

Patient and healthcare provider burden due to conventional measurement of the international normalized ratio: From a multi-dimensional perspective

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ABSTRACT

Objectives: In this study, we aimed to investigate the healthcare burden associated with hospital visits for international normalized ratio (INR) measurement from a multi-dimensional perspective.

Patients and methods: A total of 415 patients (198 males, 217 females; mean age: 54±12.7 years; range, 14 to 84 years) who were admitted to the cardiovascular surgery (CVS) outpatient clinic between March 2015 and June 2015 were included. The burden of INR measurement was assessed in two main categories: social and clinical. Data including educational status, occupational status and accompanying persons, indications for warfarin use, history of warfarin-related complications, expenses made by the patient and the accompanying persons, and the time spent were recorded.

Results: A total of 1,259 laboratory entries were found for the overall study population. Of these entries, 99.4% were only for INR measurements. An INR outside the target therapeutic range (TTR) was detected in 53.7% of the patients. Among all patients attending to the CVS outpatient clinic during the study, the sole reason for attendance was the INR measurement in 23%. The rate of complications requiring intervention was 2.1%. The daily clinical cost per patient was \$22.14, the social monetary cost was \$9.77, and the total cost was \$31.91.

Conclusion: Conventional INR measurements have a significant social and economic impact on patients and are associated with significantly increased workload and loss of resources from the perspective of the healthcare provider.

Keywords: Cost of illness, management, medication therapy, Warfarin.

The number of patients requiring oral anticoagulant therapy (OAT) has been steadily increasing worldwide, mainly due to the presence of a wide spectrum of indications for OAT therapy, most of which require lifelong use of these agents.^[1] Although novel oral anticoagulants (NOACs) are commonly used for the treatment of atrial fibrillation (AF), data from the randomized studies regarding their safety and efficacy in patients with mechanical cardiac valves (MCVs) or those with mechanical cardiac support (MCS) devices are scarce, despite initial promising studies.^[2-5] One study examining NOACs in MCV patients was terminated prematurely due to adverse effects.^[6] Thus, warfarin remains the most commonly prescribed OAT currently.^[7]

Tight and regular international normalized ratio (INR) monitoring is a prerequisite after the initiation of warfarin treatment.^[8] Conventional INR measurement methods require the attendance of the patient to a healthcare facility for blood sampling,

leading to an increased workload and costs. In this study, we aimed to investigate the workload, loss of productivity, and associated costs of the monitoring of patients on warfarin treatment from a multi-dimensional perspective.

PATIENTS AND METHODS

This prospective, observational study was conducted at Ankara Türkiye Yüksek İhtisas Training and Research Hospital, Department of Cardiovascular

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Surgery (CVS) between March 2015 and June 2015. Initially 418 patients who were on warfarin treatment and admitted to the CVS outpatient clinic were screened. Three patients were excluded due to coagulopathy confirmed by genetic testing. Finally, a total of 415 patients (198 males, 217 females; mean age: 54 ± 12.7 years; range, 14 to 84 years) were included. Exclusion criteria included treatment with additional anticoagulant agents rather than warfarin, having a diagnosis of coagulopathy, unwillingness to participate in the study, inability to follow the warfarin treatment regimen, and inability to answer the questions in the quality of life questionnaire. A written informed consent was obtained from each patient. The study protocol was approved by the Ankara Numune Training and Research Hospital Ethics Committee (date, no: 09/02/2015, E-15-541). The study was conducted in accordance with the principles of the Declaration of Helsinki.

The following parameters were examined in patients attending to the unit for conventional INR measurements: time spent for official procedures at the laboratory, the monitoring frequency and interval, costs associated with the transportation, accommodation, examination, and laboratory work-up, INR-related complications, and treatment costs associated with the treatment of these complications. Also, a questionnaire was filled out to determine whether patients received any education on warfarin use, as well as to find out whether the quality of life was an important factor for the level of INR stability. Additionally, quality of life tools (EuroQoL-5 Dimensions [EQ-5D], Turkish Version) were administered and information on portable point-of-care devices (POCDs) were gathered.^[9,10] Patients were classified into two categories based on their location of residence: those residing in Ankara province or other provinces. The distance covered by those paying a visit to the healthcare facility from outside the Ankara province was calculated as the distance from the district/village of residence to Ankara provincial center. The time spent on transportation was recorded based on the patients' declaration. The mean INR target values of anticoagulation therapy were as follows: 2.5 ± 0.5 for aortic valve replacement (AVR), AF, deep venous thrombosis (DVT), and pulmonary thromboembolism (PTE) and 3.0 ± 0.5 for mitral valve replacement (MVR) and double valve replacement (AVR-MVR).^[11,12]

The costs were considered in two main categories: clinical costs and social costs. Clinical costs included

the registration fee to the hospital, costs associated with the interventional treatment of complications, and the cost of blood and blood product replacement. These costs were recorded according to the invoice prepared by the financial unit of the hospital. For social costs, the daily wage loss was calculated based on the daily income of the employed patients and accompanying persons. Information provided by the patient were used to calculate the costs associated with transportation and accommodation. For the study period, an exchange rate of 1 United States Dollar = 2.66 Turkish Lira was used as the current currency rate of the start date of the study.

Statistical analysis

Statistical analysis was performed using the SPSS for Windows version 11.5 software (SPSS Inc., Chicago, IL, USA). The normal distribution of continuous numerical variables was tested using the Kolmogorov-Smirnov test. Continuous data were expressed in mean \pm standard deviation (SD) and median (interquartile range [IQR]: 25th-75th percentile), while categorical data were expressed in number and frequency. The significance of the difference in median values between the groups was tested using the Mann-Whitney U test. Categorical variables were assessed using the Pearson chi-square, Fisher's exact, or probability ratio test. A p value of <0.05 was considered statistically significant.

RESULTS

A total of 415 patients included in the study were followed for three months, during which a total of 1,259 attendances to the CVS outpatient unit were recorded. The median number of visits per patient to the outpatient unit during this period was 3.0 (IQR: 2.0 to 4.0). Of the patients, 88 (21.2%) received no formal education, while 27 (6.5%) had a university or higher degree. The most common reason for warfarin treatment was cardiac valvular surgery (72.8%, $n=302$) (Table 1). No significant associations between the number of visits and indication of warfarin use were detected ($p=0.86$).

The complication most frequently associated with the need for invasive treatment was gastrointestinal tract (GI) bleeding in 2.1% of the patients (Table 2). Fifty-six patients who had an INR over the target therapeutic range (TTR) had blood and blood product replacement. Also, 14.5% of the patients reported at

Table 1
Sociodemographic and clinical characteristics of the patients (n=415)

Variables	n	%	Mean±SD	Range
Age (year)			54.1±12.7	14-84
Sex				
Male	198	47.7		
Female	217	52.3		
Educational status				
No formal education	88	21.2		
Primary School	198	47.7		
Secondary School	52	12.5		
High School	50	12.0		
University or higher	27	6.5		
Place of residency				
Ankara province	376	90.6		
Outside Ankara province	39	9.4		
Indications for warfarin use				
Cardiac valve replacement or repair	302	72.8		
Atrial fibrillation	12	2.9		
Intracardiac thrombus	1	0.2		
Pulmonary thromboembolism	2	0.5		
Deep venous thrombosis	97	23.4		
Ventricular support device	1	0.2		
Distribution of patients who had cardiac valve replacement or repair (n=302)				
AVR	89	29.4		
MVR	150	49.5		
AVR-MVR	56	18.5		
Valve repair	4	1.3		
Bio-prosthesis valve replacement	1	0.3		
MVR-TVR	1	0.3		
AVR-TVR	1	0.3		
AVR	89	29.4		
MVR	150	49.5		

SD: Standard deviation; AVR: Aortic valve replacement; MVR: Mitral valve replacement; TVR: Tricuspid valve replacement.

Table 2
Distribution of complications

Complications	Total		Requiring intervention or hospitalization	
	n	%	n	%
Gingival bleeding	51	12.2	0	0.0
Epistaxis	55	13.2	1	0.2
Hematuria	13	3.1	0	0.0
Menstrual bleeding	16	3.8	1	0.2
Hemorrhagic cerebrovascular accident	0	0.0	0	0.0
Gastrointestinal bleeding	13	3.1	9	2.1
Mechanical valve thrombosis	0	0.0	0	0.0
Total	148	35.6	11	2.6

least one occasion where they altered warfarin dosage without asking for a specialist's opinion.

For clinical cost estimation, invoices sent to the social security institution were examined. Invoices prepared by different healthcare facilities were compared for the treatment of similar complications. Of the complications that were intervened, the highest costs were associated with GI bleeding. Of note, for outpatient services, an invoice of \$18.79 is issued for each outpatient visit due to a contract with the social insurance institution.

The median monthly income of the employed patients was \$714.28 (range: \$187.96 to \$1,879.69) of the overall patient group attending to a control visit, 42.7% were attended by an accompanying person. Of these accompanying persons, 28.8% were actively employed with a monthly median income level of \$563.9 (range: \$338.34 to \$1,879.69). The total loss of wages per visit was \$5.33.

The patients used the following means of transportation at least once for attending to the hospital: 316 patients with mass transportation (range, 1 to 7), 99 patients with a private car (range, 1 to 4), 26 patients with a cab (range, 1 to 4), and three patients on foot (range, 1 to 1). The median distance covered by patients coming from locations other than Ankara province was 250 (range, 80 to 1,398) km. The duration and cost of transportation were 45 (IQR: 30 to 80) min and \$1.12 (IQR: \$0.62 to 2.19) and 240 (IQR: 120 to 240) min and \$5.01 (IQR: \$0 to 8.77) for patients attending from Ankara and outside Ankara, respectively (Table 3). The median

Variables	Median	IQR
Transportation fee (\$)		
Ankara	1.12	0.62-2.19
Other	5.01	0-8.77
Transportation time (min)		
Ankara	45	30-80
Other	240	120-240
Accommodation and food fee (\$)		
Ankara	0	0-0
Other	6.26	2.5-10.02

IQR: Interquartile range.

duration for having an INR measurement within the healthcare facility was 1.0 (range, 1 to 5) days.

The total cost was the sum of the social and clinical costs and the mean total cost was \$31.91±24.7 per patient (Table 4).

Quality of life measurements usually showed a good level of quality of life, as documented by the responses to the questionnaire administered, while less than 2% of the patients were found to have a significantly impaired quality of life (Table 5).

Cost (\$)	Mean±SD
Clinical costs	22.14±14.99
Gastrointestinal bleeding	1.33±6.3
Blood products	1.69±4.28
Outpatient clinic registration	19.12±11.39
Social costs	9.77±29.23
Transport	3.05±6.7
Accommodation, food	1.2±6.12
Loss of wages, patient	3.75±11.48
Loss of wages, accompanying person	1.77±6.93
Total	31.91±24.7

SD: Standard deviation.

Variables	n	%
Mobility problems		
None	312	75.2
Partial	103	24.8
Severe	-	-
Problems of self-care		
None	393	94.7
Partial	18	4.3
Severe	4	1.0
Problems in daily chores		
None	348	83.9
Partial	59	14.2
Severe	8	1.9
Pain-discomfort		
None	264	63.6
Partial	143	34.5
Severe	8	1.9
Anxiety/depression		
None	256	61.7
Partial	154	37.1
Severe	5	1.2

Table 6
Demographic and clinical characteristics of patients within and out of the target therapeutic range of INR

Variables	INR in target value (n=223)		INR out of target value (n=192)		p†
	n	%	n	%	
Educational status					0.396
Illiterate	51	22.9	37	19.3	
Primary School	108	48.4	90	46.9	
Secondary School	29	13.0	23	12.0	
High School	25	11.2	25	13.0	
University	10	4.5	17	8.9	
Employment					0.044
Unemployed	195	87.4	154	80.2	
Employed	28	12.6	38	19.8	
Cares about nutrition	173	77.6	156	81.3	0.358
Trained on warfarin use	139	62.3	131	68.2	0.209

INR: International normalized ratio; † Pearson's chi-square test.

Table 7

Clinical, transportation, accommodation, food, and total cost in patients within and out of the target therapeutic range of INR

Cost (\$)	Mean±SD	p†
Clinical cost		0.005
INR out of TTR	24.02±15.98	
INR in TTR	11.24±13.47	
Social cost		0.894
INR out of TTR	11.24±20.27	
INR in TTR	8.06±11.43	
Total cost		0.044
INR out of TTR	35.26±28.69	
INR in TTR	28.08±18.37	

SD: Standard deviation; INR: International normalized ratio; TTR: Therapeutic target range; † Mann Whitney U test.

Of the overall patient group, 53.7% had INR values outside the TTR. The TTR of INR did not exhibit any associations with the educational status ($p=0.39$) or monthly income ($p=0.096$). On the other hand, actively employed patients had a significantly better TTR of INR ($p=0.04$) (Table 6).

The cost comparison between the patients with the inside TTR or out of the TTR showed a significantly higher clinical and total cost for those out of the TTR, while the difference in social costs was not statistically significant (Table 7).

DISCUSSION

The estimated number of individuals with paroxysmal or persistent AF is around 2.2 million in the United States.^[13] In a study by Uyarel et al.,^[14] each year 35,000 new cases of AF are diagnosed in Turkey, and the annual number of cardiac valve surgeries is approximately 10,000 as reported by Kervan et al.^[15] Another patient group requiring tight monitoring of warfarin therapy consists of those with MCS implantation. Considering the cost of artificial cardiac devices implanted, as well as the fact that cardiac transplantation represents the only therapeutic option in these patients, one may readily acknowledge the significance of INR monitoring in these individuals. In a study by Sharma et al.,^[16] 2% of the general population was found to be on long-term OAT, corresponding to a population segment of 1.6 million subjects in Turkey. As these figures suggest, a continuous increase occurs in the number of individuals on warfarin therapy both globally and also in our country. Regular INR monitoring in patients on warfarin therapy helps to prevent simple, but potentially life-threatening complications. From an economic perspective, regular visits to a healthcare facility for INR control are associated with a certain amount of costs, while treatment of complications arising from inappropriate use may lead to even larger costs and loss of productivity.

Our study population attended to our hospital on an average of 3.0 (IQR: 2.0 to 4.0) occasions within three months. There were some interesting results

observed in this study. As such, 2.6% of the patients had a delay of approximately one year for their initial follow-up laboratory assessment, either since these patients preferred not to spend a considerable amount of time in waiting queues or due to transportation difficulty.

A total of 99.4% of 1,259 outpatient visits were performed only for INR monitoring. Data acquired from hospital management revealed that the total number of outpatient visits to the CVS unit were 5,440 during the study period, implying that 23% of all outpatient visits were performed for INR measurement alone, leading to a serious workload for the outpatient setting. When the presence of an only-INR measurement outpatient clinic (conducted by the cardiology department) is taken into consideration, this workload becomes more serious and overwhelming for clinicians.

According to the data obtained from the Turkish Statistical Institution (TUIK) as of May 2015, the rate of employment in individuals between 15 and 64 years of age is 90.5% in the general Turkish population, compared to an employment rate of only 20.2% for the same age group in our study.^[17] These data suggest that majority of the employed individuals requiring INR monitoring actually do not attend for INR measurements, probably due to the difficulties such as time constraints or getting permission from the workplace or, in other point of view, these patients are not able to secure a job due to their conditions.

Since our clinic represents one of the referral centers in Turkey, individuals residing in locations other than Ankara province represented 9.4% of the total study population. Although initially it was assumed that the majority of these patients had their follow-up examination in our center due to a previous surgical intervention performed here, 97.4% were found to pay a visit to the outpatient facility only for INR measurements. Contrary to our expectations, only 2.6% had attended for routine follow-up of the disease.

A detailed examination of the patients' history revealed that after initiation of warfarin treatment, 4.6% of the patients had at least one complication such as a hemorrhagic cerebrovascular accident or MCV thrombosis requiring an intervention. Although no such complications were observed during the study period, their occurrence would certainly be associated with the significantly increased costs.

Attendance of patients on warfarin therapy to a healthcare center for each INR measurement is associated with a financial and workload burden. Until now, no studies in Turkey have been conducted to assess the financial and workload burden on the National Social Insurance Organization arising from the care of these patients. In our study, the total, clinical, and social costs per attendance to our unit were \$31.91, \$22.14, and \$9.77, respectively. These figures include complications that can be prevented with a better regulation of INR. In a study by Chen et al.^[18] from China, the approximate cost of each INR measurement was found to vary between \$9.8 and \$150.5, depending on the distance between the place of the residency and hospital. In the aforementioned study, such a wide range of costs could be accounted for by the higher level of expenses for transportation and accommodation for patients coming from peripheral areas, compared to those coming from the urban locations. However, the cost of the management of associated complications was not taken into consideration.

Although conventional INR tests are considered the gold-standard approach for evaluating the efficacy of warfarin therapy, technological advances allow the introduction of more practical and more rapid measurement devices targeting better monitoring rates. Such devices enable patients to measure their INR measurements at home and take more active responsibility in their treatment, ultimately leading to improved treatment compliance based on a more individualized strategy. This, in turn, may result in a better regulation of the anticoagulant therapies and decrease the dependency of the patients on healthcare centers. Comparative studies on such novel devices versus conventional INR measurements also showed the reliability of this new-generation POCDs.^[19,20] However, two major questions remain on the use of POCDs. The first question refers to the provider and content of the professional assistance, and the second refers to the possibility that INR measurements with POCDs may actually be costlier. Wells et al.^[20] found an increased monitoring frequency of INR in patients using POCDs, while this increase was also associated with a decreased complication rate. On the other hand, Sharma et al.^[16] found similar average costs with standard monitoring or home monitoring systems, while the latter was associated with a reduced likelihood of thrombotic events and all-cause mortality. Considering the cost of the acute treatment

of the reduced complication, it may be assumed that POCDs may prove to be increasingly more advantageous over time in terms of cost, compared to standard monitoring procedures. The POCDs may allow a decreased need for outpatient visits to the hospital and permit more frequent and regular INR measurements. In our study, only 7.5% of the patients had some information on POCDs. Such a few number of patients who are familiar with POCDs is another obstacle to home-based measurement of INR by patients and consequent dissemination of POCDs. We believe that patients should be informed more about this alternative measurement tool.

The fact that almost half of the patients visiting outpatient clinics come to the clinics with attendants causes an increased cost and loss of labor force, although 53.7% of the patients were detected to be outside the TTR values. Besides, 19.7% of them were not informed about nutrition and complications, and the way of administration of warfarin were not explained to 32.8% of the patients. This necessitates an urgent action plan. We believe that the number of patients within the TTR values would increase with a consequent reduction in complications through patient education about warfarin use and nutrition, enhanced availability and accessibility to informative brochures, and clarification of the importance of regular INR measurements.

Nonetheless, there are several limitations to this study. Some complications associated with warfarin due to a short period were unable to be monitored. Patients who failed to attend to their follow-up visits for any reasons could not be included and their social and medical conditions still remain unclear. Prescription costs were not able to be considered in this study, as the patients were not willing to wait for submitting these data after receiving their results and prescriptions. Economic and social burden analyses could not be performed for patients requiring home care. Also, patients using POCSs were unable to be followed, as they did not attend to the outpatient clinic.

In conclusion, conventional INR measurements have a significant social and economic impact on patients, while they are associated with a significant increase in workload and loss of productivity from the perspective of the healthcare provider. We believe that increased availability of POCDs may play a role in reducing costs associated with laboratory

measurements and complications, and also improve patient compliance with the treatment. However, further studies are warranted to elucidate this issue.

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REFERENCES

1. Ansell J, Hirsh J, Poller L, Bussey H, Jacobson A, Hylek E. The pharmacology and management of the vitamin K antagonists: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126(3 Suppl):204S-233S.
2. Eikelboom JW, Wallentin L, Connolly SJ, Ezekowitz M, Healey JS, Oldgren J, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: An analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. *Circulation* 2011;123:2363-72.
3. Kaerberich A, Reindl I, Raaz U, Maegdefessel L, Vogt A, Linde T, et al. Comparison of unfractionated heparin, low-molecular-weight heparin, low-dose and high-dose rivaroxaban in preventing thrombus formation on mechanical heart valves: Results of an in vitro study. *J Thromb Thrombolysis* 2011;32:417-25.
4. McKellar SH, Abel S, Camp CL, Suri RM, Ereth MH, Schaff HV. Effectiveness of dabigatran etexilate for thromboprophylaxis of mechanical heart valves. *J Thorac Cardiovasc Surg* 2011;141:1410-6.
5. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: A meta-analysis of randomised trials. *Lancet* 2014;383:955-62.
6. Eikelboom JW, Connolly SJ, Brueckmann M, Granger CB, Kappetein AP, Mack MJ, et al. Dabigatran versus warfarin in patients with mechanical heart valves. *N Engl J Med* 2013;369:1206-14.
7. Ahrens I, Lip GY, Peter K. New oral anticoagulant drugs in cardiovascular disease. *Thromb Haemost* 2010;104:49-60.
8. Butchart EG, Payne N, Li HH, Buchan K, Mandana K, Grunkemeier GL. Better anticoagulation control improves survival after valve replacement. *J Thorac Cardiovasc Surg* 2002;123:715-23.
9. Rabin R, de Charro F. EQ-5D: A measure of health status from the EuroQol Group. *Ann Med* 2001;33:337-43.
10. Kahyaoglu Süt H, Unsar S. Is EQ-5D a valid quality of life instrument in patients with acute coronary syndrome? *Anadolu Kardiyol Derg* 2011;11:156-62.
11. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for

- the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63:e57-185.
12. Baglin TP, Keeling DM, Watson HG; British Committee for Standards in Haematology. Guidelines on oral anticoagulation (warfarin): Third edition--2005 update. *Br J Haematol* 2006;132:277-85.
 13. Feinberg WM, Cornell ES, Nightingale SD, Pearce LA, Tracy RP, Hart RG, et al. Relationship between prothrombin activation fragment F1.2 and international normalized ratio in patients with atrial fibrillation. *Stroke Prevention in Atrial Fibrillation Investigators. Stroke* 1997;28:1101-6.
 14. Uyarel H, Onat A, Yüksel H, Can G, Ordu S, Dursunoğlu D. Türk halkında kronik atriyal fibrilasyon insidansı, prevalansı ve mortalitesine ilişkin tahminler. *Türk Kardiyol Dern Ars* 2008;36:214-22.
 15. Kervan Ü, Koç O, Özatik MA, Bayraktar G, Şener E, Çağlı K, et al. Türkiye'deki kalp damar cerrahisi kliniklerinin dağılımı ve hizmetlerinin niteliği. *Türk Gogus Kalp Dama* 2011;19:483-9.
 16. Sharma P, Scotland G, Cruickshank M, Tassie E, Fraser C, Burton C, et al. Is self-monitoring an effective option for people receiving long-term vitamin K antagonist therapy? A systematic review and economic evaluation. *BMJ Open* 2015;5:e007758.
 17. Türkiye İstatistik Kurumu (TÜİK) İş gücü İstatistikleri, Mayıs 2015. Available at: <https://data.tuik.gov.tr/Bulten/Index?p=Isgucu-Istatistikleri-Mayis-2015-18640>
 18. Chen QL, Dong L, Dong YJ, Zhao SL, Fu B, Wang YQ, et al. Security and cost comparison of INR self-testing and conventional hospital INR testing in patients with mechanical heart valve replacement. *J Cardiothorac Surg* 2015;10:4.
 19. Bardakci H, Altıntaş G, Çiçek OF, Kervan U, Yılmaz S, Kaplan S, et al. Comparison of the CoaguChek XS handheld coagulation analyzer and conventional laboratory methods measuring International Normalised Ratio (INR) values during the time to therapeutic range after mechanical valve surgery. *J Card Surg* 2013;28:254-7.
 20. Wells PS, Brown A, Jaffey J, McGahan L, Poon MC, Cimon K. Safety and effectiveness of point-of-care monitoring devices in patients on oral anticoagulant therapy: A meta-analysis. *Open Med* 2007;1:e131-46.