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ORIGINAL RESEARCH

Cost of hemophilia A in Turkey: an economic disease burden analysis

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ABSTRACT

Objective: Hemophilia A is the second most common bleeding disorder causing patients to have life-long follow-up and treatment. Despite being a rare disease, hemophilia A has a high economic burden on individuals and the public. The purpose of this study was to estimate the total disease cost of hemophilia A in Turkey.

Materials and Methods: Data used in this analysis were collected through literature review, including studies conducted in Turkey in December 2018. A disease burden analysis was performed by modeling hemophilia A-related costs among patients, their relatives, and the social security system. Two expert panels were held to evaluate real-world data sources and to provide further information. All direct medical and non-medical costs were calculated annually from the Social Security Institution of the Republic of Turkey perspective, while indirect costs were estimated from the patient and community perspective.

Results: For the calendar year of 2018, the number of hemophilia A patients in Turkey were estimated to be 5,055, with an average weight of 64.7 kg. The average annual direct medical, direct non-medical, and indirect costs of hemophilia A were calculated as €93,268 ($109,286; ₺502,717), €2,533 ($2,968; ₺13,655), and €7,957 ($9,323; ₺42,888) per patient, respectively, with a total annual cost of €103,759 ($121,578; ₺559,259). For the management of patients with inhibitors (4.9%), the average annual total cost was calculated to be €325,439 ($381,330; ₺1,754,117) per patient. The total annual disease burden of hemophilia A in 2018 was estimated to be about €524 million ($614 million; ₺2.82 billion), which corresponded to 1.6% of the total health expenditure in Turkey.

Conclusion: The most important reason hemophilia A has a significant economic burden in Turkey is that replacement therapy is expensive. The major cost contributor was identified as factor replacement therapy. With inhibitor development, the average annual cost increased more than 3-fold.

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Introduction

Hemophilia A is an X chromosome-linked bleeding disorder characterized by the deficiency of clotting factor VIII (FVIII). Hemophilia A has a recessive genetic pattern and is almost always seen in males. The general incidence of hemophilia A is 17.1 (14.8–19.3) in 100,000 male births[1]. Bleeding episodes involving joints and surrounding soft tissue constitutes the hallmarks of the disease and might lead to arthropathy in the long-term if insufficiently treated[2]. Randomized clinical trials and real-world evidence have demonstrated that prevention prevents joint bleeding and deterioration of joint status, and primary prevention with FVIII has, therefore, been recognized as the standard of care for individuals with severe hemophilia A in countries with adequate resources. Prophylactic therapy also reduces the incidence of central nervous system bleeds (intracranial and spinal hematoma), which are less common than joint bleeding but much more life-threatening. Additional advantages of prophylaxis vs. on-demand treatment include reduced hospitalizations and absenteeism from school or work, greater participation in social activities and, overall, improved health-related quality-of-life[3].

In developed countries, hemophilia A patients are expected to have a lifespan similar to that of the general male population[4]. Given the overall increase in life expectancy, anticipated new treatment modalities, including gene therapy, and a substantial cost associated with factor replacement, analysis of the economic burden of hemophilia A, is of importance for making reimbursement policy decisions[5,6].

The general health insurance system of the Social Security Institution of Turkey covers all citizens regardless of age or employment status. Private insurances in Turkey constitute less than 5% of all healthcare-related expenditure[7], while

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Social Security Institution covered 78% of all healthcare expenditure in 2018[8]. The sustainability of this public reimbursement model is therefore crucial with evidence-based guidance. The objective of this study was to provide an analysis of direct and indirect costs related to hemophilia A in Turkey from a social security perspective.

Materials and methods

Data sources

National tables and study reports were used where possible. The number of hemophilia A patients in 2018 was estimated based on the World Federation of Hemophilia 2010–2016 surveys[9–15] and Turkish Statistical Institute population information and projections[16,17]. Percent distributions of hemophilia A severity and prophylactic or on-demand factor replacement regimens along with annual rates of bleeding episodes, surgeries, and other hemophilia-related complications were calculated with previously reported results of pediatric and adult population studies in Turkey[18–26]. Additional data were obtained from studies reporting findings in patients with inhibitors[27]. Patients' weight was estimated using the Turkish Statistical Institute national health surveys and available literature on national pediatric anthropometry findings and age distribution of hemophilia A patients[14,28,29]. Rates of surgical procedures for the management of hemophilic arthropathy were estimated per year based on the available national study findings[21–23,30,31].

Healthcare practice service costs were calculated using the Official Health Notification (1 February 2019) of the Social Security Institution[32]. These services include inpatient and outpatient diagnostic tests and imaging, consultation, consumables, and surgical and medical intervention procedures. Medicine reimbursement costs were obtained from the registries and lists of the Turkish Medicine and Medical Device Agency and RxMedia Pharma database[33,34]. National hemophilia diagnosis and treatment guideline recommendations were used for schedules of factor treatment[35]. Factor utilization information for 2017 and 2018 in Turkey was obtained from IQVIA (Danbury, CT). Data regarding survival, employment, retirement, and wage and pension payments were obtained from the statistical annals 2017–2019 of the Social Security Institution[36]. Two panels with six local experts in the field were held in January 2019 to assess available data sources and provide practical insight and disease characteristics of hemophilia A patients in routine clinical practice. In addition to the fact that the participants of the expert panel were members of the Turkish Pediatric Hematology Association, and they were physicians who treat hemophilia in tertiary hospitals, the epidemiological data from the literature were also in the expert panel. Four of the experts are also the authors of this article. The last search for data sources was carried out in March 2019.

Definitions

The severity of hemophilia A was defined according to plasma levels of FVIII as mild (>5 to <40%), moderate (1–5%), and severe (<1%)[37]. The Social Security Institution reimburses prophylactic factor replacement (up to 4,500 IU/week) in severe hemophilia A and patients with more than three bleeding episodes per month[32]. Bleeding episodes and surgeries were classified as minor or major following national guidelines[38,39]. Prevention was not expected to be applicable in mild cases. Immune tolerance induction (ITI) treatment (50 IU/kg three times per week for a maximum duration of 1 year) is reimbursed for patients under the age of 11 years with a plasma FVIII activity ≤1% and an inhibitor level ≤10 Bethesda units/mL[32].

Cost analysis

Direct medical cost assessment was performed using the methodology provided by Cowley et al.[40]. Indirect disease-related costs were calculated for labor absenteeism of adult patients and caregivers, disability pensions, and early retirement or death[41,42]. Other direct costs were calculated for intercity travel and daily payments, the requirement of a professional caregiver, transportation, accommodation, meals during travels to healthcare facilities, and out-of-pocket medical expenses[41,42]. Mean values were calculated with available data sources for the calendar year of 2018. Cost calculations and analyses in TRY (₺) currency were carried out with Microsoft Excel 2016 (Microsoft Corporation; Redmond, WA). All monetary figures in Turkish, EU, and US currencies for international readership were also given (the 2018 exchange rate was 1€ = 5.39₺; 1$ = 4.60₺)[43].

Sensitivity analysis

To observe the effect of the variables included in the calculation on the analysis, the reflections of the ±10% changes in the values used in the basic analysis were investigated. A tornado graphic was used to compare the effects of one-way sensitivity analysis.

Results

Epidemiology and patient characteristics

The prevalence of hemophilia A in Turkey was previously reported to be 8.9–12.5/100,000 in the male population[9–15]. The number of hemophilia A patients in 2018 in Turkey was estimated to be 5,055. The number of adult patients was calculated to be 3,148 (62.3%). The average age was estimated to be 25, and the mean patient weight was 64.7 kg. The number of patients and mean weight estimates per age group are presented in Table 1.

Hemophilia A severity was mild in 30%, moderate in 15%, and severe in 55% of patients. Of all hemophilia A patients, 52.3% were estimated to be on prophylactic FVIII treatment, 4.9% to be patients with inhibitor, and 2.6% to be with inhibitor and on prophylactic regimens with bypassing agents. Prophylactic treatment was found to represent 86% and 33% of factor replacement regimens in severe and moderate disease, respectively. Rates of radiosynovectomy,

Table 1. Number of hemophilia A patients and mean patient weights in Turkey, 2018.

	Age groups					Overall
	0–4 years	5–13 years	14–18 years	19–44 years	45 years and older	
Male population, *n*	3,327,780	6,518,785	3,299,449	16,012,457	11,981,509	41,139,980
Hemophilia A patients, *n* (% in total)	301 (6.0)	983 (19.4)	623 (12.3)	2,372 (46.9)	776 (15.4)	5,055 (100.0)
Mean weight, kg	13.6	31.3	68.9	79.6	78.0	64.7

Table 2. Estimates for annual hospitalization requirements and bleeding rates of hemophilia A patients.

Hemophilia A patients ($n = 5,055$)	Hospitalization rate (%) (average length of hospital stay-days)
Hemarthrosis	49.0% (2 days)
Muscle bleeding	3.5% (3 days)
Intracranial hemorrhage	1.7% (17 days)
Throat and neck bleeding	7.5% (14 days)
Gastrointestinal bleeding	3.9% (13 days)
Urinary tract bleeding	5.3% (4 days)
Deep laceration	4.0% (6 days)
Major surgery	4.0% (10 days)
Minor surgery	60.0% (2 days)
Central venous catheter placement	0.7% (1 day)
Bleeding episodes (%)	
Major bleeding	22.1%
Minor bleeding	59.9%

arthroscopic synovectomy, and arthroplasty in 1 year were calculated to be 5.1%, 1.6%, and 5.3%, respectively. The annual mean number of bleeding episodes was four in patients on prophylaxis treatment, whereas it was seven bleeding episodes in patients treated on-demand. It was estimated that 59.9% and 22.1% of hemophilia A patients would annually develop a minor and major bleeding episode, respectively. Annual rates of hospitalization requirements and bleeding episodes are presented in Table 2.

Direct medical costs

Clotting factors and other medications

Management of a major bleeding episode or major surgery was found to require 960 IU/kg of factor VIII, which corresponds to an average cost of €12,874 ($15,085; ₺69,393) per major episode/surgery for a treatment duration of 10 days. The average cost of factor replacement for a minor bleeding episode or surgery was calculated to be €2,337 ($2,738; ₺12,596) for a treatment duration of 2–3 days.

The annual mean number of prophylactic infusions was calculated to be 127.3 per patient, with a mean factor dose of 30 IU/kg (maximum 4,500 IU per infusion). Cost of factor VIII was found to be €0.32/IU (0.37 $/IU; 1.71 ₺/IU) and average prophylactic factor replacement cost per patient was calculated to be 63,227 €/year (74,086 $/year; 340,796 ₺/year).

For the prophylactic management of patients with inhibitors, it was calculated that aPCC was used in 85% of patients and rFVIIa in 15%. The average bypassing agent dose was estimated to be 85 units/kg every other day, and the average cost was found to be 0.95 €/unit (1.11 $/unit; 5.10 ₺/unit). The annual average cost of prophylactic treatment in a hemophilia A patient with inhibitor was calculated to be €319,663 ($374,561; ₺1,722,981). rFVIIa was utilized in 97.6% of the cases with inhibitors for the management of bleeding episodes. The average bypassing agent cost was calculated as €19,162 ($22,452; ₺103,281) for every bleeding episode or surgery. ITI treatment was found to be applicable in 0.3% of hemophilia A patients as per reimbursement criteria. Cost of annual ITI treatment was calculated to be €61,542 ($72,111; ₺331,710). Additional annual average cumulative medication costs of tranexamic acid, desmopressin, analgesics, topical antiallergic medications, and fibrin sealant were estimated to be €55.12 ($61.07; ₺280.9) per patient. Mean annual total cost of medications administered to a hemophilia A patient was calculated to be €91,858 ($107,634; ₺495,116).

Management of further complications

Surgeries, rehabilitation procedures, and medical treatments for seizure neuropathic pain, and chronic hepatitis were considered for the cost calculation of hemophilia A-related complications other than inhibitor development. The cumulative cost was 660 €/year (773 $/year; 3,558 ₺/year) on average per patient.

Other medical costs

Additional average costs of admissions and other medical procedures were calculated to be 853 €/year (1,000 $/year; 4,600 ₺/year) for a patient with inhibitor and 836 €/year (980 $/year; 4,508 ₺/year) for a patient on prophylactic regimen.

Direct non-medical costs

Intercity travel and daily payments

Patients in Turkey are eligible for a daily payment from the Social Security Institution for intercity travels required for medical care. It was estimated that 53% of hemophilia A patients received medical care within their home city, while 47% needed transportation to a medical facility in another city. The total intercity travel and daily payments for hemophilia A patients were estimated to be 58,408 €/year (68,439 $/year; 314,820 ₺/year).

Informal and professional caregivers

It was estimated that 55% of hemophilia A patients were accompanied by an informal caregiver during their hospital visits. Cumulative payment loss of caregivers was calculated to be 2,007,513 €/year (2,352,282 $/year; 10,820,497 ₺/year). The expert panel estimated that 5% of hemophilia A patients require a full-time professional caregiver. The average professional caregiver cost was found to be 361€/month (423 $/month; 1,945 ₺/month) and the overall cost of caregiver

wage was calculated to be 606,234 €/year (710,348 $/year; 3,267,600 ₺/year).

Transportation, meals, and accommodation

The average weighted one-way travel distance was calculated to be 485 km. The transportation cost of hemophilia A patients was estimated to be 5,967,747 €/year (6,992,643 $/year; 32,166,158 ₺/year).

On average, a hemophilia A patient requiring intercity transportation to a medical facility was estimated to have spent 36 days on outpatient visits, necessitating 2 days of hotel stay. Cumulative cost of meals was calculated to be 31,959 €/year (37,448 $/year; 172,260 ₺/year) and accommodation cost was 89,927 €/year (105,370 $/year; 484,704 ₺/year).

Out-of-pocket expenses

Patients in Turkey need to pay a portion of their healthcare expenses, subject to service and type of healthcare facilities and medication requirements. Total cost of out-of-pocket expenses of hemophilia A patients was calculated to be 1,905,707 €/year (2,232,991 $/year; 10,271,760 ₺/year).

Indirect costs

Early retirement and disability pension

The average retirement age in Turkey was found to be 52.6 years, and the average pension was 358 €/month (419 $/month; 1,927 ₺/month). It was estimated that 9% of hemophilia A patients would retire early at the mean age of 41.0 years, resulting in an average productive loss of 12 years per patient. Cost of pension payments and tax revenue loss was calculated to be 3,265 €/year (3,826 $/year; 17,601 ₺/year) per an early retired hemophilia A patient and cumulative public cost was 15,959,861 €/year (18,700,794 $/year; 86,023,651 ₺/year).

Nine percent of hemophilia A patients were estimated to receive a disability pension per social security laws. The total annual cost of disability pension payments to hemophilia A patient was estimated to be €729,685 ($855,000; ₺3,933,002).

Labor absenteeism

The overall employment rate of hemophilia A patient was estimated to be 53%. The mean number of working days missed for an adult patient or a parent of a pediatric patient due to the medical management of hemophilia A was calculated to be 98.4 days/year. When calculated based on the legal minimum wage, the cumulative public cost of labor absenteeism was calculated to be 19,692,640 €/year (23,074,637 $/year; 106,143,331 ₺/year). Cumulative payment loss of employed hemophilia A patients was calculated to be 437,166 €/year (512,245 $/year; 2,356,326 ₺/year).

Early death

While it was expected that the average life expectancy of a hemophilia A patient would be similar to the overall national life expectancy, hemophilia A patients with inhibitors would have a 1.6-times higher risk of death. On average, a patient with an inhibitor was expected to lose 15 years of lifespan. A hemophilia A-related early death was expected to result in a 25% decline in family income. Overall cost of income loss due to early deaths was estimated to be 2,855,691 €/year (3,346,125 $/year; 15,392,174 ₺/year).

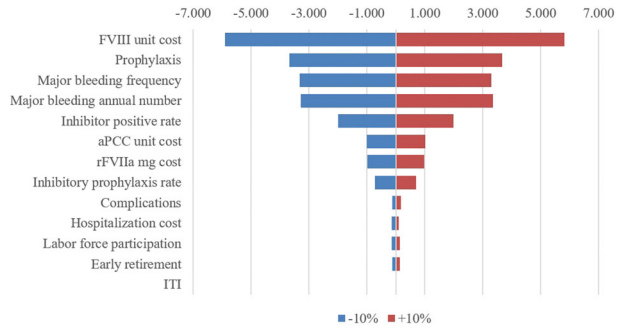

Figure 1. One-way sensitivity analysis.

Sensitivity analysis

The variables that had the highest impact on the results were determined as the FVIII unit cost, the rate of patients treated with prophylaxis, the incidence and annual incidence of major bleeding and the inhibitor positive patient rate, respectively, in one way sensitivity analysis. aPCC and FVIIa unit costs were found to be similarly effective in the analysis, followed by the rate of prophylaxis and frequency of complications used in inhibitor-positive patients (Figure 1).

Total cost of hemophilia A

The total direct medical cost of hemophilia A was found to be 93,268 €/year (109,286 $/year; 502,717 ₺/year) per patient, 75,120 €/year (88,021 $/year; 404,896 ₺/year) per patient on prophylactic therapy, and 310,682 €/year (364,038 $/year; 1,697,574 ₺/year) per patient with inhibitor, whilst total direct non-medical cost was 2,533 €/year (2,968 $/year; 13,655 ₺/year) and indirect cost was 7,957 €/year (9,323 $/year; 42,888 ₺/year) per patient. Overall average annual cost of hemophilia A was estimated to be €103,759 ($121,578; ₺559,259) per patient, of which €95,802 ($112,255; ₺516,371) (93%) was for direct costs, while €91,806 ($107,573; ₺494,835) (88.5%) was the cost of factor VIII and bypassing agents (Table 3). Besides, the annual cost of hemophilia A stratified by severity is shown in Table 4.

The total annual economic burden of hemophilia A in 2018 was estimated to be €524,499,645 ($614,576,758; ₺2,827,053,087), corresponding to 1.6% of the estimated total health expenditure in Turkey.

Discussion

This study was conducted to analyze the annual direct and indirect costs of hemophilia A in Turkey. To the best

Table 3. Annual average direct and indirect costs of hemophilia A per patient (2019).

Direct medical costs	EUR (€)	US ($)	TRY (₺)
Medications	91,859	107,635	495,120
Factor VIII replacement	68,623	80,408	369,878
Bypassing agents	23,183	27,165	124,957
Other	53	62	285
Complications	660	774	3,558
Other	749	878	4,038
Subtotal for direct medical costs	93,268	109,286	502,717
Direct non-medical costs			
Intercity travel and daily payments	12	14	62
Caregivers	940	1,102	5,067
Transportation	1,181	1,383	6,363
Meals	6.3	7.4	34
Accommodation	18	21	96
Out-of-pocket expenses	377	442	2,032
Subtotal for direct non-medical costs	2,533	2,968	13,655
Subtotal for direct costs	95,802	112,255	516,371
Indirect costs			
Early retirement	3,265	3,826	17,601
Disability pension	144	169	778
Labor absenteeism	3,982	4,666	21,464
Early death	565	662	3,045
Subtotal for indirect costs	7,957	9,323	42,888
Total	103,759	121,578	559,259

knowledge of the authors, this is the first comprehensive economic analysis of hemophilia A management in Turkey, and the overall cost was estimated to be over €524 million ($614 million; ₺2.82 billion). As a comparison, the economic burden of cardiovascular diseases in Turkey, affecting 3.4 million patients in 2016, was calculated to be €9.2 billion Intercity travel and daily payments[44]. This comparison indicates that the total cost of hemophilia A per patient was about 38-times higher. Hemophilia A-related direct medical cost per patient was also found to be more than 250-times the average health expenditure per capita of about €359 ($420; ₺1,935) in 2018[8]. Labor and school absenteeism, early retirement, and complications were also considered a considerable social burden on patients.

Previous reports from Europe have highlighted the high cost associated with optimal hemophilia A management. While these studies differ in their cost calculation models and included expense items, the annual medical cost of hemophilia A was usually found to be within a range of €40,000–100,000 per patient[45–47]. In studies that have included direct and indirect cost analyses, clotting factor concentrates accounted for up to 90% or more of overall hemophilia A-related costs[46–51].

The BURQoL-RD study on hemophilia provides an update of patients' QoL, and for the first time in Italy, offers an estimation of average total unit cost from the social perspective. This study also shows a significant relationship between age and QoL and costs other than drugs. Assuming a society perspective, the estimated mean annual total cost per patient in 2012 is €117,732. Drugs represent 92% of total costs[52].

Our findings are in line with these reports that the overall average cost per patient associated with hemophilia A was about €103,759 ($121,578; ₺559,259) per year, and expenses on clotting factors represented 88.5% of it. It should be noted that medical costs other than medications accounted for only 1.5% of direct medical costs. This finding should be interpreted within the dominant public nature of both

Table 4. Annual cost of hemophilia A stratified by severity (2019).

Hemophilia A patients ($n = 5,055$)	Mild ($n = 1,517$)			Moderate ($n = 758$)			Severe ($n = 2,780$)		
	EUR (€)	US ($)	TRY (₺)	EUR (€)	US ($)	TRY (₺)	EUR (€)	US ($)	TRY (₺)
Subtotal for direct medical costs	8,349,467	9,783,397	45,003,625	39,434,246	46,206,650	212,550,588	423,687,941	496,451,739	2,283,678,000
Subtotal for direct non-medical costs	415,135	486,429	2,237,575	1,909,399	2,237,318	10,291,661	10,481,479	12,281,559	56,495,172
Subtotal for indirect costs	2,531,955	2,966,790	13,647,235	5,248,140	6,149,451	28,287,475	32,441,884	38,013,425	174,861,756
Total	11,296,556	13,236,616	60,888,436	46,591,785	54,593,418	251,129,723	466,611,304	546,746,724	2,515,034,929

healthcare and reimbursement systems in Turkey, with relatively low prices associated with hospital services and the absence of high physician charges.

Our results indicate that medical treatment of hemophilia A with inhibitors is more than 4-times more costly than the cost of hemophilia A prophylaxis without inhibitor development. Similarly, higher costs for hemophilia A with inhibitors were reported repeatedly[6,46,47,53–57]. More frequent bleeding episodes, higher cost of bypassing agents, and potential eligibility for ITI therapy could explain the additional expenses associated with hemophilia A with inhibitor development[27,47,55].

Direct non-medical costs were found to be 2.4% of the total cost in our study. Transportation was the highest non-medical direct cost. This could be explained by the finding that about half of all hemophilia A patients needed to travel for healthcare services, probably with the intent of access to specialist care, with long travel distances. This finding is consistent with earlier reports indicating that transportation is the major non-medical direct cost for hemophilia A patients[49]. Labor absenteeism was the highest indirect cost of hemophilia A, a finding which is also similar to previous results[48,49].

Optimal clinical management of hemophilia A should be considered the desired achievement to optimize costs and decrease disease burden on patients and caregivers. Prophylaxis should be initiated in severe hemophilia A, and bleeding episodes should be prevented rather than treated with factor replacement in emergency services. Less frequent bleeding episodes, in turn, would decrease absenteeism and burden on the social security system. Increased factor costs associated with prevention could be balanced by avoiding direct and indirect costs of managing bleeding episodes and complications[58,59]. The non-economic benefit of this approach would be improved quality-of-life for patients along with their caregivers and families[60,61]. Compliance with factor replacement regimens must be optimized as well to fully actualize these expected benefits. Compliance should be the key aspect of patient training programs[62,63]. Training should additionally cover education on lifestyles, psychosocial needs, and the living environment of the patient and caregiver. Multidisciplinary training environments where social service specialists, psychologists, nurses, physiotherapists, dentists, and clinicians work together should be established. This multidisciplinary approach would also help avoid caregiver burnout[64].

Our study has several strengths as well as limitations. We used observational or official data representing Turkey for the main parameters of patient demographics, disease characteristics, and cost calculations where available. While we did not undertake a patient-level data collection, available data sources were deemed sufficient to draw a reliable picture of hemophilia A management in Turkey. Estimates from the expert panels were limited to subgroup features, daily living and occupational activities, and associated calculations. From the social security and public reimbursement system perspective, we consider that this methodology provided accurate findings of average cost per patient and national economic impact. An additional economic evaluation of patient subgroups could be performed in the future with prospective designs using metrics such as disability-adjusted life years. With the introduction of new treatment options for hemophilia A, comparative cost-effectiveness analyses would be of value for making rational reimbursement decisions and optimizing treatment-related budget effects. Alternative reimbursement models, such as risk-sharing agreements with the pharmaceutical industry, could benefit from lower medication costs.[65]

Conclusion

While classified as a rare disease, the economic impact of hemophilia A is significant on the social security system of Turkey. The key driver of cost is clotting factor replacement, and inhibitor development drastically increases the overall cost. We hope that our findings will contribute to patient support, resource allocation, and reimbursement strategies in Turkey to better hemophilia A patients experiences.

Transparency

Declaration of funding

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MCA has received research funding from Pfizer, Roche, Novartis, and Bayer, and is a member of the board of directors/speaker's bureau/advisory committee for Roche, Takeda, Pfizer, Novo Nordisk, Novartis, Sanofi-Genzyme, CSL Behring, Octapharma, and Bayer.

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Previous presentations

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