

## INCIDENCE OF HOSPITAL-ACQUIRED VENOUS THROMBOEMBOLIC DISEASE.

## INCIDENCIA DE LA ENFERMEDAD TROMBOEMBOLICA VENOSA ADQUIRIDA EN LA INTERNACIÓN

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**Abstract:**

Background: There is limited knowledge of the incidence of venous thromboembolic disease (VTE) during hospitalization, since most of these are community-based data. Purpose: To estimate the incidence rate (IR) of VTE developed during hospitalization. Methods: Retrospective cohort of all inpatients admitted in a university tertiary hospital, in Argentina. The inclusion criteria were defined as: adult patients consecutively admitted from July/2006 to August/2013, for any cause. Patients admitted for VTE were excluded; all patients at the time of admission were free of event. Each person was followed contributing time at risk, from admission to event, discharge or death. VTE incident cases were captured from the Institutional Registry of Thromboembolic Disease (ClinicalTrials.gov Identifier NCT01372514). Incidence rate was calculated with 95% confidence intervals. Results: The crude incidence rate of VTE for clinical patients was 0.49 (95%CI 0.45-0.55) per 1,000 cases person-days, and IR adjusted for WHO was 0.23 (95%CI 0.19-0.26). The crude IR of VTE for surgical patients was 0.25 (95%CI 0.23-0.27), and IR adjusted for WHO was 0.13 (95%CI 0.10-0.17). The incidence rate ratio (IRR) for VTE shows that surgical admission reduces the IRR and age categories increases the thrombosis rate risk, after adjustment for age category, sex and surgical admission. Conclusions: This study suggests that there is a high risk of VTE in hospitalized patients and is still a frequent problem.

*Keywords: epidemiology; hospital medicine; venous thromboembolism.*

**Resumen:**

Antecedentes: Existe limitado conocimiento sobre la incidencia de enfermedad tromboembólica venosa (ETV) durante la hospitalización, dado que la mayoría de los son datos basados en la comunidad. Objetivos: Estimar la tasa de incidencia de ETV incidente durante la hospitalización. Material y métodos: Cohorte retrospectiva de todos los pacientes internados en un hospital de alta complejidad, en Argentina. Los criterios de inclusión fueron definidos como: pacientes adultos consecutivamente admitidos entre Julio 2006 y Agosto 2013, por cualquier causa (clínica o quirúrgica). Se excluyeron los pacientes ingresados por ETV, todos los pacientes al momento de la admisión estaban libres del evento. A cada paciente se lo siguió en tiempo de contribución de riesgo, desde la admisión hasta el evento, el alta o la muerte intrahospitalaria. Los casos incidentes de ETV fueron capturados desde el Registro Institucional de Enfermedad Tromboembólica (ClinicalTrials.gov Identifier NCT01372514). La tasa de incidencia se calculó con intervalos de confianza del 95%. Resultados: La tasa de incidencia (TI) cruda de ETV para los pacientes clínicos fue de 0,49 (IC95% 0,45-0,55) por 1.000 pacientes persona-día, y la TI ajustada para la OMS fue de 0,23 (IC95% 0,19-0,26). La TI cruda de ETV para pacientes quirúrgicos fue de 0,25 (IC95% 0,23-0,27), y la TI ajustada para la OMS fue 0,13 (IC95% 0,10-0,17). La razón de tasas de incidencias muestra que la admisión quirúrgica reduce y la edad aumenta el riesgo de trombosis. Conclusiones: Este estudio sugiere que existe un alto riesgo de ETV en pacientes hospitalizados y sigue siendo un problema frecuente.

*Palabras clave: epidemiología; medicina hospitalaria; tromboembolismo venoso.*

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**Introduction**

Deep vein thrombosis (DVT) and acute pulmonary embolism (PE) are two types of manifestations, historically referred together as venous thromboembolism (VTE). VTE can either lead to hospitalization or either complicate it and delay the length of stay. This is why it is still a common, treatable although sometimes fatal, but potentially preventable medical problem<sup>[1]</sup>. Nowadays, preventing intrahospital VTE as a complication of medical care has become an international imperative<sup>[2]</sup>.

The overall average annual incidence of VTE adjusted by age and gender in a cohort of patients who resided in Minnesota was 117 per 100000 (DVT, 48 per 100000; PE, 69 per 100000)<sup>[3]</sup>. The incidence rates of a first episode of VTE according to different series were between 0.71 and 1.17 cases per 1,000 persons of the Caucasian population<sup>[4-7]</sup>. From the Institutional Registry of Thromboembolic Disease (IRTD Home-ClinicalTrials.gov, NCT01372514), the incidence of DVT is 1.03, and 0.32 per 1,000 person-years of PE, with a mortality of 25% in patients with confirmed PE<sup>[1]</sup>. In Argentina, the VTE crude IR was 1.65 (95%CI 1.56 to 1.75) per 1,000 person-years. The IRs adjusted to the population of the city of Buenos Aires were 0.90 (95%CI 0.84 to 0.95) for VTE, 0.71 (95%CI 0.66 to 0.76) for DVT, and 0.34 (95%CI 0.31 to 0.37) for PTE<sup>[2]</sup>.

Unfortunately, most studies on the incidence of VTE are community-based data, leaving us with limited knowledge regarding the incidence of VTE developed during hospitalization, where patients are exposed to an increased risk<sup>[3]</sup>. In this regard, VTE has been extensively studied in surgical patients. The benefit of thromboprophylaxis is now generally accepted because prophylactic treatment with 40mg per day of subcutaneous enoxaparin safely reduces the risk of VTE in patients with acute medical illnesses<sup>[8]</sup>.

However, the greatest percentage of the hospital population is represented by clinical patients. Clinical patients differ from surgical in terms of health and the pathogenesis of thromboembolism, and the impact that preventative measures can have. The extensive experience from thromboprophylaxis studies in surgical patients is therefore not necessarily applicable to non-surgical patients<sup>[9]</sup>.

From an internal medicine point of view, it is important to determine the intrahospital incidence of VTE to assess the magnitude of the risk of VTE associated with hospitalization, and the rational use of resources for prevention. The aim of this study is to estimate the incidence rate (IR) of VTE developed during hospitalization, in a cohort of clinical and surgical patients between 2006 and 2013.

**Methods**

A retrospective cohort of all inpatients admitted in a tertiary university hospital between July 2006 and August 2013, in Buenos Aires, Argentina. The inclusion criteria were defined as follows: adult patient >17 years, consecutively admitted to the Hospital Italiano de Buenos Aires (HIBA) between July 2006 to August 2013, for any clinical or surgical causes<sup>[10-12]</sup>. Patients admitted for VTE were excluded; all patients at the time of admission to the hospital were free of event. Each patient was followed contributing time-at-risk, from admission to discharge or death.

The HIBA is composed of two university hospitals of high complexity, with 750 inpatient beds (200 critical care), with approximately 42,300 hospitalizations annually. All medical care of patients is recorded centrally in a computerized data repository that includes a single electronic health record (EHR) per patient.

The cases were captured from the secondary database from a clinical registry. The Institutional Registry of Thromboembolic Disease (IRTD-Home-ClinicalTrials.gov, NCT01372514) is a prospective VTE registry ongoing since 2006, and includes all consecutive patients older than 17 years with confirmed PE and/or DVT diagnosed in all areas of the hospital (outpatient clinics, inpatient general ward and critical care areas)<sup>[1]</sup>.

The IRTD was done in compliance with the Helsinki Declaration; oral informed consent was obtained when patients decided to participate, and the institutional Ethics Committee on human research approved the study. This study did not require an additional consent.

## Definitions

VTE cases were defined as PE and/or DVT (proximal or distal) developed during hospitalization. We define as an intrahospital event to that which occurred 48 hours after clinical admission or 24 hours after surgical admission (date of event diagnosis versus date of hospital admission).

Case detection was performed through IRTD according to diagnostic tests required by physicians [13]. We use an electronic alert that is generated whenever the physician requests the following studies for an adult patient: computed pulmonary angiography, computed pulmonary tomography, ventilation/perfusion lung scan, lower/upper limbs venous ultrasonography, d-dimer lab test, and/or angiography of the lungs, veins of the lower/upper limbs.

Surgical admissions were defined as patients who underwent surgery at the hospital during the hospital stay or within at least 30 days prior to the hospital admission date. Surgery was defined as major procedures with at least 45 minutes of duration. Minor procedures such as biopsies or endoscopy were excluded. All surgical units were included (general surgery, gynecology, orthopedics, urology).

Clinical admissions (non-surgical patients) were defined as admitted patients who did not undergo surgery during hospitalization or in the previous 30 days.

Fatal PE event was included too by legal representatives of patients who die. Intrahospital death for all causes was defined as patients who die during hospitalization episode.

## Statistical methods

The incidence rate (IR) was calculated for inpatients admitted at the Hospital Italiano de Buenos Aires according to the incident cases of VTE (DVT or PE) in the IRTD. Incidence rates were reported as: crude IR, adjusted and specific by age and gender.

The IR was adjusted by direct standardization to the age and gender distribution of the populations of Argentina to the Census 2010 [14] and WHO [15]. The IR is expressed per 1,000 person-days, with 95% confidence intervals for the entire period. Access and Excel software from Microsoft Office 2007 version were used to estimate the incidence and confidence intervals.

We conducted a Poisson regression model to evaluate the determinants of VTE, and adjusted for the following variables: age category, gender and surgical admissions. Incidence rate ratios (IRRs) were obtained for this model with 95% confidence intervals. The analysis was conducted using STATA version 13.

## Results

Among 110,069 admissions which occurred in 7-years of the study period; 46 % (50,841/110,069) of hospitalizations were clinical and 54 % (59,228/110,069) surgical.

The basic characteristics of the study population were: global median of age 53 years (IQR 18–111), global median of stay 19 days (IQR 1–705), and 19.73% had concomitant cancer. Other variables are shown in Table 1.

**Table 1.** Baseline characteristics of patients admitted (n: 110,069)

	Clinical admissions	Surgical admissions
	50,841	59,228
<b>Median stay, in days (interquartile range)</b>	7 (1-370)	31 (2-705)
<b>Median age, in years (interquartile range)</b>	53 (18-111)	52 (18-104)
<b>Deaths</b>	2,011 (3.95%)	678 (1.14%)
<b>Venous thromboembolic disease</b>	363 (0.71%)	709 (1.19%)

Each person was followed contributing time-at-risk from admission to event manifestation, discharge or death. The clinical hospital mortality was 2011/50,841, 3.95 % (95%CI 3.78–4.12) and surgical 678/59,228, 1.15 % (95%CI 1.06–1.23)<sup>[7]</sup>.

VTE (PE and/or DVT) occurred in 1072 hospitalizations, 34% (363) belonged to clinical patients. The entire cohort of inpatients was followed and contributed a total of 2,812,035 days for inpatient surgical cause, and 734,738 for inpatients clinical cause.

Crude and adjusted VTE incidence rates are reported by cause of hospitalization: clinical and surgical (Table 2).

**Table 2.** Crude global incidence rate and adjusted for Argentina and world standard population, per 1000 cases person-days

	Number of cases	Person-days at risk	Crude IR (95% CI)	Adjusted IR to Argentina (95% CI)	Adjusted IR to WHO standard (95% CI)
<b>Clinical</b>					
VTE	363	734,738	0.49 (0.45 - 0.55)	0.23 (0.20 - 0.27)	0.23 (0.19 - 0.26)
DVT	300	735,611	0.41 (0.36 - 0.46)	0.2 (0.17 - 0.23)	0.19 (0.16 - 0.22)
PE	100	737,960	0.14 (0.11 - 0.16)	0.06 (0.05 - 0.08)	0.06 (0.04 - 0.08)
<b>Surgical</b>					
VTE	709	2,812,035	0.25 (0.23 - 0.27)	0.14 (0.11 - 0.17)	0.13 (0.1 - 0.17)
DVT	577	2,815,205	0.2 (0.19 - 0.22)	0.11 (0.08 - 0.13)	0.1 (0.08 - 0.12)
PE	211	2,824,464	0.07 (0.07 - 0.09)	0.04 (0.02 - 0.07)	0.04 (0.02 - 0.07)

Abbreviations: IR, incidence rate; VTE, venous thromboembolic disease; DVT, deep venous thrombosis; PE, pulmonary embolism; CI, confidence interval.

Gender-specific IRs per 1,000 person-days for VTE in clinical admissions was 0.47 (95%CI 0.41 to 0.54) in the female group and 0.52 (95%CI 0.44 to 0.61) in the male group; while in surgical admissions was 0.23 (95%CI 0.20 to 0.25) in the female group and 0.27 (95%CI 0.25 to 0.31) in the male group. The female/male IR ratios were 0.90 for VTE (95%CI 0.73-1.10) in clinical admissions, and 0.82 for VTE (95%CI 0.71-1.95) in surgical admissions.

Table 3 shows the IRR crude and adjusted by female, surgical and age category. The data shows that surgical admissions reduce IRR by 40%, and increase across age categories.

**Table 3.** Crude and adjusted incidence rate ratio for VTE by: female, surgical and age category.

	IRR crude	95% CI	p	IRR adjusted	95% CI	P
Female	0.85	0.76 - 0.96	0.011	0.93	0.83 - 1.05	0.270
Surgical	0.51	0.45 - 0.58	0.001	0.60	0.53 - 0.68	0.001
Age category						
18-29 years	1			1		
30-39 years	1.29	0.80 - 2.09	0.030	1.32	0.82 - 2.14	0.251
40-49 years	3.14	2.02 - 4.90	0.001	3.23	2.07 - 5.03	0.001
50-59 years	4.58	3.02 - 6.97	0.001	4.64	3.06 - 7.05	0.001
60-69 years	5.85	3.90 - 8.77	0.001	5.84	3.90 - 8.76	0.001
70-79 years	7.36	4.92 - 11.01	0.001	7.22	4.82 - 10.81	0.001
> 80 years	10.11	6.76 - 15.11	0.001	9.14	6.11 - 13.67	0.001

Abbreviations: CI, confidence interval; IRR, incidence rate ratio; VTE, venous thromboembolic disease.

**Discussion**

This study demonstrates, consistent with the literature<sup>[3-5,7,16]</sup>, the high risk of VTE in hospitalized patients, which is still a major health problem. Additionally, the data presented in person-days constitutes the first of this kind to cover data of hospitalized VTE incidence in Argentina.

VTE event rate adjusted for Argentina resulted in 0.23 per 1,000 person-days for clinical and 0.14 for surgical admissions; this is >100 times higher than expected<sup>[2]</sup>. This difference could be explained by the method of data capture: the patients included in our study were only inpatients, while other studies considered thromboembolic events detected in different areas (outpatient and inpatient). Additionally, it is already known in literature that the risk of developing VTE increases 100 times in hospitalized patients compared with the general population<sup>[3,6]</sup>, and they have a higher risk of fatal PE than in ambulatory setting; it is known also that hospital-acquired VTE potentially includes DVT of lower or upper extremity, as commonly as central venous catheter (CVC)-related thrombosis, or peripherally inserted central catheter (PICC)-related thrombosis.

Regarding the type of hospitalization, the data showed that the IR was lower for surgical admissions. This data might suggest that taking VTE preventive measures during the perioperative time might prevent VTE during hospitalization, and in consequence improve survival, according to the mortality rate for the same cohort explored in another study<sup>[5]</sup>. Another interesting factor to recognize in this context: thromboprophylaxis status during hospitalizations given the clinical implications it could have on the IR; but we do not have that information on this particular population. However, we know from a previous study in Argentina that the adequacy of antithrombotic prophylaxis was provided to 66.9% of the patients, and was more frequent in surgical (71%) compared to clinical (63.6%) subjects ( $p < 0.001$ )<sup>[11]</sup>. Moreover, VTE remains a common complication of cancer surgery, with a remarkable proportion of events occurring late after surgery<sup>[17]</sup>; while this study evaluate intrahospital event.

Additionally, age stratification allowed observing an increasing trend in the intrahospital incidence rate of VTE in accordance with increasing age, similarly, the studies by Silverstein<sup>[4]</sup> and Anderson<sup>[5]</sup> reported increased VTE IRs among older patients. Although we might infer that this finding is associated with greater comorbidity or concomitant risk factors inherent of clinical patients (previous VTE, cancer, immobility, hypercoagulability, congestive heart failure, exacerbation of chronic obstructive pulmonary disease, sepsis, inflammatory bowel disease, cerebrovascular accident), due to the study design we do not have this data.

There are certain differences to consider between our results and other reports, detailed below. First, we included patients with both PE and/or DVT hospital-acquired (developed during hospitalization: occurred 48 hours after clinical admission, or 24 hours after surgical admission), which contrasts with the majority of published studies, which include outpatients and/or inpatients. Second, the definition of case includes only symptomatic VTE and that may underestimate true numbers by not accounting asymptomatic cases. This study has some limitations to consider. Some additional data on the characteristics of the patients included were not available, for example could be of interest to know: reason for admission, risk-stratification, antithrombotic prophylaxis status<sup>[18-20]</sup>, previous VTE, comorbidities and concomitant risk factors. Additionally, our study was conducted in a single center, although this is a closed cohort, by being a tertiary university hospital in Argentina and referral center, patients treated are from Buenos Aires and surrounding areas, that increase external validity.

The data collection process is reliable because it is part of the institutional registry, which collects information in a systematic and rigorous manner, with a standardized process and prospectively, with particular emphasis on quality control. Additionally, our results are presented as IRs adjusted for Argentina and WHO population, and allow comparison with other populations or the same population over time. This is important because often we compare rates of VTE between different populations, or the same populations in different time periods, but populations are distributed differently in relation to the associated factors -such as age and gender- with the event studied (VTE this case).

To our knowledge, there are few data in Argentina reporting intrahospital incidence rate of VTE. The variability in reported incidences of VTE in literature would be a good argument to reinforce the importance of having local data. Each hospital should evaluate their own reality, to make correct decisions.

In conclusion, these findings provide population-based evidence that patients during hospitalization have a substantially increased risk of VTE, independent of type of admission. Awareness and increased vigilance of this potentially fatal, but preventable complication is still recommended. This information is valuable in assessing the inpatient risk and implementing preventive measures.

## Conclusions

The incidence of 0.49 per 1,000 cases person-days suggests a high risk of VTE in hospitalized patients; incidence rate was minor in surgical admissions. This study, although its similarity in results found in other geographical areas, constitutes the first of its kind to cover data of hospitalized VTE incidence in Argentina.

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