

Planning, Implementation, and Evaluation of a Glycoprotein IIb/IIIa Inhibitor Protocol for the Treatment of Acute Coronary Syndromes

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ABSTRACT

The glycoprotein IIb/IIIa inhibitors (GPIs) represent a relatively new therapy for acute coronary syndromes. In this article the authors share their experience with planning, implementing, and evaluating a protocol for GPI use in a community hospital. A working group conducted a literature review and recommended tirofiban as the formulary GPI; the working group also developed guidelines for use of the drug, including patient selection criteria. Medical records for 68 patients with unstable angina, admitted to the hospital over a 3-month period, were used to characterize the hospital's patient population. Patient selection criteria included refractory ischemia or presentation with high-risk features such as chest pain at rest of less than 24 h duration, electrocardiographic changes, and troponin I level above 4.9 µg/L. Based on the hospital's patient population, the annual estimated cost of treatment was almost \$50,000. Drug use was evaluated for the first 20 patients treated with the drug. Eighteen (80%) of the patients receiving tirofiban met the predefined patient selection criteria. An outcomes assessment revealed that readmission for any reason and for acute myocardial infarction (within 7 and 30 days of discharge after admission for unstable angina) declined over time, although introduction of tirofiban was not the only factor in this change. The approach described here could be applied by other institutions considering the implementation of high-cost drug therapies.

Key words: unstable angina, drug use evaluation, outcomes assessment

RÉSUMÉ

Les inhibiteurs des glycoprotéines IIb-IIIa (IGP) représentent un traitement relativement nouveau des syndromes coronariens aigus. Dans cet article, les auteurs partagent leur expérience de la planification, de la mise en oeuvre et de l'évaluation d'un protocole d'utilisation des IGP au sein d'un hôpital communautaire. Un groupe de travail a passé en revue la littérature et a recommandé d'inscrire le tirofiban au formulaire thérapeutique; ce groupe a également émis des lignes directrices sur l'utilisation de cet agent, comprenant des critères de sélection des patients. Les dossiers médicaux de 68 patients souffrant d'angine de poitrine instable et hospitalisés au cours d'une période de trois mois ont servi à caractériser la population de patients de l'hôpital. Les critères de sélection des patients comprenaient l'ischémie réfractaire ou des facteurs de risque élevé comme des douleurs thoraciques au repos d'une durée inférieure à 24 heures, des modifications du tracé ECG ainsi qu'un taux de troponine I supérieur à 4,9 µg/L. En se fondant sur la population de patients de l'hôpital, on a estimé les coûts annuels du traitement à près de 50 000 \$. Une évaluation de l'utilisation du médicament a été effectuée pour les 20 premiers patients traités ; 18 (80%) des patients qui ont reçu le tirofiban ont satisfait aux critères de sélection prédéfinis. Une évaluation des résultats a révélé que les réhospitalisations, peu importe la cause et pour un infarctus aigu du myocarde (survenant dans les 7 et 30 jours suivant la sortie du patient hospitalisé pour une angine instable), ont diminué avec le temps, bien que l'introduction du tirofiban n'était pas le seul facteur expliquant ce changement. La présente démarche pourrait être mise en oeuvre par d'autres établissements qui envisagent le recours à des traitements médicamenteux coûteux.

Mots clés : angine instable, évaluation de l'utilisation des médicaments, évaluation des résultats

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INTRODUCTION

The treatment of acute coronary syndromes has evolved over time, in particular with the introduction of innovative drug therapy. In the acute care setting, the current standard of treatment includes a variety of antiplatelet and antithrombotic agents used in combination.^{1,2} As a result, the complexity and the cost of treating patients with acute coronary syndromes have increased. The glycoprotein IIb/IIIa inhibitors (GPIs) are a relatively new addition to the list of therapeutic options. These agents target platelet activation and aggregation on the unstable coronary plaque. Although the first GPI to become available, abciximab, was used primarily in the setting of percutaneous coronary intervention, increasing evidence supporting the use of these agents in acute coronary syndromes has been reported over the past few years.^{3,5}

Consensus guidelines available at the time this drug therapy was being evaluated supported the use of GPIs for the treatment of acute coronary syndromes in selected patients.¹ With an average cost of treatment estimated at close to \$1,000 per patient, cost-effective strategies for drug use were required. The Toronto East General Hospital faced the challenge of reviewing the evidence and applying it to the hospital's own patient population. In this article, the authors share their experience with planning, implementing, and evaluating a protocol for GPI use in the treatment of acute coronary syndromes. This approach could probably be applied by other institutions facing similar challenges with GPIs or other new, high-cost drug therapies.

METHODS

Toronto East General Hospital is a 420-bed community teaching hospital in southeast Toronto, providing service to approximately 200 000 people. The hospital receives approximately 65 000 visits to the Emergency Department each year and treats over 500 patients with acute coronary syndrome annually. At the initiation of this project, the hospital was referring all patients who required cardiac catheterization to neighbouring institutions. In November 1999, the Department of Pharmaceutical Services and the Division of Cardiology recognized that a GPI should be added to the hospital formulary to improve the outcomes of patients presenting with acute coronary syndromes.

Protocol Development

A working group was formed, consisting of a pharmacist, a nursing administrator, and a cardiologist,

with the mandate of recommending a GPI for the formulary, along with guidelines for its use. A literature review to determine the most appropriate GPI targeted trials involving early medical management of acute coronary syndrome. On the basis of evidence derived from this review, tirofiban was selected as the GPI to be added to the formulary.

Drug use guidelines for tirofiban were developed, including patient selection criteria. Recommendations from consensus guidelines available at the time were considered. In addition, the hospital's medical records were reviewed to quantify the clinical characteristics of the patient population. The Health Records Department used the codes for unstable angina of the International Classification of Diseases, revision 9 (ICD-9), to identify all patients treated at the hospital over a 3-month period, and serum creatine kinase (CK), CK-MB fraction, and troponin concentrations were extracted from these patients' records. For troponin I, both peak serum concentration and time to reach peak concentration were noted. For all patients with elevated serum troponin I, the medical record was reviewed to determine whether ST-segment depression was apparent on electrocardiography. A cost analysis was performed, based on projected patient volumes and an average cost of \$945 per patient (a 70-kg patient treated for a total of 72 h). Recommendations were made to the Pharmacy & Therapeutics Committee on the basis of the clinical and economic findings. An education strategy for the new GPI protocol was also developed.

Postimplementation Drug Use Evaluation and Outcomes Assessment

A prospective drug use evaluation was conducted for the first 20 patients treated with tirofiban. The pharmacists in the Coronary Care Unit collected data relating to demographic characteristics, high-risk clinical features, and drug administration. The data were reviewed, and statistical analysis was applied to determine adherence to the GPI treatment guidelines.

For the outcomes assessment, 2 criteria were recorded: readmission to the hospital for any reason and readmission to the hospital with acute myocardial infarction (AMI). All patients discharged from hospital between April 1997 and December 2000 with a diagnosis of stable angina (as defined by ICD-9 codes) were included in the analysis. Average 7-day and 30-day readmission and AMI rates were calculated for every 3-month interval starting in April 1997 and were plotted



over time. The overall average rates of readmission and AMI were also determined.

RESULTS

Protocol Development

The literature review identified 3 large, randomized, double-blind, placebo-controlled clinical trials using tirofiban^{3,4} or eptifibatide⁵ for the treatment of acute coronary syndromes. Detailed reviews and evaluations of these clinical trials have been published elsewhere.^{6,7} To summarize, both agents were effective in reducing the incidence of the composite endpoint of death and AMI⁵ or the composite endpoint of death, AMI, and refractory ischemia.^{3,4} The benefit was attributed primarily to reduction in the incidence of AMI and recurrent ischemia. In March 2000, the Pharmacy & Therapeutics Committee approved the use of tirofiban for the treatment of acute coronary syndromes.

A joint consensus statement from the American Heart Association (AHA) and the American College of Cardiology (ACC) supported early treatment with GPIs.¹ Suitable candidates included patients experiencing continuing ischemia, patients for whom interventions were planned, and those presenting with other high-risk features, such as clinical features (shock or pulmonary edema), electrocardiographic abnormalities (such as ST-segment changes), and elevations in cardiac markers.

A total of 68 patient charts were reviewed for analysis of the hospital's patient population. More than half of the patients (36 or 53%) presented with a detectable serum troponin I concentration of greater than 0.3 µg/L, whereas 8 (12%) presented with a concentration greater than 4.9 µg/L (Table 1), with 2.5–4.9 µg/L indicating intermediate probability of myocardial infarction and greater than 4.9 µg/L indicating high probability of myocardial infarction. Of the 8 patients presenting with serum troponin I concentration above 4.9 µg/L, 7 (88%) also had ST-segment depression.

Tirofiban cost estimates ranged from \$45,360 to \$204,120 per year, depending on the critical concentration of troponin I (Table 1). Peak serum troponin I concentrations occurred with the first measured blood sample in approximately half of the patients; peak concentration occurred in either the first or the second sample (approximately 12 h apart) in 12 of 14 patients (86%).

After reviewing the consensus statements, along with the hospital-specific data and cost analysis, the working group agreed on 2 indications for tirofiban

Table 1. Cost Evaluation of Tirofiban Therapy According to Critical Serum Troponin I Concentration

Concentration of Troponin I, (µg/L)	No. (and %) of ACS Patients (n = 68)	Estimated No. of Patients/Year	Annual Cost to Treat (\$)
>4.9	8 (12)	48	45,360
>2.4	14 (21)	84	79,380
Detectable	36 (53)	216	204,120

ACS = acute coronary syndromes.

Table 2. Frequency of High-Risk Features among 20 Patients Receiving GPI Treatment

High-Risk Feature	No. (and %) of Patients
Chest pain at rest for < 24 h	16 (80)
ECG changes	15 (75)
Above-normal troponin I	17 (85)
Positive CK-MB	15 (75)
Chest pain at rest for < 24 h, ECG changes, and above-normal troponin I (in combination)	10 (50)
Anticipated transfer for cardiac catheterization	7 (35)

GPI = glycoprotein IIb/IIIa receptor inhibitor, ECG = electrocardiography, CK = creatine kinase.

Table 3. Characteristics of 20 Patients Receiving Tirofiban

Characteristic	Data
Mean age (years)	64.5
Sex (no. and % male)	13 (65)
Mean weight (kg)	76.4
Patients requiring cardiac catheterization	12 (60)
Patients requiring cardiac intervention	4 (20)
Adverse drug reactions	
Need for transfusion	1 (5)
Hematuria	3 (15)
Mean treatment duration and range (h)	44.7 (3–106)

therapy: treatment of acute coronary syndromes in patients with ongoing chest pain despite maximal medical therapy and treatment of patients presenting within 24 h of onset of chest pain, with troponin I concentration greater than 4.9 µg/L and ST-segment depression. The Pharmacy & Therapeutics Committee accepted the recommendations of the working group for the use of tirofiban in April 2000. Tirofiban prescribing was restricted to the Division of Cardiology.

Planning for the implementation of tirofiban use included preprinting of medication orders and an extensive education initiative. Preprinted orders included the guidelines for use, instructions on



preparation of the drug, dosing guidelines, monitoring parameters, and a nomogram for concomitant IV administration of heparin (Appendix 1). The approach to education was multidisciplinary. The working group arranged initial presentations to key nursing, pharmacy, and medical staff, who in turn conducted follow-up inservices for their respective colleagues. Targeted patient care areas included the Emergency Department, the Coronary Care Unit, and the step-down Cardiac Care Unit.

Postimplementation Drug Use Evaluation and Outcomes Assessment

Chest pain of less than 24 h duration, ST-segment depression, and troponin I concentrations above 4.9 µg/L occurred in 15 (75%) to 17 (85%) of the 20 patients in the drug use evaluation; 10 of the patients exhibited all 3 characteristics (Table 2). Combining the patients with all 3 high-risk characteristics with those experiencing ongoing chest pain despite medical therapy resulted in a total of 16 (80%) patients who met the drug use criteria. Additional clinical information was obtained regarding patient weight, infusion times, and rates of adverse events (Table 3).

In the outcomes assessment of patients discharged with a diagnosis of unstable angina, there was some variability in the rates of readmission for any cause and for AMI, but both indicators appeared to improve over time (Figures 1 and 2).

DISCUSSION

Although the selection of a formulary GPI was an important initial step in the implementation of GPI therapy for management of acute coronary syndromes at the Toronto East General Hospital, the focus in this article has been the planning, implementation, and monitoring of GPI therapy. Thus, the process and procedures described here could be applied in any institution, irrespective of the GPI chosen.

Substantial effort was expended in determining the patient selection criteria for tirofiban therapy. The AHA/ACC guidelines support the use of risk stratification for patients presenting with acute coronary syndromes, the highest-risk patients benefiting most from more aggressive intervention.¹ During the review period, evidence was accumulating to support the use of serum troponin I or troponin T concentrations as a guide for treatment decisions. Post-hoc subgroup analyses of 2 independent clinical trials categorized patients as “troponin positive” (troponin T above 0.1 µg/L or

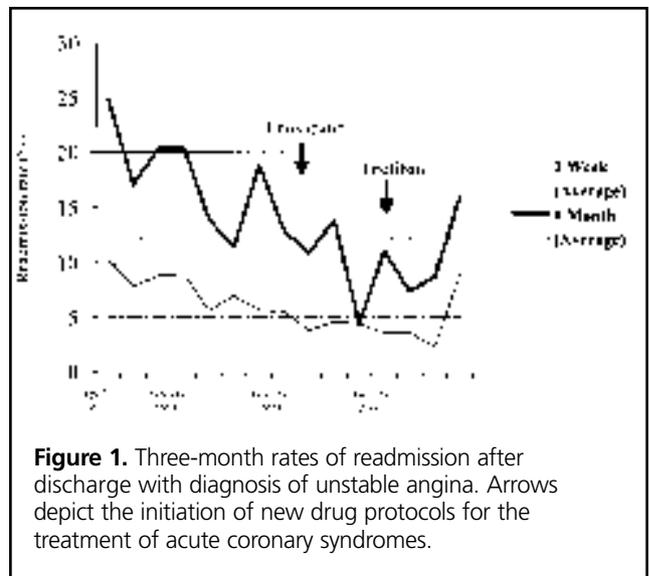


Figure 1. Three-month rates of readmission after discharge with diagnosis of unstable angina. Arrows depict the initiation of new drug protocols for the treatment of acute coronary syndromes.

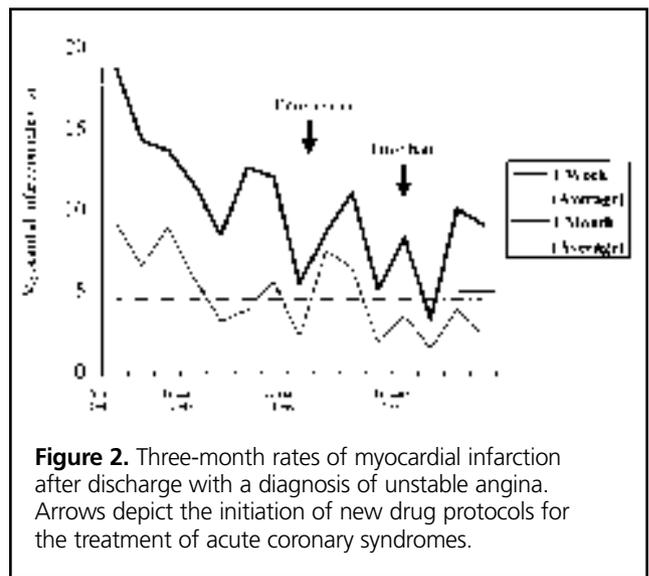


Figure 2. Three-month rates of myocardial infarction after discharge with a diagnosis of unstable angina. Arrows depict the initiation of new drug protocols for the treatment of acute coronary syndromes.

troponin I above 1 µg/L) or “troponin negative”, with the treatment effect measured in both groups.^{8,9} Patients categorized as troponin positive were at higher risk of death or AMI, and appeared to benefit most from GPI therapy. Those categorized as troponin negative had a relatively low incidence of death or AMI and did not benefit from GPI treatment. The authors concluded that serum troponin concentrations might be a powerful indicator for success with GPI treatment.

The review of medical records conducted at Toronto East General Hospital supported several key features of the hospital’s drug use guidelines for tirofiban. The use of a range of critical values for troponin I (see Table 1) gave the working group several different scenarios, each associated with a cost estimate. The critical value



of greater than 4.9 µg/L aided in the identification of several high-risk patients for early aggressive therapy that could be undertaken within the existing drug budget. Although the threshold of 4.9 µg/L was somewhat arbitrary, it was a critical component of the guidelines for identifying the highest-risk patients. The addition of ST-segment depression as a criterion for use was justified, as these 2 high-risk features often occurred together. Because serum troponin I concentrations reached their peak early in the course of treatment, initiating therapy within 24 h of the onset of chest pain gave physicians a reasonable amount of time in which to make their decision.

The goals of treatment with tirofiban were to stabilize the patient upon presentation to the Emergency Department and to improve the outcome of percutaneous intervention for patients waiting for emergency cardiac catheterization. The goal of early, aggressive treatment of high-risk patients with acute coronary syndromes was to prevent negative outcomes such as progressive chest pain, hemodynamic instability, and the need for urgent transfer for percutaneous intervention. Because this hospital had no access to on-site cardiac catheterization at the time of this evaluation, preventing the need for emergency catheterization was important.

Evaluation of the first 20 patients to receive tirofiban provided immediate feedback regarding the application of the hospital-specific guidelines. From this analysis, it was concluded that the use of tirofiban in these patients was generally appropriate, as defined by the authors' institution. Only 4 (20%) of the patients did not have all of the prespecified criteria for tirofiban use. The duration of therapy was consistent with that of clinical trials, obviating concerns that patients might receive extended infusions while awaiting transfer to the cardiac catheterization laboratory. The frequency of adverse events was consistent with that reported in the literature.^{3,4}

The impact of drug use guidelines on patient outcomes is often difficult to measure but is critically important in determining the success of a new drug therapy. Given the evidence that GPIs reduce the incidence of AMI and recurrent ischemia, it was assumed that GPI treatment would translate into a reduction in hospital readmission rates, and the outcomes assessment revealed positive trends in this regard (Figures 1 and 2). Since April 1997, there was an improvement in outcome for both variables. Because many factors influence patients' outcomes, it is difficult to attribute improvements to any one factor. New drug

therapies, such as enoxaparin (start date indicated in Figures 1 and 2), and improved access to cardiac catheterization facilities are just 2 of the confounding variables in this analysis. Another limitation was the wide variation in readmission rates from one time period to another. Given the small sample size during each time period, small fluctuations in readmissions or AMIs might have profoundly affected the rate for any individual time period. Nevertheless, considering all contributing factors, the quality of care indicated by these outcome measures appears to have improved.

This model of formulary review and evaluation has several advantages. Although reviews and evaluations of GPIs exist in the literature,^{6,7} they may not apply to specific institutional patient populations and practice patterns. The working group was able to incorporate hospital-specific information into the decision-making process and ultimately to determine a realistic strategy for GPI use at this hospital. With the methodology in place, it will be possible to repeat the drug use evaluation and the patient outcome assessment on an ongoing basis. A similar approach will be applied to other major formulary decisions to facilitate protocol planning, drug use evaluation, and evaluation of impact on patient care outcomes. Since this methodology included routines that are well established at the institution, such as drug use evaluation and benchmarking of readmission and AMI rates, generating data was not difficult. Given the financial difficulties facing hospitals today, the experience at Toronto East General Hospital provides valuable information to both clinicians and administrators in support of new, more effective drug therapies. The justification of resource allocation to high-cost drugs is facilitated by data suggesting improved patient outcomes.

One of the biggest challenges in developing guidelines is keeping up with the literature. Since the Pharmacy & Therapeutics Committee approved use of tirofiban for patients with acute coronary syndromes, additional information on risk stratification has been reported. For example, the Thrombolysis in Myocardial Infarction (TIMI) risk score is another strategy for assessing patient characteristics, performing risk stratification, and determining treatment alternatives.¹⁰ As in the categorization of patients as troponin positive or troponin negative, the presence of diabetes may also affect decisions about GPI treatment. In a meta-analysis of several clinical trials, the 30-day mortality rate for diabetic patients was lower with GPIs than with placebo.¹¹ In addition, more recent clinical trials have provided new theories regarding patient selection for



GPIs and early invasive treatment with percutaneous intervention.^{12,13} As a result, the ACC/AHA guidelines for the treatment of acute coronary syndromes have been modified to reflect the recent literature.¹⁴ Specifically, recommendations for use of GPIs in the medical management of acute coronary syndromes have been modified to include a more selective approach to treating high-risk patients. These are only some of the many references highlighting the need for ongoing review of the literature to determine the impact of new evidence on an existing treatment protocol.

CONCLUSIONS

This article has described a process for planning, implementing, and evaluating a protocol for incorporating a new drug therapy for the treatment of acute coronary syndromes into practice in a community teaching hospital. The results of the drug use evaluation and the outcomes assessment indicated that the implementation of tirofiban for the treatment of acute coronary syndromes was a success. An initial medical record review allowed the working group to make an informed decision, based on risk stratification, as to which patients should be treated with tirofiban. The high rate of compliance with evidence-based guidelines, as measured in the first 20 patients receiving tirofiban, suggested general acceptance of those guidelines within the Division of Cardiology. Finally, acknowledging the confounding variables that could affect readmission and AMI rates, it was reassuring to see positive trends in patient outcomes after implementation of tirofiban treatment. Given the dynamic nature of treatment of acute coronary syndromes, ongoing revisions and evaluations will be necessary to ensure continued high-quality care.

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Appendix 1. Preprinted order for use of tirofiban for patients with acute coronary syndromes



Tirofiban for Acute Coronary Syndromes Pre-printed Orders (IV Heparin Included)

Body weight: _____ kg

Allergies:

No known allergies

Patient Identification

ORDERS	✓ Check (☐) if applicable	CHANGES TO BE INITIALLED BY MD	NOTED
Tirofiban Pre-Printed Orders to be used in addition to the Cardiology Admission Protocol			
<p>Criteria for Use (Restricted to Cardiology):</p> <p>1. Ischaemia refractory to aggressive medical treatment (ECASA, nitroglycerin, heparin) for > 24 h OR</p> <p>1. Patients presenting within 24 h of the onset of ischaemia and both of the following features: a) ST depression b) Troponin I > 4.9 µg/L</p> <p>Medication Orders:</p> <p>1. Tirofiban (see reverse for weight-adjusted dosing): Prepare tirofiban 50 µg/mL solution</p> <p>a) Remove 50 mL from NaCl 0.9% 250 mL bag</p> <p>b) Add tirofiban 12.5 mg (50 mL vial) into bag Bolus: tirofiban 0.4 µg/kg/min IV = _____ mL/h over 30 min Infusion: tirofiban 0.1 µg/kg/min IV _____ mL/h (Therapy beyond 72 hours to be reassessed daily by Cardiologist) Reduce bolus dose and continuous infusion by 50% if creatinine clearance < 30 mL/min (See reverse for creatinine clearance calculation) Clcr = _____ mL/min</p> <p>2. Heparin For patients already on Heparin IV, continue infusion as per Heparin Titration Guidelines below. For patients initiating Heparin IV Heparin 5,000 units IV bolus, followed by heparin 1,000 units/h IV (10 mL/h) Draw aPTT 6 h after bolus, then as per Heparin Titration Guidelines below.</p>			
Heparin Titration Guidelines			
aPTT	Action	Repeat aPTT	
< 50 seconds	Increase rate by 2 mL/h (200 units/h)	6 h	
50–75 seconds	No change in rate	Next AM	
76–110 seconds	Hold infusion for 30 minutes, then decrease rate by 1 mL/h (100 units/h)	6 h	
> 110 seconds	Hold infusion for 1 h, then decrease rate by 2 mL/h (200 units/h)	6 h	
Monitoring			
1. CBC within 6 h of bolus, then daily. Continue for 24 h after tirofiban infusion discontinued			

Date: _____

Signature: _____ M.D.

Time: _____

Print Name: _____

ECASA = enteric-coated acetylsalicylic acid, Clcr = creatinine clearance, aPTT = activated partial thromboplastin time, AM = morning, CBC = complete blood count.

