Clinical and Economic Effectiveness of an Inpatient Anticoagulation Service

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We conducted a prospective cohort study to evaluate clinical and economic end points achieved by a pharmacist-managed anticoagulation service compared with usual care (50 patients/group). The primary therapeutic end point was the time between starting heparin therapy and surpassing the activated partial thromboplastin time therapeutic threshold. The primary economic end point was the direct variable cost of hospitalization from admission to discharge. No significant differences between groups were noted for the primary therapeutic end point. Total hospital costs were significantly lower for patients receiving pharmacist-managed care than for those receiving usual care ($1594 and $2014, respectively, 1997 dollars, p=0.04). Earlier start of warfarin (p=0.05) and shorter hospital stay (5 and 7 days, p=0.05) were associated with the pharmacist-managed group.
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Venous thromboembolism, specifically, deep vein thrombosis (DVT) or pulmonary embolism (PE), is a life-threatening condition resulting in approximately 300,000 hospitalizations and at least 50,000 deaths/year in the United States.[1–3] It is estimated that direct medical costs alone cost the country's health care system at least $600 million annually. It is imperative that treatment be initiated quickly and effectively to avoid fatal complications. Agents of choice for immediate and long-term anticoagulation are intravenous unfractionated heparin (UFH) and oral warfarin, respectively, for DVT and PE.[4] Although much interest has been expressed in subcutaneous low-molecular-weight heparin (LMWH) for outpatient treatment of DVT, substantial numbers of patients with proximal DVT require inpatient treatment.

Failure to achieve adequate anticoagulation with UFH within the first 24 hours of therapy may compromise care and put the patient at 5–15 times the relative risk of developing recurrent thrombi.[5, 6] Unfortunately, UFH's complex pharmacokinetics result in tremendous variability in dosing.[7–9] In 1995, a drug use evaluation of UFH therapy conducted at the Detroit Medical Center (DMC) revealed that only 42% of patients evaluated surpassed the therapeutic threshold within 24 hours of starting therapy with a 5000-U bolus followed by a 1000-U/hour continuous infusion. A weight-based

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nomogram[10] is superior to standard dosing in calculating initial dosages that rapidly exceed the therapeutic threshold and achieve a greater proportion of therapeutic activated partial thromboplastin times (aPTTs).[10, 11]

Once the therapeutic threshold of UFH is surpassed, often within the first 2 days of therapy in standard practice, oral warfarin is considered for at least 3 months. However, complex pharmacokinetics, potential adverse effects, and numerous drug-drug interactions complicate its administration and may lead to inappropriate dosages, unnecessarily long hospitalization, and avoidable adverse events. Clinical evidence suggests that starting warfarin on the same day as UFH is safe and effective,[12] having the potential to shorten the duration of heparin therapy and length of hospital stay. Applying a flexible induction nomogram for warfarin dosing is safe and effective.[13]

We evaluated clinical and economic end points achieved by a comprehensive pharmacist-managed anticoagulation consult service. Results were compared with those in patients receiving usual care. It was hypothesized that the anticoagulation service would result in improved clinical end points, reduced length of stay, and lower total cost of hospitalization.

Adjusted Raschke Heparin Weight-Based Nomogram[10]

Initial dose:	80 U/kg bolus, then 18 U/kg x hr
aPTT < 37 sec (< 1.2 x control):	80 U/kg bolus, then increase infusion rate by 4 U/kg x hr
aPTT 37 to 47 sec (1.2–1.5 x control):	40 U/kg bolus, then increase infusion rate by 2 U/kg x hr
aPTT 48–71 sec (1.5–2.3 x control):	No change
aPTT 72–93 sec (2.3–3 x control):	Decrease infusion rate by 2 U/kg x hr
aPTT > 93 sec (> 3 x control):	Hold infusion 1 hr, then decrease infusion rate by 3 U/kg x hr

Adjusted Fennerty Warfarin Dosing Nomogram[19]

Day	INR	Warfarin Dose (mg)
1	< 1.4	10.0
2	< 1.8	10.0
	1.8	1.0
	> 1.8	0.5
3	< 2.0	10.0
	2.0–2.1	5.0
	2.2–2.3	4.5
	2.4–2.5	4.0
	2.6–2.7	3.5
	2.8–2.9	3.0
	> 3.0	0
	Predicted Dose	
4	< 1.4	> 8.0
	1.4	8.0
	1.5	7.5
	1.6–1.7	7.0
	1.8	6.5
	1.9	6.0
	2.0–2.1	5.5
	2.2–2.3	5.0
	2.4–2.6	4.5
	2.7–3.0	4.0
	3.1–3.5	Miss next day's dose, then give 3.5 mg
	3.6–4.0	Miss next day's dose, then give 3.0 mg
	4.1–4.5	Miss next day's dose, then give 2 mg
	> 4.5	Miss 2 days' doses, then give 1 mg

Figure 1. Adjusted nomograms for managing heparin and warfarin therapy.

Methods

Study Design

A prospective, observational cohort study was conducted to reflect real-world practice and assess effectiveness rather than efficacy of the anticoagulation service. The study was conducted simultaneously at two teaching hospitals in the DMC.

A 24-hour, 7-day/week pharmacist-managed anticoagulation service was established in May 1996 by the Department of Pharmacy Services to provide dosing and monitoring of UFH and warfarin therapies at the request of a physician. The Raschke weight-based UFH dosing nomogram[6] and a modified Fennerty flexible induction warfarin nomogram[13] were approved by the institutions' Pharmacy and Therapeutics and Medical Executive Committees (Figure 1). Pharmacists could deviate from the nomograms based on professional judgment. Once consulted, they also could adjust UFH and warfarin dosages and order appropriate monitoring tests. The UFH dosing nomogram was modified by the hematology laboratory to correspond to ranges of values of the original weight-based nomogram.[6] Before implementation, all clinical pharmacists were trained through a certification process in UFH and warfarin therapeutics and dosing strategies. Health care professionals were informed of this service through in-service programs conducted by pharmacists and by written notification.

Patients

Patient data were collected sequentially from medical charts as a convenience sample until 50 evaluable patients in each group were identified from June 1996–April 1997. Patients were considered eligible if they were admitted for treatment of a DVT or PE and received intravenous UFH. Exclusion criteria were thrombolytic therapy, LMWH, subcutaneous adjusted-dose UFH, thrombectomy or embolectomy, less than 24 hours of intravenous heparin administration, delay of greater than 48 hours from hospital admission to start of heparin therapy, discharge against medical advice, and events unrelated to anticoagulation therapy that would unnecessarily prolong hospital stay by more than 48 hours.

Demographic information recorded for each patient included actual body weight, age, gender, race, and smoking history. Baseline aPTT, prothrombin time (PT), hemoglobin, hematocrit, platelet count, risk factors for thrombosis and bleeding, discharge diagnosis related to heparin therapy, medical service providing patient care, comorbidity, and frequency of adverse events were also noted. Risk factors for thrombosis were defined as concurrent diagnosis of malignancy,[14, 15] history of venous thromboembolism or disorder associated with thromboembolism (e.g., documented protein C deficiency, antiphospholipid antibody syndrome),[16] and prolonged immobilization due to traumatic spinal cord injury (e.g., paraplegia).[17]

Risk factors for bleeding included history of stroke or surgery within 14 days before admission, history of peptic ulcer disease or gastrointestinal or genitourinary hemorrhage, and platelet count below 100 x 10^3/mm^3.[18] Major hemorrhage was defined as overt bleeding with one of the following criteria: decrease in hemoglobin of more than 2 g/dl, transfusion of 2 U or more of blood, or location of hemorrhage in the retroperitoneum, cranium, or prosthetic joint. Minor hemorrhage was defined as overt bleeding that did not meet preceding criteria.[18]

Comorbidity was assessed using the Charlson comorbidity index.[19] Heparin-induced thrombocytopenia was defined as a decrease in platelet count to less than 100 x 10^3/mm^3 or, in patients whose baseline platelet count was below that value, a drop of 50% from baseline.[5, 6] All subsequent aPTTs, platelet counts, hemoglobins, hematocrits, international normalized ratios (INR), and heparin and warfarin dosage adjustments were recorded with respective times of collection.

Economic and efficiency information recorded for each patient included hospital length of stay, UFH and warfarin dosages and duration, number of aPTT and INR values to monitor anticoagulant therapy, estimated pharmacist time involved in providing patient care, interval between blood sampling for aPTT measurements and UFH dosage adjustment when necessary, total cost of hospitalization as determined by the department of finance, and compliance with the nomograms.

Therapeutic and Economic End Points

The primary therapeutic end point was time elapsed between starting UFH therapy and surpassing the therapeutic threshold, which was defined as an aPTT of 48 seconds. Secondary therapeutic end points for UFH therapy were time elapsed before achieving an aPTT within the defined therapeutic range; proportion of

subtherapeutic, therapeutic, and supratherapeutic aPTT values (blood samples drawn < 4 hrs after dosage adjustments were excluded); and number of aPTT values/patient. Secondary therapeutic end points for warfarin therapy were duration between starting warfarin and starting UFH therapy, proportion of patients with a therapeutic INR on day 5 of warfarin therapy and at discharge, and number of INR values/patient receiving warfarin. Nomogram compliance and adverse events associated with anticoagulation therapy were also assessed.

Compliance with the UFH nomogram was defined as absence of deviations in initial bolus doses, maintenance infusion rates, and subsequent dosing. Compliance with the warfarin nomogram was defined as absence of any deviation with respect to warfarin dosing.

The primary economic end point was the direct variable cost of hospitalization from admission to discharge, as determined by the central finance department using a cost accounting system. Secondary economic end points were length of hospital stay and opportunity cost of pharmacist time involved in providing clinical services in the pharmacist-managed anticoagulation group.

Opportunity cost can be defined as the amount that a resource could earn in its highest valued alternative use; it is the value of the alternative that must be foregone when something is produced.[20] Since clinical pharmacists are routinely involved in cost-saving interventions and are paid an annual salary irrespective of these interventions, an opportunity cost is incurred. It was estimated that hourly savings due to drug interventions for the average pharmacist at our institution range from $10.71–48.28 with a weighted average estimate of approximately $16.41/hour.[21] In contrast to opportunity cost, the pharmacist's salary also could be used to assess the economic impact of the service. This was taken into consideration through sensitivity analyses that encompassed these values.

The impact of the anticoagulation service on pharmacist time and workload in the anticoagulation service was evaluated by a written questionnaire that asked clinical pharmacists to estimate the amount of time involved daily in providing clinical services to patients with venous thromboembolism. Areas of interest were amount of time spent writing notes in medical records, writing orders for laboratory tests and changes in regimens, checking laboratory values, consulting with the medical team regarding patient care issues, and miscellaneous activities not covered by the questionnaire (e.g., reviewing patient histories, handling pump failure, communicating with nurses about interventions). All cost data were based on nominal dollars.

The primary a priori economic model considered two gross measures of economic activity—opportunity cost of lost pharmacist intervention time and cost of hospitalization—based on the equation below:

$$\text{Cost}_{\text{pharmacist-managed care}} = \text{cost}_{\text{hospitalization}} + \text{cost}_{\text{pharmacist intervention time}}$$

$$\text{Cost}_{\text{usual care}} = \text{cost}_{\text{hospitalization}}$$

Measurements

Heparin sodium (porcine derived; Wyeth Ayerst, Elkins-Sinn Division, Chicago, IL) was diluted in 5% dextrose solution and administered with infusion pumps. All blood specimens for aPTT and INR values were collected in siliconized Vacutainer tubes (Becton-Dickinson, Rutherford, NJ) containing buffered citrate. The IL Test aPTT-C Activated Partial Thromboplastin Time and IL Test PT-Fibrinogen thromboplastin reagents (Instrumentation Laboratory Co., Lexington, MA) were used to determine aPTT and INR values, respectively, on automated coagulation systems (ACL 3000; Instrumentation Laboratory Co.). The thromboplastin reagent had an international sensitivity index of 1.99.

Statistical Analyses

The independent samples *t* test and the Mann-Whitney U test were used to detect differences between groups for parametric and nonparametric continuous variables, respectively. The χ^2 and Fisher's exact tests were used to compare discrete variables where appropriate. Kaplan-Meier time-to-event analysis was conducted to assess differences between groups with respect to the time required to surpass the therapeutic threshold and to obtain an aPTT within the therapeutic range. Bivariate correlations using Pearson's correlations for parametric data and Spearman's rho statistic for nonparametric data were conducted to assess relationships between clinical and economic variables and aid in constructing efficient regression models. Multiple regression models were constructed and tested through forward selection and backward elimination methods to examine potential determinants of UFH therapy requirements, time of starting warfarin therapy relative to UFH

Table 1. Baseline Patient Demographics

Characteristic	Usual Care (n=50)	Pharmacist-Managed Care (n=50)	p Value
Mean age, yrs	60.4 (19.1)	56.7 (18.3)	0.50
Median weight, kg[a]	73.2 (29.4)	79.8 (30.5)	0.12
Men (%)	42	44	0.84
Race (%)			0.22
African-American	72	86	
Caucasian	22	10	
Other	6	4	
Smokers (%)	32	40	0.36
Thrombosis tendency (%)	70	64	0.52
Bleeding tendency (%)[b]	14.3	16.7	1.0
Baseline hematology laboratory results[c]			
Median aPTT, sec	26.1 (5.6)	27.3 (6.2)	0.12
Median PT, sec	12.7 (1.5)	13.1 (1.6)	0.31
Median hemoglobin (mg/dl)[d]			0.20
Men	13.7 (3.6)	12.0 (3.3)	
Women	12.4 (2.5)	12.6 (1.9)	
Median hematocrit (%)[d]			0.22
Men	40.3 (11.7)	36.4 (10.1)	
Women	38.3 (7.1)	37.8 (6.3)	
Median platelet count, x 10^3/mm^3	223 (102)	226 (123)	0.37
Diagnosis (%)			0.66
PE	16	20	
DVT	76	68	
PE and DVT	8	12	
Patient service (%)			0.35
Internal medicine	82	92	
Oncology	4	2	
Surgery	4	4	
Other	10	2	
Median index of comorbidity	2	2	0.56

PE = pulmonary embolism; DVT = deep vein thrombosis.
Numbers in parentheses are SDs for mean values and interquartile ranges for median values.
[a]Forty-eight patients in the usual care group were evaluable.
[b]Forty-nine and 48 patients, respectively, in the usual care and anticoagulation service groups were evaluable.
[c]Baseline hematology laboratory data were available for 45 and 46 patients, respectively, in the usual care and anticoagulation service groups.
[d]Twenty men were evaluable in each treatment group; 24 and 25 women, respectively, were evaluable in the usual care and anticoagulation service groups.

therapy, length of stay, and total hospitalization cost. Both methods yielded identical final models. The SPSS, version 6.1, was used to conduct the analyses. Sensitivity analyses were performed with a computer software program (DATA; TreeAge, Boston, MA).

A 10,000-iteration Monte Carlo simulation using Latin hypercube sampling was conducted to assess total variability in economic data observed for the primary economic model using a software package (Crystal Ball; Decisioneering, Boulder, CO). Best-fit distributions were generated using available data for cost of hospitalization, length of stay, pharmacist time requirements, and hourly savings from interventions by pharmacists had the service not existed. Correlations among variables were incorporated into the model when available.

A power analysis assuming a significance level of α equal to 0.05 and power of at least 90% revealed that 100 patients (50/group) would be required to detect expected differences in primary clinical and economic end points.

Results

Patient Characteristics

To obtain 50 patients for analysis in the usual care group, 92 charts were reviewed. Forty-two patients were excluded for the following reasons:

Table 2. End Points of UFH Therapy

End Point	Usual Care	Pharmacist-Managed Care	p Value
Median initial bolus dose, U	5000 (1000)	5000 (1250)	0.32
Median initial infusion rate, U/hr	1000 (300)	1100 (363)	0.45
Percentage of patients in whom first aPTT was			
> Therapeutic threshold	78	84	0.44
Within therapeutic range	18	24	0.46
Percentage of patients surpassing therapeutic threshold within			
12 hrs of starting heparin	82	88	0.40
24 hrs of starting heparin	88	92	0.74
48 hrs of starting heparin	92	98	0.36
Median time to first therapeutic aPTT[a], hrs	25.3 (29.3)	23.6 (24.4)	0.14
Median infusion rate of first therapeutic aPTT, U/hr[a]	1000 (388)	1000 (400)	0.82
Number of aPTT values examined	489	476	
Percentage of aPTT values			< 0.001
Subtherapeutic	21.3	15.8	0.03
Therapeutic	41.5	47.7	0.05
Supratherapeutic	37.2	36.6	0.83
Median duration of UFH therapy/pt, days[b]	4.8 (3.04)	4.9 (2.05)	0.92
Median amount of UFH/pt, U[b]	112,300 (87,775)	124,750 (71,575)	0.84
Median number of aPTT values ordered/pt[b]	9 (7)	9 (4)	0.78
Median number of dosage adjustments/pt[c]	4 (3)	4 (3)	0.42
Median time from blood draw to regimen adjustment if necessary, hrs[b]	4.4 (2.9)	2.8 (1.5)	< 0.001

Numbers in parentheses are interquartile ranges.
[a]Two patients receiving usual care did not achieve a therapeutic aPTT or reach a therapeutic state.
[b]One patient in each group was excluded from the analysis due to death.
[c]No regimen adjustments were made in two patients receiving usual care.

therapy with LMWH (3 patients) or subcutaneous UFH (5) for primary treatment, receipt of a thrombolytic agent (11), less than 48 hours of UFH therapy (6), prolonged hospitalization unrelated to anticoagulation therapy (5), premature discharge against medical advice (2), no anticoagulants (3), physician intentionally not desiring a therapeutic aPTT (1), misdiagnosis (2), immediate death (2), and thrombectomy (2).

For the pharmacist-managed group, 83 charts were reviewed before 50 evaluable patients were obtained. Thirty-three patients were excluded for the following reasons: less than 48 hours of UFH therapy (10), delay of more than 48 hours administering UFH from time of admission (2), prolonged hospitalization unrelated to anticoagulation therapy (4), premature discharge against medical advice (4), misdiagnosis (4), absence of laboratory or drug information in the medical record (3), consultation of the anticoagulation service and subsequent discontinuation before completion of therapy (3), thrombectomy (2), and embolectomy (1).

Baseline demographics data for both groups were similar (Table 1).

Therapeutic Outcomes

UFH Therapy

The anticoagulation service was consulted after starting UFH therapy for 70% of patients enrolled in the pharmacist-managed group. The proportion of patients surpassing the therapeutic threshold within 12, 24, and 48 hours of starting UFH was not significantly different between groups (Table 2).

The pharmacist-managed group had a significantly greater proportion of therapeutic aPTT values than the usual care group (47.7% vs 41.5%, p=0.05) and a significantly lower proportion of subtherapeutic aPTT values (15.8% vs 21.3%, p=0.03). Two patients receiving usual care never achieved a therapeutic aPTT throughout UFH therapy, compared with none in the pharmacist-managed group. The median amount of time between a blood draw and response to a nontherapeutic aPTT differed significantly: 2.8 hours in the pharmacist-managed group and 4.4 hours in the usual care group (p<0.001).

In assessing resource use with respect to total inpatient UFH therapy, two patients (one from each group) were excluded from the analysis due to death. Bivariate analyses revealed age, male gender, and weight to be significantly associated

Table 3. Therapeutic End Points of Warfarin Therapy

End Point	Usual Care	Pharmacist-Managed Care	p Value
Percentage of patients treated with warfarin	76	90	0.10
Percentage of patients in whom warfarin was begun within 2 days of heparin	63	82	0.05
Therapeutic INR[a]			
By day 5 of therapy (%)	40	47	0.51
At discharge (%)	58	71	0.21
Median duration of warfarin therapy, days[b]	6 (3.5)	5 (2)	0.49
Median dose of warfarin at discharge, mg[b]	5 (4.4)	5 (2.5)	0.10

Numbers in parentheses are interquartile ranges.
[a]Two patients receiving usual care were excluded, one due to death, one due to lack of warfarin monitoring.
[b]One patient receiving usual care was excluded from the analysis due to death.

with UFH requirements ($r = -0.327$, $p=0.001$; $r = 0.501$, $p<0.001$; $r = 0.291$, $p=0.004$, respectively). After controlling for age and weight in multivariate analyses, gender was no longer significantly associated with UFH requirements at the $\alpha = 0.05$ level, but a trend for greater requirements in men persisted ($\beta = 0.169$, $p=0.064$). Age had an inverse relationship to UFH requirement ($\beta = -0.215$, $p=0.02$) and weight had a directly proportional relationship ($\beta = 0.400$, $p<0.001$). These three factors accounted for approximately 29% of variation in amount of UFH required/patient (adjusted $R^2 = 0.289$).

Warfarin Therapy

Ninety percent of patients in the pharmacist-managed group and 76% in the usual care group received warfarin ($p=0.10$; Table 3). A significantly greater proportion of patients received the drug within 2 days of UFH initiation in the pharmacist-managed group than in the usual care group (82% vs 63%, $p=0.05$). Multiple regression analysis examining the influence of age, gender, diagnosis, amount of time to reach a therapeutic aPTT, bleeding risk, and comorbidity index on the day of starting warfarin relative to UFH revealed no significant associations.

Nomogram Compliance in the Pharmacist-Managed Group

Of the 196 UFH dosage adjustments made after initial dosing, 86 (43.9%) were consistent with the UFH nomogram.

For the 45 patients receiving warfarin, no deviations from the nomogram were observed for 14 patients (31.3%). Of the 31 patients in whom deviations occurred, the nomogram did not apply to 9. Seven of these patients required greater than 10 mg/day to attain a therapeutic INR (the nomogram does not account for such patients), one had previously received warfarin and the maintenance dosage was known and given, and one had warfarin held due to a minor bleeding event.

Adverse Events

Major bleeding did not occur in any patient receiving pharmacist-managed care but did occur in two (4%) receiving usual care. One of these patients had a therapeutic aPTT at the time of bleeding and was not receiving warfarin. The other patient whose INR rose to 16.8 and whose aPTT was slightly supratherapeutic at the time of bleeding, suffered a major intracerebral bleed that resulted in death. One patient in the pharmacist-managed group died due to a PE that was suspected to have developed during hospitalization. The patient was not receiving warfarin and the aPTT was slightly subtherapeutic at the time of death. No statistically significant differences were observed between groups with respect to minor bleeding complications (8% each group). No patient in either group developed thrombocytopenia.

Economic Outcomes

Cost of Hospitalization

In assessing differences in cost of hospitalization, accurate financial data were readily available for 89 of the 100 patients, after excluding 2 deaths. Median cost was approximately 21% less for the pharmacist-managed (n=42) group than for the usual care (n=47) group ($1594 and $2014, respectively, $p=0.04$). Bivariate analyses revealed length of stay, day starting warfarin therapy, and proportion of aPTT values above therapeutic threshold to be statistically significantly associated with cost of hospitalization ($r = 0.61$, $p<0.001$; $r = 0.328$, $p=0.005$; $r = -0.276$, $p=0.009$, respectively). The proportion of aPTT values

Table 4. Composition of Anticoagulation Service Workload[a]

Activity (%)	Shift		
	Morning (n=18)	Afternoon (n=6)	Midnight (n=4)
Writing progress notes in patient charts	31	31	34
Writing orders and changing anticoagulation regimens	24	31	31
Checking laboratory results	17	17	18
Consulting with medical team regarding patient issues	28	21	17
Total estimated time, minutes (range)	22 (12–62)	19 (12–52)	16 (22–47)

[a]Figures represent estimated daily times as a proportion of total daily times in the respective work shift spent by clinical pharmacists in caring for an average patient for whom clinical services were provided in the nomogram-based care group.

above therapeutic threshold and day of starting warfarin relative to UFH were inversely correlated (r = -0.326, p=0.005). In multivariate analyses, only length of stay was significantly associated with cost of hospitalization and accounted for approximately 47% of the observed variation (adjusted R^2 = 0.466, β = 0.687, p<0.001 for length of stay).

Length of Hospital Stay

Median overall length of stay, excluding two deaths, was significantly shorter for the pharmacist-managed group than for the usual care group (5 and 7 days, respectively, p=0.05). Bivariate analyses for the 89 patients with sufficient financial data revealed weight, day of starting warfarin relative to UFH initiation, and comorbidity index to be statistically significantly associated with length of stay (r=0.263, p=0.013; r=0.353, p=0.002; r=0.221, p=0.038, respectively). On multivariate analyses, however, only weight and day of starting warfarin therapy had a significant, positive relationship to length of stay and accounted for approximately 24% of the observed variability (adjusted R^2 = 0.235; β = 0.254, p=0.01 for weight, β = 0.422, p<0.001 for day of starting warfarin).

Analysis of patients excluded from cost assessments showed no significant differences between groups regarding length of stay.

Pharmacist Opportunity Cost

Average daily total time attributable to providing anticoagulation management services by pharmacists was estimated to be approximately 1 hour/patient (range 33–80 min, Table 4). Given an opportunity cost of $16.41 ($10.71–48.28)/hour from lost interventions for a median of 5 days/patient, it was estimated that $82 would be lost in providing services for the average patient managed in the anticoagulation service group. Since the difference in median cost of hospitalization between groups was $420, a benefit:cost ratio of 5:1 for providing the service was calculated and an approximate net savings/patient of $338 (17% reduction in net costs/patient) was expected.

One-way sensitivity analysis showed cost savings in favor of pharmacist management if the average patient required less than an average of 5 hours of care/day. Two-way sensitivity analysis examined the interaction between amount of time required/day/patient and hourly savings that would have been realized had the pharmacist-managed service not been implemented (i.e., opportunity cost; Figure 2). Results of the Monte Carlo simulation were consistent with our original analyses and indicated a mean net savings/patient of $340 (95% confidence interval [CI] for the mean $313–368) and an overall benefit:cost ratio of 5.0.

Discussion

The results of this study indicate possible significant clinical and economic benefits in implementing a pharmacist-managed anticoagulation service for inpatient treatment of DVT or PE relative to usual care. A greater proportion of therapeutic aPTT values, earlier start of warfarin therapy relative to UFH therapy, faster response to nontherapeutic aPTT values, shorter hospitalization, and lower total hospital costs were significantly associated with the pharmacist-managed group. A major determinant of hospital length of stay and, in turn, cost of hospitalization was the day of starting warfarin, if indicated, relative to UFH initiation. Starting warfarin earlier was associated with a shorter hospital stay. The day of starting warfarin was inversely related to the proportion of aPTT values above the therapeutic threshold, both of which were significantly more favorable in the pharmacist-managed group. Given an annual admission of approximately 300 patients with a primary diagnosis of DVT or PE between the two institutions and an estimated reduction in net

costs of 17% in the pharmacist-managed group, annual savings of approximately $101,000 may be realized from providing anticoagulation services.

Although these findings are encouraging and support implementation of similar services, several methodologic limitations of this study must be addressed before generalizations can be made. An observational design was chosen for its ease of implementation and real-world appeal. An observational study collects data from an existing system and does not intentionally interfere with the operation of the system.[22] As with any observational design that does not employ blinding or randomization, the issues of bias, confounding, and chance must be explored.[23]

Selection bias may result in an uneven allocation of patients to study groups and unfair comparison. Baseline patient demographics, however, indicate reasonable comparability between groups with respect to measured variables. Information bias may result in different data collected between groups and threaten a valid analysis. All clinical data were collected with a standard form to allow for consistent, objective information. Since patient data were collected as a convenience sample through chart review based on availability, it is possible that differential chart selection may have occurred. All efforts were made, however, to include all sequentially available charts regardless of study group status. If a sequential chart was excluded, the reason for exclusion was documented and reviewed to ensure legitimate exclusion according to a priori exclusion criteria.

Since the anticoagulation service was provided on a consult basis, it is possible that physicians consulted pharmacists according to perceived difficulty in managing the patient themselves. The impact of this potential phenomenon on our results is difficult to evaluate. Financial data were reported independently by the finance department without knowledge of study group designation.

Our results may be significantly confounded by a cross-contamination effect.[22] Nomograms were given to requesting physicians regardless of their use of the anticoagulation service. Pharmacists also provided educational services to other clinicians regarding the nomograms. Although prestudy data from 1993 revealed that only 42% of patients evaluated surpassed the therapeutic threshold within 24 hours of starting heparin therapy, the results of the current study indicate that this statistic for the usual care group more than doubled to 88%. Furthermore, 82% of heparin orders were begun with a traditional bolus dose of 5000 U and a continuous infusion of 1000 U/hour according to 1993 data compared with 44% in the usual care group for this study. Although these contrasts may represent natural progression in physician practice patterns, they may be more likely related to heightened awareness and use of nomograms. Given this contamination effect, clinical differences between study groups may have been weakened.

Sample sizes were calculated based on expected clinical differences between groups according to previous studies.[6, 11] Significant differences in certain clinical end points may not have been found due to confounding effects. Differences in less common outcomes, for example, major bleeding, also may not be apparent due to the small sample. Larger samples are necessary to detect such important differences.

Compliance with nomograms in the pharmacist-managed group was poor. Although

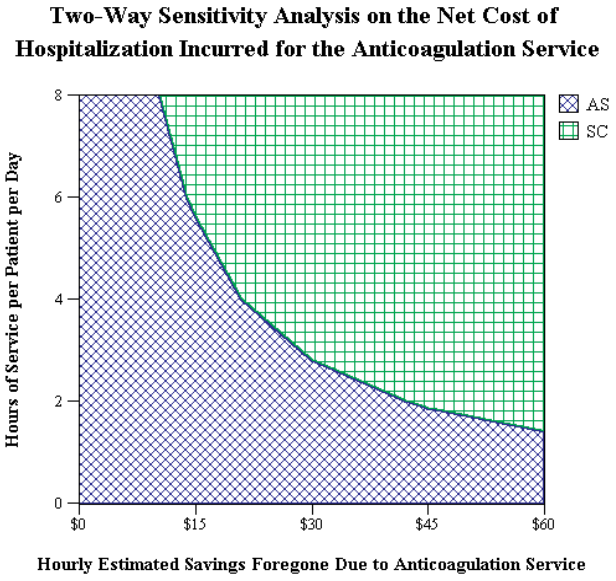

Figure 2. Two-way sensitivity analysis has two shaded areas, each corresponding to a different region of preference. The line separating the areas represents economic break-even points for various combinations of the two variables. At these points, costs associated with either strategy will be approximately the same. For example, if it were expected that 2 hours/patient/day would be required at an opportunity cost of $30/hour in providing anticoagulation services, this combination of values would fall in the region of preference corresponding to pharmacist-managed care. In this case, cost savings would be realized from such a service relative to usual care.

deviation from the nomograms was discouraged, clinical judgment by the pharmacist was recommended whenever uncertainty arose. Physicians consulted the anticoagulation service after initial UFH bolus dosing and establishment of continuous infusion rate for approximately 70% of patients, leading to immediate, uncontrollable deviation from the nomogram. As a result, data analysis for the pharmacist-managed group during the first 24 hours may be inaccurate. Although these outcomes reflect real-world practice, efforts must be made to improve nomogram compliance and enhance earlier nomogram implementation through the anticoagulation service.

The results may be limited to the particular nomograms. Since compliance was poor and a significant proportion of dosage adjustments were based on pharmacists' clinical judgment rather than nomograms, qualitative factors characteristic of clinicians at a particular institution must be taken into consideration. Generally, clinicians are most likely to accept guidelines that are easy to implement and that increase efficiency.[24] Much discussion has evolved around the initial dosing of warfarin. Although many experts now recommend 5 mg rather than 10 mg, this information was not available at the time the study was conducted. The pharmacists were trained, however, to deviate from the nomogram and give a 5-mg starting dose in elderly patients and those receiving drugs with a high interaction potential with warfarin.

Estimation of pharmacist time was based on a questionnaire rather than time-motion studies. The opportunity cost was assessed using data derived from an established computerized system at our institutions.[21] Both methods may be fairly inaccurate and highly variable. Sensitivity analyses were conducted to assess the impact of this variability on the results more accurately and strengthen the economic findings. Also, patients in whom a diagnosis of DVT or PE was ruled out were excluded from the analysis. Although these patients required a limited amount of service time until the diagnosis was ruled out, sensitivity analyses revealed that this should not significantly affect the economic findings.

Ability to generalize our findings may be limited depending on the institution, disease states treated, and nomograms used. All institutions must assess the feasibility of implementing a similar anticoagulation service. Such a service may be provided more practically by institutions that are well staffed with trained pharmacists to provide daily, 24-hour service. Commitment from leadership, workload demands, cooperation with other health care personnel, institution environment, and potential costs all must be considered before such an initiative can be undertaken. Other health care professionals, for example nurses,[6] have successfully implemented such a practice with clinical benefits. Support of the coagulation laboratory also may be a significant consideration. Finally, our results pertain to patients diagnosed with DVT or PE and may not be extrapolated to those with other disorders.

Although much interest has been expressed in subcutaneous LMWH for outpatient treatment of DVT[25, 26] and PE, approximately one-half of patients with proximal DVT may not be eligible for such treatment in a typical environment and may require inpatient treatment based on trial criteria.[27] Such patients would include intravenous drug abusers, those who are noncompliant, and patients with bleeding disorders, complex thrombosis, or poor access to hospitals. Depending on the nature of the institution, such a service may be more valuable if a significant proportion of patients require inpatient treatment.

Despite these limitations, our findings suggest potential clinical and economic benefits associated with a pharmacist-managed anticoagulation service relative to usual care. Continual monitoring of both clinical and economic outcomes after establishing such a service is essential in ensuring its real-world effectiveness and in identifying areas for improvement in patient care.

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