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Deep-vein thrombosis in Europe - Burden of illness in relationship to healthcare resource utilization and return to work

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Abstract

OBJECTIVES: Deep-vein thrombosis (DVT) forms a major healthcare burden in Europe, but exact estimates concerning the economic burden on society are lacking. This study reports results from the PREFER in VTE study concerning resource utilization and absence from work in DVT patients.

METHODS: The PREFER in VTE registry was a prospective, observational, multicenter study carried out in Europe (France, Italy, Spain, the UK, and DACH [Germany, Switzerland and Austria]), designed to provide data concerning treatment patterns, resource utilization, mortality and quality of life. Patients with a first-time and/or recurrent DVT, were recruited and followed for 12 months. Data about resource utilization concerns resource utilization related to DVT. Specifically, treatment pattern, re-hospitalization rate, length of hospital stay, ambulatory/office visit, and proportion of patients returning to work, were analyzed and presented. Subgroup analysis by country and active cancer were also conducted. The length of hospital stay was analyzed as a function of demographics, previous events and co-morbidities using zero-inflated binomial negative regression. Similarly, time until return to work was analyzed using Cox regression.

RESULTS: A total of 2056 patients with DVT were recruited, with an average age of 60 years. Patients with active cancer were mostly treated with heparin (83.9%), while patients without active cancer were treated with combinations of heparin, VKA and DOACs. DOACs were less often used in Spain and Italy (<7.0%). Following the management of their initial DVT 20.5% of the patients with and 12.2% of patients without active cancer (n=88; n= 1462) were hospitalized for on average 8.2 and 10.1 days, respectively. The hospitalization-rate was highest in Italy (16.7%) and lowest in France (7.7%). Furthermore, the average length of stay was highest in Italy (16.6 days) and lowest in DACH (5.2 days). Physician visits were highest in DACH (9.3), lowest in the UK (2.6). Of those working, 50% returned to work at 1 month; more than 30% did not return to work within the year.

CONCLUSIONS: Medical treatment of DVT differed between patients with active cancer and those without. Post-VTE or VTE-related resource utilization differs remarkably between countries. Work-loss seems high, but questions may be raised concerning the causality due to the presence of co-morbidities.

Key Words: Deep-vein thrombosis, burden of illness, Europe, healthcare resource utilization, return to work, work-loss

Introduction

Acute venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common disorder with an annual incidence of approximately 1 or 2 cases per 1000 persons in the general population [1–3]. Patients with VTE have increased morbidity and mortality, at first related directly to these conditions but secondly also as a complication of underlying diseases such as cancer, medical conditions and surgical procedures [4].

Most of the evidence concerning the burden of VTE has been generated in the United States (US); it has been estimated that 547,596 VTE events (hospitalized) occur annually among US adults (18 years and above) with 348,558 DVT, and 78,511 PE with DVT events [5]. Moreover, a recent review estimated the costs associated with the annual incidence of VTE events at $7-10 billion each year (limited to direct medical cost only) [6]. More specifically, a cost modelling study estimated that US VTE annual costs (including indirect costs) range from $13.5 to 69.3 billion (2011 US Dollars) with $4.5 to 39.3 billion of these costs being preventable if improved prophylaxis measures were put in place [7]. Publications on the burden of VTE in Europe are relatively scarce. A previously published modeling study – based on the data from 6 European countries - estimated that 684,019 DVT events (new and recurrent) occur per annum in the EU, with a prevalence of610,138 post-thrombotic syndrome (PTS) patients. The number of VTE-related deaths was estimated at 543,454 across the EU per annum [3]. The annual VTE costs for the EU, using the same decision tree model as previously reported in the US [7], range from €1.5 to 13.2 billion while preventable costs range from €0.5 to 7.3 billion (2014 Euros) [8]. However, due to the cost assumptions applied in the study, for instance the use of median costs, the total EU cost is likely to be underestimated.

Such epidemiologic modelling studies [3,8] offer valuable insights into the burden of VTE in Europe. To supplement these modelling findings, real life observational data are worthwhile. The PREFER in VTE registry was partly set up to offer such data. This study assessed the real-life acute and long-term management of patients with VTE, the use of health care resources, and provided data to estimate the costs for 12-months treatment following a first-time or recurrent VTE diagnosis in hospitals or specialized centers in Europe [4]. In addition, data was collected about clinical outcomes, treatment satisfaction, and health related quality of life (HrQoL) resource utilization and absence from work.

The aim of this study was to contribute to the current scientific knowledge regarding the burden of DVT in Europe, using the PREFER data. The focus is on resource utilization and absence from work. Specific attention is given to the differences per country, the difference between patients with active cancer and those without and the association between the burden of the disease and baseline patient characteristics. A separate paper concerning mortality and health related quality of life of patients with DVT is available elsewhere [9].

Data and methods

Setting and study population

The PREFER in VTE registry was a prospective, observational, multicenter study. 3,545 consecutive enrolled patients were followed for up to 12 months at 311 active centers in seven European countries including Austria, France, Germany, Italy, Spain, Switzerland, and the UK between January 2013 and July 2014. The outline of the study has been previously described [4]. Prior to study commencement, the registry protocol was approved by the responsible ethics committees for the participating countries and the relevant hospital-based institutional review boards. All patients enrolled in the registry first provided written informed consent.

Briefly, patients were eligible to be enrolled into the registry if they were at least 18 years old, had a symptomatic, objectively confirmed first time or recurrent acute VTE defined as either distal or proximal deep vein thrombosis, pulmonary embolism or both. Eligible patients were recruited within two weeks of the occurrence of the index event. At baseline patients were assessed in terms of their demography, disease, previous clinical events, risk factors, co-morbidities and presenting PE/DVT symptoms, as well as previous treatments. At 1, 3, 6 and 12 months follow up, information regarding the occurrence of clinical events, treatment, resource utilization, health-related quality of life and treatment satisfaction during each follow up interval was measured. The current study concerned DVT patients only, for which a total of 2,056 patients were recruited in the registry.

Data quality control

The validity of the data entered into the database was assured by training the investigators on data collection ensuring a uniform method. Furthermore, a random audit was performed on the centers included in the registry. During these visits the monitor verified informed consent documentation, performed source data verification against patient's medical records and checked for the inclusion of consecutive patients at the sites. The data collection comprised two different sources. These sources included the hospitals or specialized centers at the time of diagnosis of acute VTE and, as hospital based investigators do not always see patients in the following 12 months for routine clinical care, patients were also asked to participate in follow-ups by phone, safeguarding the collection of resource consumption data. Information was collected directly from the patients during standardized phone calls at 1, 3, 6 and 12 months after baseline. The data entered in the database were checked electronically for completeness and plausibility at the time of data entry and additional validation was performed on datasets.

Analyses and Statistics

Descriptive statistics of baseline information are provided by country, including demographics (age, gender, body mass index [BMI], marital status and country), clinical factors (with/without previous VTE event, distal vs. proximal,

[un]provoked[1]), previous clinical event (within 3 years prior to enrollment: myocardial infarction, coronary heart disease, percutaneous coronary intervention, atrial fibrillation, transient ischemic attack, stroke and bleeding event), risk factors (within past 3 months or ongoing: active cancer, prolonged immobilization[2], >5 days in bed, varicose veins, history of major surgery or trauma,), comorbidities (hypertension, congestive heart failure, vascular disease, dyslipidemia, diabetes mellitus, chronic venous insufficiency, renal disease, liver disease, chronic respiratory disease, arthritis, lower extremity paralysis, bone fracture/soft tissue trauma, thrombophilia, alcohol use, smoking history, and cardiovascular disease), and the presence of DVT symptoms. For regional comparisons, Austria, Switzerland, and Germany were combined into one pre-specified region label (DACH). The DACH countries were grouped in a cluster as the patient population, practice patterns and healthcare systems were assumed to be similar. The number of sites for Germany, Austria and Switzerland were 74, 5 and 3, respectively. More detail of clinical variables can be found elsewhere [10].

Healthcare resource utilization

Treatment medications at baseline and each follow up, i.e. the use of heparin (including both low-molecular weight heparins and unfractionated heparin), VKA or DOACs, were recorded. Accumulated post-VTE or VTE-related healthcare resource utilization, in terms of the number of hospitalizations, duration of hospital stay (LOS), the use of intensive care unit (ICU), and ambulatory/office visit at 12 months follow up, was estimated. This accumulated post-VTE or VTE-related healthcare resource utilization did not include both the diagnosis of DVT and any hospitalization related to the initial DVT. Post-VTE healthcare resource utilization referred to the number of hospitalizations, LOS and the use of ICU. VTE-related healthcare resource utilization was specifically for medication and ambulatory/office visit. In addition to the total sample, descriptive statistics for country and cancer subgroups were also presented. The difference between compared subgroups was evaluated using chi-square test, Kruskal-Wallis equality-of-populations rank test or Wilcoxon rank-sum test (no normal distribution was assumed), when appropriate.

The dependency between baseline characteristics and LOS were examined using zero-inflated negative binomial regression to address the issue of the outnumbered zero hospitalization day and over-dispersion of the distribution. The zero-inflated negative binomial regression consisted of two parts: the first (inflate) part is to predict whether there is an occurrence of LOS (probability of zero or none-zero), whereas the second part is to predict the duration of LOS above zero (non-zero value). The examined baseline characteristics included demography factors (age, gender, BMI), previous clinical events, clinical factors, co-morbidities, risk factors and presented PE symptoms.

[1] Provoked DVT was defined as having prolong immobilization, >5 days in bed, or history of major surgery or trauma.

[2] Prolonged immobilization was defined as immobilization within the last 3 months or ongoing (e.g., travelling for more than 4 hours).

Female specific risk factors, i.e. pregnancy and exogenous estrogen use, were not included ~~in the current analysis~~as potential risk factors in the current analysis in order to permit a single analysis encompassing both genders. A separate model was fitted to explore country variation by adding country as an additional co-variate. These analyses were limited to the total sample.

Return to work

Return to work was expressed as the proportion of patients returning to work during the follow up and when they returned to work. In the study, patients were asked whether they returned to work during the follow up, and, if applicable, how soon they returned to work and their productivity level after return in terms of working hours. The analysis was limited to employed patients and an age limit of 65 years at baseline, and a variable indicating how soon patients returning to work was derived. Kaplan-Meier survival analysis was executed to present the rate and time of employed patients retuning to work. Furthermore, multivariate Cox proportion hazards regression was implemented to assess the association between baseline characteristics (the same as those listed above) plus country and returning to work.

Missing data

Due to loss to follow up including death or incomplete information, there was missing data at each cross-sectional measurement. No imputation was conducted for any missing value. However, the difference in terms of baseline characteristics between patients who completed the follow up questionnaires and those who did not was tested, using chi square test, Wilcoxon rank sum test, or t-test when appropriate.

Results

Patients characteristics

Table 1 presents patient characteristics at baseline stratified by country. Amongst the 2,056 DVT patients at baseline, 30.3% patients were recruited from DACH, 28.0% from Italy, 18.2% from the UK, 12.0% from Spain and 11.6% from France. Mean age differed significantly - with the highest in Italy, approximately 64 years (SD: 16.68) and the lowest in DACH, about 57 years (SD: 16.30). Significant differences per country were also found for gender and BMI. More than 79% of patients had proximal DVT in Italy, Spain and the UK, whereas the proportion was much lower in France (47.5%). The proportion of patients with provoked DVT was similar across countries (25-31%). Patients in Italy had a higher number of previous clinical events and risk factors, as well as the highest comorbidity rates. For example, they had higher frequencies of active cancer (15.8%), prolonged immobilization (20.9%) and >5 days in bed (18.5%) compared to the other countries. In addition, the prevalence of congestive heart failure, vascular disease, diabetes mellitus, renal disease, liver disease, and chronic respiratory disease were also highest amongst patients from Italy. The most commonly reported DVT symptoms included pain and swelling, with over 72% and 54%, respectively, across all countries. The baseline characteristics of the total sample and cancer subgroup can be found elsewhere [9].

Missing data

The study sample with complete observations concerning hospitalizations (n=1446) in comparison with those with missing data (n=610) showed a higher prevalence of dyslipidemia and a lower prevalence of previous atrial fibrillation, cancer, liver disease and chronic respiratory disease. People with missing data were younger, and were more likely to smoke. Additionally, data were most often incomplete in the UK.

Healthcare resource utilization

Medication

As shown in Table 2, at baseline the proportion of patients initially treated with heparin, vitamin K antagonists (VKA) and direct oral anticoagulants (DOACs)s was 64.9%, 42.7% and 26.8%, respectively. (33.5% of patients treated with both heparin and VKA.) The use of DOACs was the highest in DACH (54.4%), whereas Spain and Italy had lowest rates: 7.0% and 4.0% (p-value<0.0001). (At the time of the data collection of the PREFER in VTE registry, not all DOACs were reimbursed in Spain and Italy.) Patients with active cancer were treated differently from those without active cancer – more heparin treatment was given in patients with active cancer (p-value<0.0001). In addition, table 2 also presents the proportion of patients who continued to use the baseline treatment at 1-, 3-, 6- and 12-months follow up. Whereas patients with active cancer continued to use heparin after baseline, >60% up to 3 months, the rate dropped to <13% for patients without active cancer. Moreover, amongst the total sample the proportion of patients who continued to use VKA or DOACs after baseline were 62.4% and 38.9 % at 6 months and 42.1% and 24.4% at 12

months, respectively. More than 17% of patients who continued to use VKA or DOACs had provoked DVT. In comparison to other countries, France, Spain and Italy had a higher proportion of patients who continued to use heparin after baseline (21.8, 23.0 and 32.8% at 3 months). Patients in Spain without active cancer had a higher rate of heparin treatment (31.2%, 17.4% and 9.7% for 3, 6 and 12 months).

Post-VTE hospitalization

Table 3 presents the cumulative frequency (percentage) of post-VTE re-hospitalization and VTE-related ambulatory/office visit by cancer and country subgroups. (The average number of visits and LOS can be found in Appendix Table 1.) By the end of the 12-month follow up, 197 out of 1552 patients (12.7%) had been re-hospitalized (VTE-related). The reasons for re-hospitalization can be found in Appendix Table 2. The average number of repeat hospitalizations was 1.4, with an average LOS of 9.9 days (calculated as the total number of days in hospital divided by the number of patients who have had hospitalizations). A substantial country variation was observed: the re-hospitalization rate ranging from 16.7% in Italy to 7.7% in France (*p*-value <0.0001) and a LOS of 16.6 days in Italy to 5.2 days in DACH (*p*-value =0.0001). Figure 1 presents the cumulative percentage of patients who needed re-hospitalization and the cumulative number of hospital days of those who were hospitalized. From month one the hospitalization rate in Italy was substantially higher compared to other countries. We also found that not only were patients in Italy hospitalized more often, their hospital stays were longer. The differences between the other countries were much smaller. Furthermore, patients with active cancer were more often re-hospitalized than patients without active cancer (20.5% vs. 12.2%, *p*-value=0.037) during the 12-month follow up. However, the average LOS was longer for patients without active cancer than for those with active cancer (10.1 vs. 8.2, *p*-value= 0.723, Appendix Table 1).

Modeling of risk factors associated with increased length of hospitalization found patients with active cancer, previous CAD, chronic respiratory disease, vascular disease, or arthritis were more likely to be hospitalized. When modeling for risk factors associated with duration of hospitalization, we found that patients with previous PCI and patients living in Italy were likely to have a longer hospital stay. However, with the relative low variance explained by the models, the result should be interpreted with caution. Details can be found in Table 4.

VTE-related ambulatory/office visit

During the 12-month follow up, the majority of patients visited a physician (84.2%), with an average number of visits of 7.0 (SD: 7.6). Of those who had at least one visit, the recruiting physician and the general practitioner were most often visited: by 69.6% and 55.1% respectively. In comparison, relatively few visits were made to venous institutions or other healthcare professionals. Amongst investigated countries, great variation existed in terms physician type that patients visited during the follow up period (Table 3). For instance, Spain had a relatively lower percentage of

visiting general practitioners, but a higher percentage of visiting internists. In Italy, it was more common to visit vascular physicians than in other countries. In addition, the occurrences of ambulatory/office visits were less in patients with active cancer than in those without. Visiting any physician was 72.7% vs. 84.9% in the two groups, respectively. 10.0% of the study population did not have any ambulatory/office visit during 12-months follow up; the proportion was higher in countries such as Italy 17.4% and the UK 17.1%.

Finally, a possible selection bias should be considered. As noted in the missing data section above, the study sample differed from the non-study sample. The additional analyses show that the re-hospitalization rate and average LOS at any particular follow up point were higher in the group of patients who did not participate in the next follow up compared to those who were followed up.

Return to work

Amongst 756 patients who were employed at baseline and under 65 years old (average age 46.84), 70.5% had returned to work by the end of the one-year follow up. The highest number of patients returned to work in DACH (75.85%), the lowest in Spain (61.25%) (*p*-value= 0.056). Of the active cancer patients, only 32% had returned to work after one year (total active cancer sample = 25) (*p*-value<0.0001). Figure 2 presents the Kaplan-Meier estimate of returning to work after the index event in the total study sample (both active and non-active cancer patients). As shown in figure 2, more than half of study population had returned to work after a month. The median time for returning to work was 34 days. Amongst patients who reported returning to work, 23.4% (120/514) had reduced working hours at first return. Initially work hours reduced from an average of 36.8 hours per week prior to DVT, to an average of 29 hours per week for the prior 4 weeks of the first assessment. At the time of last follow up 17.6% (92/523) continued to have reduced working hours, with an average of 31 hours per week for over the previous 4 weeks. The data suggested that patients still experienced some level of limited productivity after returning to work. The results are presented per country and cancer subgroups in Appendix Table 3.

The Cox regression results suggested that being older, having active cancer, having been in bed for more than 5 days is associated with a lower probability of returning to work (OR<1). Adding country variables the results suggested that patients in France and Spain were less likely to return to work, whereas patients from Italy were more likely to do so. Detailed analysis results can be found in Table 5.

Discussion

This study investigated the burden of DVT in Europe in terms of post-VTE or VTE-related healthcare resource utilization and work-loss. The study demonstrated significant country variation in a number of factors. Post-VTE re-hospitalization rate and LOS varied substantially between countries. The regression results confirmed the country variation in LOS. In terms of work-loss, half of the employed patients returned to work within a month but around thirty percent had still not returned after one year. Active cancer was a significant predictor for not returning to work, whereas country also played a significant role in determining their return to work.

Post-VTE or VTE-related healthcare resource use

Significant country variation in terms of post-VTE or VTE-related healthcare resource use was observed. For example, the use of DOACs varied substantially across the countries which can partly be explained by the licensing and reimbursement status of DOACs at the time of the data collection (Spain and Italy had limited access). However, even amongst the countries where DOACs were fully accessible, DOACs use varied, probably due to different national or local guidelines/recommendations. For instance, the UK had a much lower DOAC use, compared to DACH and France. Country variation in the use of heparin after the baseline varied greatly among countries. Patients in France, Spain and Italy continued to use heparin after baseline much more often than other countries. After limiting the analysis to patients without active cancer, the higher rate of using heparin was still observed in Spain. Local treatment recommendations and limited access to DOACs explain this observation. Furthermore, a large proportion of patients who received VKA or DOACs at baseline continued their treatment after 3 months (mostly patients with unprovoked DVT, as recommended in the guidelines [11]), where the standard treatment duration according to treatment guidelines is usually 3 months, but longer periods of treatment are more often recommended. Thus, the proportion of patients who continued to use VKA or DOACs as observed in the data represent those receiving extended treatment. It should be noted that the observed medication use in the current study, to a great extent, reflected the specific case mix of patients included in the PREFER in VTE registry, as well as the variation in the disease management across countries.

Similarly, the frequency of re-hospitalizations and the average length of stay also differs per country, as does the frequency of ambulatory/office visits. It may reflect different treatment patterns but it may also be a reflection of a different mix of patients. The regression results suggest that after controlling for baseline characteristics of patients, patients in Italy were associated with a longer hospital stay in comparison to patients in the UK. However, it should be noted that other factors, such as pressure on budget, cost containment, the healthcare reimbursement system, the level of adoption for outpatient VTE treatment in clinical practices, as well as other relevant clinical factors which were not recorded in the current study, might all contribute to the observed variations.

The key cost driver of the economic burden associated with DVT is VTE-related LOS [12]. While most studies examining VTE hospitalization rates and LOS emerged from the US, very few current studies reported those numbers in the European setting. A modeling study in France in 1999 reported an average LOS of 3.3-6.4 days [13] and an Italian study collecting data from 160 VTE patients in 2010 reported a LOS of 12.5 days [14]. A recent study utilizing the data of 1452 DVT patients in Italy from year 2006 to 2013, collected as part of the REITE registry, reported the average of LOS as 9 days (SD: 8 days) and the average LOS in 2013 is 7.02 days [15]. In the current study the post-VTE re-hospitalization was reported. It was not possible to ensure that all hospitalizations were directly related to the initial DVT despite the registry asking investigators to record all VTE related re-hospitalizations. A range of new hospitalizations under that heading were also collected (Appendix Table 2).

In about 10% of patients there was no recorded follow up visits for DVT. This number is likely due to visits not registered as DVT-related. One would expect that DVT patients have regular follow up for other reasons than their DVT-history and that visits weren't registered as related to a DVT. This implies that the resource utilization may well be underestimated. The European Society of Cardiology recommends that patients on DOACs are followed on a regular basis for on-going review of their treatment, preferably after 1 month initially, and later every 3 months. This study demonstrated that patients were followed-up less regularly than recommended by these guidelines.

Return to work

Our study demonstrated that 70.5% of DVT patients (limited to those employed and under age 65 at baseline) return to work within one year, with a lower rate for patients with active cancer. This figure is consistent with return to work rate following other major illnesses. The return to work rate within the first year after stroke was reported between 45% to 75%, based on self-reported employment outcomes [16,17]. A more recent Swedish publication, using insurance sickness leave data, reported return to work rate following stroke was 74.7%, at the end of 6-year follow up [18]. Following myocardial infarction (MI), a US study utilizing the data gathered from the VIRGO study reported 84% of patients return to work by 12 months [19]. However, this observed high work-loss for patients with DVT may at least in part reflect the presence of co-morbidities.

The regression results further suggested that, after adjusting baseline characteristics, patients from France and Spain were more likely to return to work compared to patients from the UK, whereas patients from Italy were less likely to return to work. This result should be interpreted with caution. It is likely that the results reflect different retirement ages, sickness/disability benefits and the prevalence of early retirement across each compared county, rather than the impact of DVT alone. Nevertheless, the excess burden adds to the indirect costs and emphasizes the need for reducing recurrence rates more effectively and improving the care of DVT patients.

Strengths and limitations

The PREFER in VTE registry provides a rich data source of epidemiology, management and outcomes of VTE patients in a real-world setting. It is one of the largest prospective disease registries in VTE and its focus on seven European countries provides a much-needed addition to the relatively scarce data on DVT from this continent. In addition, the PREFER registry represents "real life" data by including consecutive patients presenting with PE/DVT with few exclusion criteria, in contrast to data from randomized clinical trials, which typically will include patients with less co-morbidities, who are more median aged and where the disease definition is more restricted. In other words, this current data represents the real-world practice. To the authors' best knowledge, there are no other studies that have explored country variation in post-VTE or VTE-related HCRU.

However, due to the design of the registry, it is difficult to make a direct comparison between observed countries. The results in this registry, nevertheless, are not aiming to accept or reject a predefined hypothesis, they offer a reference point to compare other data, such as in more selected patients, data from other countries, data with and without the use of DOACs and data in patients with and without cancer. The data may also help in forming expectations for future studies when considering subgroups. As such it may be helpful in the further development of defining the best treatment pattern/management for DVT patients. Furthermore, a typical limitation of most observational studies is that data may be missing. No corrections such as multiple imputations were made, and this needs to be considered in the interpretation of the results, as it is likely that the patients with co-morbidities are more often missing, and therefore the burden of DVT may be underestimated. A recall bias might play a role in this study as the follow-up data was collected through telephone calls few months after the recruitment. Finally, in this study the level of significance at 0.05 was used throughout the whole analyses. No adjustment was made in the significance level for multiple comparisons. As a result, potential false-positive results cannot be ruled out.

Conclusion

This study concluded that post-DVT or DVT-related healthcare resource utilization and return to work differed markedly between countries and between patients with active cancer and those without. A large amount of country specific information on patient characteristics, re-hospitalization, length of hospital stay, ambulatory/office visits and work-loss, all of which concern the excess burden of illness for DVT patients was provided to enhance current knowledge on health economics in Europe.

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Table 1 Patient characteristics at baseline

Baseline	Total n=2056	France n=238	DACH n=623	Italy n=575	Spain n=246	UK n=374	
Age, years, mean (SD)	59.8 (16.8)	58.6(16.0)	57.4(16.3)	64.5(16.7)	59.3(18.1)	57.6(16.3)	*
Male	52.9	47.9	53.0	49.6	55.7	59.4	*
BMI, mean (SD)	27.8 (5.3)	26.8 (4.7)	28.2(5.2)	26.4(4.9)	28.4(5.0)	29.5(5.9)	*
Highest graduation							*
Primary school	26.7	19.7	22.5	41.0	48.4	1.9	
Secondary school	47.67	49.6	47.0	41.2	30.5	68.7	
Above	20.91	25.6	21.8	13.9	19.1	28.3	
Marital status							*
Single	13.8	10.5	18.0	11.8	13.4	17.9	
Married/living as married	65.7	75.2	61.2	66.1	66.7	65.8	
Separated/divorced	5.7	5.0	6.7	3.8	4.1	8.6	
Widowed	10.8	6.7	7.7	17.0	13.4	7.0	
Other	1.1	0.0	1.6	0.9	0.0	1.9	
Previous clinical event (within 3 yr. prior to enroll.)							
Myocardial infarction	3.1	2.1	1.6	5.4	3.3	2.4	*
Coronary artery disease	3.8	2.5	2.9	5.9	2.0	4.0	*
Percutaneous coronary intervention	1.8	0.4	1.3	3.3	0.4	2.1	*
Atrial fibrillation	2.6	1.3	1.0	5.2	2.4	2.4	*
Transient ischemic attack	2.0	0.0	0.5	5.1	1.2	1.6	*
Stroke	2.2	0.8	1.6	3.1	3.3	1.9	
Bleeding event	3.6	3.8	2.9	5.2	3.3	2.4	
DVT symptoms present							
Pain	82.8	88.2	89.1	72.7	83.3	84.2	*
Discoloration	16.2	6.7	13.6	12.7	19.9	29.4	*
Calf tenderness	29.4	19.3	15.4	26.1	35.8	59.9	*
Swelling	73.4	54.2	75.9	65.4	85.0	85.8	*
Collateral superficial veins	7.3	6.3	3.5	9.9	12.6	6.4	*
Other	5.8	5.5	3.2	6.4	3.7	11.0	*

* p-value <0.05 chi-square test, Kruskal-Wallis equality-of-populations rank test, anova

Table 1 (continue) Patient characteristics at baseline

France	Total n=2056	France n=238	DACH n=623	Italy n=575	Spain n=246	UK n=374	
Comorbidities							
Hypertension	39.7	27.7	39.0	49.7	40.4	32.4	*
Congestive heart failure	2.8	2.9	1.3	6.1	1.6	1.1	*
Vascular disease	5.5	3.8	2.9	11.7	3.7	2.4	*
Dyslipidemia	17.5	15.5	11.1	23.8	28.2	12.8	*
Diabetes	9.7	7.6	10.0	12.4	7.8	8.0	
Chronic venous insufficiency	16.6	18.1	13.7	23.7	25.3	3.7	*
Renal disease	6.0	3.4	5.3	8.4	4.5	6.1	*
Liver disease	2.6	2.1	1.1	5.2	1.6	1.9	*
Chronic respiratory disease	7.6	3.8	3.1	12.2	7.3	10.4	*
Arthritis	8.8	5.9	2.9	9.7	4.5	21.7	*
Bone fracture/soft tissue trauma	12.4	13.0	12.7	10.3	9.0	17.1	*
Lower extremity paralysis	1.2	0.4	1.3	1.0	2.4	0.8	
Alcohol use	18.4	7.6	14.6	11.0	7.8	50.0	*
Smoking history	30.3	25.6	27.0	30.0	29.0	40.1	*
Thrombophilia	7.5	5.9	8.8	8.9	7.7	4.3	*
Cardiovascular disease	62.9	48.1	69.4	66.0	60.9	58.6	*
Risk factors (within past 3 month or ongoing)							
Active cancer	8.5	12.2	4.0	15.8	4.9	4.5	*
Prolong immobilization	15.9	13.0	13.2	20.9	16.3	14.2	*
>5 day in bed	9.9	6.3	5.8	18.5	11.0	5.3	*
Varicose veins	22.1	19.3	20.7	24.7	30.5	16.8	*
History of major surg. or trauma	14.4	18.1	15.0	13.6	12.6	13.4	
Previous VTE event	25.7	33.6	27.4	20.2	21.1	29.4	*
Proximal	71.3	47.5	63.1	79.3	85.0	78.6	*
Provoked	27.5	27.3	24.6	31.0	30.1	25.1	

Table 2 Treatment overtime, by with/without active cancer and country

	Total sample		Without active cancer		With active cancer	
	%	n	%	n	%	n
Heparin						
BL	64.9	(1,327 /2,046)	63.1	(1,181 /1,872)	83.9	(146 /174)
Continue. 1 m	30.5	(345 /1,130)	25.2	(254 /1,009)	75.2	(91 /121)
Continue. 3 m	18.4	(188 /1,023)	13.8	(128 /927)	62.5	(60 /96)
Continue. 6 m	10.3	(101 /983)	7.6	(69 /906)	41.6	(32 /77)
Continue. 12 m	3.8	(35 /928)	2.8	(24 /868)	18.3	(11 /60)
VKA						
BL	42.7	(874 /2,047)	45.0	(843 /1,873)	17.8	(31 /174)
Continue. 1 m	94.9	(760 /801)	94.8	(732 /772)	96.6	(28 /29)
Continue. 3 m	82.1	(588 /716)	82.1	(567 /691)	84.0	(21 /25)
Continue. 6 m	62.4	(431 /691)	61.8	(413 /668)	78.3	(18 /23)
Continue. 12 m	42.1	(255 /606)	41.6	(246 /592)	64.3	(9 /14)
DOACs						
BL	26.8	(549 /2,050)	28.7	(539 /1,876)	5.8	(10 /174)
Continue. 1 m	92.0	(451 /490)	92.1	(442 /480)	90	(9 /10)
Continue. 3 m	61.4	(282 /459)	61.7	(277 /449)	50	(5 /10)
Continue. 6 m	38.9	(169 /435)	38.8	(165 /425)	40	(4 /10)
Continue. 12 m	24.4	(103 /422)	24.5	(101 /413)	22.2	(2 /9)

BL: baseline, VKA: vitamin K antagonists, DOAC: direct oral anticoagulants. Heparin includes both low-molecular weight heparins and unfractionated heparin.

Table 2 (Continue) Treatment overtime, by with/without active cancer and country

	France			DAH			Italy			Spain			UK		
	%	n		%	n		%	n		%	n		%	n	
Heparin															
BL	54.6	(130	/238)	43.7	(269	/615)	72.0	(413	/574)	89.8	(220	/245)	78.9	(295	/374)
Continue. 1 m	44.1	(49	/111)	17.3	(39	/225)	38.7	(142	/367)	44.9	(87	/194)	12.0	(28	/233)
Continue. 3 m	21.8	(24	/110)	9.8	(20	/204)	23.0	(72	/313)	32.8	(61	/186)	5.2	(11	/210)
Continue. 6 m	13.3	(14	/105)	3.1	(6	/192)	12.76	(38	/298)	19.2	(36	/188)	3.5	(7	/200)
Continue. 12 m	3.1	(3	/96)	0.5	(1	/198)	5.1	(14	/276)	8.3	(14	/168)	1.6	(3	/190)
VKA															
BL	34.9	(83	/238)	23.2	(143	/616)	50.9	(292	/574)	44.5	(109	/245)	66.0	(247	/374)
Continue. 1 m	95.0	(76	/80)	94.4	(117	/124)	93.8	(258	/275)	96.0	(97	/101)	95.9	(212	/221)
Continue. 3 m	76.6	(59	/77)	75.4	(86	/114)	89.5	(214	/239)	88.9	(88	/99)	75.4	(141	/187)
Continue. 6 m	49.4	(38	/77)	55.1	(59	/107)	73.1	(174	/238)	63.2	(60	/95)	57.5	(100	/174)
Continue. 12 m	31.9	(23	/72)	43.3	(45	/104)	51.6	(96	/186)	40.5	(36	/89)	35.5	(55	/155)
DOACs															
BL	42.0	(100	/238)	54.4	(337	/619)	4.0	(23	/575)	7.0	(17	/244)	19.3	(72	/374)
Continue. 1 m	89.9	(89	/99)	90.9	(271	/298)	95.2	(20	/21)	92.9	(13	/14)	100.0	(58	/58)
Continue. 3 m	56.1	(55	/98)	59.6	(161	/270)	89.5	(17	/19)	61.5	(8	/13)	69.5	(41	/59)
Continue. 6 m	30.1	(28	/93)	39.3	(103	/262)	75.0	(12	/16)	33.3	(4	/12)	42.3	(22	/52)
Continue. 12 m	14.6	(13	/89)	25.2	(66	/262)	41.7	(5	/12)	18.2	(2	/11)	35.4	(17	/48)

BL: baseline, VKA: vitamin K antagonists, DOAC: direct oral anticoagulants. Heparin includes both low-molecular weight heparins and unfractionated heparin.

Table 3. Cumulative post-VTE or VTE-related healthcare resource utilization by cancer/non-cancer and by country

	Total		Without active cancer		With active cancer	
	N= 1552		N= 1464		N= 88	
	n	%	N	%	n	%
Re-hospitalization	197	12.7%	179	12.2%	18	20.5%
Ambulatory/office visits						
Physician	1307	84.2%	1243	84.9%	64	72.7%
Original site	910	69.6%	870	70.0%	40	62.5%
General practitioners	720	55.1%	692	55.7%	28	43.8%
Cardiologists	71	5.4%	65	5.2%	6	9.4%
Internists	206	15.8%	201	16.2%	5	7.8%
Vascular physicians	260	19.9%	241	19.4%	19	29.7%
Pulmonologists	37	2.8%	36	2.9%	1	1.6%
Other physicians	293	22.4%	277	22.3%	16	25.0%
Venous institutions	59	3.8%	56	3.8%	3	3.4%
Other healthcare professionals	130	8.4%	122	8.3%	8	9.1%
None	155	10.0%	136	9.3%	19	21.6%

Table 3 (continue). Cumulative post-VTE or VTE-related healthcare resource utilization by cancer/non-cancer and by country

	France N = 196		DACH N = 500		Italy N = 407		Spain N = 198		UK N = 251	
	n	%	n	%	n	%	n	%	n	%
Re-hospitalization	15	7.7%	52	10.4%	68	16.7%	24	12.1%	38	15.1%
Ambulatory/office visits										
Physician	193	98.5%	457	91.4%	311	76.4%	178	89.9%	168	66.9%
Original site	167	86.5%	381	83.4%	142	45.7%	118	66.3%	102	60.7%
General practitioners	132	68.4%	301	65.9%	132	42.4%	65	36.5%	90	53.6%
Cardiologists	24	12.4%	16	3.5%	18	5.8%	11	6.2%	2	1.2%
Internists	1	0.5%	66	14.4%	70	22.5%	58	32.6%	11	6.6%
Vascular physicians	49	25.4%	58	12.7%	101	32.5%	38	21.4%	14	8.3%
Pulmonologists	6	3.1%	12	2.6%	4	1.3%	13	7.3%	2	1.2%
Other physicians	65	33.7%	115	25.2%	53	17.0%	42	23.6%	18	10.7%
Venous institutions	4	2.0%	5	1.0%	39	9.6%	1	0.5%	10	4.0%
Other healthcare professionals	11	5.6%	31	6.2%	39	9.6%	11	5.6%	38	15.1%
None	-		24	4.8%	71	17.4%	17	8.6%	43	17.1%

Table 4 The results of zero-inflated negative binomial regression (length of hospital stay)

	Coef.	Std. Err.	P>z	[95% Conf.	Interval]
Inflate part					
Constant	2.254	0.125	0	2.009	2.498
Active cancer	-0.844	0.305	0.006	-1.442	-0.247
Previous coronary artery disease	-1.154	0.356	0.001	-1.852	-0.456
Chronic respiratory disease	-0.774	0.301	0.01	-1.364	-0.184
Vascular disease	-1.088	0.300	0	-1.675	-0.500
Arthritis	-0.898	0.266	0.001	-1.419	-0.377
Second part					
Constant	1.706	0.130	0	1.451	1.960
Previous percutaneous coronary intervention	0.812	0.379	0.032	0.069	1.555
Italy	1.002	0.194	0	0.623	1.381

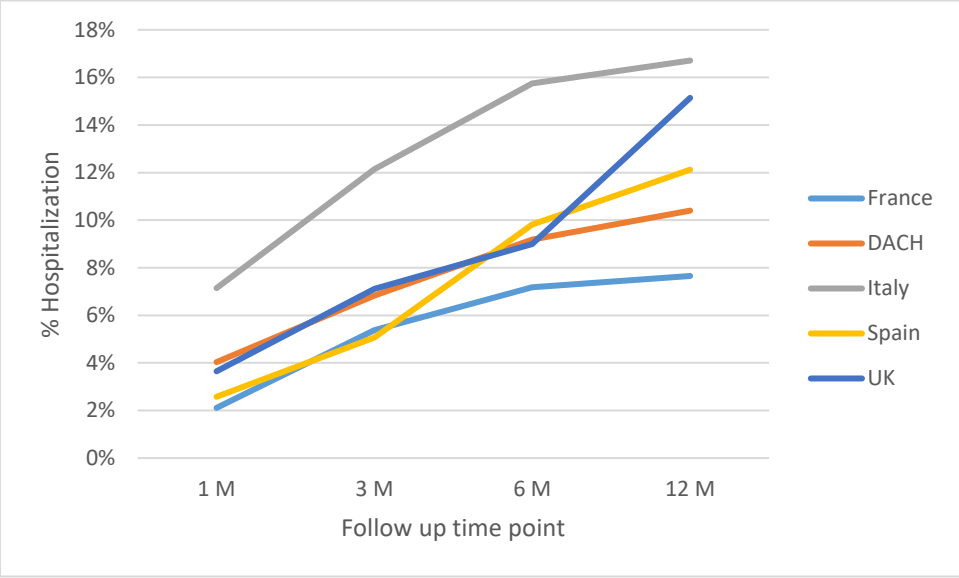
The zero-inflated negative binomial regression results suggested that for the first (inflate) part (estimating the probability of having no hospital stay) patients with active cancer, previous CAD, chronic respiratory disease, vascular disease or arthritis were associated with a lower probability of having no hospital stay, i.e. they were more likely to be hospitalized. The second part of the analyses (estimating non-zero values) found that patients with previous PCI and patients living in Italy were likely to have a longer hospital stay.

Table 5. Factors determining return to work - Cox regression result

	Hazard ratios	Std. Err.	P>z	[95% Conf.	Interval]
Age	0.988	0.005	0.009	0.979	0.997
Active cancer	0.178	0.104	0.003	0.057	0.558
France	0.593	0.114	0.007	0.406	0.865
> 5 day in bed	0.610	0.136	0.026	0.395	0.944
Italy	1.365	0.179	0.017	1.056	1.764
Spain	0.658	0.118	0.019	0.463	0.935

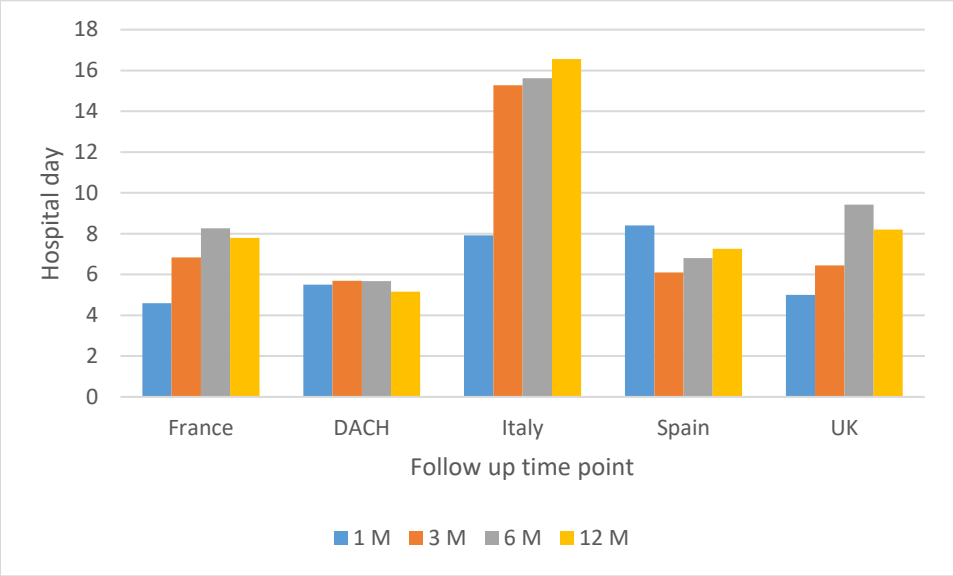
Figure 1. Hospitalization by follow-up and country

Figure 1.a Percentage of patients being hospitalized



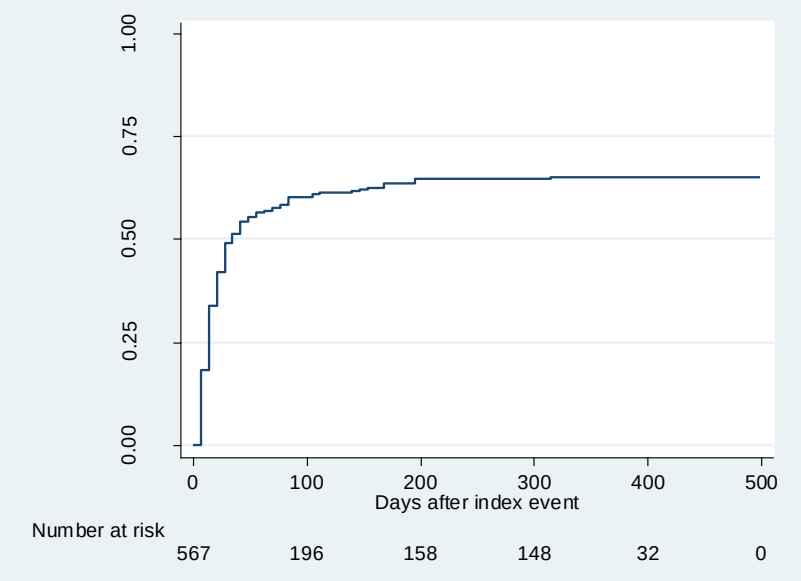
M: month

Figure 1.b Average total hospitalization duration if hospitalized



DACH: Germany, Switzerland and Austria

Figure 2. Kaplan-Meier survival estimate of how soon returning to work after index event



Number at risk: number of patients returning to work at given time point

Appendix

Table 1. Accumulated post-VTE or VTE-related healthcare resource utilization by each country (magnitude)

	Total N=1552			Without active cancer N=1464			With active cancer N=88			France N=196		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
Re-hospitalization												
Number of hospitalization	184	1.4	1.0	166	1.4	1.0	18	1.3	1.0	15	1.4	1.1
Length of hospital stay, total	174	9.9	13.3	156	10.1	13.8	18	8.2	7.6	15	7.8	7.2
Length of hospital stay, per stay	174	7.1	8.3	156	7.1	8.4	18	7.2	7.2	15	5.9	4.5
Days in ICU, total	134	0.2	1.3	118	0.2	1.4	16	0.2	0.5	12	0.1	0.3
Ambulatory / office visits												
Any physician	1208	7.0	7.6	1145	6.9	7.6	63	6.1	6.1	193	6.3	5.6
Original site	864	3.6	4.3	824	3.6	4.3	40	3.3	3.5	167	2.5	1.3
General practitioners	674	5.1	6.4	646	5.1	6.4	28	5.8	5.4	132	3.8	4.5
Cardiologists	67	1.3	0.8	61	1.3	0.7	6	1.8	1.6	24	1.5	1.1
Internists	193	2.9	2.8	189	2.9	2.8	4	1.8	1.5	1	3	-
Vascular physicians	242	1.9	1.8	223	1.9	1.8	19	2.2	1.2	49	1.9	1.4
Pulmonologists	36	1.6	1.0	35	1.6	1.0	1	1	-	6	1.7	0.8
Other physicians	278	2.4	2.7	262	2.4	2.8	16	1.9	2.5	65	2.5	3.7
Venous institutions	55	2.2	2.2	52	2.2	2.2	3	1	0	4	1	0
Any other healthcare professionals	109	8.2	13.7	101	8.0	13.8	8	10.1	12.3	11	9.2	9.6

ICU: intensive care unit

Table 1. (continue) Accumulated post-VTE or VTE-related healthcare resource utilization by each country (magnitude)

	DACH N=500			Italy N=407			Spain N=198			GB N=251		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
Re-hospitalization												
Number of hospitalization	50	1.2	0.6	65	1.6	1.1	23	1.2	0.5	31	1.6	1.4
Length of hospital stay, total	49	5.2	5.2	57	16.6	18.2	23	7.3	7.4	30	8.2	13.0
Length of hospital stay, per stay	49	4.4	4.4	57	10.6	9.0	23	5.8	5.1	30	6.6	12.3
Days in ICU, total	43	0.1	0.4	33	0.1	0.5	19	0.8	3.4	27	0	-
Ambulatory / office visits												
Any physician	424	9.3	8.3	285	7.2	9.3	171	4.4	3.5	135	2.6	2.5
Original site	362	4.1	4.4	134	5.9	7.2	116	2.1	1.5	85	1.9	1.5
General practitioners	285	6.6	7.0	125	6.4	8.2	61	2.3	1.9	71	2.2	2.7
Cardiologists	15	1.3	0.6	17	0.9	0.4	10	1.3	0.5	1	1	-
Internists	62	4.2	3.5	64	2.7	2.7	58	2.1	1.7	8	1	-
Vascular physicians	53	2.2	2.9	92	1.9	1.2	37	2	1.6	11	1.2	0.6
Pulmonologists	12	1.7	1.3	4	1.3	0.5	13	1.7	1.0	1	1	-
Other physicians	109	1.9	1.4	49	2.7	3.0	42	3.4	3.4	13	1.5	0.9
Venous institutions	5	1	0	36	2.1	1.4	1	1	-	9	3.7	4.4
Any other healthcare professionals	26	17.4	20.8	31	3.2	6.8	11	12.6	16.9	30	3.4	3.7

ICU: intensive care unit

Table 2. Reasons for re-hospitalization (Multiple choice is possible)

	%	N	
Venous thromboembolism	24.7	(48	/194)
Myocardial infarction	2.7	(5	/184)
Transient ischemic attack	1.6	(3	/184)
Stroke	2.2	(4	/185)
Arterial embolism	0.6	(1	/183)
Bleeding event	12.3	(23	/187)
Major surgery or trauma	25.8	(49	/190)
Other reasons	66.7	(152	/228)

Table 3. Return to work and working hour/duration, by cancer and country subgroups

	Total		Without active cancer		With active cancer		France		DACH		Italy		Spain		UK	
	n=756		n=731		n=25		n=102		n=265		n=145		n=80		n=164	
Return to work																
Yes, n	533		525		8		66		201		105		49		112	
No, n	223		206		17		36		64		40		31		52	
First return with reduced work																
Yes, n	120		118		2		9		31		46		8		26	
No, n	394		389		5		57		159		52		41		85	
First return reduced work, hours																
n	118		116		2		9		30		45		8		26	
Hour per week, mean (SD)	29.0	(14.0)	28.91	(14.0)	32.50	(17.7)	28.83	(10.1)	27.55	(14.6)	32.61	(12.7)	14.38	(18.0)	28.87	(12.8)
First return reduced work, duration																
N	109		107		2		9		28		39		8		25	
week, mean (SD)	3.9	(4.4)	3.93	(4.4)	4.00	(5.7)	3.89	(2.6)	4.36	(4.9)	3.74	(4.7)	3.38	(2.1)	3.92	(4.8)
Current work same as before																
No, n	92		90		2		9		26		39		4		14	
Yes, n	431		425		6		57		168		64		45		97	
Current work reduced, hours																
n	92		90		2		9		26		39		4		14	
Hour per week, mean (SD)	31.3	(14.0)	31.24	(14.1)	32.50	(17.7)	28.83	(10.1)	26.42	(14.7)	35.50	(13.5)	22.75	(18.1)	32.50	(12.9)
Current work reduced, duration																
n	80		78		2		9		21		33		4		13	
week, mean (SD)	4.3	(4.4)	4.33	(4.5)	4.00	(5.7)	3.89	(2.6)	4.62	(5.4)	3.82	(3.6)	3.50	(1.7)	5.69	(6.1)