

Clinical Pharmacy Anticoagulation Service

"This model shifts the majority of anticoagulation therapy management to a clinical pharmacist working in partnership with the physician and within written guidelines."

The commonly prescribed anticoagulant warfarin requires meticulous laboratory monitoring and follow-up and is the drug most frequently associated with drug-induced hospitalization. The Clinical Pharmacy Anticoagulation Service (CPAS), originated in 1991 with the objectives of assisting physicians and patients in the systematic management of anticoagulation therapy, shifts most anticoagulation therapy management to a clinical pharmacist. In addition to warfarin management, later additions to CPAS included low molecular weight heparin therapy for deep venous thrombosis. The system, one of the largest in the US, manages over 4200 anticoagulated persons with daily 24-hour availability. Analysis of data regarding thromboembolism and bleeding episodes related to warfarin before and after CPAS showed substantial benefits. For example, 1) the percentage of patients with INR values > 6 who developed major bleeding decreased from 6.31% to 1.19%/year (relative risk reduction = 82%; 95% confidence interval 47% to 94%), 2) the risk of hospitalization for a complication of anticoagulation therapy was reduced by 30%, and 3) there was a 77% reduction in the risk of death attributable to complications/failure of anticoagulation medications. After CPAS, the annual rate of major thromboembolism was 2.5%/patient-year, compared with a reported global average of 4.1%/patient-year. The use of low molecular weight heparin therapy for deep venous thrombosis resulted in substantial reductions in number and costs of hospitalizations. In conclusion, the CPAS has improved the quality of anticoagulation therapy by reducing rates of major bleeding, thromboembolism, hospitalization, and death.

The Clinical Pharmacy Anticoagulation Service (CPAS) project was initiated in the Rocky Mountain Division, Denver/Boulder Colorado Local Market in November, 1996. Team member names/titles are provided in Table 1.

Background

The anticoagulant warfarin is among the most commonly prescribed medications in the US. Warfarin is distinguished by being the drug with greatest potential for clinically significant drug interactions and is the agent most frequently associated with drug-induced hospitalization (secondary to bleeding or clotting complications). The difference between an effective dose and a dangerous dose of warfarin is small. Consequently, patients receiving warfarin therapy require meticulous laboratory monitoring and follow-up to assure compliance, and detect bleeding episodes so as to minimize potential for an unfavorable outcome. A patient's response to warfarin therapy is monitored by using the international normalized ratio (INR), a measure of how long it takes the patient's blood to clot.

Our Clinical Pharmacy Anticoagulation Service (CPAS) originated in 1991, when a model for anticoagulation therapy management by clinical pharmacists was developed by a clinical pharmacy specialist at our Westminster Medical Office. This model shifts the majority of anticoagulation therapy management to a clinical pharmacist working in partnership with the physician and within written guidelines. All related activities and outcomes are documented in a comprehensive computerized patient profile and monitoring system. Subsequent internal medicine quality improvement audits and the results of a retrospective outcomes analysis (see Publications) showed improved anticoagulation management at Westminster compared with other medical offices in this Local Market.

In 1996, at the request of CPMG and KFHP leadership, our pharmacy department—in collaboration with nursing, laboratory, and the Medical Group—developed a plan to expand CPAS to the rest of the Local Market (11 medical offices and over 200 physicians). Rollout of the marketwide service began in November, 1996. Our CPAS now manages over 4,200 anticoagulated patients and is staffed by 11 FTEs (1 chief, 2 clinical pharmacy specialists, 6 clinical pharmacists, and 2 pharmacy technicians). Our CPAS has expanded the basic model described to include a comprehensive list of anticoagulation services, including: 1) Outpatient management of approximately 200 episodes of deep vein thrombosis (DVT) each year; 2) Prevention and treatment of venous

Table 1. Clinical Pharmacy Anticoagulation Service (CPAS)

Team member names/titles: Daniel Witt, PharmD, CPAS Chief; Donald Tillman, PharmD, Clinical Pharmacy Specialist; Michael Rapp, RPh, Clinical Pharmacist; Keith Wallin, RPh, Clinical Pharmacist; Debra Wilkinson, PharmD, Clinical Pharmacist; Robyn LeDoux, Pharmacy Technician; Mary Alarcon, Pharmacy Technician; Kent Nelson, PharmD, Clinical Pharmacy Services Administrator; Dennis Helling, PharmD, Pharmacy Operations Director; Hal Spritzer, MD, Medical Director of Pharmacy Utilization and Therapeutics; Nikki Carroll, MS, Pharmacy Analyst

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thromboembolism in about 12 high-risk pregnancies annually by using self-administered unfractionated heparin; 3) Prevention of DVT after orthopedic surgery for the patients of 8 surgeons; 4) Management of anticoagulation therapy in over 100 patients residing in over 50 nursing homes; management of excessive anticoagulation; and 5) Interruption of anticoagulation therapy for invasive procedures (eg, surgery, endoscopy, colonoscopy, and biopsy).

Objectives

The primary objectives of the CPAS are to:

- Assist the physician and patient in systematic management of anticoagulation therapy;
- Decrease the possibility of untoward effects (ie, bleeding and clotting) due to anticoagulation therapy failure or complications, including hospital admissions, emergency department visits, and medical office visits;
- Improve quality and consistency of care through development and implementation of anticoagulation therapy guidelines.

Scope and Significance

Scope of Quality Issues and Member Impact

Our anticoagulated members receive intensive monitoring, including prompt notification of test results, reminder notifications of missed laboratory visits, and after-hours notification of critical test values. Our anticoagulated members have confidence in the advice of the CPAS staff and routinely contact the service with questions related to their anticoagulation therapy (eg, drug, food, and vitamin interactions, compliance issues, goals of treatment, coordination of therapy during travel, etc). Our anticoagulated members receive written and verbal instructions regarding safe use of anticoagulation medications and become actively involved in managing their disease. All aspects of anticoagulation therapy are coordinated through our CPAS, a procedure which results in seamless continuity of care: therapy initiation; patient education; schedule for drawing blood (including visiting nursing or mobile phlebotomy services if necessary); adjustment of anticoagulation medication dosages; management of adverse events; and discontinuation of therapy when appropriate. The care provided by our CPAS reduces potential for bleeding and clotting complications.

Magnitude

Our CPAS is among the largest in the US and manages over 4200 anticoagulated members in the

Denver/Boulder Market—more than tenfold greater than the mean number of patients followed by other anticoagulation services (amount based on a 1997 survey reported in proceedings of The Anticoagulation Forum).

Our CPAS staff personally phones over 300 patients daily.

Our CPAS staff manages the patients of more than 200 physicians (internists, family practitioners, orthopedists, cardiologists, obstetricians, perinatologists, rheumatologists, pediatricians, pulmonologists, gerontologists, oncologists, hematologists).

Our CPAS model has recently been implemented in the Kansas City KP Local Market and is being considered by national KP leadership (Division Presidents/Executive Medical Directors) for widespread implementation as a pharmacy/medical quality improvement best practice.

Relevance of Project to Direct Patient Care

Coordination of all aspects of anticoagulation therapy from a centralized service has resulted in favorable operational changes in several departments, including:

- Laboratory: consolidation of prothrombin time processing with resultant reduction in equipment and personnel costs, simplification of critical INR laboratory value reporting, switch to more accurate thromboplastin reagent;
- Nursing: elimination of need for role in time-consuming day-to-day management of anticoagulation therapy;
- Medical Group: simplification of transition between inpatient and outpatient care for anticoagulated patients, elimination of need for role in time-consuming day-to-day management of anticoagulation therapy, delegation of responsibility for managing anticoagulated orthopedic and nursing home patients, elimination of need to hospitalize most DVT patients;
- Pharmacy: simplification of procedure for managing anticoagulation therapy drug interactions, streamlining of refill authorization process for anticoagulation medications, creation of expanded and more satisfying role for pharmacists and pharmacy technicians;
- Patients, caregivers, and medical staff are able to contact our CPAS 24 hours a day, 7 days a week.

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Practice Innovation/Leadership; Member/Community Impact

A descriptive overview of our CPAS was chosen to highlight the extent to which anticoagulation services are occurring in managed care settings. Dr. D.J. Tillman is nationally recognized for his role in successful implementation and documentation of the cost impact of our outpatient treatment of DVT program. Our CPAS is the keystone for continuing success of this program. Our CPAS has published research in major medical journals (see Publications).

Methodology

Management of Excessive Anticoagulation

Prior to implementation of our CPAS, we assessed management and outcomes of excessive anticoagulation (INR >6.0) within our organization (see Publications). Data were collected for all episodes identified through a laboratory computer search during a 9-month interval by using a standard form. Information for cost analyses were collected concurrently. After implementation of our CPAS, the above analysis was repeated for all episodes of excessive anticoagulation during a 6-month interval.

Outpatient Treatment of Deep Vein Thrombosis with Low Molecular Weight Heparin

In 1996, a multidisciplinary team consisting of representatives from the pharmacy, hematology/oncology, internal medicine, family medicine, alternate care, pathology, and quality improvement departments developed a guideline for outpatient treatment of DVT with the low-molecular-weight heparin agent enoxaparin. This innovative program allowed patients who formerly would have been hospitalized for a minimum of five days to be treated at home. Comprehensive outcome data were collected by using a standard form for the first 131 patients to receive treatment according to the guideline.

Repackaging Enoxaparin in Patient-specific Dosages

Much of the initial pilot project involved educating patients in preparation of enoxaparin doses. This difficult and time-consuming process involved transferring the correct amount of enoxaparin from multiple prefilled 30-mg syringes into a single tuberculin syringe. This process also resulted in much waste, because only 30-mg increments could be dispensed from the pharmacy. Concerns about sterility and stability prevented the pharmacy from repackaging enoxaparin for patients. To reduce waste, a study evaluating stability of enoxaparin in tuberculin syringes was completed (see Publications).

National Benchmark Cost Savings

The associated cost savings entirely offset the costs of operating the CPAS. We project annualized cost savings of \$700,000 from this innovative outpatient treatment of DVT with low-molecular-weight heparin program alone.

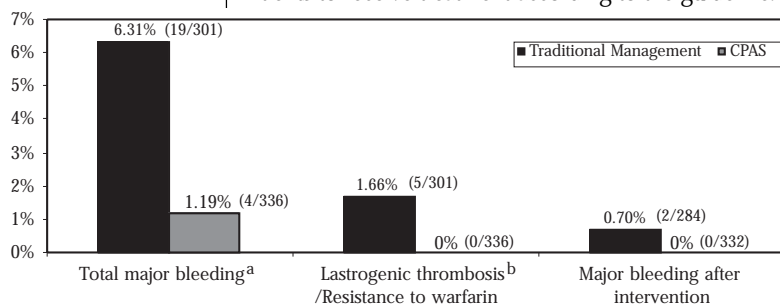
Anticoagulation Therapy Outcomes

The rollout of our CPAS occurred sequentially over time. The initial group of primary care patients was enrolled beginning in the 4th quarter of 1996; the final group was enrolled in the 1st quarter of 1998. This enrollment procedure afforded the unique opportunity to compare, in a parallel fashion, anticoagulation therapy outcomes of patients enrolled in our CPAS with patients managed by their primary care physician (traditional management).

Outcome data for the calendar year 1997 were collected for all patients comprising the first medical office enrolled in the service (East Denver Medical Office). During the same time, similar data were collected for all patients managed by primary care physicians at the last medical office enrolled in the service (Skyline Medical Office). Information was extracted from clinic and hospital medical records, death certificates, and various computerized databases by using standard forms. Data relating to the following variables were collected for each group: demographic information; patient-years of anticoagulation therapy; mean length of anticoagulation therapy during the study period; incidence and costs of every hospitalization and emergency room visit due to complications or failure of anticoagulation therapy; incidence of deaths directly attributable to complications or failure of anticoagulation therapy.

The occurrence of adverse outcomes was verified through objective evidence in all but two cases. Defini-

"The 6-month results from reanalysis demonstrated dramatic improvement in the clinical outcomes and management of excessive anticoagulation."



^a Overt hemorrhage associated with decrease of ≥ 2 g/dl in hemoglobin concentration, transfusion of ≥ 2 units of blood, or any intracranial, gastrointestinal, intraarticular, or retroperitoneal bleeding.
^b Embolic cerebrovascular accident, pulmonary embolism, DVT, or other systemic thromboembolic event documented through objective evidence.

Figure 1. Clinical Pharmacy Anticoagulation Service (CPAS). Adverse clinical outcomes of excessive anticoagulation (INR > 6.0): CPAS vs traditional management.



Table 2. Vitamin K use patterns before and after implementation of CPAS

Route	Percentage total vitamin K doses		Mean dose \pm SD ^a		Comment
	Before CPAS	After CPAS	Before CPAS	After CPAS	
Subcutaneous	39	30	11.76 \pm 9.40 mg	3.92 \pm 3.60 ^b	Correct dose = 1 mg; route not recommended due to unpredictable absorption
Intramuscular	38	0	12.73 \pm 14.62 mg	NA	Route contraindicated due to potential for bleeding at injection site
Intravenous	7	0	5.50 \pm 5.20 mg	NA	Correct dose = 1 mg
Oral	16	70	11.25 \pm 5.82 mg	3.03 \pm 1.06 ^c	Correct dose = 2.5-5 mg

^a Administration of large (>3 mg) doses increases the risk of iatrogenic resistance to the effects of warfarin and subsequent clot formation
^b Includes one 10-mg dose administered without consultation with our CPAS
^c Statistically significant (p < .001)

“Compared with traditional management, for every 20 episodes of excessive anticoagulation managed by our CPAS, one major hemorrhage is prevented.”

tions for major bleeding and thromboembolism were as described previously (Figure 1). Risk ratio estimates for the occurrence of hospitalization and death were calculated along with 95% confidence intervals. Cost minimization analysis was performed on the hospitalization data.

Global Benchmark Clinical Outcomes

We also compared frequency of adverse outcomes experienced by patients cared for by our CPAS with those reported in the medical literature by other anticoagulation services (Table 6).

Results

Management of Excessive Coagulation

The results of our analysis identified opportunities to improve management of excessive anticoagulation within our organization (Table 2, Figure 1). Frequent administration of vitamin K (reverses the anticoagulant effect of warfarin) in excessive doses resulted in three cases of resistance to the effects of warfarin, all of which required hospitalization for administration of alternative forms of anticoagulation medication. New clotting complications occurred in two of these cases. For INRs between 6.0 and 10.0, incremental cost effectiveness analysis determined that overzealous treatment with vitamin K is about seven times more costly than conservative management (temporary discontinuation of warfarin therapy until INR declines to within the therapeutic range). Therefore, to prevent one major bleeding episode, an additional \$70,500 would be spent treating with vitamin K compared with temporary withdrawal of warfarin therapy.

The 6-month results from reanalysis demonstrated dramatic improvement in the clinical outcomes and management of excessive anticoagulation (Table 2, Figure 1). Because vitamin K was used sparingly (12.4% of episodes before vs 5.4% after CPAS implementation) and in appropriate doses, no patient required hospitalization for iatrogenic thrombosis or for resistance to the effects of warfarin. The percentage of patients receiving vitamin K intramuscularly (a route of administration contraindicated in excessively anticoagulated patients) decreased from 38% to 0%. The total percentage of patients who developed major bleeding decreased from 6.31% (19/301) to 1.19% (4/336) after implementation of our CPAS (relative risk reduction of 82%; 95% confidence interval 47% to 94%). Compared with traditional management, for every 20 episodes of excessive anticoagulation managed by our CPAS, one major hemorrhage is prevented. No major bleeding occurred once the decision to administer vitamin K or to temporarily withhold warfarin therapy was made by CPAS pharmacists compared with two such episodes before implementation of the service. No INR exceeded 20 (a critical value) compared with 17 such episodes before implementation of the service.

Outpatient Treatment of Deep Vein Thrombosis with Low-Molecular-Weight Heparin

Outcomes for outpatient treatment were equivalent to those expected for inpatient treatment of DVT (Table 3). Average cost to the organization for managing a patient according to the guideline was \$855



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± 443 (includes cost of enoxaparin, visiting nursing, laboratory, ECC/urgent care visits, clinic visits, hospitalization, and personnel). Hospitalization cost avoided for each patient treated according to the guideline was \$4197 ± 1142, yielding a cost savings per patient of \$3342 ± 1196. For the initial 131 patients, the total cost savings was \$437,788.

Beginning in September 1997, our CPAS assumed complete responsibility for administration of the outpatient treatment of DVT program. Through June 30, 1998, an additional 163 patients were treated according to the guideline, resulting in additional \$544,728 in cost savings to the organization.

Repackaging Enoxaparin

Results indicated that sterility and potency of repackaged enoxaparin are maintained for 10 days under refrigeration. Now all patients receiving enoxaparin for the outpatient therapy of DVT receive prefilled syringes with the correct dose of enoxaparin repackaged by the pharmacy. Repackaging enoxaparin in patient-specific dosages has resulted in provision of an aseptic product, en-

hanced patient compliance with ease of administration, and projected cost savings of \$40,000 annually through decreased waste.

Anticoagulation Therapy Outcomes

Table 4 summarizes baseline characteristics of the study groups. The groups were comparable with regard to sex and average duration of anticoagulation therapy. The group managed by the CPAS was older on average than the traditional care group. We believe this age difference would predispose the CPAS group to more complications, as increasing age generally increases risk for major bleeding and thromboembolism. Thus, the favorable effects demonstrated on the incidence of adverse outcomes are probably underestimated.

Summary of Improved Risk Reduction, Complication Rates, and Associated Costs

Table 5 summarizes the impact of our CPAS on occurrence of anticoagulation-therapy-related adverse events:

- The relative risk of being hospitalized for a complication of anticoagulation therapy was reduced by 30% overall.

Table 3. Outpatient treatment of DVT outcomes for first 131 patients

Length of enoxaparin therapy (days)	5.8 ± 1.3
Uncomplicated completion of therapy (90 days)	125 (95.4%)
Increased thromboembolic symptoms:	
DVT	7 (5.3%)
Pulmonary embolus	5 (3.8%)
	2 (1.5%)
Major bleeding	0 (0%)
Minor bleeding	6 (4.6%)
Thrombocytopenia	0 (0%)
INR >2.0 by day 7 of therapy	112 (85.5%)
Admitted to hospital	5 (3.8%) ^a
Average KP cost per patient treated according to guideline	\$855 ± 433
Hospitalization cost avoided per patient	\$4,197 ± 1,142
Net cost savings per patient	\$3,342 ± 1,196
Total cost savings	\$437,788

^a 1 pulmonary embolus on day 5 of therapy; 1 questionable pulmonary embolus on day 2 of therapy (patient with concurrent lung pathology and moderate probability V/Q scan); 2 extensions of DVT; 1 patient unable to tolerate enoxaparin injections

**Table 4. Summary of baseline characteristics**

Characteristic	CPAS (n=663; 516 patient-years)	Traditional care (n=311; 241 patient-years)	P Value
Sex (% male)	47.78	52.92	NS
Age (years ± SD)	69.08 (13.54)	66.21 (12.40)	0.001
Mean LOT ^a (years ± SD)	0.78 (0.34)	0.78 (0.33)	NS

^a LOT = Length of anticoagulation therapy during the one-year study period.

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Table 5. Summary of anticoagulation therapy adverse outcomes

Outcome	CPAS	Traditional Care	Risk Ratio	95% Confidence interval
Hospitalization ^a :				
Major bleeding	0.90% (6/663)	1.29% (4/311)	0.70	0.20 to 2.50
Thromboembolism	1.66% (11/663)	2.57% (8/311)	0.64	0.25 to 1.61
Total	2.71% (8/311)	3.86% (12/311)	0.70	0.33 to 1.46
Death	0.15% (1/663)	0.64% (2/311)	0.23	0.02 to 2.60

^a Categorized as none, or 1 hospitalization (1 patient in Traditional Care group had 2 hospitalizations for major bleeding; 2 patients in CPAS group had 2 hospitalizations for thromboembolism)

“The thromboembolic rate for our CPAS was lower than for all other reported services (except one), and 40% lower than the global average.”

- Cost minimization analysis showed hospitalization cost savings of \$70.30 for each patient-year of management by our CPAS.
- This amount equates to more than \$280,000 in annualized hospitalization cost savings when applied to the total number of patients managed by our CPAS.
- Improved management of therapy by our CPAS resulted in a 77% relative reduction in risk of death directly attributable to complications or failure of anticoagulation medication (Table 5). This risk reduction is equivalent to prevention of one therapy-related death for every 204 patients managed by our service (approximately 19 lives each year).

Global Benchmark Clinical Outcomes

- The major hemorrhage rate for our CPAS was less than half of any comparable anticoagulation service reported in the literature, and one fifth that of the global average (Table 6).

- The thromboembolic rate for our CPAS was lower than for all other reported services (except one), and 40% lower than the global average.
- Fatal event occurrence for our CPAS was less than half of any comparable anticoagulation service reported in the literature, and just under one fifth that of the global average.

Conclusions

As summarized in Figure 2, our CPAS has improved the quality of providing anticoagulation therapy to members in the Denver/Boulder Market. Our CPAS has decreased the rate of:

- Major bleeding due to excessive anticoagulation;
- Hospitalization due to major bleeding;
- Hospitalization due to thromboembolism;
- Total hospitalization;
- Death.

"We believe that our CPAS model epitomizes the unique power of a group-model managed care organization like Kaiser Permanente to identify and manage high-risk drug therapy patients and to achieve unparalleled clinical outcomes and cost savings."

Figure 3 summarizes how CPAS has documented annualized cost savings of \$1,020,000 by providing anticoagulation therapy to members in the Denver/Boulder Local Market.

Total cost savings include:

- \$700,000 for the outpatient treatment of deep vein thrombosis (DVT);
- \$40,000 for re-packaging of enoxaparin in patient-specific doses;
- \$280,000 for reduced hospitalization costs.

The collaborative model of our CPAS as developed and implemented by the pharmacy department with assistance and multidisciplinary cooperation of nursing, laboratory, and the Medical Group is currently being considered by national Kaiser Permanente leadership for widespread implementation as a pharmacy/medical quality improvement best practice.

Most health care organizations are either still in the process of implementing similar low-molecular-weight heparin programs or are still in the conceptualization phase. Our program is not only operational—it is a model

for other programs nationwide. Our CPAS has garnered local and national recognition for the preeminent care provided to our members needing anticoagulation. We believe that our CPAS model epitomizes the unique power of a group-model managed care organization like Kaiser Permanente to identify and manage high-risk drug therapy patients and to achieve unparalleled clinical outcomes and cost savings. ❖

Publications

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- Lousberg TR, Witt DM, Beall DG, Carter BL, Malone CD. Evaluation of excessive anticoagulation in a group model health maintenance organization. *Arch Intern Med* 1998;158:528-34.
- Charland SL, Davis DD, Tillman DJ. Activity of enoxaparin sodium in tuberculin syringes for 10 days. *Am J Health Syst Pharm* 1998;55:1296-8.
- Charland SL, Tillman DJ, Davis DD. The use of low-molecular weight heparin in the outpatient treatment of venous thrombosis. *Pharmacotherapy* 1997;17:183.

Table 6. Frequency comparison of adverse outcomes associated with oral anticoagulation therapy

Complication	Global benchmark range ^{ab}	Global average ^{ab}	CPAS
Major hemorrhage	2.5-13.4%/pt-year	6.1%/pt-year	1.16%/pt-year
Thromboembolism	0.7-7.5%/pt-year	4.1%/pt-year	2.5%/pt-year
Fatal events	0.4-1.4%	0.7%	0.15%

^a Ansell JE, Buttaro ML, Thomas OV, Knowlton CH. Consensus guidelines for coordinated outpatient oral anticoagulation therapy management. *Anticoagulation Guidelines Task Force Ann Pharmacother* 1997;31:604-15

^b Includes only reports having sufficient patient-years (300) of follow-up to detect major hemorrhage, thromboembolism, and fatal events

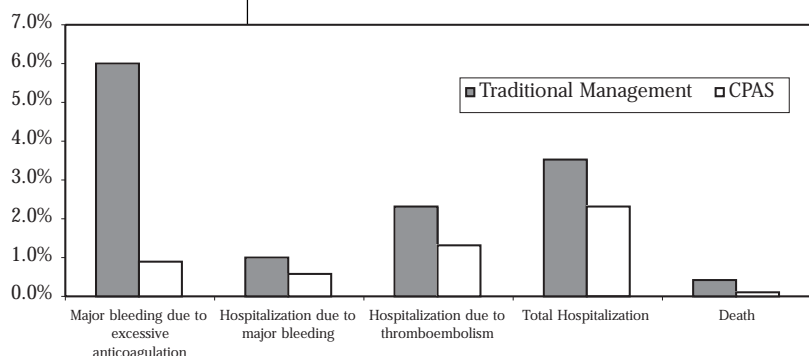
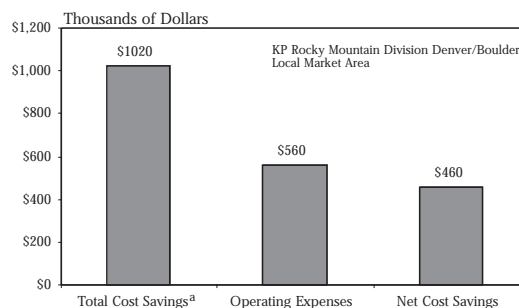


Figure 2. Clinical Pharmacy Anticoagulation Service (CPAS). Adverse clinical outcomes of anticoagulant therapy: CPAS vs traditional management.



^a Total Cost Savings includes \$700,000 for DVT, \$40,000 for repackaging of enoxaparin, and \$280,000 for hospitalization costs

Figure 3. Clinical Pharmacy Anticoagulation Service (CPAS). \$1,020,000 annualized cost savings of program.