

Estimated Prevalence of Venous Thromboembolism in Iran: Prophylaxis Still an Unmet Challenge

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Background: Inappropriate thromboprophylaxis is a serious problem in Iran. Venous thromboembolism (VTE) is one of the most important causes of morbidity in patients in surgical and obstetrics departments and intensive care units (ICUs). It is a leading preventable cause of mortality among in-patients. This study was designed to determine the prevalence of VTE and its epidemiology in an Iranian population for the first time.

Materials and Methods: There is no national registry system for keeping VTE records in Iran. To statistically calculate the annual prevalence of VTE, we used the prevalence of VTE in presence of each VTE predisposing condition and the annual prevalence of each VTE predisposing condition in Iran.

Results: The average annual number of total adult patients with predisposing conditions of deep vein thrombosis (DVT) in Iran was 5,288,272 people. The mean annual prevalence of DVT in Iran was between 686,928 and 2,089,738 cases. The mean annual prevalence rate of DVT among the hospitalized Iranian adult patients with the risk of DVT was approximately between 129.90 and 395.16 cases per 1000 patients.

Conclusion: The mean annual prevalence of DVT among the hospitalized Iranian adult patients not receiving prophylaxis is high. We also found that appropriate prophylaxis was provided for less than half the patients in need.

Key words: Venous thromboembolism, Prophylaxis, Prevalence, Iran

INTRODUCTION

Venous thromboembolism (VTE) is one of the most important causes of morbidity in medical, surgical, and obstetrics patients as well as those in the ICUs. It is a leading preventable cause of mortality among in-patients (1). Pulmonary embolism alone is the third most common cause of death from cardiovascular diseases after coronary artery disease and stroke (2). In 2006, the overall prevalence of VTE in the general population of the United States was 422 per 100,000 and it is estimated to reach 567 per 100,000 people in 2050 (3).

Up to 70% of VTE cases can be asymptomatic (4). Moreover, around 6% of cases of DVT and 12% of cases of pulmonary embolism lead to death within one month of

diagnosis (5). Notwithstanding, VTE is treatable and its complications can be avoided safely. Currently, there are many VTE prophylaxis guidelines available. Unfortunately, the guidelines are not utilized properly and many patients with the risk of VTE, who are in need of thromboprophylaxis, do not receive appropriate prophylaxis (6).

More than 10 centuries ago Avicenna described DVT (7), but Virchow was the first to mention the three factors contributing to thrombosis namely hypercoagulability, hemodynamic changes (stasis or turbulence) and endothelial injury and/or dysfunction. These 3 factors are now known as Virchow's triad (8).

Recognizing the epidemiology of VTE is fundamental in its management. This study was designed to determine the prevalence of VTE and its epidemiology in an Iranian adult population.

MATERIALS AND METHODS

There is no national registry system for keeping VTE records in Iran. Therefore, to statistically calculate the annual prevalence of VTE in case of no prophylaxis, we used the prevalence of VTE in presence of each VTE predisposing condition and the annual prevalence of each VTE predisposing condition in Iran.

On the basis of Virchow's triad, prevalent conditions that predispose patients to VTE include major general surgery, major orthopedic surgery, spinal cord injury, hip fracture, multiple trauma, malignancy, myocardial infarction, congestive heart failure, respiratory failure (1, 9), obesity, immobility, varicose veins, pregnancy and puerperium, oral contraceptive use, specific hereditary conditions (9), vascular surgery, gynecologic surgery, thoracic surgery, neurosurgery, long-distance travel and critical care (1).

Prevalence of asymptomatic DVT in each VTE predisposing condition

We searched the medical literature for studies reporting the prevalence of VTE in presence of each VTE predisposing condition published in the past 10 years. We searched PubMed for every predisposing condition associated with the words "venous thromboembolism" and "prevalence". The most formal reference we found about the VTE prevalence was the 2008 guideline for the prevention of VTE published by the American College of Chest Physicians (1).

Objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis by Geerts et al.(1) yielded the results, which we used as the basis of our study. Since VTE can be asymptomatic in 70% of the cases (4), and considering the high prevalence of VTE without any thromboprophylaxis, we used these data to achieve practical results. The most important predisposing conditions for DVT and prevalence of DVT in presence of

each condition, according to Geerts et al (1), are described in Table 1.

Table 1. Approximate risks of DVT in hospitalized patients^a (1)

Patient group	DVT prevalence (%)
Medical patients	10-20
General surgery	15-40
Major gynecologic surgery	15-40
Major urologic surgery	15-40
Neurosurgery	15-40
Stroke	20-50
Hip or knee arthroplasty and HFS	40-60
Major trauma	40-80
Spinal cord injury	60-80
Critical care patients	10-80
Vascular surgery	15-25
Thoracic surgery ^b	18-51
Coronary artery bypass surgery ^c	16-48

a: All rates except for thoracic surgery and coronary artery bypass surgery are based on objective diagnostic screening for asymptomatic DVT in patients not receiving thromboprophylaxis.

b: Thoracic surgery rate is based on objective diagnostic screening for asymptomatic DVT, but thromboprophylaxis received by patients is not clarified.

c: Coronary artery bypass surgery rate is based on objective diagnostic screening for asymptomatic DVT and in patients receiving thromboprophylaxis.

DVT: Deep vein thrombosis, HFS: Hip fracture surgery

Annual prevalence of each VTE predisposing condition in Iran

To estimate the annual prevalence of each VTE predisposing condition in Iran, we presented to the Department of Statistics and Information Technology (DSIT) of Deputy of Treatment of Iran's Ministry of Health and Medical Education and requested the abovementioned statistics in the past three years. To find out about the population of Iran, we presented to the Statistical Centre of Iran. Statistical Centre of Iran is an official institute affiliated to the Iran's government vice-presidency for strategic planning and supervision. It is the official reference of statistical information dissemination in Iran. According to the Statistical Centre of Iran, the population of the country in the years of 2010, 2011, and 2013 was 74,232,843, 75,149,669 and 76,066,495, respectively (10, 11).

RESULTS

According to the DSIT records, the statistics of hospitalized Iranian adult patients with the risk of DVT, on the basis of categories defined by Geerts et al. (1), are listed in table 2. The average annual number of total adult patients with DVT predisposing conditions in Iran was 5,288,272. Using statistical calculation, approximate

prevalence of DVT in presence of each predisposing condition in the hospitalized Iranian adult patients in case of receiving no prophylaxis can be estimated as listed in table 3. The mean annual prevalence of DVT in Iran was between 686,928 and 2,089,738 cases. Gynecologic surgery patients were the group with the highest annual DVT rate in these series (minimum of 243,074 and maximum of 648,197 patients annually).

The annual prevalence rates of DVT among the hospitalized Iranian adult patients at risk of DVT, all hospitalized adult patients and general population are listed in table 4. The mean annual prevalence rate of DVT

among the hospitalized Iranian adult patients at risk of DVT was approximately between 129.90 and 395.16 cases per 1000 patients. The approximate mean annual prevalence rate of DVT in all hospitalized Iranian adult patients was between 83.24 and 253.23 cases per 1000 patients. The mean annual prevalence rate of DVT in the Iranian general population was estimated to be between 914.08 and 2,780.77 cases per 100,000 people. Since up to 70% of DVT cases can be asymptomatic (4), approximate annual prevalence rate of symptomatic DVT in the Iranian population is listed in table 5.

Table 2. Number of hospitalized Iranian adult patients with the risk of DVT

Patient group	Number of cases in three years		
	2010	2011	2012
Medical patients	1,489,771	1,631,490	1,356,970
General surgery	1,104,401	1,128,439	962,473
Major gynecologic surgery	1,577,426	1,768,853	1,515,196
Major urologic surgery	175,249	187,435	173,837
Neurosurgery	145,059	156,206	145,007
Hip or knee arthroplasty and HFS	526	1,068	940
Critical care patients	647,435	742,018	604,319
Vascular surgery	12,341	12,612	11,883
Thoracic surgery	14,336	15,726	14,487
Coronary artery bypass surgery or open heart surgery	85,081	103,923	80,308
Total	5,251,625	5,747,770	4,865,420

DVT: Deep vein thrombosis, HFS: Hip fracture surgery

Table 3. Approximate prevalence of DVT among the hospitalized Iranian adult patients in three years

Patient group ^a	2010		2011		2012	
	Min.	Max.	Min.	Max.	Min.	Max.
Medical patients	148,977	297,954	163,149	326,298	135,697	271,394
General surgery	165,660	441,760	169,266	451,376	144,371	384,989
Major gynecologic surgery	236,614	630,970	265,328	707,541	227,279	606,078
Major urologic surgery	26,287	70,100	28,115	74,974	26,076	69,535
Neurosurgery	21,759	58,024	23,431	62,482	21,751	58,003
Hip or knee arthroplasty and HFS	210	316	427	641	376	564
Critical care patients	64,744	517,948	74,202	593,614	60,432	483,455
Vascular surgery	1,851	3,085	1,892	3,153	1,782	2,971
Thoracic surgery ^b	2,580	7,311	2,831	8,020	2,608	7,388
Coronary artery bypass surgery or open heart surgery ^c	13,613	40,839	16,628	49,883	12,849	38,548
Total	682,296	2,068,307	745,268	2,277,983	633,221	1,922,925

a: All cases except for thoracic surgery and coronary artery bypass surgery are estimated in case of no thromboprophylaxis.

b: Thoracic surgery cases are estimated according to undetermined thromboprophylaxis conditions.

c: Coronary artery bypass surgery cases are estimated in case of receiving thromboprophylaxis.

DVT: Deep vein thrombosis, HFS: Hip fracture surgery, Min: Minimum, Max: Maximum

Table 4. Approximate prevalence rate of DVT in the Iranian population in three years

DVT prevalence	2010		2011		2012	
	Min.	Max.	Min.	Max.	Min.	Max.
Per 1000 hospitalized adult patients at risk of DVT	129.92	393.84	129.66	396.32	130.15	395.22
Per 1000 hospitalized adult patients	85.01	257.71	82.96	253.57	81.73	248.19
Per 100,000 general population	919.13	2,786.24	991.71	3,031.26	832.46	2,527.95

DVT: Deep vein thrombosis, Min.: Minimum, Max.: Maximum

Table 5. Approximate prevalence rate of symptomatic DVT in the Iranian population in three years

Symptomatic DVT prevalence	2010		2011		2012	
	Min.	Max.	Min.	Max.	Min.	Max.
Per 1000 hospitalized adult patients at risk of DVT	38.98	118.15	38.90	118.90	39.04	118.57
Per 1000 hospitalized adult patients	25.50	77.31	24.89	76.07	24.52	74.46
Per 100000 general population	275.74	835.87	297.51	909.38	249.74	758.39

DVT: Deep vein thrombosis, Min: Minimum, Max: Maximum

DISCUSSION

To our knowledge, this is the first study to estimate the prevalence of VTE among the Iranian population. Our findings are compatible with those of Deitelzweig et al, who estimated the annual prevalence rate of symptomatic VTE in the general population of the United States to be 432 and 453 per 100,000 people in 2010 and 2015, respectively (3).

Meanwhile, other studies in the United States, Australia, Norway, and Korea have reported different results showing that VTE, DVT and pulmonary embolism have annual prevalence rate ranges of 13.8 to 117, 5.31 to 98, and 7.01 to 34 per 100,000 general population, respectively (12-15). This discrepancy might be related to race differences, age standardization, the date of studies and operator-dependent diagnostic methods. Because of our statistical method of calculation and lack of information about the exact age of cases provided by DSIT, age standardization was not possible. Moreover, our study is based on statistical estimation in case of no prophylaxis, while the abovementioned studies included actual cases.

Although the prevalence of VTE in gynecologic patients is not the highest among different patient groups, considering the great number of gynecologic surgeries and the high rate of Cesarean sections which account for 35% of

total deliveries in Iran - twice the maximum rate accepted by the WHO (16)- it seems reasonable to argue that Iranian gynecologic patients deserve much more attention and even a special guideline for VTE prophylaxis.

Orthopedic surgery is one of the most important predisposing conditions to VTE (17). Hip and knee arthroplasty and hip fracture surgery as the most immobilizing orthopedic surgeries are accounted as VTE predisposing factors (1). Although isolated lower-extremity injuries distal to knee are accounted as a VTE risk factor in the 2008 guideline for prevention of venous thromboembolism published by the American College of Chest Physicians (1), we were unable to use the data provided by the Iranian Ministry of Health in this regard. That is because the accurate statistics of cases of hip or knee arthroplasty, hip fracture surgery and isolated lower-extremity injuries distal to knee are not reported separately and are included in overall statistics of hospitalization in orthopedic wards and may be even more than what is indicated in table 2. We need statistics of isolated cases of lower-extremity injuries distal to knee in the Iranian hospitals for calculation of asymptomatic DVT cases based on the results of 2008 guidelines by Geert et al. (1). DSIT reports 461,162, 508,507 and 457,111 orthopedic cases in years of 2010, 2011, and 2012, respectively which include

cases of isolated lower-extremity injuries distal to knee. This amount of orthopedic cases indicates the serious need for specific attention to VTE prophylaxis and field guided registry in Iran.

The highest prevalence rate of DVT among patient groups belongs to patients with spinal cord injury (SCI) (1). Rahimi-Movaghar et al. showed in a population based study in Tehran city, that the estimated annual prevalence of traumatic SCI was 4.4 new cases per 100,000 general population and its point prevalence was 44 per 100,000 people; but DSIT does not have any specific records on SCI. According to their findings, it can be estimated that the prevalence of asymptomatic DVT related to traumatic SCI is 26.4 to 35.2 cases per 100,000 Iranian general population (18).

Studies on the prevalence of VTE in transplantation patients are scarce. Solid organ transplantations not only have a VTE risk similar to major surgeries, but many of them seem to carry specific VTE risks because of particular characteristics of organs transplanted. Prevalence of symptomatic VTE in lung transplantation recipients ranges from 8% to 22% (19). Additionally, Burns and Iacono have found pulmonary thromboembolism in 27% of autopsies of the lung and heart-lung transplant recipients (20). The prevalence of VTE in renal transplantation recipients has been reported to vary from 0.6% to 25% (21). It has also been reported that the prevalence of intraoperative pulmonary embolism in liver transplantation is 4% (22). According to DSIT records, a total annual number of 5,413 solid organ transplantations are performed in Iran. These data indicate the need for special attention to thromboprophylaxis in transplantation as a VTE risk factor.

Despite the existence of major guidelines on VTE prophylaxis, it is still a leading preventable cause of mortality among in-patients (1). A large number of patients are missed according to the VTE prevention guideline recommendations (23). Although there are no clinical trials to be used as reference, it is known that many of these patients need thromboprophylaxis (24). The

abovementioned shortcomings lead researchers to different VTE risk assessment models and subsequently, lead physicians to different practical results. Bikdeli et al. have shown that Goldhaber's risk assessment model and Harinath and St. John's risk assessment models detect only 59.85% and 68.46% of patients at-risk of VTE, respectively in comparison with the guidelines of the American College of Chest Physicians (8th edition) (25).

There is a significant difference in VTE prophylaxis practice among different countries (23). At least in developing countries, VTE prophylaxis guidelines like the one by the American College of Chest Physicians are not being implemented correctly (26). Although thromboprophylaxis guidelines are being applied in Iran, appropriate prophylaxis (in terms of correct type of regimen, dosing, and duration) is given only to 47.60% of patients prone to VTE (27). Under-prophylaxis and over-prophylaxis are major issues related to VTE in developing countries including Iran (23). In a study in an Iranian university hospital, we demonstrated that only 63.40% of patients in need of VTE prophylaxis received it (27). This is consistent with the findings of Heidarnezhad et al, demonstrating under-prophylaxis in Tabriz university hospital wards even in the ICUs (28). Mokhtari et al. demonstrated that on the basis of the American College of Chest Physicians' guidelines (8th edition), only 78.8% of patients in need of thromboprophylaxis in the Middle Eastern hospitals receive thromboprophylactic drugs (26).

Moreover, over-prophylaxis is not uncommon in Iran and developing countries. Administration of thromboprophylaxis in patients not in need of it can lead to serious complications. In the Middle Eastern hospitals, 66% of patients with any contraindications to thromboprophylaxis and 78% of patients who do not require any thromboprophylaxis receive inappropriate prophylaxis (26).

CONCLUSIONS

Evidence suggests that appropriate prophylaxis is not received by all patients in need of it resulting in high

prevalence of VTE in Iran. This indicates VTE as a considerable cause of morbidity in the Iranian Hospitals.

Presently, there is no national VTE registry system in Iran. A national registry system based on ICD codes is a basic requirement for evaluating the prevalence of VTE and deciding on how to deal with it. In addition to the urgent need for such a registry system, solving the problems related to under-prophylaxis and over-prophylaxis requires a synchronized guideline-based protocol to be used by the specialist committees in every hospital. Currently we are working to develop an Iranian VTE prophylaxis guidebook (we just released its 2nd edition). We also established a national VTE day in the Persian calendar on which we launch different programs to draw the attention of physicians and the general population to this issue.

REFERENCES

1. Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest* 2008; 133 (6 Suppl): 381S- 453S.
2. Goldhaber SZ, Bounameaux H. Pulmonary embolism and deep vein thrombosis. *Lancet* 2012; 379 (9828): 1835- 46.
3. Deitelzweig SB, Johnson BH, Lin J, Schulman KL. Prevalence of clinical venous thromboembolism in the USA: current trends and future projections. *Am J Hematol* 2011; 86 (2): 217- 20.
4. Vardi M, Steinberg M, Haran M, Cohen S. Benefits versus risks of pharmacological prophylaxis to prevent symptomatic venous thromboembolism in unselected medical patients revisited. Meta-analysis of the medical literature. *J Thromb Thrombolysis* 2012; 34 (1): 11- 9.
5. White RH. The epidemiology of venous thromboembolism. *Circulation* 2003; 107 (23 Suppl 1): I4- 8.
6. Rothberg MB, Lahti M, Pekow PS, Lindenauer PK. Venous thromboembolism prophylaxis among medical patients at US hospitals. *J Gen Intern Med* 2010; 25 (6): 489- 94.
7. Bikdeli B, Sharif-Kashani B. Venous thromboembolism: a Persian perspective to prevention, diagnosis, and treatment. North American thrombosis forum (serial online). 2010. Available from: <http://www.natfonline.org/media/15133/persianvteperspectiveformat.pdf>. Accessed June 14, 2013
8. Bagot CN, Arya R. Virchow and his triad: a question of attribution. *Br J Haematol* 2008; 143 (2): 180- 90.
9. Anderson FA Jr, Spencer FA. Risk factors for venous thromboembolism. *Circulation* 2003; 107 (23 Suppl 1): I9- 16.
10. Iran SCo. National Population and Housing Census 2011 Selected Findings. Statistical Centre of Iran (online). 2012. Available from: <http://www.amar.org.ir/Default.aspx?tabid=500>. Accessed June 7, 2013.
11. Population Clock. Statistical Centre of Iran (online).2013. Available from: <http://www.amar.org.ir/Default.aspx?tabid=654>. Accessed June 10, 2013.
12. Spencer FA, Emery C, Joffe SW, Pacifico L, Lessard D, Reed G, et al. Incidence rates, clinical profile, and outcomes of patients with venous thromboembolism. The Worcester VTE study. *J Thromb Thrombolysis* 2009; 28 (4): 401- 9.
13. Jang MJ, Bang SM, Oh D. Incidence of venous thromboembolism in Korea: from the Health Insurance Review and Assessment Service database. *J Thromb Haemost* 2011; 9 (1): 85- 91.
14. Ho WK, Hankey GJ, Eikelboom JW. The incidence of venous thromboembolism: a prospective, community-based study in Perth, Western Australia. *Med J Aust* 2008; 189 (3): 144- 7.
15. Naess IA, Christiansen SC, Romundstad P, Cannegieter SC, Rosendaal FR, Hammerstrøm J. Incidence and mortality of venous thrombosis: a population-based study. *J Thromb Haemost* 2007; 5 (4): 692- 9.
16. Ahmad-Nia S, Delavar B, Eini-Zinab H, Kazemipour S, Mehryar AH, Naghavi M. Caesarean section in the Islamic Republic of Iran: prevalence and some sociodemographic correlates. *East Mediterr Health J* 2009; 15 (6): 1389- 98.
17. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians

- Evidence-Based Clinical Practice Guidelines. *Chest* 2012; 141 (2 Suppl): e278S- 325S.
18. Rahimi-Movaghar V, Saadat S, Rasouli MR, Ganji S, Ghahramani M, Zarei MR, et al. Prevalence of spinal cord injury in Tehran, Iran. *J Spinal Cord Med* 2009; 32 (4): 428- 31.
 19. Yegen HA, Lederer DJ, Barr RG, Wilt JS, Fang Y, Bagiella E, et al. Risk factors for venous thromboembolism after lung transplantation. *Chest* 2007; 132 (2): 547- 53.
 20. Burns KE, Iacono AT. Pulmonary embolism on postmortem examination: an under-recognized complication in lung-transplant recipients? *Transplantation* 2004; 77 (5): 692- 8.
 21. Poli D, Zanazzi M, Antonucci E, Marcucci R, Rosati A, Bertoni E, et al. High rate of recurrence in renal transplant recipients after a first episode of venous thromboembolism. *Transplantation* 2005; 80 (6): 789- 93.
 22. Sakai T, Matsusaki T, Dai F, Tanaka KA, Donaldson JB, Hilmi IA, et al. Pulmonary thromboembolism during adult liver transplantation: incidence, clinical presentation, outcome, risk factors, and diagnostic predictors. *Br J Anaesth* 2012; 108 (3): 469- 77.
 23. Bikdeli B, Sharif-Kashani B. Prophylaxis for venous thromboembolism: a great global divide between expert guidelines and clinical practice? *Semin Thromb Hemost* 2012; 38 (2): 144- 55.
 24. Caprini JA. Individual risk assessment is the best strategy for thromboembolic prophylaxis. *Dis Mon* 2010; 56 (10): 552-9.
 25. Bikdeli B, Sharif-Kashani B, Shahabi P, Raeissi S, Shahrivari M, Shoraka AR, et al. Comparison of three risk assessment methods for venous thromboembolism prophylaxis. *Blood Coagul Fibrinolysis* 2013; 24 (2): 157- 63.
 26. Mokhtari M, Salameh P, Kouчек M, Kashani BS, Taher A, Waked M; et al. The AVAIL ME Extension: a multinational Middle Eastern survey of venous thromboembolism risk and prophylaxis. *J Thromb Haemost* 2011; 9 (7): 1340- 9.
 27. Sharif-Kashani B, Shahabi P, Raeissi S, Behzadnia N, Shoaraka A, Shahrivari M, et al. AssessMent of ProphylAxis for VenouS Thromboembolism in hospitalized patients: the MASIH study. *Clin Appl Thromb Hemost* 2012; 18 (5): 462- 8.
 28. Heidarnezhad H, Zendehtel N, Kolahi S, Pirzeh A, Eslampanah S. Practice of deep vein thrombosis prophylaxis in teaching hospitals of Tabriz. *Tanaffos* 2003; 2(6): 31- 7.