1.71 (1.6, 1.3, 2, 0.7)	< 0.001
PT, s, mean (median, p25, p75 IQR)	19.3 (16.9, 15.3, 19.2, 3.9)	20.5 (19.2, 16.5, 23.2, 6.7)	0.463
PADUA predictive score [40] (mean $\pm$ SD)	4.3 (2.17)	3.5 (2.25)	< 0.001
Etiology of cirrhosis, %			
Alcohol induced	49	37	
Non-alcoholic steatohepatitis	27	42	
Virus associated	30	22	
Idiopathic	3	4	
Autoimmune hepatitis	4	5	
Alpha-1 antitrypsin deficiency	2	1	
Wilson's disease/hemochromatosis	2	1	
Cardiac cirrhosis	1	1	
Other*	4	3	

MELD, Model for End-stage Liver Disease; INR, international normalized ratio; PT, prothrombin time; SD, standard deviation; p25, 25th percentile; p75, 75th percentile; IQR, interquartile range.

* Alagille's syndrome, hereditary telangiectasia, HIV, nodular hyperplasia of the liver, transfusion siderosis, congestive hepatopathy, amyloidosis.

Baseline characteristics of patients who received pharmacological VTE prophylaxis and experienced or did not experience a bleeding event

Table 2

	Bleeding event (n = 24 admissions)	No bleeding event (n = 272 admissions)	P value
Age, years, mean (median, p25, p75, IQR)	59.4 (60.5, 51.0, 64.5, 13.5)	59.3 (57.0, 50.0, 65.0, 15.0)	0.940
Male, n (%)	14 (58)	133 (48)	0.402
Platelets $9 \times 10^3 \text{ IL}^{-1}$, mean (median, p25, p75, IQR)	148.0 (127.0, 61.0, 162.0, 101.0)	170.1 (120.0, 76.0, 186.0, 110.0)	0.290
MELD score, mean (median, p25, p75, IQR)	17.6 (16.2, 10.5, 22.5, 11.9)	12.8 (13.8, 7.8, 19.8, 12.0)	0.008
Total bilirubin, mg dL^{-1} , mean (median, p25, p75, IQR)	3.3 (2.2, 1.0, 5.2, 4.2)	2.8 (1.8, 0.7, 3.9, 3.2)	0.600
Serum creatinine, mg dL^{-1} , mean (median, p25, p75, IQR)	1.7 (1.1, 0.7, 1.9, 1.2)	1.6 (1.0, 0.7, 1.6, 0.9)	0.940
INR, mean (median, p25, p75, IQR)	1.7 (1.6, 1.4, 2.0, 0.6)	1.4 (1.4, 1.2, 1.8, 0.6)	<0.001
PT, s, mean (median, p25, p75, IQR)	20.3 (19.4, 17.3, 23.4, 6.1)	19.2 (17.6, 15.6, 21.2, 5.6)	0.850

MELD, Model for End-stage Liver Disease; INR, international normalized ratio; PT, prothrombin time; SD, standard deviation; p25, 25th percentile; p75, 75th percentile; IQR, interquartile range.

Table 3Risk of in-hospital bleeding event according to prophylaxis strategy^{*}

	Odds ratio [†]	95% CI
Heparin at all		
In-hospital bleed	2.40	1.13–5.08
Non-GI bleed	2.95	1.13–7.68
GI bleed	1.74	0.64–4.73
Heparin only		
In-hospital bleed	2.88	1.34–5.84
Non-GI bleed	3.35	1.20–9.36
GI bleed	2.14	0.79–5.80
LMWH at all		
In-hospital bleed	0.84	0.36–1.98
Non-GI bleed	2.37	0.81–6.94
GI bleed	0.24	0.05–1.11
LMWH only		
In-hospital bleed	1.04	0.44–2.46
Non-GI bleed	2.85	0.97–8.39
GI bleed	0.29	0.06–1.35

GI, gastrointestinal; LMWH, low molecular weight heparin; CI, confidence interval.

^{*} Adjusted for total bilirubin, AST, ALT, alkaline phosphatase, MELD, creatinine, platelets, age, INR, and length of stay.[†] These odds ratio were calculated by comparing patients who received different types and combinations of VTE prophylaxis (heparin at all, heparin only, LMWH at all, and LMWH only) to patients who did not receive any prophylaxis.

Table 4

Adverse events according to VTE prophylaxis status

	VTE prophylaxis (<i>n</i> = 296 admissions)	No VTE prophylaxis (<i>n</i> = 304 admissions)	<i>P</i> value
VTE, <i>n</i> (%)	7 (2.4)	5 (1.7)	0.537
In-hospital bleed, <i>n</i> (%)	24 (8.1)	17 (5.5)	0.258
GI bleed, <i>n</i> (%)	9 (3.0)	10 (3.3)	0.851
Non-GI bleed, <i>n</i> (%)	15 (5.1)	7 (2.3)	0.074
PRBC transfusion, <i>n</i> (%)	30 (10.1)	19 (6.3)	0.087
PRBC units, <i>n</i> , median (IQR)	4.17 (2.25)	2.42 (2)	0.082
In-hospital death, <i>n</i> (%)	25 (8.4)	22 (7.3)	0.599

VTE, venous thromboembolism; GI, gastrointestinal; PRBC, packed red blood cell.

Table 5

Predictors of in-hospital VTE *

	<i>P</i> -value
Age	OR 1.03, 95% CI 0.97–1.08, <i>P</i> = 0.261
Platelet count	OR 1.00, 95% CI 0.99–1.00, <i>P</i> = 0.592
MELD score	OR 1.08, 95% CI 0.37–3.71, <i>P</i> = 0.245
Serum creatinine level	OR 0.39, 95% CI 0.12–1.29, <i>P</i> = 0.126
INR	OR 1.09, 95% CI 0.18–6.45, <i>P</i> = 0.919
Total bilirubin level	OR 1.00, 95% CI 0.84–1.19, <i>P</i> = 0.961
VTE thromboprophylaxis (yes or no)	OR 0.94, 95% CI 0.23–3.71, <i>P</i> = 0.931
Length of stay	OR 1.04, 95% CI 1.00–1.09, <i>P</i> = 0.032 [†]

MELD, Model for End-stage Liver Disease; INR, international normalized ratio; VTE, venous thromboembolism; CI, confidence interval. For continuous variables, odds ratios are in terms of changes in odds as a result of a one-unit change in the variable.

* Adjusted for presence of chemical VTE prophylaxis, type of VTE prophylaxis, total bilirubin, AST, ALT, alkaline phosphatase, MELD, creatinine, platelets, age, INR, and length of stay.

[†] Significant at a *P* value of 0.05.

Table 6Predictors of in-hospital bleeding events^{*}

	OR, 95% CI, <i>P</i> value
Age	OR 1.00, 95% CI 0.972–1.03, <i>P</i> = 0.914
Length of stay	OR 1.01, 95% CI: 0.992–1.03, <i>P</i> = 0.283
Platelet count	OR 0.99, 95% CI: 0.995–1.00, <i>P</i> = 0.684
MELD score	OR 1.04, 95% CI: 0.952–1.136, <i>P</i> = 0.39
Serum creatinine level	OR 0.77, 95% CI: 0.474–1.25, <i>P</i> = 0.298
INR	OR 1.94, 95% CI: 0.936–4.02, <i>P</i> = 0.075
Total bilirubin level	OR 0.98, 95% CI: 0.917–1.04, <i>P</i> = 0.565
VTE thromboprophylaxis (yes or no)	OR 2.355, 95% CI: 1.116–4.971 <i>P</i> = 0.025 [†]

MELD, Model for End-stage Liver Disease; INR, international normalized ratio; VTE, venous thromboembolism; CI, confidence interval. For continuous variables, odds ratios are in terms of changes in odds as a result of a one-unit change in the variable.

^{*} Adjusted for presence of chemical VTE prophylaxis, type of VTE prophylaxis, total bilirubin, AST, ALT, alkaline phosphatase, MELD, creatinine, platelets, age, INR, and length of stay.

[†] Significant at a *P* value of 0.05.