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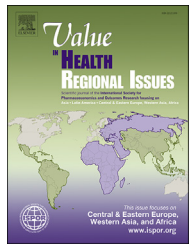

Economic Evaluation

Cost of Healthcare Associated With Deep Vein Thrombosis in Patients Treated With Warfarin in Turkey: 2010-2013 Database Analysis of a Tertiary Care Center

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ABSTRACT

Objectives: To evaluate the cost of healthcare with respect to the quality of anticoagulation in patients with deep vein thrombosis (DVT) treated with warfarin in daily practice via the database analysis of a tertiary care center in the period 2010 to 2013. **Methods:** Of 258 307 records in total, 42 582 unique patients with DVT and 32 012 patients with international normalized ratio (INR) measurements were included. Overall, 6720 unique patients with DVT diagnosis and one or more INR measurements were identified, and the records of 4377 out of 6720 unique patients were validated and included in the analysis data set. The cost analysis was based on direct medical costs from the payer's perspective. Cost items were related to healthcare resource utilization (inpatient and outpatient services) during the study period, which provided a basis for calculation of per-patient, outpatient, inpatient, and total direct medical costs. **Results:** Mean outpatient, inpatient, and total hospital admission costs were $578, $2195, and $2785, respectively, for patients with time in the therapeutic range of 70% or more, whereas the same costs were $571, $2163, and $3192, respectively, for patients with time in the therapeutic range of less than 70%. **Conclusions:** Our findings for a retrospective cohort of patients with DVT undergoing warfarin therapy reveal that patients spent 70% or more, as opposed to less than 70%, of follow-up time within the therapeutic INR range and that outpatient care, as opposed to inpatient care, was associated with lower healthcare costs. Given the significant contribution that hospital stay makes to the cost burden of DVT, our findings also highlight the association between poor warfarin anticoagulant control and increased hospitalization costs.

Keywords: cost of healthcare, deep vein thrombosis, follow-up, INR monitoring, therapeutic range, Turkey, vitamin K antagonist

Introduction

Venous thromboembolism (VTE), comprising deep vein thrombosis (DVT) and pulmonary embolism (PE), is the third most common vascular disease associated with significant morbidity and mortality.[1,2] VTE presents a substantial burden for healthcare systems, because of costs associated with the management of acute episodes, as well as long-term morbidities, the risk of recurrence, and lost productivity.[3–7] DVT has been associated with an estimated initial hospitalization cost of $9805,[8] mean daily costs of $1594 for the initial episodes,[9] and an estimated annual cumulative cost ranging from $4.9 to $7.5 billion.[10]

Despite updated current guidelines, initial anticoagulation with unfractionated heparin, low-molecular-weight heparin, or fondaparinux for at least 5 days until an international normalized ratio (INR) higher than 2.0 for 24 hours or more is reached, after administration of vitamin K antagonist (VKA), is still a widely used approach.[11,12]

Having a complex dose-response relationship and a narrow therapeutic window, warfarin treatment requires close periodic monitoring of anticoagulant efficacy, which is measured by prothrombin time and is conventionally expressed as INR.[13–15] Identification of time in the therapeutic range (TTR) is a reliable measure of the quality of anticoagulation that strongly correlates with underdosing- and overdosing-related adverse clinical outcomes.[13–17]

Although its efficacy and safety are largely dependent on the maintenance of INR within a narrow (2.0-3.0) therapeutic

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range[18–22] and a minimum TTR target threshold of at least 60% to 70%,[16,23–25] warfarin remains a widely prescribed, although challenging, anticoagulant in the management of VTE. This necessitates continual dose adjustment and routine INR monitoring, which, along with the consequences of potential poor anticoagulation, poses a considerable burden for the healthcare system.[26–28]

Even though a limited number of publications and position statements of local societies are available, to date no studies exist on the time spent in the therapeutic INR range and related healthcare costs among patients with DVT treated with warfarin in Turkey.

This study was therefore designed to evaluate, for the first time in Turkey, the cost of healthcare with respect to the quality of anticoagulation in patients with DVT treated with warfarin in daily practice, on the basis of data from the database of a large tertiary care center specialized in cardiology and cardiovascular and thoracic surgery.

Methods

Study Population

Records of patients aged 18 years and older who were diagnosed with one of the *International Classification of Diseases, Tenth Revision* (*ICD-10*) diagnosis codes/subcodes of I80 (phlebitis and thrombophlebitis), I82 (other venous embolism and thrombosis), I83 (varicose veins of lower extremities), and I87 (other disorders of veins) and who were under warfarin treatment were included in the study. Records of patients who had only 1 record in the database at a single point in time were excluded. The hospital, located in the Istanbul province, is one of the largest cardiac centers in Turkey with a remarkably large patient turnover, with approximately 3000 cardiac surgeries performed annually and 61 000 outpatients for cardiovascular surgery.[29] Its database may therefore be considered representative of the Turkish population.

Of the 258 307 records, 42 582 unique patients with *ICD-10* codes consistent with DVT and 32 012 patients with an INR measurement irrespective of the *ICD-10* code, who were registered in our hospital database with available medical history and follow-up data between January 1, 2010, and December 31, 2013, were included in this retrospective cohort study. By combining these 2 patient groups, 6720 unique patients with DVT diagnosis and 1 or more INR measurements were identified. Of the 6720 patients, 2343 patients were excluded because of having only 1 INR measurement, with no records of another INR or outpatient clinic follow-up. Finally, 4377 records out of the 6720 unique patients were validated and comprised the analysis data set (Fig. 1).

The methodology for using hospital databases has been defined by relevant law in Turkey and the entire study was conducted in full accordance with this law. Although database studies are exempt from ethical approval by local legislations in Turkey, a permission was nevertheless obtained from our institutional ethics committee for the use of patient data for publication purposes.

Annual INR Measurement Frequency ($n = 1918$)

Of the 4377 patients with INR measurement admitted as outpatients and diagnosed at least once with DVT, 1918 were determined to have been followed-up on for more than 3 months. Annual INR measurement frequency was evaluated for the 1918 patients (Fig. 1). The INR measurement count is adjusted for the follow-up duration because of the variability in follow-up durations.

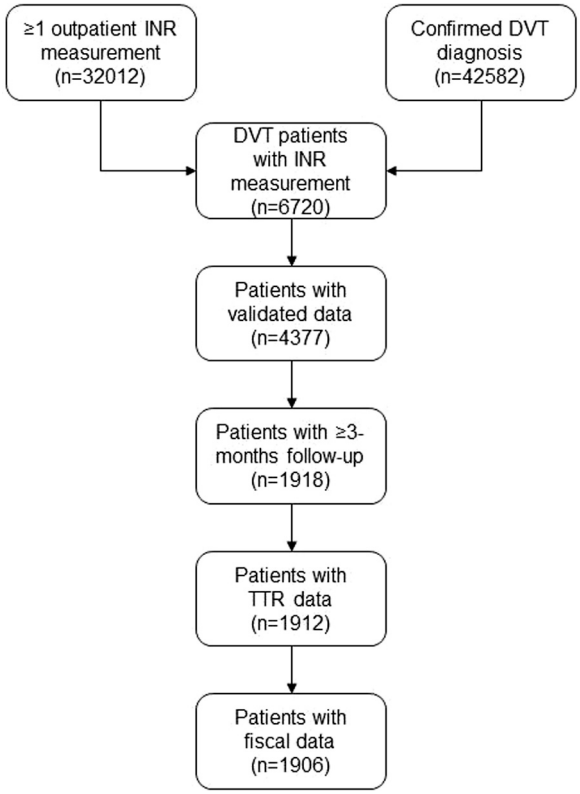

Fig. 1 – Data selection process. DVT indicates deep vein thrombosis; INR, international normalized ratio; TTR, time in the therapeutic range.

Calculation of TTR ($n = 1912$)

Of the 1918 patients, TTR could be calculated for 1912 patients, and the calculation could not be made for 6 patients because of the inappropriateness of their INR records (Fig. 1). The INR levels during warfarin use were categorized as below therapeutic range (<2), in range (2-3), or above range (>3 and >4). The proportion of follow-up time spent outside and within TTR for INR and the percentage of patients who spent 70% or more and 80% or more of follow-up time within TTR were estimated using a linear interpolation method, as described by Rosendaal et al.[30]

Annual Outpatient, Inpatient, and Total Cost ($n = 1906$)

Of the 1918 patients, records on healthcare costs were available for 1906 patients. Inpatient and outpatient costs were therefore evaluated for 1906 patients (Fig. 1).

Cost Analysis

In Turkey, the Ministry of Health General Directorate of Pharmaceuticals and Pharmacies is the sole authority in charge of registration, marketing approval/authorization, pricing, legal classification, and inspection of pharmaceuticals. The main sources of healthcare financing in Turkey are (1) the general government budget funded by tax revenues, (2) contributions obtained from the Social Security Institution (SSI), and (3) out-of-pocket payments. There are approximately 700 000 private health insurance policyholders (~1% of the population), who also have publicly provided healthcare coverage.[31]

Table 1 – Percentage of patients and follow-up time outside and within therapeutic range for INR among patients followed up for ≥3 mo with DVT diagnosis and outpatient INR measurement (n = 1912).

% of follow-up time, regarding therapeutic range	Mean (95% CI)
INR < 2	52.0 (50.5-53.6)
INR > 3	13.8 (13.0-14.6)
INR > 4	4.0 (3.6-4.4)
2 ≤ INR ≤ 3	34.3 (33.1-35.5)
% of patients, regarding therapeutic range	**n (%)**
Having INR < 2 at least once	1874 (98.0)
Having INR > 3 at least once	1260 (65.9)
% of patients, regarding time in 2 ≤ INR ≤ 3	**n (%)**
≥70%*	191 (10.0)
≥80%†	89 (4.7)

CI indicates confidence interval; DVT, deep vein thrombosis; INR, international normalized ratio.
* Patients who had ≥70% of follow-up time within the defined INR ranges.
† Patients who had ≥80% of follow-up time within the defined INR ranges.

The cost analysis included direct medical costs that were calculated on the basis of cost items related to outpatient visits, laboratory and radiological tests, hospitalizations/interventions, and inpatient drug treatments from the payer's perspective (only direct medical costs using prices of the SSI in Turkey). For drugs, retail prices from the updated price list and SSI's updated institution discount list were taken into account in the calculation of the unit costs.[32] Costs related to diagnostic tests were calculated using the Health Implementation Notification by SSI.[33] Physician visits costs were calculated by using unit prices based on the same SSI notification.[33] Hospitalization costs were calculated using unit prices based on the Healthcare Organization Price List in the Health Practice Declaration and Treatment Assist Practice Declaration.[33] Monetary results were converted using an exchange rate of $1.50 per Turkish lira. Direct nonmedical costs of different origin (transfers of patients and caregivers for examination and/or hospitalization, home care, etc) and indirect costs were not included in the cost analysis.

Statistical Analysis

Descriptive statistics were used to analyze data in accordance with the study's objectives. Data were expressed as the mean, 95% confidence interval (CI; lower and upper bounds), median, minimum and maximum, and percentage, where appropriate. Post hoc power analysis revealed a total 4.4% (±2.2) error margin based on the inclusion of 1912 patients.

Results

Annual INR Measurement (n = 1918)

Annual adjusted mean INR measurement count was 9.1 (95% CI 9.0-9.4) times among patients who were followed-up for 3 months or more.

Table 2 – Cost ($) of outpatient, inpatient, and total hospital admissions in patients followed up for >3 mo with DVT diagnosis and outpatient INR measurement.

TTR	Outpatient	Inpatient	Total
All patients (n = 1906)	571 (550-592)	2564 (2320-2808)	3143 (2894-3392)
TTR < 70%* (n = 1716)	571 (550-593)	2613 (2348-2878)	3192 (2922-3462)
TTR ≥ 70%† (n = 190)	578 (509-648)	2195 (1635-2756)	2785 (2199-3372)

Note. Results are given as mean (95% CI).
CI indicates confidence interval; DVT, deep vein thrombosis; INR, international normalized ratio; TTR, time in the therapeutic range.
* Patients who had <70% of follow-up time within 2 ≤ INR ≤ 3 range.
† Patients who had ≥70% of follow-up time within 2 ≤ INR ≤ 3 range.

Time in Therapeutic INR Range (n = 1912)

With regard to time outside of therapeutic range, patients had INR levels less than 2 in mean 52.0% (95% CI 50.5%-53.6%) of follow-up time, whereas INR levels were higher than 3 in 13.8% (95% CI 13.0%-14.6%) of follow-up time (Table 1). With regard to TTR, patients had INR levels of 2 to 3 in mean 34.3% (95% CI 33.1%-35.5%) of follow-up time (Table 1).

The percentage of patients who had 70% or more and 80% or more of follow-up in TTR (2 ≤ INR ≤ 3) was 10.0% and 4.7%, respectively. Of the 1912 patients, 98.0% had an INR less than 2 at least once and 65.9% had an INR higher than 3 at least once during the study period (Table 1).

Cost of Outpatient, Inpatient, and Total Hospital Admissions (n = 1906)

Per 4095 patient-year follow-up data for 1906 patients, the overall mean outpatient, inpatient, and total hospital admission costs were $571, $2564, and $3143, respectively. For patients who had 70% or more of follow-up time within the 2 ≤ INR ≤ 3 range, the mean outpatient, inpatient, and total hospital admission costs were $578, $2195, and $2785, respectively. For patients who had less than 70% of follow-up time within the 2 ≤ INR ≤ 3 range, the mean outpatient, inpatient, and total hospital admission costs were $571, $2163, and $3192, respectively (Table 2).

Discussion

Our findings for a retrospective cohort of patients who were followed-up for more than 3 months and who had outpatient INR measurements reveal INR monitoring of 9.1 times per year, whereas TTR (INR 2-3) composed only 34.3% of the follow-up period, with only 10.0% of patients spending 70% or more of follow-up time within the therapeutic INR range. Spending 70% or more, as opposed to less than 70%, of follow-up time within the therapeutic INR range was associated with lower direct medical costs.

In our study population, INR levels were outside the therapeutic range in 65.8% (INR < 2 in 52.0% and INR > 3 in 13.8%) of follow-up time, whereas TTR composed only 34.3% of the follow-up period. This seems to indicate poor warfarin control in our cohort, because a TTR of at least 60% is considered a benchmark to ensure high-quality warfarin anticoagulation.[16,24,25] Indeed, current European guidelines recommend efforts to achieve TTR of more than 70%.[23]

In addition, data from the Veterans Health Administration revealed that time from the onset of anticoagulation was a strong predictor of quality of anticoagulant therapy, with the mean TTR ranging from 48% in patients in the first 6 months of therapy to 61% in the treatment of experienced patients.[34]

In our analysis, TTR was evaluated in patients who were followed-up for at least 3 months. It therefore seems likely that the low TTR (34.3%) in our cohort is associated with the difficulty of reaching therapeutic INR, particularly within the initial period of treatment, and improvements in TTR in the later stages of VKA treatment.[17,35]

Similarly, data from the TROMBOTEK trial among patients with lower limb DVT in Turkey revealed the long-term efficacy and safety of once-daily enoxaparin plus warfarin for outpatient ambulatory treatment without significant bleeding risk, whereas the authors noted the failure of warfarin in keeping INR within effective limits starting with the first 3 months of long-term follow-up care.[36]

In a systematic review of 67 studies of 50 208 patients, TTR was also reported to vary depending on the anticoagulation management strategy, with values of 53.1% noted in usual care, 62.1% in anticoagulation clinics, 66.3% in clinical trials, and 71.5% in models with self-management strategy in warfarin studies.[37] In addition, retrospective studies for INR have been shown to be associated with inferior results regarding TTR achievement, compared with prospective studies and randomized controlled trials, which were associated with higher likelihood of regular and frequent follow-ups in prospective randomized trials.[13,38]

Less frequent INR monitoring was associated with poorer quality of oral anticoagulation, along with less than optimal INR and increased adverse events in patients without long-term stable INR control.[39–45] Given that TTR was achieved in only one-third of the follow-up times, with less than 10% of patients in the therapeutic range for 70% or more to 80% or more of follow-up time, our findings indicate a lack of stable INR in a remarkable percentage of patients. Notably, although an INR monitoring interval not exceeding 4 weeks in patients without stable INR is recommended,[39] the annual measurement frequency for INR was 9.1/year in our cohort. Therefore, besides the inclusion of initial treatment periods with a lower likelihood of TTR achievement, less frequent INR testing with longer INR recall intervals also seems to be associated with the low TTR noted in our cohort.

Poor warfarin control (TTR < 60%) was associated with increased mortality and adverse patient outcomes.[46] During the study period, warfarin was the only reimbursed anticoagulant in Turkey and thus all our patients were on warfarin therapy. Nonetheless, the difficulty in consistent maintenance of a target INR under warfarin therapy in our cohort highlights the potential risks associated with a subtherapeutic INR and the potential role of predicting potential warfarin TTR for an individual before considering the use of warfarin over other anticoagulants.[47–49]

The total direct medical costs per patient with DVT in our cohort ($3143) seems lower than healthcare costs associated with initial DVT or PE estimated at $3000 to $9500 in the United States, and approximately €2000 to €4000 in Europe.[7] Similar to our study, evaluation of in-hospital costs strictly related to VTE management in a past study among internal medicine patients in Italy also revealed a lower median economic cost for VTE of €1348.68 (range €838.57-€1876.82) compared with published data regarding whole hospitalization costs.[50]

Higher direct medical costs associated with inpatient ($2564) compared with outpatient ($571) admissions in our analysis support the conclusion that hospitalization costs are the main cost driver for patients with VTE, contributing to approximately half the total annualized costs per patient,[51] whereas a DVT is considered to add at least a mean cost of $7769 to a hospital stay.[52]

In accordance with standard operating procedures for ambulance services in Turkey, admission of our patients to other hospitals in the case of an emergency is quite likely. This might lead to an underestimation of costs related to disease complications. It should also be noted that the present cost analysis was based on direct costs per se and from the healthcare payer's perspective, whereas indirect costs comprised 12% to 22% of annual expenditures for VTE depending on the model studied[53] and indicated that there is potential total cost to society.[6]

Given that our cost analysis was based on expenditures for patients with more than 3 months of follow-up time, it seems notable to indicate that extended evaluation of VTE management was associated with a significant increase in estimated costs, with $5000 over 3 months, $10 000 over 6 months, and $33 000 after 1 year.[7] An increase was also noted in the annual cost per patient from $7590 to $33 200 for an initial episode of DVT[7,54] and from $11 419 to $15 000 for a recurrent event.[7,8,55,56] Moreover, long-term healthcare costs of postthrombotic syndrome complications were reported to represent approximately 75% of the total cost of managing an initial DVT event.[57]

In addition, per-patient costs for inpatient ($2613 vs $2195) and total ($3192 vs $2785) hospital admission were determined to be higher in our patients who had less than 70% versus 70% or more of follow-up time within the therapeutic INR range. This seems consistent with the 1.8-fold higher monthly medical costs (€143.6 [656.6] vs €80.3 [174.8]) and the higher monthly mean INR testing cost (€2.7 [1.9] vs €2.3 [1.1]) reported for inadequately controlled patients, compared with controlled patients, with nonvalvular atrial fibrillation under VKA therapy.[58]

It is suggested that the adoption of treatment strategies or protocols that affect the length of hospital stay and enable outpatient management could influence the immediate care and hospitalization costs of VTE populations.[9,50] Accordingly, our findings support the finding that hospital stays for DVT represent a substantial cost burden to the healthcare system.[55] This also highlights the importance of adequate VTE treatment in the inpatient setting and continued care via transition to thromboprophylaxis after discharge to avoid the need for subsequent hospital readmissions with subsequent poor outcomes and increased costs.[55]

Cost-effectiveness of novel target-specific oral anticoagulants depends on the quality of warfarin control,[59] with cost-effectiveness expected to be higher in patients with poor anticoagulation control rather than in patients with high-quality control.[59,60] The impact of novel target-specific oral anticoagulants on the reduction in hospital length of stay and frequency of INR monitoring was confirmed when compared against standard care, which likely offsets their higher acquisition cost.[9,61,62] Our findings therefore highlight the importance of compliance, monitoring, and follow-up along with timely intervention in poor anticoagulation by means of changes in warfarin dosage and administration,[63] as well as identifying patients with poor warfarin control as candidates for novel target-specific oral anticoagulants.[47–49,64]

Certain limitations to this study should be considered. First, because of the retrospective design of the study and the use of data from administrative databases and medical records, establishing the temporal relation between cause and effect, as well as the complete inclusion of all variables considered in a clinical decision, seems difficult. Second, lack of sufficient evidence that the findings are representative of the Turkish population seems another important limitation because of impossibility of drawing a generalization from a single-center study. Third, absence of data regarding subsequent INR measurements in the hospital database for a nonnegligible portion of patients is another potential limitation of the study, given that 1840 out of 4357 patients could be followed up only for 1 day. Fourth, lack of data regarding

potentially confounding variables with a likely effect on the ability to achieve a therapeutic INR such as diet, comorbidities, concomitant medications, and complications is another limitation that would otherwise extend the knowledge achieved in the present study. Finally, because of the exclusion of extreme value data (n = 4) from the analysis, the total medical care costs reported for the inpatient and outpatient subgroups are not the sums of the 2 stated components. Although the removal of outliers is based on the fact that these data points are not representative of the therapeutic INR range under study, potential implications of removing outliers for the validity (ie, sufficient evidence to support the cost relations) cannot be entirely discarded. Therefore, alongside the exclusion of externalities and patients with inappropriate INR records, a lack of sensitivity analysis, a lack of analysis regarding the robustness of the generated study results against the assumptions, and the missing data seem to be other important limitations of the study. Nevertheless, despite these certain limitations, our findings provide for the first time data on healthcare costs in patients with DVT with respect to TTR in Turkey, on the basis of an analysis of the database of a large tertiary care center specialized in cardiology and cardiovascular and thoracic surgery.

Conclusions

Our findings for a retrospective cohort of patients with DVT undergoing warfarin therapy reveal that only one-third of follow-up time is spent within the therapeutic INR range, along with an INR monitoring frequency of 9.1 times/year despite a lack of stable INR control in most of the patients. Overall, costs related to inpatient DVT management were higher than those related to outpatient management, whereas having 70% or more of follow-up time within the therapeutic INR range seemed to be more advantageous for inpatient costs than for outpatient costs. Affirming the significant contribution that hospital stay makes to the cost burden of DVT, our findings also highlight the role of adequate VTE treatment in the inpatient setting and the continued post-discharge care via transition to thromboprophylaxis, with close and regular INR monitoring decreasing the need for subsequent hospital readmissions and thus the likelihood of subsequent poor outcomes and increased costs.[8,55]

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