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**TRATTAMENTO DEL TROMBOEMBOLISMO VENOSO
CON ANTICOAGULANTI TRADIZIONALI
E DI NUOVA GENERAZIONE**

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Introduzione

Il trattamento del tromboembolismo venoso (TEV) si è basato per decenni sull'utilizzo di farmaci parenterali nella fase acuta (eparina non frazionata, eparine a basso peso molecolare, fondaparinux) e di farmaci orali (dicumarolici) per la prevenzione secondaria a medio-lungo termine. Questi ultimi sono notevolmente efficaci nel ridurre il rischio di recidiva di TEV, ma, a causa della stretta finestra terapeutica e della variabilità farmacocinetica intra- ed inter-individuale, necessitano di un monitoraggio laboratoristico, allo scopo di minimizzare sia il rischio di recidive trombotiche che quello di complicanze emorragiche.¹

Negli ultimi 15 anni circa, la ricerca farmacologica ha portato allo sviluppo e alla sperimentazione di farmaci anticoagulanti orali diretti (DOACs), che presentano, rispetto ai dicumarolici, un'azione più selettiva, un migliore profilo di efficacia/sicurezza e caratteristiche farmacocinetiche più prevedibili, tali da non richiedere uno stretto monitoraggio laboratoristico.² Negli studi di fase III per il trattamento del TEV, i DOACs si sono dimostrati, rispetto ai dicumarolici, non inferiori in termini di efficacia e hanno presentato un profilo di rischio emorragico equivalente o migliore.^{3,4,5,6,7}

¹ Ageno W, Gallus AS, Wittkowsky A, et al. Oral anticoagulant therapy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e44S-88S

² Ufer M. Comparative efficacy and safety of the novel oral anticoagulants dabigatran, rivaroxaban and apixaban in preclinical and clinical development. Thromb Haemost 2010;103:572-85

³ The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med 2010;363:2499-2510

⁴ The EINSTEIN-PE Investigators. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. N Engl J Med 2012;366:1287-97

Pertanto, la European Medicines Agency (EMA) ha approvato rivaroxaban (2011), dabigatran (2014), apixaban ed edoxaban (2015) per il trattamento del TEV e l'Agenzia Italiana del Farmaco (AIFA) ne ha successivamente autorizzato l'utilizzo in Italia, stabilendo un regime di rimborsabilità per rivaroxaban (2013), apixaban e dabigatran (2015).⁸

Tra gli ambiti clinici che possono beneficiare dall'introduzione dei DOACs, vi sono due manifestazioni comuni del TEV, cioè l'embolia polmonare (EP) e la trombosi venosa profonda distale isolata (TVPDI). In particolare, per quanto riguarda l'EP, l'utilizzo dei DOACs può portare, nella fase acuta, ad un miglioramento della gestione dei pazienti che presentano basso rischio di complicanze e, nel medio-lungo termine, ad una ottimizzazione del profilo rischio-beneficio della terapia anticoagulante. Per quanto riguarda il trattamento delle TVPDI, le cui evidenze sono più scarse ed eterogenee in termini di scelta del farmaco e durata della terapia, l'utilizzo dei DOACs, grazie alla loro semplicità di uso e al buon profilo di sicurezza, può condurre ad una semplificazione ed omogeneità terapeutica.

Infine, il profilo di rischio emorragico dei DOACs può rappresentare un vantaggio rispetto ai dicumarolici, vista la dimostrata riduzione significativa

⁵ Agnelli G, Buller HR, Cohen A, et al; the AMPLIFY Investigators. Oral Apixaban for the Treatment of Acute Venous Thromboembolism. *N Engl J Med* 2013;369:799-808

⁶ Schulman S, Kearon C, Kakkar AK, et al; RE-COVER Study Group. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med* 2009;361:2342-2352

⁷ Hokusai-VTE Investigators, Büller HR, Décousus H, Grosso MA, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med* 2013;369:1406-15

⁸ Squizzato A, Galli M, Dentali F, et al. Outpatient treatment and early discharge of symptomatic pulmonary embolism: a systematic review. *Eur Respir J* 2009;33:1148-55

delle emorragie intracraniche, che sono caratterizzate da una significativa mortalità e morbilità.

Obiettivi

Lo scopo del programma di ricerca era la valutazione dell'impatto clinico dei DOACs, sotto il profilo di efficacia e sicurezza in tre ambiti del TEV: 1) la stratificazione prognostica e l'ottimizzazione del trattamento dell'EP, 2) il trattamento delle TVPDI e 3) la gestione delle complicanze emorragiche.

In particolare, nel trattamento dell'EP, lo scopo del progetto era testare l'impatto dei DOACs nella gestione dei pazienti a basso rischio di complicanze, i quali potrebbero beneficiare di una breve ospedalizzazione o di un trattamento interamente domiciliare, grazie alla disponibilità di farmaci in grado di fornire un'adeguato livello di anticoagulazione in breve tempo e senza necessità di monitoraggio laboratoristico.

Per quanto riguarda la gestione delle TVPDI, lo scopo del progetto era valutare la possibilità di ottimizzare e standardizzare il regime di trattamento, che attualmente è controverso ed eterogeneo.

Infine, nell'ambito delle complicanze emorragiche, il progetto si prefiggeva di valutare il rischio di sanguinamento e la sua gestione nella pratica clinica, dal momento che, rispetto agli studi di fase III, i DOACs sono utilizzati in pazienti meno selezionati e per periodi di tempo potenzialmente più lunghi.

Durante il primo anno di svolgimento del progetto, è stato necessario apportare delle modifiche al piano sperimentale a causa del ritardo in Italia nell'approvazione e commercializzazione dei DOACs per il trattamento del TEV. Pertanto, sono stati progettati alcuni studi preliminari/preparatori, la

cui conduzione è proseguita nei successivi due anni. Nel corso del II anno, inoltre, poiché il regime di rimborsabilità stabilito da AIFA per rivaroxaban (unico DOAC allora approvato per il trattamento del TEV) non includeva il trattamento dell'EP e della TVPDI, non è stato possibile mantenere, come parte centrale dei progetti, gli obiettivi legati ai DOACs, che sono stati pertanto inclusi come obiettivi secondari, ove possibile. Per le medesime ragioni, è stato giudicato opportuno ampliare i progetti di ricerca già in intrapresi.

Stratificazione prognostica dell'embolia polmonare

L'embolia polmonare, che rappresenta la terza causa più frequente di patologia cardiovascolare dopo le sindromi coronariche acute e gli eventi cerebrovascolari acuti, è caratterizzata da un ampio spettro prognostico, che varia da una pronta risoluzione dei sintomi dopo alcune ore di trattamento alla morte improvvisa.

I pazienti a cui viene diagnosticata una EP vengono solitamente ricoverati in ospedale per intraprendere il trattamento anticoagulante iniziale, sebbene alcuni di loro, considerati a basso rischio di eventi avversi (mortalità intraospedaliera < 1%), possano risultare idonei per una breve ospedalizzazione (circa 72 ore) o perfino per una terapia interamente domiciliare.^{9,10,11,12}

In anni recenti vi sono stati numerosi studi che si sono focalizzati sulla stratificazione prognostica dei pazienti con EP acuta, allo scopo di adattare le strategie di trattamento e di gestione. In particolare, sono stati derivati e validati alcuni modelli predittivi (clinical prediction models, CPM), tra cui vi

⁹ Konstantinides SV, Torbicki A, Agnelli G, et al. 2014 ESC guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J* 2014;35:3033-69

¹⁰ Jaff MR, McMurtry MS, Archer SL, et al. Management of massive and submassive pulmonary embolism, iliofemoral deep vein thrombosis, and chronic thromboembolic pulmonary hypertension: a scientific statement from the American Heart Association. *Circulation* 2011;123:1788-830

¹¹ Kearon C, Akl EA, Comerota AJ, Prandoni P, et al. Antithrombotic therapy for VTE disease: antithrombotic therapy and prevention of thrombosis, 9th edition: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest* 2012;141 (2 Suppl):e419S-94S

¹² Aujesky D, Roy PM, Verschuren F, et al. Outpatient versus inpatient treatment for patients with acute pulmonary embolism: an international, open-label, randomised, non-inferiority trial. *Lancet* 2011;378:41-8

sono il Pulmonary Embolism Severity Index (PESI)¹³ e la sua versione semplificata (sPESI)¹⁴, che sono risultati associati ad un più alto livello di evidenze scientifiche¹⁵.

Tuttavia, non vi sono ancora evidenze adeguate sul fatto che l'adozione di PESI o sPESI nella pratica clinica cambi il comportamento dei medici, migliori outcome clinici importanti per i pazienti o riduca i costi¹⁶.

Pertanto, è stata pianificato un progetto che mira a valutare se la durata dell'ospedalizzazione per EP varia a seconda della stratificazione prognostica identificata da PESI e sPESI nella comune pratica clinica, partendo dall'ipotesi che l'adozione di questi CPM possa cambiare significativamente il comportamento dei medici clinici nella gestione ottimale dei pazienti con EP.

Il progetto comprende 5 fasi:

1. Osservazionale: acquisizione di dati sulla gestione dell'EP nei centri partecipanti
2. Educazionale: presentazione, ai centri partecipanti, dei risultati dello studio osservazionale; distribuzione di materiale educativo riguardante la stratificazione prognostica dell'EP; presentazione delle evidenze provenienti dai trial randomizzati controllati (RCT) dei DOACs nel trattamento del TEV

¹³ Aujesky D, Obrosky DS, Stone RA, et al. Derivation and validation of a prognostic model for pulmonary embolism. *Am J Respir Crit Care Med* 2005;172:1041-6

¹⁴ Jimenez D, Aujesky D, Moores L, et al; RIETE Investigators. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med* 2010; 170: 1383-9

¹⁵ Squizzato A, Donadini MP, Galli L, et al. Prognostic clinical prediction rules to identify a low-risk pulmonary embolism: a systematic review and meta-analysis. *J Thromb Haemost* 2012;10:1276-90

¹⁶ McGinn TG, Guyatt GH, Wyer PC, et al. Users' guides to the medical literature: XXII: how to use articles about clinical decision rules. Evidence-Based Medicine Working Group. *JAMA* 2000; 284: 79-84

3. Intervento: assegnazione randomizzata dei medici all'utilizzo formale di PESI versus sola pratica clinica standard, per la stratificazione prognostica dei pazienti con EP

4. Condotta dello studio e valutazione degli outcome

5. Analisi dei dati; diffusione dei risultati; preparazione del manoscritto.

Nella fase di intervento del progetto, al fine di poter valutare l'impatto dei DOACs sull'outcome primario (durata del ricovero ospedaliero), è stato stabilito che, prima della randomizzazione, ciascun medico debba dichiarare quale strategia di trattamento utilizzare per il paziente, cioè DOACs o trattamento "tradizionale" (randomizzazione stratificata per trattamento). In tal modo sarà possibile confrontare l'outcome tra i seguenti gruppi:

- gruppo 1 (PESI) versus gruppo 2 (pratica clinica standard) in pazienti trattati con DOACs

- gruppo 1 (PESI) versus gruppo 2 (pratica clinica standard) in pazienti che ricevono trattamento tradizionale

- gruppo DOACs versus gruppo trattamento tradizionale

- gruppo DOACs versus coorti della fase osservazionale (in cui nessun paziente ha ricevuto DOACs).

La prima fase osservazionale del progetto (Low-Risk Pulmonary Embolism and Length of Hospital-stay: the LORPELHS study), comprendente una corte "storica" (2005-2009) e una coorte "attuale" di pazienti (2010-2013), viene presentata di seguito (manoscritto in fase di sottomissione a rivista scientifica).

La fase di intervento del progetto costituisce lo studio “Impact Analysis of Prognostic stratification for Pulmonary embolism: the iAPP study”, il cui protocollo è stato recentemente approvato dal comitato etico provinciale di Varese (Ottobre 2015), ed è in fase di partenza, congiuntamente agli 8 centri partecipanti.

LOW-RISK PULMONARY EMBOLISM AND LENGTH OF HOSPITAL-STAY IN GENERAL AND SPECIAL POPULATIONS : THE LORPELHS STUDY

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Introduction

Pulmonary embolism (PE) is the third most frequent acute cardiovascular disease after acute coronary syndromes and stroke, with a prevalence of 80 to 100 cases/100.000 persons per year [1]. PE is associated with a wide prognostic spectrum, ranging from prompt resolution of symptoms after few hours of treatment to sudden death. PE patients are commonly admitted to hospital for their initial treatment, though some of them, who are at low risk of adverse outcomes (~1% of in-hospital mortality), may be suitable for a short-hospital stay or even complete home-treatment [2-8]. In recent years, research has focused on stratifying the risk of adverse outcomes after PE, in order to tailor treatment and management strategies. Although some prognostic clinical prediction models (CPM) have been adequately derived and validated, especially the Pulmonary Embolism Severity Index (PESI) and its simplified version (sPESI) [9-11], there is no evidence that its use changes clinicians behavior, improves PE patient outcomes or reduces costs [12]. Therefore, we planned to perform an impact analysis study to evaluate if length of hospital-stay for PE varies according to PE risk of adverse events defined by PESI in common clinical practice.

Methods

A retrospective cohort study was performed on consecutive adult patients objectively diagnosed with suspected or unsuspected PE within 72 hours from hospital admission. The study was conducted in eight Italian internal

medicine divisions, from 2011 to 2013. No exclusion criteria were applied, except for age > 18 years.

Suspected PE means that diagnosis was made by an imaging test (computed tomography pulmonary angiography (CTPA), pulmonary angiography, lung scan, compression ultrasonography) prescribed by a physician who had clinical suspicion of PE. Unsuspected PE means that diagnosis was made incidentally by an imaging test performed for other clinical indications (e.g. cancer staging).

Patients were identified by direct chart review or by searching the administrative database of each hospital using discharge codes according to the 9th Clinical Modification International Classification of Diseases, (ICD-9-CM). Either patients with primary and secondary diagnosis of PE were considered. Demographic, clinical, laboratory, radiological and therapeutic data were collected by reviewing clinical charts; original PESI and sPESI were retrospectively calculated. We anticipated a higher proportion of missing data for PESI as compared to sPESI, because of the higher number of variables (11 and 6, respectively). In addition, two centers could provide data on sPESI only (as previously published).

Patients were classified at low vs. high risk of adverse events according to original PESI (classes I-II vs. III-V) and to sPESI (0 vs. ≥ 1 points), as previously published. Furthermore, individual PESI classes I to V were calculated.

The primary objective of our study was to retrospectively evaluate if length of hospital-stay for PE varies according to PE risk stratification of adverse events defined by PESI and sPESI, in common clinical practice.

Secondary objectives were to identify any predictors of reduced length of hospital-stay in PE patients and to compare clinical characteristics, prognosis, and length of hospital-stay in PE special frail populations, such as those with cancer, impaired renal function (glomerular filtration rate (GFR) < 50 mL/min) and the elderly (>75 years).

In addition, a historical cohort was included as control group, consisting of patients diagnosed with PE at one center (Ospedale di Circolo, Varese) from 2005 to 2009, to evaluate a possible time-dependent trend of hospital stay duration for PE.

Statistical analysis

To calculate the sample size, we considered that the mean length of hospital-stay for PE in Lombardia region is 11.5 days (data from the Ministry of Health reports, 2010). We hypothesized that the distribution of hospital stay durations for PE would have a standard deviation of 4 days. We also hypothesized that the mean duration of hospital stay for low-risk PE patients would be shorter of, at minimum, 10% than in high-risk PE patients.

Low-risk PE patients are about 50% of the entire PE population. Therefore, with alfa 0.05 and power 80%, we calculated that 400 patients were necessary to find a statistically significant difference ($p < 0.05$) between the mean length of hospital stay of low-risk versus high-risk groups of patients. Therefore, each of the eight participating centers were asked to include 50 patients.

Descriptive data are presented as means with standard deviation (SD) or medians with interquartile range (IQR) according to the normal or non-normal distribution of the variables, respectively (Kolmogorov-Smirnov test). Student's T-test or Mann-Whitney test were used to compare means or medians between two groups, respectively. In addition, Kruskal-Wallis test was used to compare medians between more than two groups (i.e. five PESI classes).

A univariate logistic regression analysis was used to find potential predictors of the length of hospital stay (considered as a dichotomous variable based on its median). The dependent variables that resulted potentially associated ($p < 0.15$) with length of hospital stay were subsequently entered in a multivariate model.

Anticipating missing data for PESI, an analysis on the best and worst clinical scenario was planned, inputting missing data on PESI items as absence or presence of the condition, respectively.

Results

391 patients with an objective diagnosis of PE, admitted to 8 Italian internal medicine divisions from 2011 to 2013, were included in the study. Median age was 77 years (IQR 69-84), 165 patients (42.2%) were males. Active cancer were present in 87 patients (22.3%). Complete baseline characteristics are presented in Table 1.

Initial PE treatment were administered according to local practice: 332 patients (84.9%) received low molecular weight heparin or fondaparinux, 33 (8.4%) received unfractionated heparin and 7 (1.8%) received pharmacological thrombolysis. Before discharge, 247 patients (63.2%) were started on vitamin K antagonists. No patients received any direct oral anticoagulant.

Complete data on sPESI were available for 380 of 391 patients from 8 centers (97.2%) and on PESI for 150 of 299 patients from 6 centers (50.2%). According to sPESI, 94 patients (24.7%) were classified at low risk and 286 (75.3%) at high risk of adverse outcomes. Similar proportions were identified by PESI (26.7% and 73.3%, respectively) and, in particular, 8.7% of patients were classified in class I, 18% in class II, 26.7% in class III, 15.3% in class IV and 31.3% in class V.

Overall, the median hospital stay was of 10 days (IQR 7-14). The low risk and high risk groups, as identified by sPESI, presented a median hospital stay of 9 (IQR 7-11) and 10 (IQR 7-15) days, respectively ($P=0.027$). The result did not change after excluding 39 patients (10%) who died in hospital ($P=0.017$). Few patients were discharged within 5 days, 18 of 94 in the low risk group (19.1%) and 42 of 286 (14.7%) in the high risk group ($P=0.329$).

Similarly, the median hospital stay was of 9 (IQR 7-13) and 10 (IQR 8-15) days in the low risk and high risk group identified by PESI, respectively

($P=.264$). According to individual PESI classes, the median hospital stay was 9 days for class I, 9 for class II, 10 for class III, 11 for class IV, 10 for class V ($P=.662$). When missing data on PESI were analyzed according to the best and worst clinical scenarios, the difference of median hospital stay between the low risk and high risk group did not change (9 vs. 10 days, $P=.008$, and 9 vs. 10 days, $P=.019$, respectively).

Possible predictors of prolonged hospital stay were analyzed by logistic regression. In the final multivariate model, no variables were significantly associated with the length of hospital stay, with the exceptions of impaired renal failure (GFR, < 50 mL/min) and anemia (haemoglobin < 10 g/dL) that were only marginally associated with a prolonged hospitalization ($P=.057$ and $.064$, respectively).

Secondary analysis

Special populations

245 patients (62.7%) aged ≥ 75 years were included in the study. Compared to the entire study population, a lower proportion of these patients was classified by sPESI at low risk (11.3%) and a higher proportion at high risk (88.7%) of adverse outcome. The overall median hospital stay was of 10 days (IQR 7-15), similar to that of the entire study population. However, there was a non-statistically significant difference of 2 days between the low risk (9 days, IQR 7-11) and high risk group (11 days, IQR 7-15) ($P=.091$), that was slightly larger compared to the entire population (1 day).

Similar results were found in 80 patients with impaired renal function (calculated GFR < 50 mL/min), who were hospitalized for a median of 11 days (IQR 7.5-15.5), with a difference of 2.5 days between the low risk (10 days, IQR 7.5-14) and high risk group (12.5 days, IQR 7.75-15.5), although not statistically significant ($P=.466$).

Finally, 87 patients with active cancer were included in the study, none of them classified at low risk using sPESI, by definition. The median hospital stay was 10 days (IQR 6-15), similar to the entire study population.

Control group

The results of a cohort of 363 patients diagnosed with PE within 72 hours from hospital admission from 2005 to 2009 at one center (Ospedale di Circolo, Varese), were compared to the present study. The median hospital stay of the entire 2005-2009 population was 12 days (IQR 9-17), and in particular it was 11 days (IQR 8-15) in the low risk group and 12 days (IQR 9-19) in the high risk group (P=.068). In relative terms, this non statistically significant difference of 1 day between the low risk and high risk is similar to that found in the present (2011-2013) study. However, in absolute terms, there is a difference of 2 days in the overall median hospital stay between the two entire cohorts (10 days in the 2011-2013 cohort vs. 12 days in the 2005-2009 cohort) and between the groups at low risk (9 vs. 11) and high risk (10 vs 12 days), that may indicate a time-dependent trend towards shorter hospital stay for PE.

Table 1. Baseline characteristics

Patients, n	391
Age, ys (mean, SD)	74.6 (13.8)
Sex, male (%)	165 (42.2)
Asymptomatic PE	57 (14.6%)
Proximal DVT, n (%)	128 (32.7%)
Isolated distal DVT, n (%)	30 (7.7%)
Simplified PESI, n (%)	
• Low risk	94 (24.7%)
• High risk	286 (75.3%)
PESI, n (%)	
• class I	13 (8.7%)
• class II	27 (18%)
• class III	40 (26.7%)
• class IV	23 (15.3%)
• class V	47 (31.3%)
• Low risk (I-II)	40 (26.7%)
• High risk (III-V)	110 (73.3%)

Table 2. Results

Prognostic stratification	Length of hospital stay, days, median (IQR)	P
Simplified PESI, n (%)		
• Low risk	9 (7-11)	.027
• High risk	10 (7-15)	
PESI, n (%)		
• class I	9 (5.5-12.5)	.662
• class II	9 (7-15)	
• class III	10 (8-13.75)	
• class IV	11 (8-14)	
• class V	10 (7-15)	
• Low risk (I-II)	9 (7-13)	.264
• High risk (III-V)	10 (8-15)	

Discussion

The study shows that, in the clinical context of internal medicine divisions, the duration of hospital stay for PE was generally long (median 10 days) both in frail patients (eg patients with cancer, impaired renal function, advanced age) and in the general population. When patients were classified at low or high risk of adverse outcomes, by retrospectively applying sPESI, a statistically significant difference of 1 day was found between the two groups. However, this difference is not clinically meaningful.

Therefore, in clinical practice, the clinical judgment on prognostic stratification of PE does not seem to be a major determinant of the duration of hospital stay. It is also possible that the clinical feeling alone (i.e. not supported by validated tools that formally provide a prognostic stratification such as PESI) is not sufficient *per se* to take adequately informed clinical decisions on the best timing of discharge. Indeed, compared to the available evidence and current clinical guidelines, a hospital stay of 9 days for patients at low risk of adverse outcome, found in this study, is significantly longer than 72 hours or 5 days suggested by recent evidence.

Large and consistent evidence shows that patients identified to be at low risk by PESI have a short-term risk of mortality of less than 1%. Therefore, the

adoption of PESI in clinical practice may assist clinicians in correctly identifying this group of patients, who may benefit from a short hospital stay. Moreover, the calculation of PESI is simple, especially in its simplified version (being represented by commonly available anamnestic variables and vital parameters, that are already part of the initial evaluation of a patient).

Nonetheless, in addition to the clinical data included in PESI, several other variables may play an important role in the physicians' decision on the duration of hospital stay. First, PE still represents a potentially lethal disease, thus making physicians worried about an early discharge. In addition, the treatment of PE may be dangerous in itself, because of potentially severe bleeding or treatment failure, thus making a prolonged hospitalization reassuring for physicians. Second, anticoagulant therapy may not be easy to take by some patients. Indeed, heparin injections, especially if administered more than once daily, may represent an obstacle to early discharge in many contexts (unwilling patients, absence of dedicated nurses or familiar support). In addition, VKA overlapping and INR monitoring may further complicate the initial therapy, thus increasing the physicians' perception of potentially high risk of under or over anticoagulation in the crucial early treatment phase. Third, an early discharge should rely on adequate home circumstances, such as the availability of anticoagulation clinics or trained family doctors for early follow-up, an adequate distance from the hospital in case of therapy complications or suspected recurrent VTE, in addition to the already mentioned dedicated nurses and adequate family support for elderly or frail patients.

The study, therefore, seems to suggest that PESI may have a limited impact on the management of PE. However, the retrospective design of the study does not allow definitive conclusions on the impact of PESI in clinical practice, but the results provide preliminary data on the usefulness of adopting this prognostic prediction model. Indeed, even if PESI is a widely validated model, its adoption in clinical practice needs to be tested by impact analyses, i.e. to demonstrate a change in clinician behavior with beneficial

consequences, such as taking better decisions and/or improving patients' outcomes (eg quality of life) and/or reducing costs. This objectives should be evaluated prospectively in studies that ideally randomize physicians or medical divisions to adopt or not PESI in the clinical decision making process. Moreover, addressing variables related to physicians' and patients' values and to the health system organization could have a relevant impact on the length of hospital stay for PE. For instance, the time dependent trend that was found towards a reduction of hospital stay (12 days in 2005-2009 versus 10 days in 2011-2013) may reflect an impact of the increasing evidence on the safety of early discharge of PE patients at low risk of mortality, as suggested in clinical practice guidelines from 2011.

Our study has limitations. First, the retrospective design of the study was associated with missing data, especially for PESI (11 items). A secondary analysis was performed inputing missing data according to the best and worst clinical scenario and the results was comparable to those of the main analysis. Moreover, the calculation of the simplified version of PESI (6 items) was available for more than 97% of patients.

Second, some variables potentially impacting on the timing of discharge were not collected, such as the time to reach a therapeutic INR. However, in addition to PESI, several other clinical, laboratoristic and imaging variables that could be potentially associated with the length of hospital stay were collected and tested in a logistic regression analysis, without finding any statistical significant association in the multivariate model. This finding reflects also the complexity of the prognostic reasoning, that encompasses several variables of different fields.

Third, the number of patients from each centers were not equally distributed, thus potentially increasing or reducing the impact of some centers. However, this difference only reflects the size of the participating centers and it is unlikely to introduce a significant bias, since patients were consecutive, thus increasing the internal validity of the results.

Last, the centers were located in northern Italy, thus potentially limiting the generalizability of the results. However, the multicenter design of the study, including eight centers from four different regions, may increase the external validity of the results.

In conclusion, in this study the median length of hospital stay for PE was generally long. The difference of one day between the low-risk and high-risk groups of patients according to sPESI was statistically, but not clinically significant. Whether adopting PESI/sPESI in clinical practice can assist clinicians to take better decisions about the optimal duration of hospital stay needs to be prospectively evaluated.

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Trattamento delle trombosi venose profonde distali

Le trombosi venose profonde distali isolate (TVPDI) interessano una o più vene della gamba, senza coinvolgimento della vena poplitea, includendo pertanto le vene assiali (vene tibiali anteriori, tibiali posteriori e peroneali) e le vene muscolari del polpaccio (vene gemellari mediali, gemellari laterali e soleali).

Le TVPDI costituiscono una manifestazione comune del TEV, rappresentando circa il 20% e il 50% di tutti gli eventi tromboembolici venosi¹⁷. Nonostante ciò, i dati disponibili sulla storia naturale delle TVPDI sono molto eterogenei. Le TVPDI possono estendersi al distretto venoso prossimale e/o embolizzare alle arterie polmonari, possono andare incontro a risoluzione spontanea oppure si può avere una ricanalizzazione del vaso interessato nell'arco di qualche settimana o mese¹⁸.

Tradizionalmente, le TVPDI vengono considerate una patologia benigna, soprattutto se confrontate con le trombosi venose profonde (TVP) prossimali, sebbene fino al 20-25% possa estendersi al distretto prossimale¹⁹. In aggiunta, un'EP silente è presente nel 13%-33% dei pazienti con diagnosi di TVPDI²⁰.

¹⁷ Palareti G, Schellong S. Isolated distal deep vein thrombosis: what we know and what we are doing. *J Thromb Haemost* 2012;10:11-19

¹⁸ Antignani PL, Aluigi L. The calf vein thrombosis. *Reviews in Vascular Medicine* 2013;1:1-4

¹⁹ Righini M, Paris S, Le Gal G, et al. Clinical relevance of distal deep vein thrombosis. Review of literature data. *Thromb Haemost*. 2006;95:56-64

²⁰ Hughes MJ, Stein PD, Matta F. Silent pulmonary embolism in patients with distal deep venous thrombosis: Systematic review. *Thrombosis Research* 2014;134:1182-85

Per quanto riguarda il rischio di recidiva tromboembolica, l'ottenimento di informazioni adeguate è ostacolato dall'eterogeneità degli studi in termini di tipo di trattamento iniziale, durata dell'anticoagulazione, durata del follow-up e definizione degli outcome. Per esempio, stati riportati tassi di recidiva di circa il 2-3% dopo un anno dalla diagnosi di TVPDI in alcuni studi^{21,22}, mentre tassi significativamente più alti, fino al 9-19% dopo circa due anni, sono stati riportati in altri studi^{23,24}.

Vi è ancora incertezza sulla necessità di trattare tutti i casi di TVPDI e sulla durata ottimale del trattamento anticoagulante. Le linee guida sulla terapia antitrombotica del TEV dell'American College of Chest Physicians suggeriscono di trattare solo pazienti selezionati, cioè coloro che presentano sintomi severi o fattori di rischio per estensione della trombosi²⁵. Per questi pazienti è suggerito un trattamento anticoagulante della durata di minimo 3 mesi, come per i pazienti con TVP prossimale.²⁵ Tuttavia, queste raccomandazioni sono deboli, basate su un basso livello di evidenze. Infatti, un ciclo di terapia anticoagulante più breve (4-6 settimane) è stato utilizzato

²¹ Galanaud JP, Sevestre MA, Genty C, et al. Incidence and predictors of venous thromboembolism recurrence after a first isolated distal deep vein thrombosis. *J Thromb Haemost*. 2014;12:436-43

²² Pinede L, Ninet J, Duhaut P, et al, for the Investigators of the "Durée optimale du Traitement AntiVitamines K" (DOTAVK) Study. *Circulation* 2001; 103: 2453-60

²³ Astemark J, Björgell O, Lindén E, et al. Low recurrence rate after deep calf-vein thrombosis with 6 weeks of oral anticoagulation. *Journal of Internal Medicine* 1998; 244: 79-82

²⁴ Gillet JL, Perrin MR, Allaert FA. Short-term and mid-term outcome of isolated symptomatic muscular calf vein thrombosis. *J Vasc Surg* 2007; 46: 513-19

²⁵ Kearon C, Akl EA, Comerota AJ, et al. Antithrombotic therapy for VTE disease. *Chest* 2012; 141(2)(S): e419S-e494S

in diversi studi^{22,26,27}, con risultati favorevoli quanto confrontato con cicli più lunghi^{Errore. Il segnalibro non è definito.,26,28}.

In considerazione di questa eterogeneità di informazioni, è stato pianificato uno studio di coorte, con lo scopo di valutare il rischio di recidiva tromboembolica venosa in pazienti consecutivi con una diagnosi di TVPDI sintomatica, che hanno ricevuto terapia eparinica a basso peso molecolare (EBPM) secondo il protocollo terapeutico locale (1 settimana a dosaggio terapeutico, seguita da 3-5 settimane a dosaggio dimezzato).

Lo studio viene presentato di seguito (manoscritto in fase di sottomissione a rivista scientifica).

²⁶ Ferrara F, Meli F, Amato C, Cospite V, Raimondi F, Novo G, Novo S. Optimal duration of treatment in surgical patients with calf vein thrombosis involving one or more veins. *Angiology* 2006; 57: 418-23

²⁷ Parisi R, Visonà A, Camporese G, et al. Isolated distal deep vein thrombosis: efficacy and safety of a protocol treatment. Treatment of Isolated calf Thrombosis (TICT) Study. *Int Angiol* 2009; 28: 68-72

²⁸ Sartori M, Cosmi B, Legnani C, et al. Two years outcome of isolated distal deep vein thrombosis. *Thromb Res* 2014;134:36-40

**LONG-TERM RECURRENCE OF VENOUS THROMBOEMBOLISM AFTER
TREATED SYMPTOMATIC ISOLATED DISTAL DEEP VEIN THROMBOSIS:
A RETROSPECTIVE COHORT STUDY**

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Chiara Brignone, Luigina Guasti, Luigi Steidl, Walter Ageno

Introduction

Isolated distal deep vein thrombosis (IDDVT) represents a common clinical manifestation of venous thromboembolism (VTE), ranging from 20 to 50% of all VTE events [1]. Despite this high incidence, scant and heterogeneous data are available on the clinical history of IDDVT [2,3]. IDDVT is commonly considered a benign disease, in particular when compared with proximal DVT, although up to 20-25% of IDDVTs extend to the proximal vein system [4,5], in particular when IDDVT is unprovoked [6], bilateral [7], involves more than one distal vein [8], presents large thrombosed vessels diameter [9], or when it is associated with active cancer [10]. Moreover, the results of a recent systematic review of the literature show that 13% to 33% of IDDVT are associated with asymptomatic pulmonary embolism (PE) at onset, most of which represented by micro-emboli [11].

Information on the recurrence rates of the disease are hampered by the heterogeneity among studies in terms of initial treatment, duration of anticoagulation, duration of follow-up and definition of outcomes. A recurrence rate of 2-3% after 1 year was reported in some studies [12,13], whereas a higher rate up to 9-19% after about 2 years was reported in other studies [7,9].

There is still uncertainty on the need to treat all cases of IDDVT and on the optimal duration of anticoagulation [14]. Current guidelines suggest that only selected patients diagnosed with IDDVT (ie those with severe symptoms or risk factors for extension) should be treated, and that in these patients

anticoagulation should be given for a minimum of 3 months, as for patients with proximal DVT [15]. However, these recommendations are weak and mainly based on low level of evidence. Indeed, a shorter course of anticoagulation (i.e. 4 to 6 weeks) was used in several studies [6,8,12,16-18] and favourable results were found when compared to longer durations [8,12, 18].

Given the paucity and the heterogeneity of available information, we decided to perform a retrospective cohort study aimed at evaluating the long-term risk of recurrent VTE in consecutive patients diagnosed with symptomatic IDDVT, who received anticoagulant therapy according to a center-based protocol, and were followed-up for at least 2 years.

Methods

The study was conducted on consecutive patients objectively diagnosed with symptomatic IDDVT between January 2004 and December 2011 at the Thrombosis and Haemostasis Center of the university hospital of Varese, in Italy, which serves as a tertiary referral center for the diagnosis and treatment of patients with venous thromboembolism.

Patients were eligible if aged ≥ 18 years and if no concomitant proximal DVT and/or PE were diagnosed. Asymptomatic PE was not systematically searched.

Based on an internal protocol active from 2004, all patients presenting with suspected symptomatic IDDVT were evaluated by means of bilateral whole leg compression ultrasound, performed by trained physicians, according the method of Schellong [19]. All the examinations were registered on a computerized database, and patients diagnosed with IDDVT were scheduled for regular follow-up visits for up to 6 months after the diagnosis. According to the protocol, all patients were initially treated with low molecular weight heparin (LMWH) for 4 to 6 weeks (1 week full dose, followed by 3 to 5 weeks half dose). In case of contraindications to anticoagulation (eg active bleeding, high risk of bleeding, platelet count $< 30.000/mm^3$, known allergy to LMWH

or severe renal failure), treatment and follow-up strategies were left to the treating physician, who decided on a case by case basis, and patients were not excluded from the study.

Baseline characteristics were routinely collected on demographic characteristics, risk factors for VTE, site and extension of IDDVT, type and duration of anticoagulant treatment and were retrospectively retrieved from the center electronic database. Follow-up information was retrieved for all scheduled follow-up visits until 6 months from the index event and integrated by a telephone contact with all patients, up to at least 2 years from the diagnosis of IDDVT.

The primary study outcome was the composite of objectively documented recurrent VTE, including IDDVT, proximal DVT, PE or deep venous thrombosis in other sites. All events were locally adjudicated after the evaluation of specific clinical documentation. Proximal DVT was adjudicated if documented by a compression or duplex ultrasound. Recurrent IDDVT was adjudicated in the presence of thrombosis of a previously normal vessel or in a previously completely recanalized distal venous segment. PE was adjudicated when documented by a positive computed tomography pulmonary angiography or high probability perfusion lung scan.

Secondary outcomes were major bleeding (according to the definition of the International Society on Thrombosis and Haemostasis [20]) and overall mortality.

Statistical Analysis. Continuous data are presented with mean and standard deviations (SD) or median and interquartile range (IQR) according to their distribution, after applying the Kolmogorov-Smirnov test. A multivariate Cox-regression analysis was performed to calculate the hazard ratio (HR) and 95% confidence interval (CI) associated with potential predictors of recurrent VTE, after maintaining variables resulted at least marginally significant ($p < .10$) at the univariate analysis. IBM SPSS Statistics software, version 19 (SPSS, Inc., IBM corporation, U.S., Armonk, NY, USA) was used for all the analyses.

Results

A total of 321 patients with IDDVT were included in the study. Baseline characteristics are presented in Table 1. Median age was 64 years (IQR 46-76), 55.1% were female. According to underlying VTE risk factors, 165 IDDVTs (51.4%) were classified as provoked by transient risk factors (trauma 22.1%, surgery 9.3%, bed rest >3 days 8.1%, and oral contraceptives 8.4% were the most common), 55 (17.1%) were associated with cancer, and 96 (29.9%) were unprovoked; 72 patients (22.4%) had a previous VTE. Anticoagulant treatment was administered for 4 to 6 weeks in 288 patients (89.7%) (284 with LMWH alone and 4 with LMWH for at least 5 days and warfarin); 13 patients (4.2%) received LMWH for at least 5 days and warfarin for 3 to 6 months or indefinitely because of previous VTE; 20 patients (6.2%) received a shorter course of LMWH due to pre-existing anemia and/or thrombocytopenia (7 patients) or because of pre-existing (3 patients) or subsequent (6 patients) bleeding complications, or upon decision of the family doctor (4 patients). Among the 288 patients who initially received therapy for 4 to 6 weeks, 42 (14.6%) continued on prophylactic or intermediate dose LMWH for some additional weeks (range 1-104) because of the persistence of risk factors (e.g. immobilization, pregnancy and/or puerperium, cancer).

Follow-up was complete for 97.5% patients (8 patients were lost to follow-up), and data on mortality were retrieved for 99.1% of patients (3 were lost to follow-up).

During a mean follow-up of 41.5 months (SD 27.9), 48 patients (15%) experienced a recurrent VTE, for an annualized recurrence rate of 4.1 per 100 person-years. Recurrent VTE events were recurrent IDDVT in 21 patients (43.8%), proximal DVT in 10 patients (20.8%), PE in 15 patients (31.3%), and deep venous thrombosis in other sites in 2 patients (4.2%) (Table 2).

Table 3 shows the results of univariate and multivariate analysis. Among potential predictors of recurrence, only unprovoked IDDVT and the presence of active cancer remained significantly associated with recurrent VTE at multivariate analysis (HR 2.11, 95% CI 1.09-4.11, and HR 2.68, 95% CI 1.13-6.36, respectively). The annualized rate of recurrent VTE was 6.8 per 100 patient-years after unprovoked IDDVT and 9.7 per 100 patient-years after IDDVT associated with active cancer (as compared with 2.2 per 100 patient-years after provoked IDDVT, $p = .004$, log-rank test)

During anticoagulant treatment, 6 patients (1.9%) experienced major bleeding, none was fatal. During the entire follow-up period, 62 patients (19.3%) died.

Discussion

In this large retrospective cohort study of patients with symptomatic IDDVT, who were treated with a short course of anticoagulation in 90% of cases (4 to 6 weeks), and who were followed for 3.5 years on average, we found a non-negligible rate of recurrent VTE (15% of patients, 4.1 per 100 patient-years). More than half of recurrent events occurred in the proximal veins or as PE. . Recurrence rates were significantly higher in patients with an index unprovoked event or with active cancer (6.8 and 9.7 per 100 patient-years, respectively), as compared to patients with a transient provoking factor (2.2 per 100 patient-years).

Previous studies on IDDVT were quite heterogeneous in terms of number of patients enrolled, type and duration of treatment and follow-up. In two randomized controlled trials, the recurrence rate of VTE after IDDVT was found to be 4% and 2.6% after 12 and 15 months of follow-up, respectively, in patients who received anticoagulation for 12 weeks or 6/12 weeks, respectively [12,21]. Higher cumulative rates of recurrence were described in more recent observational studies, which present, however, some important limitations. In one study, a VTE recurrent rate of 18.8% was found after 27 months of follow-up, but the duration of treatment was heterogenous and

27% of patients were lost to follow-up [9]; another study found a 20% VTE recurrence after 67 months, but only 56 patients were enrolled [22]. Finally, data on a large number of patients with IDDVT (almost 2000) are available from the international RIETE registry, but the follow-up was of 3 months only, during which 2% of patients experience recurrent VTE [23]. Therefore, our study may be considered innovative and shows several strengths, being conducted on a large number of patients, who were treated homogeneously and followed for more than 3 years, with negligible loss to follow-up (< 3%). More recently, the results of a multicenter prospective cohort study (OPTIMEV study), enrolling 490 patients, were published [13]. Differently from our study, patients with cancer or a personal history of VTE were excluded and the median duration of treatment was significantly longer than in our study (92 days, IQR 61-123 and 42 days, IQR 35-42, respectively). These differences may explain the lower rate of recurrent VTE in the OPTIMEV study as compared to our study, both in the overall population (2.7 and 4.1 per 100 patient-years, respectively) and in patients with provoked IDDVT (1.4 and 2.2 per 100 patient-years, respectively) or unprovoked IDDVT (3.8 and 6.8 per 100 patient-years, respectively). One similarity between the OPTIMEV study and our study was in the failure to find any significant difference in the risk of recurrent VTE between patients presenting with axial vein involvement and patients with muscular vein involvement. Differently from the OPTIMEV study, we did not find older age and increasing number of involved veins to be predictive of recurrent VTE at multivariate analysis. In addition, our results are similar to those of a recent prospective study enrolling 90 patients, that found a 19% rate of VTE recurrence after two years from IDDVT treated with LMWH for 30 days or with VKAs for 3 months (according to the presence or absence of transient risk factors, respectively) [18].

The results of our study confirm that the risk of recurrent VTE after treated IDDVT is relevant in patients with an unprovoked event or with active cancer. In patients with unprovoked event, we found a 24% cumulative

incidence of recurrent VTE after 3.5 years. Interestingly, half of the events occurred during the first year, for a cumulative incidence of 12.5% at 1 year, an incidence that is quite similar to that of proximal DVT or PE [24]. However, our study failed to identify a subgroup of patients with unprovoked IDDVT with a higher risk of recurrent VTE, which may require an extended or indefinite treatment duration.

In patients with IDDVT and cancer we found a 12.7% cumulative incidence of recurrence at 1 year. Of particular note, recurrent events were either proximal DVT and/or PE in 7 out of 8 patient. Recent consensus guidelines on the treatment of VTE in cancer patients and clinical practice data from international surveys do not specifically consider the issue of IDDVT [25]. Given the observed risk of recurrence, further evidence is urgently needed.

Current guidelines suggest that anticoagulation for IDDVT should be given for a minimum of 3 months, as for patients with proximal DVT [15]. However, this recommendation is based on low level of evidence. The results of our study show that a short course of anticoagulation (4 to 6 weeks) can be adequate for a large proportion of patients, especially when IDDVT is associated with a transient risk factors. This approach seems to be reasonable, as confirmed by the results of other studies [18], and it also supported by some experts [14]. Moreover, several additional studies used a similar short-term treatment [6,8,12,16,17], with similar results when compared to longer durations [12]. On the other hand, an extended treatment is probably necessary for a non negligible proportion of patients at higher risk of recurrence (i.e. in presence of cancer or of an unprovoked event with additional risk factors).

Our study has limitations. First, the retrospective design can be associated with incomplete and/or inaccurate data. However, initial and follow-up information up to 6 months were prospectively collected and electronically recorded, according to a pre-existing internal protocol, so minimizing the risk of incompleteness. Moreover, all patients were called to complete at least a 2-

year follow-up and only 8 patients (2.5%) and 3 patients (0.9%) were lost to follow-up for the primary outcome and mortality, respectively.

Second, there may have been recall bias if patients reported as recurrent VTE events some episodes that were only suspected. Therefore, we asked patients to bring the clinical documentation to our center, in order to confirm only objectively diagnosed events, thus minimizing the risk of overestimating the recurrence rate. On the other hand, patients may have missed to report some recurrent VTE events: we tried minimize this risk by searching the entire databases of our center (which serves as referral center for the diagnosis of DVT and collects all ultrasound reports and clinical visits) as well as those of the radiology and emergency department units of our hospital, to look for potential records of recurrent events.

Third, treatment was not identical for all patients. Although the internal protocol indicated a course of LMWH for 4 to 6 weeks, the final decision was still left to the attending physician. However, about 90% of patients received LMWH according to the protocol. Moreover, the scheduled visit at the end of treatment made it possible to verify, at least retrospectively, the type and reasons of treatment modifications (eg low platelet count, bleeding, skin reactions)

Finally, this is a single center study, thus limiting the generalizability of the results. However, due to the retrospective nature of the study and to the presence of pre-existing treatment and follow-up protocol at our center, we had the possibility to minimize the risk of incomplete data and heterogeneous results.

In conclusion, the results of our study show that the long-term risk of recurrence after treated IDDVT is not negligible and is represented by major VTE events in more than 50% of cases. Therefore, if some IDDVTs may be regarded as transient/benign conditions, many other cases should be considered in the more complex context of major venous thromboembolic events. Indeed, patients with unprovoked IDDVT, as well as other patients at higher risk of recurrence (active cancer, history of

VTE), may benefit from an extended treatment period. Further studies are needed to better identify IDVT patients who may deserve prolonged anticoagulation and to balance the risk of recurrence with the risk of bleeding.

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Tables

Table 1. Baseline characteristics and treatment

N. of patients	321
Median age (years)	64 (IQR 46-76; range 20 -92)
Female/Male	177/144 (55.1 / 44.9%)
Clinical presentation	
Pain	266 (82.9%)
Edema	198 (61.7%)
Redness	71 (22.1%)
Extension	
Monolateral	312 (97.2%)
Bilateral	9 (2.8%)
Single vein	262 (81.6%)
Muscular	177 (55.1%)
Axial	108 (33.6%)
Both	36 (11.2%)
Concomitant SVT	53 (16.5%)
Risk factors	
Transient risk factor	165 (51.4%)
Cancer/MPN	56 (17.4%)
Unprovoked	96 (30.0%)
Personal history of VTE	72 (22.4%)
Treatment	
LMWH for 4 to 6 weeks	288 (89.7%)
Vitamin K antagonists	13 (4.0%)
Other treatment	20 (6.2%)

Legend: SVT Superficial vein thrombosis; MPN myeloproliferative neoplasm; VTE venous thromboembolism; LMWH low molecular weight heparin

Table 2. Results

Primary outcome	
Mean follow-up	41.5 months (SD 27.9)
Lost to follow-up	8 (2.5%)
Patients diagnosed with recurrent VTE	48 (15%)
PE (+/- associated DVT)	15 (31.3%)
Proximal DVT	10 (20.8%)
Isolated distal DVT	21 (43.8%)
Unusual site thrombosis	2 (4.2%)
Secondary outcomes	
Major bleeding	6 (1.9%)
Minor bleeding	8 (2.5%)
Cutaneous reactions to LMWH	4 (1.2%)

Legend: VTE venous thromboembolism, PE pulmonary embolism, DVT deep vein thrombosis, LMWH low molecular weight heparin

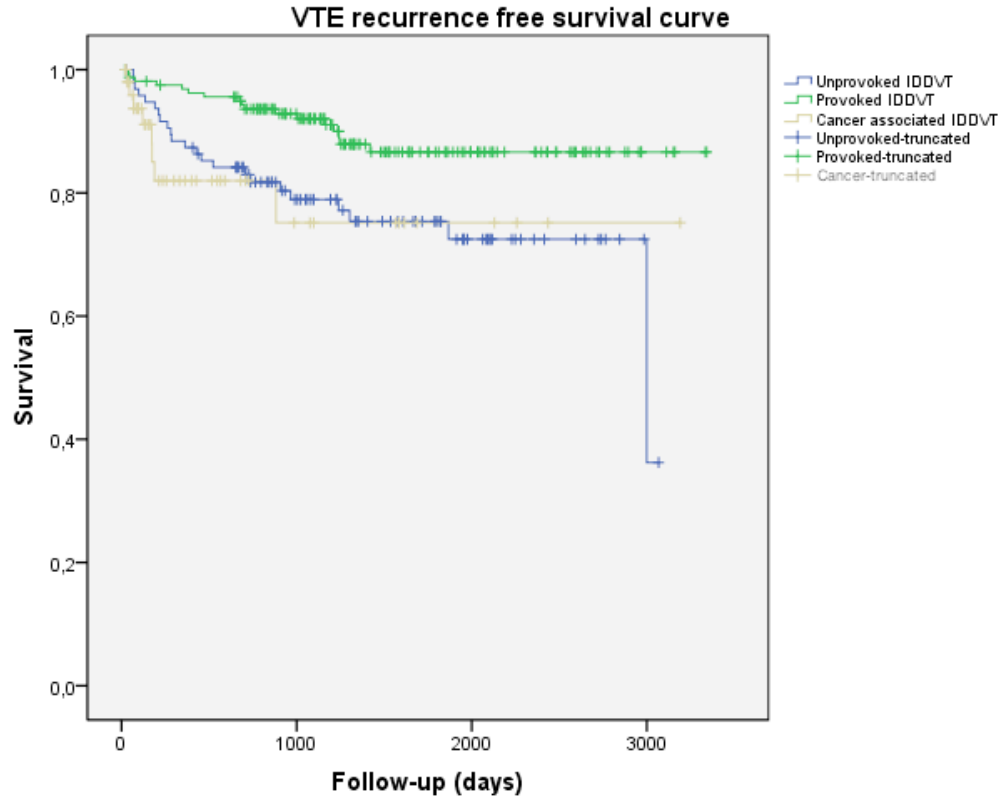
Table 3. Cox-regression analysis

Predictive factors	Univariate analysis HR, 95% CI	p value	Multivariate analysis HR 95% CI	p value
Age ≥65 ys	1.64 (0.92 - 2.9)	0.09	1.3 (0.72 - 2.36)	0.38
Male gender	1.01 (0.57 - 1.79)	0.97	-	
VTE risk factors				
- transient	1		1	
- cancer	3.02 (1.29 - 7.05)	0.01	2.68 (1.13 - 6.36)	0.03
- unprovoked	2.5 (0.33 - 4.68)	0.00	2.11 (1.09 - 4.11)	0.03
IDDDVT location				
- muscular veins	1		-	
- axial veins	1.11 (0.62 - 2.02)	0.72		
- both	0.52 (0.12 - 2.19)	0.37		
IDDDVT extension				
- 1 vein	1		-	
- ≥ 2 veins	0.53 (0.19 - 1.46)	0.21		
Unilateral IDDDVT	1			
Bilateral IDDDVT	0.05 (0 - 4476.7)	0.44	-	
Previous VTE	1.88 (1.03 - 3.42)	0.04	1.49 (0.8 - 2.77)	0.22
Anticoagulant for > 6 weeks	0.53 (0.19 - 1.49)	0.23	-	

Legend: VTE venous thromboembolism, IDDDVT isolated distal deep vein thrombosis, HR hazard ratio

Figures

Figure 1. Kaplan-Meier curve for recurrence free survival after provoked, unprovoked or cancer-associated IDDVT.



Gestione delle emorragie in pazienti anticoagulati

I farmaci anticoagulanti “tradizionali” (eparina non frazionata, eparine a basso peso molecolare, fondaparinux, dicumarolici) e quelli di nuova generazione o “diretti” (apixaban, edoxaban, rivaroxaban, dabigatran) sono associati ad un rischio non trascurabile di emorragia maggiore, intorno al 1-4% all’anno^{29,30,31}. In aggiunta, le emorragie maggiori in corso di trattamento anticoagulante sono caratterizzate da un significativo case-fatality rate, in particolare se avvengono in sede intracranica e/o nei primi mesi di trattamento³².

Le misure generali di supporto sono fondamentali in caso di sanguinamenti pericolosi per la sopravvivenza (reintegrazione dei fluidi, trasfusione di globuli rossi, identificazione e trattamento della fonte di sanguinamento), unitamente a misure specifiche per antagonizzare l’effetto dell’anticoagulante coinvolto. Tuttavia, al momento, sono disponibili degli antidoti solo per l’eparina non frazionata (solfato di protamina) e per i farmaci dicumarolici (vitamina K). Inoltre, anche in caso di trattamento dicumarolico, la somministrazione dell’antidoto spesso non è sufficiente ad interrompere un sanguinamento maggiore, per cui è necessario infondere

²⁹ Palareti G, Leali N, Coccheri S, et al. Bleeding complication of anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; 348: 423-8

³⁰ Schulman S, Beyth RJ, Kearon C, et al. Hemorrhagic complications of anticoagulant and thrombolytic treatment: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008; 133 (6 Suppl.): 257S-98S

³¹ Dentali F, Riva N, Crowther M, et al. Efficacy and safety of the novel oral anticoagulants in atrial fibrillation: a systematic review and meta-analysis of the literature. *Circulation* 2012;126:2381-91

³² Carrier M, Le Gal G, Wells PS, et al. Systematic review: case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism. *Ann Intern Med* 2010;152:578-589

fattori della coagulazione attraverso concentrati protrombinici o plasma fresco congelato. Per quanto riguarda gli antidoti specifici per i DOACs (andexanet, idarucizumab, PER977), questi sono attualmente in fase di sperimentazione, con idarucizumab che ha recentemente ottenuto una approvazione accelerata da parte della Food and Drug Administration (Ottobre 2015).

E' stata condotta una revisione della letteratura per raccogliere e presentare, con approccio clinico basato su casi clinici, le evidenze disponibili sulla gestione e trattamento delle emorragie durante terapia anticoagulante tradizionale e con DOACs.

Viene presentato di seguito il testo dell'articolo relativo revisione della letteratura sopracitato, che è stato pubblicato sulla rivista *Drugs* (Donadini MP, Ageno W, Douketis J. Management of patients who are bleeding on conventional or new anticoagulants: a practical and case-based approach. *Drugs* 2012;72(15):1965-75).

MANAGEMENT OF PATIENTS WHO ARE BLEEDING ON CONVENTIONAL OR NEW ANTICOAGULANTS: A PRACTICAL AND CASE-BASED APPROACH

Marco P. Donadini, Walter Ageno, James D. Douketis

Introduction

Anticoagulant drugs are highly effective for the prevention and treatment of venous thromboembolism (VTE) and the prevention of stroke and systemic embolism in patients with chronic atrial fibrillation (AF) or prosthetic heart valves. The need for and duration of anticoagulant therapy is driven primarily by the indication for anticoagulation but is coupled with individual patient characteristics that weigh thrombotic risks against bleeding risks.

Anticoagulant-related bleeding is characterized according to its severity as either major, clinically relevant non-major, or minor. Until recently, there was no standardized definition of bleeding, resulting in heterogeneity in the reported incidence of bleeding across studies assessing anticoagulant therapy.^[1] The International Society on Thrombosis and Haemostasis (ISTH) proposed in 2005 a definition of major bleeding in non-surgical patients which comprised fatal bleeding and/or bleeding in a critical site (intracranial, intraspinal, intraocular, retroperitoneal, intra-articular, pericardial or intramuscular with compartment syndrome) or bleeding associated with a decrease in hemoglobin ≥ 2 g/dL or transfusion of ≥ 2 units of red cells.^[2] A similar definition is proposed by the ISTH for surgical patients, with additional parameters that account for surgical site bleeding.^[3]

The management of anticoagulant-associated bleeding depends on the severity of bleeding and is anchored on general measures, which include fluid resuscitation, red blood cell transfusion and, perhaps most importantly, the diagnosis and treatment of the bleeding site. Additional specific interventions are based on the potential reversibility of an anticoagulant with blood products and the existence of drug-specific antidotes.

The objective of this review is to provide an evidence-based but practical approach to anticoagulant-associated bleeding. Specifically, we aim to juxtapose the management of patients who are receiving an 'old anticoagulant' and bleed with patients who develop bleeding while using a 'new anticoagulant'. The format of this review consists of illustrative cases of anticoagulant-related bleeding followed by an evidence-based discussion of our suggested management approach.

Management of anticoagulant associated bleeding

Case Scenario 1 - Vitamin K Antagonists

A 73-year old man who was recently hospitalized for decompensated congestive heart failure is diagnosed with proximal deep vein thrombosis (DVT) and commences conventional anticoagulant therapy, consisting of low-molecular-weight heparin (LMWH) and warfarin. After 2 weeks of treatment, the patient presents with headache and vomiting followed by a decreased level of consciousness and is transported to hospital. Computed tomography (CT) scan of the brain shows a large intra-parenchymal bleed involving the temporoparietal and occipital regions. The INR at presentation is 5.2.

Incidence, Risk Factors, and Case-fatality of VKA-associated Bleeding

In patients who are receiving vitamin K antagonists (VKAs) such as warfarin the risk for major bleeding is 1-2% per year, based on findings from cohort studies and randomized trials.^[4,5] The risk for bleeding is likely higher in unselected community-based patients, as is evidence in a Danish registry study where the annual risk for bleeding was 4.3%.^[6] Several risk factors for VKA-associated bleeding have been identified, including advanced age (>65 years), previous bleeding, cancer, renal or hepatic impairment, anemia, thrombocytopenia, concomitant use of antiplatelet drugs, previous stroke, hypertension, poor anticoagulant control, recent surgery, alcohol abuse, and frequent falls.^[7,8] The importance of prompt and effective management of such bleeding is illustrated by the case-fatality rate of VKA-associated bleeding, which is 11% (upper bound 95% confidence interval [CI]: 16%)

during the first 3 months of VKA treatment for VTE [9] and 9% (upper bound 95% CI: 22%) thereafter [10]. In patients with VKA-associated intra-cerebral bleeding, as described in the case herein, the case-fatality is approximately 50% and survivors often have major irreversible neurological deficits, thereby highlighting the importance for the prevention and prompt reversal of such bleeds. [11]

Pharmacologic Properties of VKAs and Reversal Strategies (Table 1)

Warfarin is probably the most commonly used VKA worldwide but acenocoumarol and phenprocoumon also are used widely, especially in Europe. Warfarin has an elimination half-life of approximately 36-48 hours, longer than acenocoumarol (6-8 hours) but shorter than phenprocoumon (96-140 hours).[12] Several measures should be considered for the management of VKA-associated bleeding, which depend on the severity of bleeding and, in turn, the need for urgent reversal. These measures include:

- i) interruption of VKA alone without additional interventions, typically for minor and/or self-limiting bleeds;
- ii) administration of intravenous vitamin K, 5.0-10 mg, by slow infusion, in cases of severe bleeding (e.g., gastrointestinal), or oral vitamin K, 1.0-2.5, mg for less severe, self-limiting bleeding (e.g., hemorrhoids, epistaxis);
- iii) infusion of fresh frozen plasma (FFP) or prothrombin complex concentrates (PCC); and
- iv) infusion of recombinant activated factor VII (rFVIIa).

In patients with VKA-associated major bleeding, vitamin K₁ (phytonadione) is the antidote for VKAs and should be routinely administered (the need to administer vitamin K also to patients treated with the short-acting acenocoumarol has been less investigated) to ensure neutralization of the anticoagulant effect, especially if the clinical course of the bleed is uncertain. Vitamin K can be given intravenously (1.0-2.5 mg) to obtain a more rapid reduction of the INR that begins within 2 hours and may be complete within 24 hours, depending on the baseline INR. To minimize the risk of anaphylactoid reactions caused by intravenous vitamin K

administration (approximately 3 per 10,000), vitamin K should be mixed in 50 mL of fluid and infused slowly over 20-30 minutes.^[12-15]

It is noteworthy that in patients with VKA-associated bleeding a coagulopathy exists for a considerable time after the last dose of the VKA as it takes the liver between 12 and 100 hours to restore (to at least 50% levels) the vitamin K-dependent factors II, VII, IX, and X (based on a half-life of 6 hours for factor VII and 50 hours for factor II).^[16] Consequently, in the setting of a life-threatening bleed, coagulation factor replacement is advised. FFP is one option for VKA-associated bleeding, administered at a dose of 15 mL/kg.^[17] However, the use of FFP for patients with VKA-associated bleeding has drawbacks, which include:

- i) variable quantities of vitamin K-dependent coagulation factors per unit of FFP;
- ii) need for ABO blood group cross-matching (if not already available);
- iii) time required to thaw (stored at 4°C) and infuse FFP (time from request of FFP to completion of transfusion can take several hours);^[18]
- iv) risk for volume overload with 4-8 units of FFP transfusion (1 unit FFP contains 180-300 mL fluid); and
- v) risk for transfusion associated lung injury (TRALI) - a rare form of non-cardiogenic pulmonary edema occurring with rapid FFP infusion ^[19].

In recent years, PCCs have become available for VKA-associated bleeding and have advantages over FFP, which include:

- i) providing consistent quantities of vitamin K-dependent coagulation factors;
- ii) no need for ABO blood group cross-matching (due to purification process, that also makes PCC safer in terms of the transmission of pathogens);^[20]
- iii) less time for its preparation (stored at room temperature as a lyophilized powder and reconstituted with sterile water); and
- iv) no risk for volume overload (total volume <50 mL).

PCCs are available as 3-factor (II, IX, and X) PCCs, 4-factor (II, VII, IX, and X) PCCs (e.g., Octaplex[®], Beriplex[®]), or activated 4-factor PCCs (e.g., FEIBA[®] - factor eight inhibitor bypass activity). PCCs are infused at a rate of 20-50 IU/kg over 15-30 minutes. INR correction is more rapid with PCC than FFP and can be achieved in about 3-5 hours.^[13,21] Although the absence of clinical outcome-driven trials comparing FFP and PCC for VKA-associated bleeding precludes definitive recommendations, these advantages of PCCs should be considered when managing patients with VKA-associated bleeding. Indeed, from a practical perspective, PCCs may be considered as first-line treatment for patients with life-threatening or intracranial VKA-associated bleeding where rapidity of availability and targeted clotting factor administration may be desirable.^[22] . Moreover, it should be noted that PCCs are relatively expensive, at approximately \$2,000-\$2,500 per infusion (compared with approximately \$200-\$300 for 4 units FFP) but less so than recombinant activated factor VII (rFVIIa), at approximately \$5,000-\$5,500 per infusion. From a practical perspective, it is reasonable to consider PCCs as first-line treatment to correct the coagulopathy in patients with life-threatening or intracranial VKA-associated bleeding and to consider FFP in less severe bleeding, especially if PCCs are not readily available.

Irrespective of whether FFP or PCC is administered for VKA-associated bleeding, the long half-life of VKAs coupled with the short half-lives of infused coagulation factors mandates the use of vitamin K in most VKA-treated patients as an antidote to warfarin so as to restore the endogenous production of vitamin K-dependent coagulation factors.

Finally, in the setting of VKA-associated bleeding, evidence supporting the use of rFVIIa is limited. Its use may be suggested in cases of life-threatening bleeding when coagulation factor replacement products do not have the desired effect or in patients who will not accept any blood product transfusions.^[12]

Case Scenario 2 - New Oral Anticoagulants

A 76-year old woman with hypertensive cardiomyopathy and diabetes is found to have AF on a routine medical visit, which is confirmed on repeat testing. Treatment options for stroke prevention include dabigatran, 150 mg twice-daily, or warfarin, administered to achieve a targeted INR of 2.5 (range: 2.0-3.0). Dabigatran was chosen because of its ease of administration. After 2 months of treatment, the patient presents with two episodes of melena and superimposed fatigue. On physical examination, there is palor, blood pressure was 85/50 mmHg, and the heart rate was 110 beats/minute. Hemoglobin was 7.5 g/dL. Esophagogastroduodenoscopy and colonoscopy did not reveal a source of bleeding.

Incidence and Case-fatality of Bleeding Associated with New Oral Anticoagulant

In recent years, the emergence of new oral anticoagulants (NOACs) provides clinicians with alternatives to VKAs for patients with AF or VTE. Among the NOACs, the oral factor II inhibitor dabigatran and oral factor Xa inhibitors rivaroxaban and apixaban have completed phase III trials. Dabigatran was approved by the Food and Drug Administration (FDA) in the United States in October 2010 for stroke prevention in AF, becoming the first new oral anticoagulant to be available for this clinical indication in more than 50 years. The European Medicines Agency (EMA) also approved dabigatran and, more recently, rivaroxaban for the same clinical indication. In addition, the EMA approved rivaroxaban for the treatment of acute DVT (both dabigatran and rivaroxaban were already approved in US and Europe for the prevention of VTE after orthopedic surgery).

In phase III trials involving patients with AF, dabigatran was found to be non-inferior to warfarin for preventing stroke and systemic embolism at a dose of 110 mg bid and superior to warfarin at a dose of 150 mg bid.^[23] Rivaroxaban at a dose 20 mg od was non-inferior to warfarin for the same outcome.^[24]

In terms of bleeding events, dabigatran 150 mg bid was not associated with an increased risk of major bleeding (3.11%/year vs. 3.36%/year, respectively, p=0.31) whereas dabigatran 110 mg bid was associated with

less major bleeding than warfarin (2.71%/year, $p=0.003$).^[23] Interestingly, the only dose of dabigatran approved by the FDA for patients without renal impairment (150 mg bid) was associated with an increased risk of gastrointestinal bleeding (RR 1.50, 95% CI: 1.19-1.89) and a reduced risk of intracranial bleeding (RR 0.40, 95 % CI: 0.27-0.60) compared with warfarin.^[23]

The risk of major bleeding for rivaroxaban and warfarin was similar (3.6 vs 3.4 per 100 patient-years, respectively, $p=0.58$); rivaroxaban was associated with less intracranial bleeding compared with warfarin (0.5 vs. 0.7/100 patient-years, respectively, $p=0.02$) but more gastrointestinal major bleeding (3.2% vs. 2.2%).^[24]

In phase III trials on VTE treatment, rivaroxaban was non-inferior to warfarin for the prevention of recurrent VTE ^[25,26], and the number of major bleeding events were similar among patients receiving rivaroxaban and warfarin treated for acute DVT (0.8% vs 1.2%, $p=0.21$),^[25] whereas there was less major bleeding associated with rivaroxaban in patients treated for acute pulmonary embolism (1.1% vs. 2.2%, $p= 0.003$)^[26].

Data on the case-fatality of NOAC-associated are not yet available. However, the case-fatality probably is similar (and possibly less, due to fewer intracranial bleeds) to that of VKA-associated bleeding. In support of this contention, an assessment of bleeding associated with ximelagatran, the prototype oral direct thrombin inhibitor that was withdrawn from clinical use because of hepatotoxicity, showed similar case-fatality rates compared with warfarin.^[27]

Pharmacologic Properties of New Oral Anticoagulants and Implications for Reversal (Table 1)

Dabigatran is a selective and reversible oral direct thrombin inhibitor. It is administered as a prodrug (dabigatran etexilate) that is rapidly adsorbed in the stomach and small intestine and converted to its active form, dabigatran, by rapidly acting serine esterase-catalyzed hydrolysis.^[28] The key pharmacologic properties of dabigatran include a time to peak action of 1-3

hours, blood protein binding of 30-35%, and approximately 80% clearance by the kidney. Rivaroxaban is a selective and reversible oral direct factor Xa inhibitor. Its key pharmacologic properties include a time to peak action of 1-3 hours, blood protein binding of 92-95%, and 33% clearance by the kidney for the active form of the drug (30% renal clearance of inactive form).^[29] Apixaban is another selective and reversible oral direct factor Xa inhibitor and, as with rivaroxaban and dabigatran, has a rapid peak action of 1-3 hours. Blood protein binding is approximately 80% and 25-27% of the drug is cleared by the kidney.

One of the advantages of the NOACs is their shorter half-lives compared to warfarin: 12-17 hours for dabigatran; 7-11 hours for rivaroxaban; and 8-10 hours for apixaban, as compared with 36-48 hours for warfarin.^[29] However, unlike with warfarin, the half-lives of NOACs can increase in patients with moderate-to-severe renal impairment, especially for dabigatran.^[30,31] One of the disadvantages of the NOACs is the lack of drug-specific antidotes although the development of such antidotes are in progress.

A suggested management approach to bleeding in patients who are receiving a NOAC is provided below. However, it should be emphasized that given the relatively short half-lives of NOACs, it may be sufficient to simply withhold further NOAC doses without the need for blood product administration, especially in patients with non-life-threatening bleeding or patients in whom the source of bleeding has been identified and treated (e.g., electrocautery of a bleeding peptic ulcer). In addition to the abovementioned general measures (fluid resuscitation, red blood cell transfusion, diagnostic and therapeutic procedures on the source of bleeding), other interventions may include:

- i) interruption of the drug;
- ii) FFP or PCC;
- iii) rVIIa;
- iv) hemodialysis (dabigatran only as rivaroxaban and apixaban are highly protein bound and cannot be dialyzed); and

v) activated charcoal and/or gastric lavage may be considered in selected patients, for example those with a known NOAC overdose.

In the setting of major bleeding, the interruption of dabigatran and rivaroxaban alone is not sufficient, considering their half-life and the ongoing inhibition of factors II and X. Administration of activated charcoal may prevent further drug absorption if done within a few hours of drug ingestion although NOAC-specific clinical data to support such interventions are lacking. Oral activated charcoal appears effective in absorbing dabigatran in an *in vitro* model [32], whereas no comparable data are available for rivaroxaban. Overall, there are no clinical data to support the efficacy of activated charcoal and/or gastric lavage in patients with NOAC-associated bleeding.

In studies involving a murine model of intracranial hemorrhage, FFP was tested to reduce hematoma expansion provoked by dabigatran but there was no effect on mortality.[33] It is unclear whether these results correlate with FFP use in humans. No clinical data are available on the use of FFP in patients with dabigatran- or rivaroxaban-associated bleeding.

The efficacy of 4-factor PCC to reverse the anticoagulant effect of dabigatran and rivaroxaban was tested in a randomized, placebo-controlled, crossover trial in healthy subjects.[34] The prolongation of aPTT, thrombin time and ecarin clotting time induced by dabigatran was not reversed by the 4-factor PCC. On the other hand, the prolongation of PT and endogenous thrombin potential (ETP) induced by rivaroxaban was normalized by the 4-factor PCC, suggesting the possibility to reverse rivaroxaban action by the 4-factor PCC.[34] However, the ability to arrest bleeding in rivaroxaban-treated patients needs further research. These findings on the ability of PCCs to reverse the action of rivaroxaban but not of dabigatran have been confirmed in another study on healthy volunteers; on the other hand, this study suggests a potential role of FEIBA® (4-factor activated PCC) in patients with dabigatran-associated bleeding.[35]

With regard to the use of rVIIa, it significantly reduced the bleeding time that was increased by dabigatran in a rat model; however, among coagulation tests, only the PT returned to normal after rVIIa administration, but not aPTT, thrombin time and ecarin clotting time.^[36] In a mouse model, rVIIa did not prevent intracerebral hematoma expansion in mice receiving dabigatran.^[33] With regard to rivaroxaban, rVIIa reduced bleeding time that was increased by rivaroxaban in a rat and a baboon model.^[37,38] No clinical data are available currently on the use of rVIIa for bleeding reversal or its effects on coagulation parameters in patients treated with either dabigatran or rivaroxaban.

Finally, hemodialysis can be an option only for non-highly protein-bound drugs, such as dabigatran (and not rivaroxaban or apixaban). Hemodialysis was able to remove more than 60% of dabigatran at 2 hours in volunteers receiving hemodialysis for end-stage renal disease.^[39] Hemoperfusion proved effective to eliminate dabigatran only in an *in vitro* model.^[32]

Considering the paucity of available evidence regarding the reversal of NOAC-associated bleeding, pragmatic guidance was recently provided by members of North American thrombosis and hemostasis scientific societies. The use of FFP was considered not likely to be helpful in this setting, whereas the use of PCC was considered to be a reasonable approach in the opinion of several, but not all, authors (due to absence of clinical data). The usefulness of rVIIa for new oral anticoagulation reversal was considered unclear.^[40]

Case Scenario 3 - Parenteral Anticoagulants (unfractionated heparin [UFH], low-molecular-weight heparin [LMWH], fondaparinux)

An 83-year old woman is receiving LMWH for treatment of right leg superficial vein thrombosis, diagnosed 3 weeks ago, now presents with pain and swelling of the left lower limb, which began 3 days before. On physical examination there is a large hematoma on the posterior side of the left thigh; the hemoglobin level was 8.2 g/dL. A CT-angiography confirmed the presence of a hematoma of the quadriceps, extending for about 25 cm

longitudinally; there was no arterial bleeding at that site, whereas it was not sufficiently clear whether some small venous active bleeding was present.

Bleeding Risk Associated with Parenteral Anticoagulants

The incremental risk of major bleeding associated with treatment doses of UFH or LMWH (i.e., enoxaparin 1 mg/kg bid) compared to placebo is less than 2%.^[8] In trials comparing LMWH to VKAs for the long-term treatment of VTE, the risk of major bleeding associated with LMWH was not statistically different from that associated with warfarin (RR = 0.81, 95% CI: 0.81-1.22).^[7] The risk of major bleeding associated with treatment doses of fondaparinux (i.e., 7.5 mg daily) in patients with acute VTE does not appear to differ to that of LMWH (RR = 0.93, 95% CI: 0.43-2.03 in the DVT trial; RR = 0.85, 95% CI: 0.49-1.49 in the PE trial).^[41,42] In a placebo-controlled trial assessing a 45-day course of a lower dose of fondaparinux (i.e., 2.5 mg daily) for the treatment of superficial vein thrombosis, the incidence of major bleeding was low (~1 in 1,500 patients in either arm).^[43]

Pharmacologic Properties of Parenteral Anticoagulants and Reversal Strategies (Table 1)

UFH can be administered by continuous intravenous infusion or by subcutaneous injection, with the intravenous route allowing rapid action within minutes. UFH is cleared by a rapid saturable (cellular) dose-dependent mechanism and a slower non-saturable dose-independent renal mechanism. After stopping the infusion, the time to normalize hemostasis is 3-6 hours for intravenous UFH and 8-12 after subcutaneous UFH.^[44,45]

LWMHs are administered subcutaneously and have advantages over UFH that include having higher bioavailability and providing a more predictable anticoagulant response. After absorption, the peak anti-Xa activity occurs at 3-5 hours. Differing from UFH, their elimination is predominantly by the kidney so that their half-life of 3-6 hours may be prolonged in patients with moderate-to-severe renal dysfunction.^[44]

Fondaparinux is administered subcutaneously and is rapidly and completely absorbed. It is excreted unchanged in the urine and it has a half-life of 15-17 hours.^[46]

In case of major bleeding in UFH-treated patients, the infusion should be interrupted immediately. Given the short half-life of intravenous UFH, this first step alone can normalize hemostasis in 3-4 hours. However, if a rapid reversal is needed in an emergency situation, this can be achieved by using intravenous protamine sulfate, a specific antidote to UFH. The aPTT can be used to monitor the neutralization of the heparin effect. One milligram of protamine sulfate can reverse approximately 100 units of UFH. Importantly, considering the short half-life of intravenous UFH of about 60-90 minutes, the dosage of protamine sulfate needs to be calculated based on the amount of UFH infused in the last 2-2.5 hours. The reversal of subcutaneously administered UFH may require a prolonged infusion of protamine sulfate.^[44] It should be noted that protamine, which is derived from fish sperm, is associated with allergic reactions, including cardiorespiratory collapse, especially in patients with a fish allergy or men who have had a vasectomy in whom the potential loss of the blood-testis barrier may lead to semen antibody development.^[47,48]

In LMWH-treated patients with major bleeding, apart from the interruption of LMWH (that, alone, can restore hemostasis in about 12-24 hours only), protamine sulfate is not as effective as for UFH. Indeed, protamine sulfate neutralizes the anti-thrombin activity of LMWH but only part of its predominant anti-Xa activity. There is no convincing evidence supporting or refuting a beneficial effect of protamine sulfate on LMWH-associated bleeding. In recent clinical practice guidelines it is suggested that, in cases where a LMWH effect needs to be neutralized, protamine sulfate can be infused at a dose of 1 mg per 100 anti-Xa units, if LMWH was given within 8 hours.^[44] Evidence on the use of rVIIa is limited to a single successful case report.^[49]

In fondaparinux-treated patients with bleeding, no approved antidotes are available. Interruption of sc administration is needed as the first step. The use of FFP and/or PCC is not supported by adequate evidence;^[50] activated PCC (FEIBA[®]) significantly reversed the action of fondaparinux *in vitro* in a single study.^[51] Two randomized placebo-controlled trials on healthy subjects evaluated the use of rVIIa, showing its ability to normalize the aPTT, PT and thrombin-generation time that were prolonged by fondaparinux.^[52,53] Recently, a specific antidote has been developed to neutralize the anti-Xa activity of fondaparinux *in vivo*,^[54] that need to be tested in the clinical setting of fondaparinux-associated bleeding.

The use of PCC, FFP or rFVIIa has not been assessed, to our knowledge, for UFH- or LMWH- or fondaparinux-associated bleeding. Although a clinician may not be faulted for administering one or more of these agents for life-threatening or severe intracranial bleeding, emphasis should be placed on antidote administration and other supportive measures.

New Oral Anticoagulants and Antidotes Under Investigation

Apixaban, as discussed earlier, has completed phase III trials for stroke prevention in patients with AF and approval for this clinical indication is likely forthcoming in 2012 ^[55,56]; phase III trials for the treatment of VTE are ongoing. As of mid-2012 apixaban is approved for clinical use (in Canada and Europe) only as DVT prophylaxis after hip or knee replacement surgery. No clinical strategies for the reversal of its anticoagulation effect have been tested so far. Two other oral factor Xa inhibitors, edoxaban and betrixaban, are also in earlier stages of clinical development.

A novel anticoagulant, idrabiotaparinux, has been developed by adding a biotin moiety to idraparinux, a long-lasting inhibitor of factor Xa. This modification does not change the efficacy and safety of idraparinux but allows rapid reversal of its anticoagulant effect through the infusion of avidin, which tightly binds to biotin, if bleeding occurs.^[57] If urgent reversal is needed, avidin 100 mg, diluted in 100 mL of isotonic saline, can be infused

over 30 min.^[58] Idrabiotaparinux is non-inferior to warfarin for the treatment of PE.^[59]

Moreover, new antidotes are being developed in recent years. Among them, a recombinant antithrombin variant (AT-N135Q-Pro394) and a recombinant factor-Xa variant (PRT064445) have shown to reverse the effect of fondaparinux and LMWH *in vitro* and in animal models.^[60,61] Interestingly, the recombinant factor-Xa variant PRT064445 was able to reverse the anti-Xa activity of rivaroxaban in experimental models, thus emerging as a potential antidote to new oral factor-Xa inhibitors for the clinical setting.^[60]

Conclusions

Old and new anticoagulants are associated with a clinically important, 1-4% per year, risk for major bleeding. Rapid reversal of their anticoagulant effect is desirable when major bleeding occurs to mitigate the associated morbidity and mortality. General supportive measures are fundamental in case of life-threatening bleeding (fluid resuscitation; red blood cell transfusions; diagnosis and treatment of bleeding site), along with specific measures directed to reverse the effect of the involved anticoagulant. Specific antidotes are currently available only for the oldest anticoagulants, UFH and VKAs. However, even in case of VKA-associated bleeding, the administration of the antidote alone is not sufficient to reverse severe bleeding, thus requiring the infusion of coagulation factors through PCC or FFP. The management of bleeding during treatment with new oral anticoagulants requires further clinical research, since available data mainly come from *in vitro* or animal models. New antidotes, specifically targeted to the new agents, are currently under initial investigative steps and may offer some important progress in the management of anticoagulated patients, if their efficacy and safety will be confirmed in clinical trials.

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Table 1. Pharmacological properties and suggested reversal strategies for oral and parenteral anticoagulants

Anticoagulant	Target	Half-life	Antidote	Reversal strategies	Time to normalized hemostasis
Warfarin	Vitamin K Oxide Reductase	Warfarin: 36-48 h	vitamin K	Interruption of VKA	24 h - 5/7 days
Acenocoumarol	(synthesis of	Acenocoumarol: 6-8 h	(po 1-2.5 mg	Vitamin K po/iv	24 h (po) /12-16 h (iv)
Phenprocoumon	Factor II, VII, IX, X)	Phenprocoumon: 90-140 h	iv 2.5-10 mg)	PCC (25-50 IU/kg)	15 min-5 h
				FFP (15 mL/kg)	2-7 h
				(rVIIa)	2 h
Dabigatran	Factor IIa	12-17 h (renal excretion ~ 80%)	Not available	Interruption of dabigatran	12-24 h
				Gastric lavage	-
				Oral activated charcoal	-
				Hemodialysis	(2-4 h for ~ 60-70% drug removal)
Rivaroxaban	Factor Xa	7-11 h (renal excretion ~ 66%)	Not available	Interruption of rivaroxaban	12-24 h
				Gastric lavage	-
				Oral activated charcoal	-
				PCC	15-30 min
UFH	AT-mediated inhibition of coagulation factors (anti-Xa/anti-IIa ratio 1:1)	60-90 min (iv) ~ 3 h (sc)	Protamine sulfate	Interruption of iv UFH Interruption of sc UFH Protamine sulfate (1 mg per 100 UI iv UFH given in the last 2-2.5 h)	3-4 hours 8-12 hours Immediate
LMWHs	AT-mediated inhibition of coagulation factors (anti-Xa/anti-IIa ratio 2-4:1)	3-6 h	Not available	Interruption of LMWH (Partially) protamine sulfate (1 mg per 100 anti-Xa U if LMWH given within 8 h)	12-24 hours n.a.
Fondaparinux	AT-mediated inhibition of factor Xa	15-20 h	Not available	Interruption of fondaparinux rVIIa (90 µg/Kg) Activated PCC	~ 24 hours 2-6 h -

Legend: po, per os; iv intravenously; PCC, prothrombin complex concentrate; FFP, fresh frozen plasma; rVIIa, recombinant activated factor VII; AT, antithrombin; n.a., not available

Conclusioni

I risultati del progetto di ricerca hanno portato ad una conoscenza più approfondita della prognosi di due manifestazioni comuni del TEV, come l'EP e la TVPDI. L'analisi dei risultati ha reso possibile anche la valutazione delle terapie antitrombotiche utilizzate per il trattamento di queste patologie, sia in termini di efficacia che di sicurezza. Inoltre, una migliore conoscenza del rischio e della gestione dei sanguinamenti in corso di trattamenti anticoagulanti, compresi i DOACs, è stata ottenuta grazie ad una revisione ed analisi della letteratura. L'obiettivo iniziale di valutazione dell'impatto dei DOACs nel TEV ha dovuto tuttavia subire una significativa modifica a causa delle tempistiche di approvazione ed delle indicazioni e regimi di rimborsabilità stabiliti da AIFA. Tuttavia, i risultati del progetto di ricerca hanno permesso di porre delle solide basi per valutare l'impatto dei DOACs in alcuni ambiti specifici del TEV e, in particolare, nella gestione dei pazienti con EP a basso rischio di complicanze e nella terapia delle TVPDI.

Per quanto riguarda la stratificazione prognostica dell'EP acuta, i risultati dallo studio LORPELHS hanno confermato la validità del PESI nell'identificare i pazienti a basso rischio di mortalità a breve termine. I risultati hanno altresì evidenziato come la durata del ricovero ospedaliero per EP sia ancora piuttosto lunga nella realtà italiana, anche in caso di basso rischio di eventi avversi, specialmente se confrontata con le indicazioni di linee guida internazionali ed i risultati di importanti studi recenti. E' possibile ipotizzare che il solo giudizio clinico standard non sia in grado di identificare

adeguatamente questi pazienti a basso rischio e che, pertanto, l'utilizzo di un semplice strumento di stratificazione prognostica, come il PESI, possa portare ad un significativo miglioramento nella loro identificazione e gestione. Questa considerazione ha portato a progettare lo studio iAPP (Impact Analysis of Prognostic stratification for Pulmonary embolism), recentemente approvato dal comitato etico provinciale di Varese (centro coordinatore dello studio) ed in fase di partenza.

I risultati dello studio LORPELHS non hanno evidenziato una influenza del tipo di terapia anticoagulante sulla durata del ricovero ospedaliero. Tuttavia, questo risultato può essere ascritto alle diverse caratteristiche basali dei pazienti che sono stati trattati con eparina+dicumarolico rispetto a quelli trattati con sola eparina (più frequentemente oncologici). È ipotizzabile, infatti, che la risposta individuale alla terapia dicumarolica, e di conseguenza il tempo per raggiungere un adeguato livello di anticoagulazione, influenzino la durata del ricovero ospedaliero. In quest'ottica, l'utilizzo dei DOACs, grazie alla loro rapidità d'azione e prevedibilità farmacocinetica, potrebbe portare di per sé ad una riduzione della durata del ricovero, indipendentemente dalla stratificazione prognostica. Per tale motivo, nella fase di intervento del progetto (studio iAPP) è stato deciso di adottare una randomizzazione stratificata per la scelta del farmaco anticoagulante (DOACs versus dicumarolico), al fine di compararne l'influenza sulla durata di ricovero.

Per quanto riguarda il trattamento delle TVPDI, lo studio retrospettivo di coorte condotto ha evidenziato una incidenza di recidiva di TEV non trascurabile (15% dei pazienti, 4.1 per 100 anni-paziente) e rappresentata da un evento maggiore in oltre la metà dei casi. Il tasso di recidiva è risultato significativamente più alto nei pazienti con un evento indice idiopatico o associato ad una neoplasia attiva, rispetto ai pazienti che presentavano un fattore di rischio temporaneo.

Lo studio ha anche permesso di valutare un approccio terapeutico più breve (EBPM per 4-6 settimane, utilizzato in circa il 90% dei pazienti) rispetto a quello attualmente suggerito dalle linee guida internazionali, seppur con basso grado di evidenza. I risultati mostrano come questo trattamento anticoagulante di breve durata possa essere sufficiente per una proporzione sostanziale di pazienti, come quelli con TVPDI associata a fattore di rischio temporaneo. Al contrario, un trattamento anticoagulante più prolungato sembra essere necessario in sottogruppi di pazienti a più alto rischio di recidiva, come i pazienti oncologici e quelli con TVPDI idiopatica. Tuttavia, se una durata di 3 mesi sia sufficiente per prevenire le recidive di TEV in questi sottogruppi di pazienti, rimane da essere stabilito in trial clinici.

Infine, per quanto riguarda i sanguinamenti in corso di terapia anticoagulante, la revisione della letteratura ha portato a concludere che i farmaci "convenzionali" e quelli di nuova generazione sono associati ad un rischio clinicamente importante di emorragia maggiore, intorno al 1-4%

all'anno. E' pertanto fondamentale, in questi casi, mettere in atto strategie di rapido "reversal" dell'azione anticoagulante. Le misure generali di supporto sono fondamentali in caso di sanguinamenti pericolosi per la sopravvivenza, unitamente a misure specifiche per antagonizzare l'effetto dell'anticoagulante coinvolto. Al momento, sono disponibili degli antidoti per l'eparina non frazionata (solfato di protamina) e per i farmaci dicumarolici (vitamina K). Nuovi antidoti, specificatamente indirizzati ai DOACs, sono attualmente in corso di sperimentazione (andexanet, idarucizumab, PER977) e potrebbero fornire un importante aiuto nella gestione dei sanguinamenti, se la loro efficacia e sicurezza sarà confermata dai trial clinici.