

ORIGINAL ARTICLE

Direct and indirect costs of management of long-term warfarin therapy in Canada

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Summary. *Background:* Comparisons of overall costs and resource utilization associated with anticoagulation management are important as new alternatives to warfarin are introduced. The aim of the present study was to assess total costs of warfarin-based anticoagulation in different health care models. *Methods:* Physician- or pharmacist-managed hospital- or community-based anticoagulation clinics in five Canadian provinces were asked to provide itemized information on costs for staff, laboratory, hardware and overheads associated with warfarin management. At each site, cohorts of patients were provided with diaries and participants prospectively entered all costs for warfarin medication and associated health professional contacts, travel to the laboratory, required assistance and time lost from work by patient or caregiver over 3 months. All costs were calculated for a 3-month period. *Results:* Data from 429 patients at 15 sites were evaluated. The cost from the Ministry of Health perspective ranged from \$108 to \$199 per 3 months in the different settings, the patient costs were \$40–\$80 and the total societal costs ranged from \$188–\$244. Sensitivity analyses with typical blood test intervals, the most prescribed strength of warfarin and dispensing fee from another province increased these estimates to \$230–\$302. When reimbursement for unemployed caregivers was also entered the total cost was \$308–\$503 per 3 months. *Conclusions:* The total cost for warfarin-based anticoagulation amounted to at least 10 times the lowest cost for the drug. The costs provided should be useful for comparisons with newer drugs without requirement for routine laboratory monitoring and dose adjustments.

Keywords: anticoagulants, drug monitoring, economics, health care.

The most widely used vitamin K antagonist (VKA), warfarin, has been available for more than 60 years and is inexpensive. Unlike most other types of medications VKAs require frequent monitoring with measurement of the prothrombin time (PT), which is expressed as the International Normalized Ratio (INR). A plethora of drug interactions, foods, diseases and genetic variants affecting the pharmacokinetics of warfarin, as well as the narrow therapeutic window, necessitate frequent laboratory monitoring and dose adjustments [1]. The complexity of the management of warfarin therapy has led to the establishment of specialized anticoagulation clinics, which appear to perform better than ‘usual care’ and guidelines give a careful recommendation in favor of anticoagulant management services [1]. This was supported by a systematic review of 67 studies [2]. Canadian studies have shown that hospital anticoagulation clinics provide better or equal anticoagulation control compared with family physicians and anticoagulation clinics appear to be effective in both hospital and community settings [3,4].

Many of the patients on warfarin are elderly and require assistance from family or friends or caregivers to manage the monitoring and medication administration. Therefore, the total cost of anticoagulant therapy with warfarin entails much more than the cost of the drug. Several cost analyses have been published but these have been based on only direct medical costs [5–7], direct and indirect costs excluding patient expenses [8], hospitalization and emergency department visit rates [7,9], only time- and traveling costs [10] or on a Markov model [11–13]. One study, performed at a single center in the United Kingdom, addressed both direct and indirect costs as well as expenses for managing complications of the anticoagulant treatment [14].

New, orally available anticoagulants with more predictable pharmacokinetics and therefore probably not requiring

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laboratory monitoring of anticoagulant effect are now in clinical trials [15–17], and two drugs have been approved in several countries for limited indications. With higher direct costs of these new drugs as compared with warfarin, it is important to quantify and compare the total cost of anticoagulant management. The aim of the present study was to prospectively study the current total cost of warfarin-based anticoagulation in four different models of care: hospital-based physician managed, hospital-based pharmacist managed, community-based family physician managed (e.g. traditional model) and community-based pharmacist managed care. We also aimed to include several centers for each model to achieve more generalized assessment. The total cost encompassed direct medical, direct non-medical, direct patient and productivity loss costs.

Methods

This was a multi-center, prospective, observational study to determine the cost and resource utilization associated with monitoring warfarin anticoagulation during a 3-month period in four types of clinic settings in Canada during 2006–2008. We planned to recruit both hospital- and community-based sites and for each type of setting, both physician- and pharmacist-managed clinics. Eighteen participating sites were invited to represent five populous provinces (British Columbia, Alberta, Ontario, Québec and New Brunswick) across Canada.

Patients

Patients were eligible for inclusion if they were treated with warfarin for stroke prophylaxis in atrial fibrillation or secondary prophylaxis after venous thromboembolism, if they had received this treatment for ≤ 1 month (new users) or ≥ 3 months (chronic users) and were planned to continue treatment for at least another 3 months. In addition, they had to be at least 18 years of age, able to read and write English or French and provide informed consent. Exclusion criteria were treatment with VKA other than warfarin or for another indication than the above-mentioned, participation in another clinical study, a life-expectancy of < 3 months, a history of frequent hospitalizations for another disease, planned surgery or invasive procedure requiring interruption of warfarin within 3 months, geographic inaccessibility for follow-up or documented poor compliance.

Consecutive, eligible patients starting on warfarin or with treatment for maximum 1 month (new users) were to constitute a minimum of 10% but not more than 30% of the study population. The remainder were consecutive chronic users visiting the site but adjustments of enrolment were allowed to avoid selection bias. The intention was to obtain a study sample representative of the population of anticoagulated patients at each site.

The 3-month duration of data collection from each patient was based on the fact that many patients with venous thromboembolism are only treated for about 3 months [18].

On the other hand, with a maximum recommended interval between PT tests of 4 weeks [1], at least three test occasions would be recorded per patient.

Study procedures

Study centers

Characteristics of each site were recorded at the start of the study by completion of a questionnaire. Information on type of setting, location, services provided, annual operating budget, overhead costs related to warfarin management (including depreciation of equipment and rental costs), percentage of site operations related to warfarin therapy, hours of operation per week, source of funding for the site and reimbursement for physicians, statistics on patients managed, new referrals including sources of referrals, salaries and benefits for all permanent and part-time staff involved, other related services provided (e.g. home visits), routines for laboratory monitoring, dosing decision process and staff involved, transmission of results to the patients, laboratory funding for PT tests and for other tests typically ordered as a consequence of warfarin treatment (urinalysis, occult blood in stools, liver function tests, complete blood count) and point-of-care-instruments used. The sites were asked to record the time staff was involved in three types of patient encounters (routine dosing with no change, intermediate complexity contact with change of dose and extended patient contact in case of symptoms related to warfarin therapy) prior to initiation of the study as previously described by Menzin *et al.* [8]. The time assessment also included communications with laboratories and administrative activities (updating patient chart, filing chart etc.).

Patient data collection

Information recorded on the enrolled patients included age, gender, employment status, drug plan coverage, indication for anticoagulation and start date thereof, therapeutic INR range, risk factors for bleeding and thromboembolism and concomitant medications (number, and specifically use of aspirin, clopidogrel or ticlopidine).

At the enrolment visit, participating patients received one study diary for each of the 3 months with instructions to enter data weekly and after completion of the month to return it by mail in provided envelopes with pre-paid postage. Information entered included number of visits to the site as well as to other health care professionals in relation to the management of anticoagulation, location of blood sampling for PT, number of such tests, mode of transportation to the clinic or laboratory and expenses for that or distance in kilometers, assistance by caregiver at any of those visits, time lost from work for the patient or caregiver and out-of-pocket expenses for warfarin, house calls for blood sampling or for caregiver (when applicable).

At each contact with the patients during the 3 months, the investigators recorded the type of contact (telephone, visit),

staff involved, current dose of warfarin, the INR results and any other tests performed as a consequence of the anticoagulant treatment, visits to hospitals or other physicians since the previous contact, and any complications of the treatment.

Definition of costs

The unit costs for salaries, consultations, laboratory, warfarin and wages and the sources used are shown in Table 1 and are representative for the years 2008–2009. Overhead costs were calculated using the ‘total cost’ divided by ‘total number of warfarin patients’, using only the clinics for which both data were available. ‘Total cost Hospital’ = Administration + Equipment + Energy + Staff + Depreciation + Equipment (rental); ‘Total cost Community’ = Rent + Energy + Administration + Equipment (rental) + Depreciation. Ministry of Health perspective cost is the sum of medical consultations, laboratory tests, hospitalizations (if applicable), medications and appropriate overhead costs. Patient perspective cost is in fact the sum of co-payments for medications, personal expenses, caregiver costs, homecare costs, cost of patient- and caregiver work days lost. However, co-payments can vary for each individual whether the out-of pocket maximum has been reached. For simplicity, we therefore assigned the drug cost of warfarin to the Ministry of Health and the dispensing fee to the patient. Societal cost is the sum of

Ministry of Health costs, patient costs and, if applicable, overhead costs (for free-standing community clinics). Costs are in Canadian \$ unless otherwise stated.

Analysis of costs

We used descriptive analyses to demonstrate the average total cost per 3 months of anticoagulant therapy with warfarin. After calculating the Ministry of Health costs, patient costs and site overhead costs, the total societal cost was obtained as the sum of these components, separately for the four management settings.

Results

We enrolled 16 sites for the study. We were only able to enrol one community-based pharmacist-managed center, which did not contribute complete data on the administrative costs. Costs are therefore compared costs from 15 sites at the three other types of management, the characteristics of which are shown in Table 2. The total number of patients recruited from those three settings is 429. From an epidemiological perspective, there are approximately 225 000 patients treated with warfarin in Canada at any time point as extrapolated from US statistics [19,20]. There was an obvious difference in volume between the anticoagulant clinics with the hospital-based physician-managed clinics at the high end and the community-based

Table 1 Unit costs of resource utilization items

Resource	Mean Cost (\$)	Source
Hourly salaries of staff		Study sites
Nurse	25.2	
Nurse practitioner	50.0	
Pharmacist	39.7	
Other for example receptionist	19.6	
Physician consultations	56.10	Ontario Schedule of Benefits (A005)
Other health care consultations, \$/h	25.64	Statistics Canada*
Emergency room visits	229.10	Health Costing in Alberta [†]
PT test	6.20	Ontario Schedule of Benefits for Laboratory Services [‡]
Venipuncture and handling	7.755	
CoaguChek XS test strip	5.00	BioUSA [§]
Warfarin, 10 mg tablet	0.2153	Ontario Drug Benefit [¶]
Dispensing fee	6.11	Ministry of Health and Long Term Care, Ontario**
Patient wage, \$/h	23.50	Statistics Canada ^{††}
Caregiver/homecare wage, \$/h	9.50	Ontario Government ^{†††}
Travel by private car, \$/km	0.53	Canadian Institutes of Health Research ^{§§}

PT, prothrombin time. *From 2008 average hourly wage for Health Occupations. [†]Cost for ambulatory care for management hematological (> 65 years), \$164 from Health Costing in Alberta plus a physician consultation in emergency medicine from Ontario Schedule of Benefits (\$65.10, H065). [‡]Cost is for a single PT test (L445) on venous blood with no physician consultation and for patient documentation and specimen collection fee (\$7.755, claim L700), as the vast majority of PT tests are stand-alone (http://www.health.gov.on.ca/english/providers/program/ohip/sob/lab/lab_services_sched_01_19990401.pdf). [§]For the Community based pharmacy setting, where Point-of-Care testing is used almost exclusively, a cost of \$5.00 per CoaguChek test strip is calculated. Advertised price per strip for a pack of 48 strips for CoaguChek XS USD 4.55, shipping and taxes not included (<http://www.bioussa.com/coxsbgltest.html>). [¶]Cost is for a 10-mg tab of apo-warfarin, the least expensive alternative per mg (<https://www.healthinfo.moh.gov.on.ca/formulary/index.jsp>). ^{**}Ontario Drug Benefit – based on single citizens, who pay up to \$6.11 toward the dispensing fee each time they fill an ODB eligible prescription. Notably, in Nova Scotia this fee is \$10.13 (<http://www.health.gov.on.ca/english/public/pub/drugs/dispense.html>). ^{††}Based on data on average salaries from Statistics Canada for individuals (men and women) 55 years and older as of February 2009 (<http://www40.statcan.gc.ca/l01/cst01/labr69a-eng.htm>). ^{†††}Minimum wage data from the Ontario Government Web Site (<http://www.ontario.ca/en/residents/index.htm>). Hourly rate as of March 31, 2009. ^{§§}CIHR Travel Expenses Reimbursement Guidelines, Ontario, July 1, 2009 (<http://www.cihr-irsc.gc.ca/e/16406.html>).

Table 2 Warfarin management site characteristics

Parameter	Hospital-based sites		Community
	Physician (<i>n</i> = 4)	Pharmacist (<i>n</i> = 5)	Physician (<i>n</i> = 6)
Years of operation, mean ± SD	27.8 ± 10.0	7.0 ± 2.2	24.7 ± 11.6
Funding source, % of total			
Hospital	75	65	0
Outpatient clinic budget	0	17.5	0
Provincial MoH	25	0	50
Private Practice General	0	5	50
Other	0	12.5	0
Estimated overhead costs, mean \$/patient*†	29	10	18.5
Number of full-time staff, mean	12.4	3	2.9
Number of patients managed per year, mean (range)	1475 (511–3000)	678 (102–1282)	92 (5–250)
Type of patients, %			
New users, ≤ 1 month on warfarin	7.3	28.3	17.7
Stable/chronic users, ≥ 3 months	66	68.5	66.5
On warfarin 1–3 months	26.7	3.2	15.8
Number of patient visits per month, mean (range)	610 (125–1800)	310 (8–800)	393 (18–900)
Number of new referrals per month, mean (range)	40.0 (20–60)	15.6 (1–40)	3.8 (1–10)
Number of PT tests/week, mean ± SD	363.5 ± 211.7	164.4 ± 134.9	22.2 ± 17.1
Venipuncture performed on-site, <i>n</i>	3	3	2
PT analysis performed on-site, <i>n</i>	3	5	1
PT performed on venous blood, %	98.6	87.7	100
PT performed with POCT, %	1.4	12.3	0
Sites using POCT for on-site PT tests, <i>n</i>	2	0	4
Warfarin dose adjustment procedures, <i>n</i> §			
Physician required to approve dosage	4	1	6
Pharmacist decision	1	5	0
Data documentation procedures, <i>n</i> §			
Paper copies	4	4	6
Electronic files	2	4	1
Both paper and electronic files	2	3	1

PT, prothrombin time; MoH, Ministry of Health, POCT, point-of-care-testing; SD, standard deviation. *Unknown costs are set to 0 during the calculation. Estimated overhead costs maybe underestimated. †The cost of Physician Managed – Community based site was driven up by one site operated by 69 health workers with estimated total cost of \$32700. Taking this site out considering it an outlier, the estimated overhead cost is 18.5. §Some sites used more than one procedure.

physician-managed clinics at the low end. Although two of the hospital-based physician clinics had point-of-care instruments these were only used for a small subset of patients.

The patients recruited were younger at the hospital-based sites than at the community-based sites (63–66 years vs. 70 years) and accordingly with a higher percentage of the former patients having full-time employment (24–38% vs. 12%) (Table 3). On the other hand, the proportion of patients using the help of caregivers was similar at all types of sites (21–29%). Co-morbidities and multiple chronic medications were common among patients in all management settings.

Data on direct medical resource utilization are shown in Table 4. The warfarin dose in mg/week was highest among the patients at the hospital-based physician-managed clinics, which may be related to the younger age of those patients [21]. The community-based physicians performed fewer PT tests per patient during the 3-month period than the other types of clinics and the hospital-based pharmacists performed the most frequent testing. The patients provided information in their diaries that they filled prescriptions for warfarin at least once a month. This may be a consequence of using several strengths of warfarin tablets and the need for refills at different time points.

The patient visits at the study sites and the time required for different types of contacts are shown in Table 5.

Data obtained from patient diaries and used for calculation of indirect costs for travel and loss of time from work for patients or caregivers are shown in Table 6. Costs for parking have not been calculated. This cost is probably related to the size of the community and can be substantial in the case of frequent testing.

The number of additional diagnostic tests related to warfarin management ranged from 0 to 0.02 per patient during 3 months. Among the 429 patients there were five warfarin-associated complications reported by the patients but with minimal additional costs. Therefore, none of these items were included in the total cost calculation.

The ultimate costs for each item are shown in Table 7. The total cost per patient for a 3-month period ranges from \$188 to \$244 (corresponding to \$2.06–2.68 per day).

The proportion of direct medical costs (staff, consultations, laboratory tests, drug and dispensing fee) varied from 71% at the hospital-based physician-managed clinics to 94% at the community-based physician-managed clinics.

Sensitivity analyses were performed to take into account data from published cohorts or other experience. The typical

Table 3 Characteristics of the recruited patients

Variable	Hospital-based sites		Community
	Physician (<i>n</i> = 188)	Pharmacist (<i>n</i> = 145)	Physician (<i>n</i> = 96)
Patients per site, mean ± SD	47.0 ± 15.0	16.0 ± 9.9	29.0 ± 16.7
Range	32–67	5–33	2–45
Age, mean ± SD	63.1 ± 15.2	66.1 ± 13.7	70.5 ± 11.2
Range	23.6–91.9	22.5–91.3	26.1–92.9
Females, <i>n</i> (%)	82 (44%)	62 (43%)	50 (52%)
Indication for warfarin, %*			
Atrial fibrillation	59	55	86
Deep vein thrombosis	32	38	8
Pulmonary embolism	13	15	7
Warfarin use, %			
≤ 1 month (New users)	16	7	8
≥ 3 months (Chronic users)	84	93	92
Risk factors, %*			
Stroke	13	10	12
Ulcers	4	8	2
Congestive heart failure	9	14	18
Thrombophilic defect	17	5	3
Cancer	5	6	8
Hypertension	47	52	66
Diabetes	12	14	26
Other	11	19	8
Number of chronic prescription medications, mean ± SD	4.3 ± 3.5	4.8 ± 3.2	6.1 ± 3.0
Patients with prior hemorrhagic events within last 6 months, %	2	4	0
Current employment status, %			
Active – full time	38	24	12
Active – part time	5	12	2
Unemployed	10	3	7
Retired	47	61	79
Insurance coverage (drug), %*			
Employer drug plan	40	50	19
Provincial drug plan (includes Social Assistance)	54	49	59
Other coverage	8	8	34
No insurance coverage	4	1	3
Patients with co-payments, %			
Employer plan	24	37	12
Provincial plan	23	41	21
Other plan	4	6	14
Patients using a caregiver, %	29	21	26
Proportion of unpaid caregivers, %	98	100	96

*Some patients had more than one indication, or risk factor, or insurance coverage.

interval between PT tests was 2–3 weeks. We calculated the effect of 2.5-weekly testing, which is 5.2 tests/3 months on the cost of testing and travel to the laboratory. The total cost then ranges from \$203 to \$277 per patient and 3 months (\$2.23–3.04 per day). The most commonly prescribed strength of warfarin is 2.5 mg and when that is entered, instead of 10 mg tablets, together with 2.5-weekly testing, the total cost ranges from \$215 to \$285 per patient and 3 months (\$2.36–3.13 per day). The calculated dispensing fee from Ontario is the lowest and if the fee in Nova Scotia (\$10.13) is entered instead, the total cost ranges from \$229 to \$303 (\$2.52–3.33). Finally, if we value the time spent by non-paid caregivers equal to the paid caregivers, the indirect costs increase substantially, resulting in total costs between \$309 and \$503 per patient and 3 months (\$3.40–5.53 per day).

Discussion

We present in the present study data on the total cost of management of anticoagulation with warfarin in three models of care. By including both direct and indirect costs from four to six centers of each model from five provinces across Canada, we believe that these data will generally be useful in the comparison with new alternatives for anticoagulation. In our studied population, 11% were new users of warfarin with associated higher costs of management. This proportion is probably representative of the demography at many anticoagulation clinics and a published audit reported that 20% of patients had been treated for < 1 year [22]. The maximum recommended interval between PT tests of 4 weeks in Canada follows the North American guidelines [1]. A few of our stable patients extended this interval at their

Table 4 Direct medical resource utilization during 3 months of warfarin management*

Variable	Hospital-based sites		Community
	Physician (<i>n</i> = 188)	Pharmacist (<i>n</i> = 145)	Physician (<i>n</i> = 96)
Data from investigator sites			
Patient contacts	2.5 ± 3.0	3.9 ± 2.8	2.4 ± 1.6
Type of patient contact (% of total)			
Telephone	353 (77%)	370 (66%)	124 (53%)
Site visit	10 (2%)	186 (33%)	56 (24%)
Site visit with physician consultation	98 (21%)	2 (0.4%)	55 (23%)
Other	0	2 (0.4%)	0
Warfarin dose per week, mg	42.3 ± 22.3	32.8 ± 14.9	25.1 ± 14.8
PT tests reported/patient	4.1 ± 2.7	4.7 ± 2.0	2.8 ± 1.4
Additional laboratory tests/patient	0.03 ± 0.3	0.1 ± 0.5	0.03 ± 0.2
Physician consultations/patient	1.1 ± 1.7	0.1 ± 0.4	1.4 ± 1.2
Other health care consultations/patient	4.1 ± 6.0	5.8 ± 5.3	2.6 ± 2.8
Emergency room visits/patient	0.04 ± 0.2	0.09 ± 0.4	0.03 ± 0.2
Other diagnostic tests and procedures	0.01 ± 0.1	0	0.02 ± 0.1
Min – max	0–1		0–1
Data from patient diaries			
Additional physician consultations [†]	0.14 ± 0.58	0.14 ± 0.54	1.50 ± 2.48
Other healthcare consultations [†]	0.96 ± 1.97	2.54 ± 2.41	2.67 ± 2.53
Number of warfarin prescriptions filled per 3 months	4.0 ± 7.8	3.4 ± 7.0	4.2 ± 8.0

PT, prothrombin time. *Results are given as mean ± SD. †Refers to consultations that did not take place at the study site.

Table 5 Healthcare professional time involved in patient contacts during 3 months

Variable	Hospital-based sites		Community
	Physician (<i>n</i> = 188)	Pharmacist (<i>n</i> = 145)	Physician (<i>n</i> = 96)
Patient contacts, mean ± SD	2.5 ± 3.0	3.9 ± 2.8	2.4 ± 1.6
Number of site visits per patient*	0.05	1.28	0.58
Site personnel involved in patient contacts, % of total [†]			
Nurse	79.5	35.7	53.2
Pharmacist	0.2	91.6	0.9
Physician	44.9	2.5	57.0
Other	93.0	27.0	51.5
Total time spent in patient contacts, hours			
Routine contacts	44.5	117.7	17.0
Intermediate contacts	65.2	70.2	19.8
Extended contacts	40.8	1.7	22.9
Average time involved in patient contacts (min)			
Routine contacts	6.1	5.2	6.7
Intermediate contacts	9.8	8.6	13.8
Extended contacts	25.0	40.0	28.7

*Expressed in terms of the total patient population in each setting. †More than one personnel category could have been involved at the same visit.

own decision. In some countries, for example the United Kingdom, where guidelines allow for longer intervals [23,24], the management costs for a minority of very stable patients will be lower than ours. Conversely, we excluded patients with poor compliance and that subset is likely to incur higher management costs.

The estimation of the total cost for management of warfarin, including direct and indirect costs is far from an exact science. Direct medical costs vary depending on the reimbursement for anticoagulant management, whether physicians in addition bill for visits, the level of staff involved and whether PT tests are performed on venous blood in the laboratory or with a point-of-care instrument. In addition, laboratory costs can be for the

test alone, for venipuncture (\$2.32) or for patient documentation and specimen collection (\$7.755), travel to the laboratory which varies by modes of transportation, the age of the patient population and thereby the employment status and the need for assistance. In the present study we aimed at collecting real world data from four different management systems, using information from both the anticoagulant clinics and prospectively collected from the patients. We obtained complete data from three of the four models of care demonstrating that the total cost for management of warfarin is at least 20 times (approximately \$200) the lowest possible cost for the drug (approximately \$10, excluding dispensing fee) per patient during a 3-month period. We had a high but consistent

Table 6 Non-medical resource utilization patterns, based on patient diaries*

Variable	Hospital-based sites		Community
	Physician (n = 188)	Pharmacist (n = 145)	Physician (n = 96)
Usual mode of transportation to laboratory, %			
Car	26.5	32.7	37.4
Taxi	2.4	1.2	0.4
Public transit	6.7	1.6	1.0
Walk	64.7	64.4	61.2
If traveling by car, distance to laboratory, km	7.2 ± 18.2	10.0 ± 23.7	6.5 ± 22.3
Time missed from work by patient, min/week	15.20 ± 41.28	6.16 ± 28.59	3.09 ± 14.06
Min – max	0–360	0–450	0–120
Time missed from work by caregivers, min/week†	133.38 ± 146.32	82.50 ± 66.52	3.00 ± 13.42
Min – max	0–540	0–150	0–60

*Results are given as mean ± SD. †Mean value based on all patients in each group.

Table 7 Mean costs per patient during 3 months of warfarin management

Variable	Hospital-based cost (\$)		Community based cost (\$)
	Physician (n = 188)	Pharmacist (n = 145)	Physician (n = 96)
Ministry of Health perspective			
Physician consultations	7.85	7.85	84.15
Other health care professionals consultations	24.60	65.10	68.50
Warfarin medication	11.84	9.18	7.03
PT tests*	56.70	60.41	39.07
Site overhead costs	7.25	2.25	NA
Total MoH costs	108.24	144.79	198.75
Patient perspective			
Dispensing fees	24.44	20.77	25.66
Caregiver costs	0.23	0.01	0.23
Homecare costs	0	0.54	0.06
Travel costs	18.06	23.32	12.17
Additional costs	1.89	0.75	0.11
Calculated cost for time lost from work by patients	29.41	7.53	1.89
Calculated cost for time lost from work by caregivers	5.49	0.00	0.25
Total patient costs	79.52	52.92	40.37
Societal perspective			
Site overhead costs	NA	NA	4.62
Total societal cost (MoH + Patient + Overhead)	187.76	197.71	243.74
Total costs, tests every 2.5 weeks†	202.98	204.14	277.23
... and 2.5 mg tablets†	217.49	215.39	285.84
... and dispensing fee of Nova Scotia, \$10.13	233.57	229.06	302.73
... and all caregivers reimbursed for time†	502.62	398.87	308.65

MoH, Ministry of Health; PT, prothrombin time. Bold numbers represent the sum of costs in the three main perspectives followed by the overall management cost (total societal cost) by adding these perspectives. *Calculated according to the proportions of tests done on venous blood or as Point-of-Care Test (Table 2). †Sensitivity analyses with costs recalculated incrementally with adjustments for the most typical interval between PT tests, warfarin tablet strength, dispensing fee in Nova Scotia, and finally for the scenario that volunteer caregivers would be reimbursed.

proportion of patients who reported that they walked to the laboratory (61–65%), which might be much lower in other settings and thus with higher costs incurred. Our travel costs, ranging from \$12 to \$23 per 3 months, may have been underestimated as in a European study, specifically addressing this component, the cost ranged from €3.0 (Portugal) to € 7.7 (France) per visit [10] corresponding to Can\$58–\$149 per 3 months.

In the present study, the cost for warfarin tablets was completely assigned to the Ministry of Health perspective.

Depending on employment status, this cost is in reality partly borne by the patients or third party payers. As a result of the small proportion of the total cost, the complexity of calculating the individual proportions with different levels of co-payments and the fact that the total cost still is the same, we did not determine the real distribution of this cost.

In other studies on the actual cost (rather than Markov modeling) of anticoagulation management, there is a considerable range, which at least partly depends on the items included. Menzin *et al.*[8] reported direct costs corresponding

to US\$54–85 per 3 months, based on staff, laboratory and overhead but not drug. Anderson calculated the direct costs, including drug, laboratory and clinical pharmacist, to US\$153 per 3 months [5]. Abdelhafiz and Wheeldon included costs for drug, laboratory, nurse visits, traveling and work missed at a United Kingdom center, arriving at a cost of £11 per month, corresponding to Can\$58 per 3 months and if cost for complications was added, Can\$1570 per 3 months [14]. Their calculations did not include overheads which may differ in the United Kingdom as monitoring of INRs may be extended to every 8–12 weeks in stable patients according to national guidelines [23,24], whereas in North America a maximum of a 4-week interval is recommended [1]. Chiquette *et al.* [9] compared anticoagulant clinics with usual care and arrived at costs of US\$136 and US\$542, respectively, for a 3-month period, based on hospitalizations and visits to the Emergency Department, and also included costs to obtain refills of the prescription. Björholt *et al.* [6] estimated the direct costs in primary care during different periods from initiation of treatment and reported for the first 3 months, the first and the second year costs of Swedish Krona 6811, 16 244 and 8904, respectively, which converted to 3-month periods corresponding to Can\$ 994, 593 and 325, respectively.

A limitation to our study is that we did not include costs for bleeding or thromboembolic complications as was studied by others [9,14]. We had too short a time horizon and few events, which would result in great uncertainty in such cost estimates. Taking into account adverse events would obviously have increased the total cost. Nevertheless, new treatment alternatives that do not require laboratory monitoring may still result in similar rates of complications. In addition, the risk of bleeding or thromboembolism is dependent on the patient population and the time in therapeutic range [1,25], and comparisons of such costs have to be made head-to-head. Another limitation is that we did not include patient self-management in our models of care. Connock *et al.* [26] concluded in a systematic review that patient self-management is probably not more cost-effective than specialized anticoagulation clinics. In addition, we excluded patients with planned surgical procedures and the costs do therefore not include those associated with peri-operative bridging of anticoagulation. Such costs may be lower with oral anticoagulants with rapid onset and offset of action.

Treatment with warfarin is fraught with a multitude of interactions with other drugs and with food [1]. Minor bleeding events are common and cause great concern to the patients [27]. The patients therefore require frequent contacts with the staff for advice and reassurance, which is illustrated by the relatively high cost accounted for by consultations with health care professionals in the present study. New anticoagulant drugs without or with very few interactions, fixed dosing, a single tablet strength and no need for routine laboratory monitoring should reduce or eliminate the overall costs for medical advice and consultations, laboratory tests, transportation, parking, time lost from work by patients or caregivers and perhaps also dispensing fees. With reduced need for support staff at the

anticoagulation clinics, the space and overhead that can be accounted for should also diminish. These new drugs will without doubt be much more expensive than warfarin. It is then crucial to bear in mind the additional costs associated with warfarin management, in order to make a justified comparison. Cost analyses similar to ours should be performed with the new anticoagulants when available for long-term use. Such studies should include the corresponding number of newly anticoagulated patients and also register all costs pertaining to any safety monitoring mandated by regulatory authorities such as creatinine levels or liver function tests.

Addendum

All of the authors contributed to the design of the study and interpretation of the data. S. Schulman prepared the initial draft of the manuscript. The Steering Committee (Schulman, Anderson, Bungard, Kahn, Wells, Wilson) wrote the protocol and analyzed the data together with McKesson Specialty. All of the authors critically revised the manuscript and approved the final version submitted for publication.

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Disclosure of Conflict of Interests

S. Schulman is chairman of the steering committee for studies on dabigatran in the treatment of venous thromboembolism, and chairman of the data safety monitoring boards for studies on rivaroxaban in the treatment of venous thromboembolism. He has participated at advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, GlaxoSmithKline and Octapharma. D. Anderson has received honoraria for presentations, consultations and research funding from AstraZeneca, Bayer, Boehringer Ingelheim, Pfizer and Sanofi Aventis. T. Bungard has participated at advisory boards for AstraZeneca, Bayer, Boehringer Ingelheim, Pfizer and Roche Diagnostics. She has had travel and speaker honoraria funded by Boehringer Ingelheim. T. Jaeger is an employee of McKesson Specialty Pharmaceutical Solutions. S. Kahn has participated at advisory boards for Bayer, Boehringer Ingelheim and

Sanofi-Aventis. She has received grant support from Sanofi-Aventis and Sigvaris Corp. and honoraria for talks from Leo Pharma, Pfizer and Sanofi-Aventis. P. Wells has received honoraria for presentations made for BioMerieux, Dade Behring, Leo Pharma, Organon and Sanofi Aventis. J.-A. Wilson has no conflicts of interest to disclose. Of the additional investigators S. Solymoss has received honoraria for presentations for Leo Pharma and Pfizer. The study was sponsored by AstraZeneca and coordinated with the assistance of McKesson Specialty. The sponsor and McKesson Specialty had no influence on the writing of the manuscript. McKesson Specialty is an independent company that was reimbursed by AstraZeneca for its assistance to carry out the study by printing case report forms and diary sheets, provide study material, recruit and monitor study sites, collect data, reimburse investigators per patients completed, and analyze the data together with the authors.

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