

Economic assessment of tirofiban in the management of acute coronary syndromes in the hospital setting

An analysis based on the PRISM PLUS trial

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Aims We analysed whether generalized use of tirofiban plus heparin and aspirin might save direct healthcare costs, as compared with heparin and aspirin alone, in patients with acute coronary ischaemic syndromes in Switzerland.

Methods and Results We conducted an incremental cost-consequence analysis from the perspective of the admitting hospital for the period of the first 7 days. Costs were analysed for the management of refractory ischaemic conditions and myocardial infarctions, including incremental days on the general ward or intensive care unit, as well as necessary revascularization procedures, and expressed in Swiss francs (CHF) and European currency units (ECU). Drug costs were based on a loading dose of $0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and a maintenance dose of $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for tirofiban at a cost of CHF 273.55 (ECU 166.50) per vial. Heparin was administered at a loading dose of 5000 U and a maintenance dose of $1000 \text{ U} \cdot \text{h}^{-1}$. All calculations were standardized to 100 treated patients. The costs of managing ischaemic complications were based on typical practice patterns in Swiss

hospitals. The incremental costs per patient of managing unstable angina patients with recurrent ischaemia or myocardial infarction were calculated as CHF 23 325 (ECU 14 198) and CHF 18 599 (ECU 11 321), respectively. The incremental drug costs amounted to CHF 82 065 (ECU 49 954). The additional use of tirofiban resulted in net savings of CHF 54 899 (ECU 33 418) per 100 patients, achieved through a reduction in the cost of treating refractory ischaemic conditions (CHF 79 306, ECU 48 275) and myocardial infarctions (CHF 57 658, ECU 35 097).

Conclusion Tirofiban is cost-saving in acute coronary ischaemic syndromes and improves the economics of managing these patients during the initial hospitalization. (*Eur Heart J* 1999 20: 1253–1260)

Key Words: Costs, economic evaluation, unstable angina pectoris, tirofiban, percutaneous transluminal coronary angioplasty, Switzerland.

See page 1217 for the Editorial comment on this article

Introduction

Within the spectrum of coronary heart disease, unstable coronary artery disease or acute coronary ischaemic syndromes consume a considerable portion of healthcare costs. Patients with acute coronary ischaemic syndrome account for approximately 40% of the admissions to coronary care units. Each year, 3 million patients worldwide will suffer an acute myocardial infarction and over 1 million will be hospitalized with unstable angina.

In acute coronary ischaemic syndrome patients there is a substantial risk of recurrent ischaemia, infarction, and death when early angiography and/or revascularization are deferred. Conversely, it has also been suggested that early angiography and revascularization are more dangerous than deferred procedures. A critical appraisal of the literature, however, suggests that there is no specific risk inherent in early intervention; rather, that patients who cannot wait are at higher risk anyway^[1]. The most valuable data on the comparison of an early invasive and a conservative strategy in acute coronary ischaemic syndrome came from the Thrombolysis in Myocardial Infarction (TIMI) IIIb study^[2–4]. The results show no major differences in the outcomes between groups, except for a shorter hospital stay, lower drug use, and fewer rehospitalizations in the group treated

Revision submitted 8 January 1999, and accepted 15 January 1999.

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according to an early invasive strategy. In addition, since the inception of the TIMI IIIb study, there have been major improvements in the field of angioplasty, such as the increased use of stents and the availability of safe and effective glycoprotein IIb/IIIa inhibitors. Recently, the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) Trial Investigators suggested that most patients with non-Q wave myocardial infarction do not benefit from routine, early invasive management consisting of coronary angiography and revascularization^[5]. They concluded that a conservative, ischaemia-guided initial approach is both safe and effective. All available studies in acute coronary ischaemic syndrome show that routine angiography and revascularization do not reduce the incidence of non-fatal reinfarction or death as compared with the more conservative, ischaemia-guided approach^[6].

Many cardiologists rely primarily on catheterization to evaluate, and revascularization to treat, patients with acute coronary ischaemic syndrome. However, under the constraints of cost containment, it might be useful to determine whether some patients might benefit sufficiently from non-invasive testing and medical therapies, such as glycoprotein IIb/IIIa inhibitors^[7]. This clinical benefit is based mainly on the prevention of refractory ischaemia and myocardial infarctions.

While medical and interventional innovations have helped improve the outcomes of patients with acute coronary conditions, they have also fuelled a substantial rise in costs. Coronary artery bypass graft and PTCA procedures have been reported as the primary cost drivers in hospitalized patients with unstable angina. Evaluation of glycoprotein IIb/IIIa inhibitors as primary therapy for these patients suggests that good value for money is possible, especially if the use of these agents results in a reduction in revascularization procedures^[8–13].

Promising early results have been achieved with GP IIb/IIIa inhibitors as primary therapy in patients with acute coronary ischaemic syndrome. Three large trials have assessed the impact of GP IIb/IIIa blockade in patients with acute coronary ischaemic syndrome: **PRISM**^[14], **PRISM PLUS**^[15], **PARAGON**^[16] and **PURSUIT**^[17]. A pooled analysis of the efficacy of these results has recently been presented^[18]. The combined effect was an absolute risk reduction of 1.7% (95% CI 0.78; 2.7).

Tirofiban (Aggrastat[®]) is a reversible, highly selective non-peptide inhibitor of platelet glycoprotein IIb/IIIa receptors^[19–21]. Pre-clinical and clinical studies have confirmed that tirofiban inhibits ex vivo platelet aggregation in response to a variety of agonists, including ADP, collagen, epinephrine, and thrombin. Potential advantages of such a drug include immediate onset of action, rapid reversal of antiplatelet activity after drug discontinuation, suitability for multiple repeat administrations, and high specificity for the GP IIb/IIIa receptor.

The measurement of the value of health improvements resulting from the use of new drugs can be done using

one of several types of economic studies^[22–25]. These differ in the way in which costs and benefits are quantified, although the greatest variation is in the determination of 'benefits'. Economic evaluation of drugs is concerned with comparing the effects or outcomes and the costs of a treatment with its next best alternative. This means that the costs and benefits of two or more therapies are compared. There are studies which consider costs or benefits independently. These are partial evaluations and while less complex than a full evaluation, (which examines both costs and benefits), are of significant interest to governments. A further definitional note relates to the use of the term 'cost-effectiveness study' which shares some of the same problems of misuse described above. Cost-effectiveness analyses refer to economic evaluations that consider both the comparative costs and clinical effects measured in pure clinical units (effectiveness), preferences (utility or Quality Adjusted Life Years), or dollars (benefits). Cost-consequence analysis is a special type of analysis which is generally used to compute the costs of a single option. In cost analyses (or cost-minimization analyses) outcomes are assumed to be equal between competing interventions and are measured in monetary terms. In contrast to the cost-benefit analysis, however, the scope of benefit is usually less broad. Ideally, cost-benefit analyses should have a societal perspective.

The aim of the present study was to conduct an incremental cost analysis of tirofiban plus heparin and aspirin vs standard treatment with heparin plus aspirin alone from the perspective of Swiss hospitals on the basis of the randomized, double-blind controlled clinical study **PRISM PLUS**^[15].

Methods

Economic study design

The economic benefit of tirofiban was determined by conducting an incremental cost consequence analysis on the basis of the recently completed **PRISM PLUS** trial^[15]. Using a hypothetical cohort of 100 patients with acute unstable angina pectoris and/or non-Q wave myocardial infarction a strategy of tirofiban plus heparin was compared with heparin alone. All patients received aspirin as conventional therapy. The main hypothesis to be tested was whether the costs of additional tirofiban treatment would be partially or completely offset by a reduction in additional inpatient resource use due to complications of refractory ischaemic conditions and myocardial infarctions. The perspective of the study was purely addressed from the admitting hospital's point of view. Thus, we focussed on the index hospitalization over a period of 7 days, which is well within the range of an ordinary hospital stay for unstable angina pectoris without complications. Another reason to consider the first 7 days was due to the fact that the primary efficacy

Table 1 Outcome events in the PRISM PLUS trial

Results at 7 days	Heparin (n=797)	Tirofiban plus heparin (n=773)	Odds ratio	P-value
Composite end-point	17.9%	12.9%	0.66	0.004
Components of composite end-point:				
Refractory ischaemic condition	12.7%	9.3%	0.685	0.022
Myocardial infarction (MI)*	7.0%	3.9%	0.528	0.006
Death	1.9%	1.9%	1.011	0.98
MI/death	8.3%	4.9%	0.565	0.007

*fatal and non fatal

variable was defined as a composite end-point of death, myocardial infarction and refractory conditions at 7 days after randomization.

Efficacy of tirofiban

The clinical efficacy of tirofiban was taken from the PRISM PLUS trial^[14]. This study was a multicentre, international, randomized, double-blind trial in patients with unstable angina or non-Q wave myocardial infarction. Unstable angina was defined as prolonged or repetitive angina at rest with 12 h prior to randomization and ECG evidence of ischaemia or elevated cardiac enzymes. The main results of the PRISM PLUS trial are displayed in Table 1. There were no statistically significant differences between the treatment groups with respect to major bleeding (TIMI criteria), decreases in haemoglobin, required transfusions, reductions in platelet counts or discontinuations.

Analysis of costs

The determination of costs was based on the additional hospital days required to treat complications (refractory ischaemic conditions and myocardial infarctions) during the first 7 days. We also took into consideration the need for additional days in the intensive care unit and revascularization procedures for each complication. All costs are expressed in Swiss francs (CHF), as well as in European currency units (ECU), applying an exchange rate of CHF 1.6428 for 1 ECU (average exchange rate in April 1998). In order to quantify the costs of these complications we had to analyse typical clinical practice patterns in Swiss hospitals. Using a structured questionnaire, we obtained data on the probability and quantity of additional days on the normal ward and intensive care units, including the probability of revascularization procedures, from six cardiologists, representing larger university teaching hospitals and smaller hospitals. The use of expert opinion as an approach to obtain consensus has been well acknowledged in pharmacoeconomic research^[26]. The additional days were weighted in accordance with average costs per day, published by the

association of Swiss hospitals (CHF 1000 (ECU 609) per day on the normal ward, CHF 2500 (ECU 1.522)) in the intensive care unit^[27]. The costs for revascularization procedures were obtained from published secondary sources^[28] and were CHF 10 000 (ECU 6087) for PT-CAs and CHF 30 000 (ECU 18 262) for coronary bypass operations. The drug costs were based on a loading dose of $0.4 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ and a maintenance dose of $0.1 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ for tirofiban. Heparin was administered with a loading dose of 5000 U and a maintenance dose of $1000 \text{ U} \cdot \text{h}^{-1}$. The treatment costs of tirofiban were CHF 821 (ECU 499.8) per patient for a complete treatment course, including three vials for an infusion period of 3 days. The corresponding costs for heparin were CHF 10 (ECU 6.09) per patient per day. Discounting was not required on the basis of the short follow-up period of 7 days.

Sensitivity analysis

The robustness of the results of this economic analysis was tested using a series of sensitivity analyses. These tests take into consideration uncertainties and the lack of precise cost data. We conducted three types of sensitivity analyses: a univariate analysis covering a broad range of plausible values between -50% and $+50\%$ for the unit resource costs, a threshold analysis to obtain the drug cost at which the results change from net savings to net investments between the treatment groups, and an analysis considering the 95% confidence intervals of the absolute risk reduction between the two treatment groups.

Results

Management of complications

An important first step was to analyse the proportion of patients with complications receiving either revascularization treatment or no treatment (Fig. 1). Interestingly, the differences between the hospitals were not significant from each other, which suggest homogenous treatment patterns and high consistency. Not all patients require

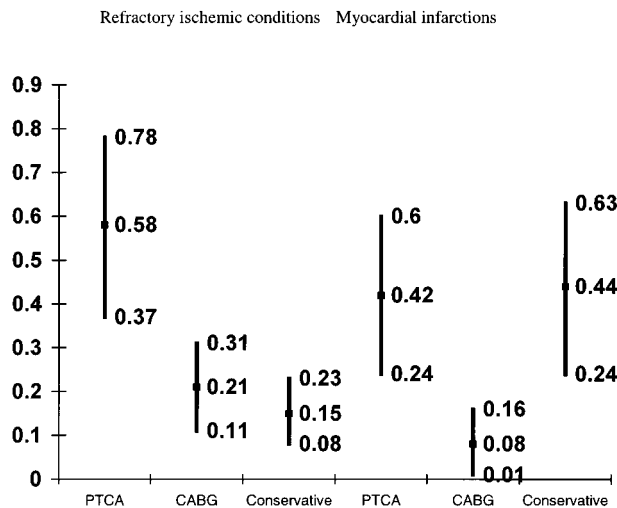


Figure 1 Treatment strategies for complications in patients in with unstable angina pectoris/non-Q wave infarction expressed in probabilities, with upper and lower 95% confidence intervals.

Table 2 Additional days of care for managing complications in patients in with unstable angina pectoris/non-Q wave infarction for each treatment category

	Refractory ischaemic condition	Myocardial infarction
Non-interventional treatment		
General ward	8.8 (4.8; 12.7)	8.1 (5.2; 11.0)
Intensive care unit	2.8 (1.2; 4.4)	2.8 (1.2; 4.3)
PTCA		
General ward	4.2 (1.7; 6.7)	5.6 (3.1; 8.0)
Intensive care unit	2.0 (0.72; 3.3)	2.1 (1.0; 3.2)
Bypass operation		
General ward	12.6 (6.8; 18.4)	13.7 (8.1; 19.3)
Intensive care unit	3.9 (1.7; 6.1)	4.1 (1.9; 6.2)

All values are means (95% confidence limits).

admission to the intensive care unit, so the corresponding admission rates were also determined. Fifty-six percent of patients with refractory ischaemic conditions, not requiring any revascularization procedures, were admitted (95% CI: 25%; 87%), 79% patients with PTCA (95% CI: 56%; 100%) and 91% of patients with coronary bypass operations (95% CI: 80%; 100%). The corresponding figures for patients with myocardial infarctions were 80% (95% CI: 55%, 100%), 80% (95% CI: 60%; 100%) and 96% (95% CI: 90%, 100%). The additional days of care for each treatment option of complications in patients with unstable angina pectoris/non Q-wave infarction are given in Table 2.

Costs and effectiveness

The cost of treating the complications amounted to CHF 23 325 (ECU 14 198) for refractory ischaemia and

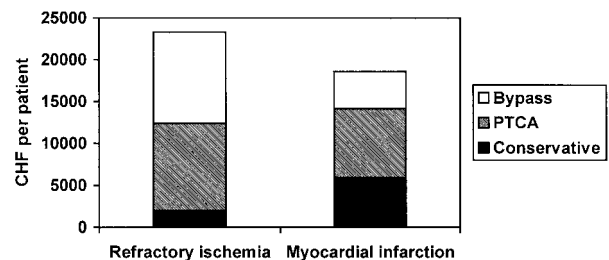


Figure 2 Total costs to treat complications in patients in with unstable angina pectoris/non Q-wave infarction according to treatment strategy.

CHF 18 599 (ECU 11 322) for myocardial infarctions. The breakdown of total costs per patient according to treatment strategy is given in Fig. 2.

The additional use of tirofiban plus heparin vs heparin alone in 100 patients is capable of preventing 3.4 (95% CI: 0.3; 6.5) refractory ischaemic complications and 3.1 (95% CI: 0.9; 5.3) myocardial infarctions. The economic benefit associated with the reduction of these complications translates into savings of CHF 136 964 (ECU 83 372) per 100 patients. By including the costs of the medication (CHF 3000 (ECU 1826) for heparin and aspirin, CHF 85 065 (ECU 51 780) for tirofiban, heparin and aspirin), the net savings amount to CHF 54 899 (ECU 33 418), i.e. CHF 549 (ECU 334) per patient. Table 3 gives a comparative overview of costs and benefits of the two treatment groups, including upper and lower 95% confidence intervals. Interestingly, even with the pessimistic assumption of the lower confidence interval, more than 61% of the initial drug costs of tirofiban are offset by preventing complications.

Even though we did not consider the efficacy at 30 days as a primary objective of the economic analysis, we calculated expected 30-day savings of CHF 316 (ECU 193) per patient for tirofiban.

Sensitivity analysis

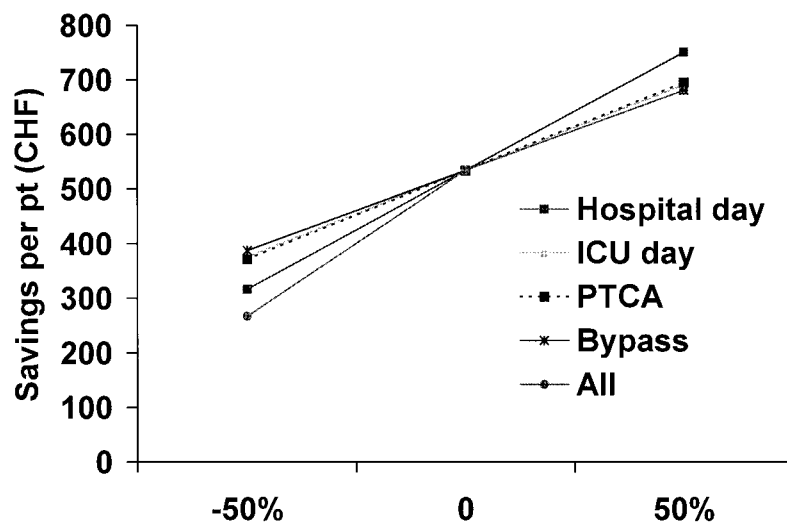
The uni- and multivariate sensitivity analysis (Fig. 3) demonstrated that the results of the present analysis are stable across a wide range (from -50% to +50%) of input values. The costs of tirofiban obviously has the greatest influence on economic outcomes. The value at which the costs of managing acute coronary ischaemic syndrome patients with tirofiban will turn cost-neutral, i.e. the threshold value lies at CHF 1370 (ECU 834) per patient. When taking the 95% confidence limits of the absolute treatment effects into account, the net difference lies between CHF 583 (ECU 355) and CHF 1681 (ECU 1023) per patient.

Discussion

While the present study is limited by the fact that it was a retrospective analysis and that the cost-structure was

Table 3 Cost comparison of treating patients with unstable angina pectoris/non-Q wave infarction with conventional therapy (heparin plus aspirin) vs tirofiban plus conventional therapy (in CHF per 100 patients, ECU in italics)

	Mean			Lower 95% CI			Upper 95% CI		
	Conventional	Conventional plus tirofiban	Difference	Conventional	Conventional plus tirofiban	Difference	Conventional plus tirofiban	Difference	
Refractory ischaemia	296 230	216 924	79 306	122 663	89 824	32 839	416 935	152 428	
	180 320	132 050	48 275	74 667	54 677	19 989	253 795	92 785	
Myocardial infarction	130 196	72 538	57 658	38 851	21 645	17 205	154 806	123 051	
	79 252	44 155	35 097	23 649	13 176	10 473	94 233	74 903	
Medication	3000	85 065	82 065	3000	85 065	82 065	85 065	82 065	
	1826	51 780	49 954	1826	51 780	49 954	51 780	49 954	
Total	429 426	374 527	54 899	164 514	196 535	- 32 021	656 806	193 414	
	261 399	227 980	33 418	100 142	119 634	+19 492	399 808	117 734	
Difference per patient			549			- 320		1934	
			334			- 194		1177	



costs varied between -50% and +50%

Figure 3 Univariate and multivariate sensitivity analysis of results with unit resource.

principally determined by expert opinion from interviews with a limited number of physicians, it provides an interesting insight into the cost-structure of treating patients with acute coronary syndromes. We found that the main cost drivers in the treatment of these conditions are the costs for managing complications, mainly additional days of hospitalization on the general and intensive care ward. When the contribution of the different costs included in the present analysis are compared between the two treatment regimens, it can be seen that complication-related costs accounted for the greatest difference between the treatment groups. The magnitude of the difference in hospitalization costs between the regimens can be explained by the fact that tirofiban was effective in reducing complications within the first 7 days of treatment.

The health economic benefit of glycoprotein IIb/IIIa inhibitors has been confirmed by the findings of previous economic analyses^[29,30]. A direct comparison, however, is not possible, because of differing follow-up periods, differing perspectives and different indications (e.g. the periprocedural management of angioplasties vs primary non-invasive treatment). However, a recent unpublished analysis of the GUSTO IIb data showed hospital costs comparable with ours, although they did not discriminate between the different complications of refractory ischaemia and myocardial infarctions. The hospital costs for managing patients with acute coronary ischaemic syndrome have been estimated at \$8600 per patient for patients receiving conservative treatment, \$15 500 for patients undergoing PTCA and \$32 000 for patients requiring coronary artery bypass operations^[31]. The economic analysis of the ESSENCE trial identified net cost savings of \$763 per patient given low molecular weight heparin vs unfractionated heparin in acute coronary syndrome patients during the initial hospitalization^[32]. This difference, however, was not statistically

significant. To the best of our knowledge no economic analyses have been published on the benefit of glycoprotein IIb/IIIa inhibitors in patients with acute coronary ischaemic syndrome.

Since the goal of modern medicine is to improve patients' quality, as well as the quantity, of life, a potential limitation of the PRISM PLUS study (on which the present economic analysis was based) is that patients' quality of life during the extended survival period associated with therapy was not assessed. Indeed, an improvement in life expectancy does not necessarily confer an improvement in quality of life among patients since long-term complications can diminish a patient's quality of life; furthermore, the management of such complications may incur additional resource costs.

Potential other limitations of this study are acknowledged. The incremental estimated costs relate only to the first 7 days after treatment onset, due to the chosen perspective of the study. There is the possibility that additional costs will become evident later. Offsetting this are the likely lower costs from fewer repeat revascularizations. It may thus be theoretically argued that a long-term perspective is required. In practice, however, this will not work in many health care environments due to the strict separation of sectoral healthcare budgets. Even if rehospitalizations for future interventions are considered, this may only be relevant from a third party payer or societal perspective and not for the individual hospital, because each admission is considered to be a (financially) independent event. Thus, the decision to include these types of drugs onto a hospital formulary can only be truly justified when addressing the economics of the index admission. Obviously, things become different in settings where capitation arrangements or diagnosis related groups prevail. Furthermore, these results are most applicable to patients with similar inclusion criteria, as defined in the PRISM PLUS study.

Another problem might be the use of expert opinion to determine clinical practice patterns. This may, in our case, be only of minor relevance, since the results indicate a high degree of consistency, suggesting little variation between hospitals in Switzerland. On the other hand, however, our results may also partially underestimate the true economic savings. This is mainly due to the fact that many patients with acute coronary ischaemic syndrome presenting in hospitals without the facilities for initial revascularization procedures may have to be transferred to secondary or tertiary care clinics. The costs of this transport, according to present practice in Switzerland, have to be covered by the referring hospital and not by the third party payer. Thus, hospital administrators are keen to reduce unnecessary patient transport as much as possible. Furthermore, caution should be exerted when extrapolating our results to other countries and healthcare settings without taking local practice patterns and technology availability into consideration.

Further economic research is certainly warranted in the field of managing patients with acute ischaemic syndromes, mainly because the economics is closely related to baseline cardiovascular risk and the force of the selected intervention(s). For example, the economic benefit of drug and non-drug interventions may vary according to various patient characteristics, e.g. sex, age, troponin T levels, cardiovascular risk factors. Thus, we might be able to identify patient categories, in which glycoprotein IIb/IIIa inhibitors are more or less cost-effective and incorporate these findings into subsequent clinical management pathways. Even additional, long-term, pharmacoeconomic studies may be useful, depending on the healthcare system in which the research is undertaken and in which subsequent health care decisions have to be made.

Despite several methodological challenges, economic analyses will be critical to the rational allocation of resources by health care providers and payers. Many questions may be answered with economic studies. The rational use of new and established technology is also going to require increased technology assessment^[33,34], a better assessment of patient preferences, and more rigorous pharmacoeconomic analyses. The benefit of such assessments, however, will certainly be worth their cost. On the grounds of best available epidemiological knowledge, we can thus assume an overall population benefit of CHF 11 million (ECU 6.7 million) in Switzerland on the basis of a conservative estimate of 20 000 hospitalizations annually.

In conclusion, tirofiban has been shown to reduce the rate of early complications in the management of patients with documented unstable angina pectoris or non-Q wave myocardial infarction. In addition, the clinical efficacy of tirofiban translates into immediate economic benefits for the hospital at net savings of more than CHF 500 per patient. Thus, primary therapy with tirofiban is an economically justified intervention in the initial management of patients with acute coronary ischaemic syndrome in the Swiss hospital setting.

The study was supported by an unrestricted educational grant by Merck Sharp & Dohme Chibret AG, Glattbrugg, Switzerland.

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