International Journal of Technology Assessment in Health Care, **18:3** (2002), 555–565.

IN VITRO TESTS FOR ASSESSING HEPARIN-INDUCED THROMBOCYTOPENIA IN PATIENTS AFTER ELECTIVE HIP REPLACEMENT

A Medico-economical Evaluation

Frédéric Sobas
Edouard Herriot University Hospital

Cyrille Colin
Hospices Civils de Lyon

Patrick Ffrench
Louis Pradel University Hospital

Marie Christine Trzeciak
Marc Dechavanne
Claude Négrier
Edouard Herriot University Hospital

Abstract

Objectives: Considering the previously published incidences of heparin-induced thrombocytopenia (HIT) in patients receiving a thromboprophylactic therapy, the role of the hemostasis laboratory is essential in making a clinical decision. The purpose of this project was to compare the strategies of diagnosis and associated care of patients with suspected HIT after elective hip replacement using platelet aggregation assay, carbon 14-serotonin release, and "doing nothing."
Methods: The authors used an incremental cost-effectiveness analysis based on data extracted from the literature. The effectiveness of the strategies was represented by the number of deep venous thromboses prevented. Cost data were collected from the observation of biological and medical practice at Edouard Herriot University Hospital, Lyon, France, in 1999.
Results: In comparison with the strategies of doing nothing using no biological test for diagnosis, and clinical care of HIT-suspected patients, the strategy using platelet aggregation test was more expensive and less effective. With respect to the strategy using carbon 14-serotonin release assay, the incremental cost-effectiveness ratio, expressed as U.S. dollars per deep venous thrombosis prevented, reached $200,000, with a marginal effectiveness of eight deep venous thromboses prevented for 10,000 HIT-suspected patients.
Conclusion: This study suggests that clinical hemostasis laboratories might consider replacing the platelet aggregation test with the carbon 14-serotonin release assay or should use another functional assay such as the flow cytometric assay for the diagnosis and care of patients with suspected HIT.

Keywords: Thrombocytopenia, Heparin, Thrombosis, Cost-effectiveness analysis

Heparin-induced thrombocytopenia (HIT) is a side effect of heparin therapy. In contrast to other drug-associated thrombocytopenias, the most frequently observed complication is not hemorrhage but thrombosis. Thomboses are mediated by an antigen–antibody complex that causes platelet activation in the presence of heparin, referred to as heparin-dependent antibody. The antigenic target of the antibody is a multimolecular complex formed by platelet factor 4 and heparin, which subsequently binds to the FcγRII platelet receptor (1). These antibodies are heterogeneous since platelet activation was shown in the presence of antiheparin–platelet factor 4 antibodies and heparin, as well as the result of the contact with a superactive heparin–platelet factor 4 antibody that does not require the presence of heparin (14). The presence of the antibody detected by an enzyme-linked immunosorbent assay (ELISA) is not predictive of either heparin-induced thrombocytopenia or thromboembolic complication (26;41). The functional methods used for the identification of heparin-dependent antiplatelet antibodies have been designed to detect platelet activation. Danaparoid sodium (Orgaran®, Organon, Inc., West Orange, NJ) can also be tested with the functional methods. This anticoagulant is licensed in France as a prophylactic antithrombotic drug in the absence of cross-reactivity. For these reasons, this study focuses on the cost-effectiveness analysis of functional tests. The platelet aggregation test (PAT) (6) and the carbon 14-labeled serotonin release assay (SRA) (36) are the two main functional methods to detect heparin-dependent antibodies, with PAT being more commonly used than SRA (28) and heparin-induced platelet activation assay (17). Although the prevalence of HIT was found to be equal to or less than 1% in patients receiving low-molecular-weight heparin (LMWH) (29), dramatic venous and arterial thrombotic complications have been reported in cases of HIT (29;45). In addition, in a period of budget constraints, we cannot ignore the substantial cost associated with diagnosis and clinical care of patients with deep venous thrombosis (26,153 French francs [FF] or US $4,000; French national cost scale, 1999). For these medical and economical reasons, hemostasis laboratories are essential for helping the medical decision in patients with suspected HIT. The objective of this study was to compare the strategy of diagnosis and associated care of HIT-suspected patients using PAT, SRA, and doing nothing, using a cost-effectiveness analysis.

METHODS

The method used is an incremental cost-effectiveness analysis with a decision model using Bayesian logic (Figure 1) (31;32). We used the decision analysis software DATA^{TM} 3.0 (TreeAge Software, Inc., Williamstown, MA) to create a decision tree.

Construction of the Cost-effectiveness Model

At the origin of the decision tree is a patient with an isolated thrombocytopenia at day 5 of LMWH treatment after elective hip replacement. The assumptions of our model are as follows: a) the clinician's strategy depends on the functional laboratory test results; b) if the test is positive, the clinician replaces LMWH by danaparoid sodium in case of absence of cross reactivity; c) the clinician suspends the anticoagulant therapy in case of danaparoid sodium cross-reactivity; d) as venous thrombotic events predominated over arterial thrombotic events by a ratio of 4 : 1 (45), the thrombotic risk is mainly represented by deep venous thrombosis; and e) in case of danaparoid sodium cross-reactivity, the risk of thrombotic event is similar to that of LMWH treatment (16).

In 1,000 patients with suspected HIT, our model computes the number of patients who may develop a deep venous thrombosis. Thus, the effectiveness of the strategy is represented by the number of deep venous thromboses prevented.

The parameters used in the analysis are shown in Table 1. The sensitivity and the specificity of the laboratory tests were estimated by Chong et al. (6). These authors emphasized the

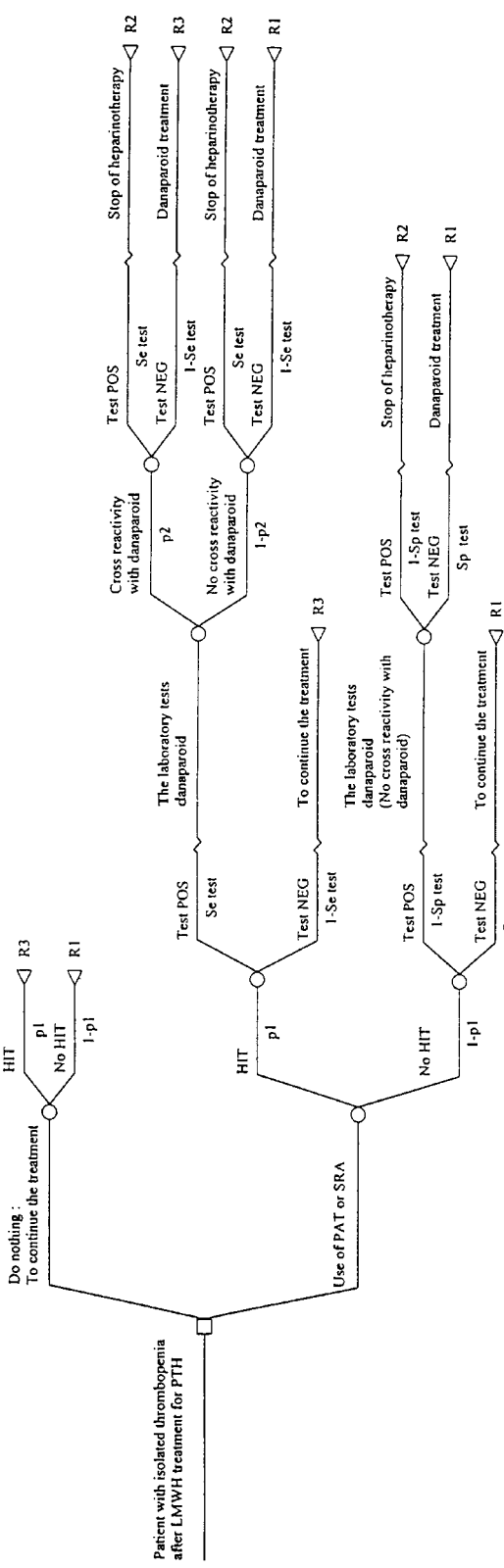

Figure 1. Decision tree comparing the strategies of care of patients with suspected HIT based on laboratory HIT diagnostic tests to the strategy of doing nothing. PTH = total hip replacement; PAT = platelet aggregation test; SRA = serotonin release assay; HIT = heparin-induced thrombocytopenia; P1 = HIT prevalence; Se test = test sensitivity; Sp test = test specificity; P2 = probability of cross-reactivity with danaparoid; R1 = residual thrombotic risk with LMWH treatment; R2 = thrombotic risk in the absence of treatment; R3 = thrombotic risk with HIT responsible treatment; test POS = positive test result; test NEG = negative test result; □ = decision node with choice; ○ = chance node; ◁ = terminal node; ∼ = decision node.

https://doi.org/10.1017/S0266462302000399 Published online by Cambridge University Press

Table 1. Data Source Used in the Analysis

	Mean	Range	Study by reference no.
Sensitivity of platelet aggregation test (%)	60	39–81	6
Sensitivity of serotonin release assay (%)	80	65–94	6
Specificity of platelet aggregation test (%)	91	82–100	6
Specificity of serotonin release assay (%)	97	94–100	6
Thrombotic risk in the absence of treatment (%)	50	46–55	2;3;11;13;15;16;18;19;20;25;27;30;33;35;37;42
Residual thrombotic risk with LMWH treatment (%)	16	13–19	2;3;11;13;15;16;18;19;20;25;27;30;33;35;37;42
Thrombotic risk with HIT responsible treatment (%)	70	52–89	9;46
Probability of cross-reactivity with danaparoid sodium (%)	14	10–19	7;8;22;43
HIT prevalence with LMWH treatment (%)	0.5	0–1	29

importance of the platelet reactivity among normal donors as assessed by functional laboratory tests. The estimates of the risk of deep venous thrombosis after elective hip replacement came from the LMWH clinical trials (2;3;11;13;15;16;18;19;20;25;27;30;33;35;37;42). The postoperative thrombotic risk in the absence of LMWH treatment was considered to be the number of deep venous thromboses in the control groups of these trials. When a preventive treatment with LMWH was given, the postoperative thrombotic risk was considered to be the number of deep venous thromboses in patients who received LMWH. The risk of thrombosis in case of suspected HIT when thromboprophylactic treatment was not stopped has been the subject of several reports (45). In a heterogeneous population, 52% of patients with biologically confirmed HIT developed thrombosis (45). Among a high risk population of patients admitted for elective hip replacement, 89% with confirmed HIT had a thrombotic complication (46). These studies demonstrated that the frequency of thromboembolic events may vary dramatically compared with the baseline risk of thrombosis in the patients' group (5).

The frequency of HIT in patients who received LMWH is equal to or less than 1% (29). The frequency of danaparoid sodium cross-reactivity has been the subject of several reports (Table 1) (7;8;22;43).

Sensitivity Analysis

The variables in our decision analysis model were analyzed over a range of values using a process known as sensitivity analysis. This was done for determining the stability of our results and to evaluate the effects of uncertainty on the values that were assigned to these variables. The clinical decision analysis is based on the thrombotic risk and on both the sensitivity and the specificity of the laboratory tests. We used a Tornado diagram (DATA 3.0) to select the parameters for the sensitivity analysis. The Tornado diagram classifies the variables according to their aptitude to modify the strategy score.

Cost Variables

Costs were assessed in the hospital perspective (12). The average costs of one test per patient, preventive danaparoid sodium treatment, and clinical care for patients with deep venous thrombosis were calculated. The cost of one test per patient consists of the addition of the reagent costs, the laboratory technician workload (number of hours per diagnostic test per patient $\times$ 1 hour laboratory technician working cost) and equipment cost (annual depreciation cost + annual maintenance cost). At our institution, 100 tests are realized

per year. The mortgage on the equipment is paid off in 7 years and there is no maintenance contract (annual depreciation cost = market equipment price /7).

The laboratory technician salary ranges from 6,000 to 24,000 FF monthly (US 1,000 to $4,000) (national collective agreement of French medical analysis laboratory). We used in our analysis an average monthly technician salary of 15,000 FF (US $2,500).

The estimation of danaparoid sodium preventive treatment cost depends on the average treatment duration, the number of danaparoid sodium vials administered, and the market price of danaparoid sodium.

We estimated the cost of care for a patient with deep venous thrombosis according to the Diagnosis-Related Group (DRG) in French hospitals (or GHM in French). A number of synthetic activity index (ISA) points are assigned to each GHM. The value of each GHM is fixed by the median cost of hospitalization of each GHM in a French national hospital setting. An ISA point was equal to FF 13.7 at our institution in 1999.

We assigned to each terminal node of the decision tree the cost of each decision way for 1,000 patients with suspected HIT. Then our decision model calculated the expected cost of each strategy.

The incremental cost-effectiveness ratio (CE) was calculated as follows:

$$CE = \Delta C/\Delta E = (Ct - Co)/(Et - Eo),$$

with Ct = the expected cost of a strategy using a biological test, Co = the expected cost of the strategy of doing nothing, Et = the effectiveness of a strategy using a biological test, and Eo = the effectiveness of the strategy of doing nothing.

RESULTS

The expected effectiveness of PAT, SRA, and doing nothing were 835.5, 838, and 837.2, respectively, of deep venous thrombosis prevented per 1,000 patients with suspected HIT. All the costs were evaluated according to the references of 1999. From the hospital perspective, the overall cost of care for a patient with a deep venous thrombosis was 26,153 FF (US $4,358) (GHM 185 on the French medical cost scale). The cost of using a preventive treatment with danaparoid sodium was 3,750 FF ($625). The manufacturer that produces both aggregometers and β-radioactivity counters (Bekman Coulter) does not recommend a maintenance contract for the aggregometer. The price of an aggregometer or a β-radioactivity counter was 150,000 FF ($25,000). The costs per patient of PAT and SRA were 315 and 820 FF ($52 and $136), respectively. The expected costs of the strategy using PAT, SRA, and doing nothing were 4,957,011, 5,195,826, and 4,255,093 FF ($826,168, $865,971, and $709,182), respectively, for 1,000 HIT-suspected patients. The strategy using PAT is less effective and more expensive than the strategy of doing nothing, with the latter being *a priori* clinically unacceptable. In comparison with doing nothing, the incremental cost-effectiveness of the strategy using SRA per deep venous thrombosis prevented was 1,175,916 FF ($195,986) (Table 2).

DISCUSSION

The present analysis was based on data extracted from the international literature that were used to perform a local analysis. However, within the variation range of our variables, the sensitivity analysis demonstrated the robustness of our results. To confirm the validity of our results, we estimated the effects of uncertainty on the values that were assigned to each variable. The univariate sensitivity analysis on each variable demonstrated that the strategy ranking was not invalidated by variations in the residual thrombotic risk, the

Table 2. Cost Components of the Three Strategies of Our Model

	Strategy using the platelet aggregation test	Strategy using the serotonin release assay	Strategy of doing nothing
Number of deep venous thrombosis per 1,000 patients with suspected HIT	164.5	162	162.8
Expected effectiveness = number of deep venous thrombosis prevented per 1,000 patients with suspected HIT	835.5	838	837.2
Reagent costs per patient (c1) (FF 1999)	5	10	
Cost of laboratory technician work per patient (c2) (FF 1999)	96	96	
Analyzer market price (FF 1999)	150,000	150,000	
Annual depreciation cost (FF 1999)	21,430	21,430	
Annual maintenance contract cost (FF 1999)	0	50,000	
Equipment working cost (FF 1999) (c3)	214	714	
Cost of one test per patient = c1 + c2 + c3 (French Francs 1999)	315	820	
Strategy expected cost for 1,000 patients with suspected HIT (FF 1999)	4,957,011	5,195,826	4,255,093
Incremental CE per deep venous thrombosis prevented (FF 1999)	Not done: strategy dominated by strategy of doing nothing	1,175,916	

thrombotic risk in the absence of treatment, the thrombotic risk with HIT induced by treatment, the danaparoid sodium cross-reactivity probability, or the PAT sensitivity. The three first variables that would invalidate our results were the PAT specificity, the HIT prevalence, and the residual thrombotic risk (Figure 2).

We have not examined the role of the antigen assay (ELISA) in this study because ELISA is not a functional assay. So, with ELISA, it is impossible to test the cross-reactivity of Orgaran®, which is required in case of drug substitution because of HIT suspicion.

The strategy using PAT was more effective than the strategy of doing nothing when PAT specificity was greater than 0.95 (Figure 3). However, in the last study assessing PAT, the specificity was 0.77 despite a high degree of technique expertise (34). The lack of specificity when using PAT, wrongly inducing a discontinuation of heparin prophylaxis and a subsequent thrombotic event by cessation of heparin treatment, is responsible for the lack of effectiveness of the strategy using this test. This is why, without treatment, the thrombotic risk indirectly affects the strategy ranking (44).

The strategy of doing nothing was more effective than the strategy using SRA when the HIT prevalence was less than 0.3% (Figure 3). The sensitivity analysis showed the effect of HIT prevalence on the incremental CE ratio. Indeed, when the strategies of doing nothing and SRA were compared, the SRA incremental cost-effectiveness per deep venous thrombosis prevented varied from 836,125 to 1,581,885 FF (US $139,354 to $263,647) (Table 3). In the study of Warkentin et al. (46), no patient developed HIT after LMWH treatment. At our institution, we diagnose approximately 5 HIT per 100 HIT-suspected patients with thrombocytopenia after LMWH treatment. The diagnosis of HIT is retrospectively confirmed because platelet count recovers when LMWH is discontinuated. The HIT prevalence with LMWH treatment is less than 1% but not equal to zero. Despite some uncertainty about HIT prevalence, our results may be considered valid and demonstrate the interest of SRA.

When a clinical laboratory is asked to test danaparoid sodium because of a positive result obtained with the initial treatment, the use of the test is redundant. The result of

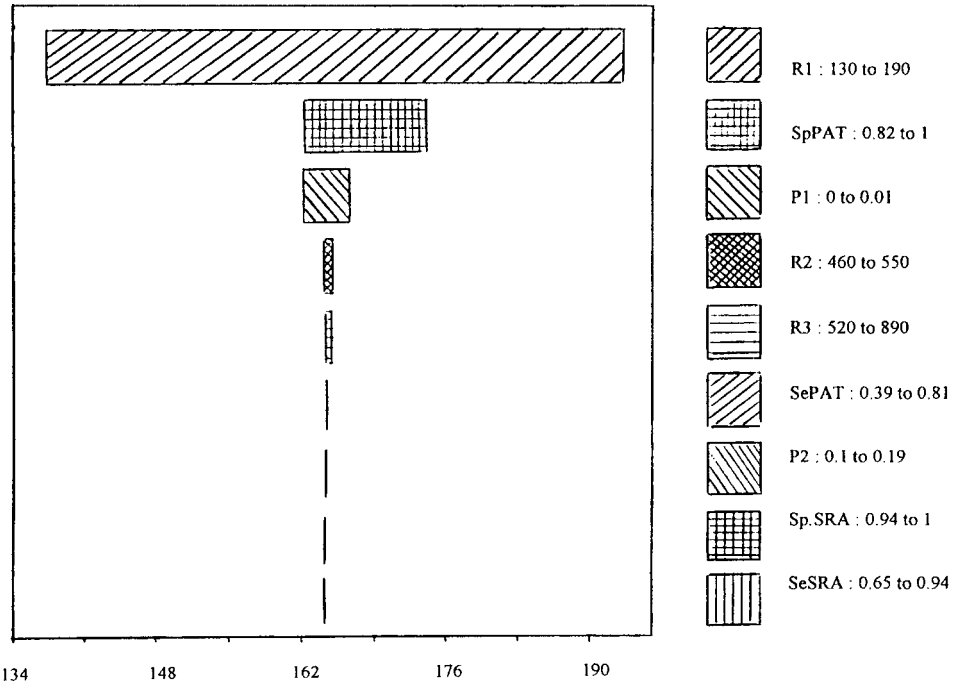

Figure 2. Tornado diagram ranking the different variables of our model according to their capacity of inducing strategy score variations. R1 = residual thrombotic risk with LMWH treatment; SpPAT = platelet aggregation test specificity; P1 = HIT prevalence with LMWH treatment; R2 = thrombotic risk in the absence of treatment; R3 = thrombotic risk with HIT responsible treatment; SePAT = platelet aggregation test sensitivity; P2 = probability of cross-reactivity with danaparoid sodium; SpSRA = serotonin release assay specificity; SeSRA = serotonin release assay sensitivity.

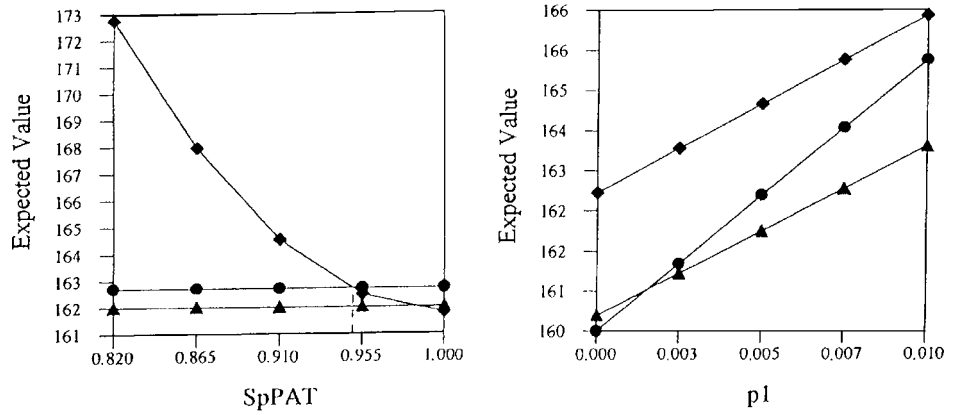

Figure 3. Univariate sensitivity analysis on platelet aggregation test specificity (SpPAT) and HIT prevalence (p1) ♦ = PAT; ▲ = SRA; ● = doing nothing.

a danaparoid sodium test depends on the result of the first test realized with the initial treatment. If HIT is present, the selection operated by the first positive test brings to the next test a subgroup of patients among whom the probability of a positive test with danaparoid sodium is high. This suggests that the sensitivity of the second test can be overestimated. In the same subgroup of patients, the false-positive patients will reduce the specificity of

https://doi.org/10.1017/S0266462302000399 Published online by Cambridge University Press

Table 3. Sensitivity Analysis on the Incremental CE Ratio (French Francs, 1999) of the Strategy Using the Serotonin Release Assay in Comparison with the Strategy of Doing Nothing

HIT prevalence with LMWH treatment (%)	Effectiveness differential between the SRA strategy and the strategy of doing nothing	Cost differential between the SRA strategy and the strategy of doing nothing	Incremental CE ratio in comparison with the strategy of doing nothing
0.3	0.6	949,131	1,581,885
0.5	0.8	940,733	1,175,916
1	1.1	919,738	836,125

the functional method used to test danaparoid sodium. However, our results remained valid because the sequential use of the tests was restricted (40).

In our study, the effectiveness of the strategy is determined by the number of deep venous thromboses prevented for 1,000 patients with suspected HIT. However, other clinical complications of HIT have been described (5). Though venous thrombosis is the most frequent complication, arterial thrombosis has also been associated with HIT (4). A strategy using a test lacking specificity is disadvantaged because it induces a discontinuation of treatment, which is more pejorative for the patient considering the potential outcomes. Arterial thrombosis is more pejorative from both a medical (23) and economical viewpoint than deep venous thrombosis (French medical cost scale, version 5, 1999). Thus, integration of arterial thrombosis in a similar model would confirm and even reinforce the validity of our results.

The incremental CE per deep venous thrombosis prevented varied from 836,125 to 1,581,885 FF. We have compared this ratio to those of other prevention programs to estimate the medico-economical acceptability of the strategy using SRA (10). We can evaluate this medico-economical acceptability by comparing the respective CE ratio with the number of affected patients. From a medico-economical point of view, a program with a high CE ratio is as acceptable as a program with a low CE ratio if the number of affected patients is proportionally lower. As an example, we compared the strategy using a combination of a transaminase assay and tests for antibodies to hepatitis B core antigen and antibodies to hepatitis C virus versus an approach using only a transaminase assay and a test for antibodies to hepatitis B core antigen. The incremental CE was 14,256 FF (US $2,376) per additional infected donor detected in the transfusion centers (10). Even though the strategy using SRA is expensive with regard to the strategy of doing nothing, it is nevertheless the most acceptable figure considering the potential side effects related to HIT. In other words, when the pretest probability, e.g., the HIT prevalence, is high or low because of a high or low suspicion of HIT, the CE ratio may vary by twice as much (Table 3).

The cost induced by the care of patients with deep venous thrombosis represents the greatest part of the direct costs in patients with HIT. Treating 1,000 HIT-suspected patients without laboratory tests costs 4,255,093 FF (US $709,182). Thus, a sensitivity analysis performed on range values of laboratory reagents, equipment, and staff costs would induce insignificant variations of our results and would not invalidate these results.

Considering the trend to reduce the use of radioactive products, it is commonly considered that the effectiveness differential between SRA and PAT is too weak to promote SRA in the hospital. Recently, the functional flow cytometric assay (FCA) was shown to be valuable in HIT diagnosis (38). The sensitivity and the specificity of this assay were reported to be 0.95 and 1, respectively. In the two comparative studies, Pouplard et al. (34) and Tomer (38) did not use the same gold standard. There is some uncertainty about the possibility of comparing clinical scoring of with suspected HIT patients in studies that

assessed the HIT diagnosis tests (34;38). Nevertheless, we consider this new functional method promising because of its capacity to detect the discrete platelet activation states. Tomer et al. (39) found three patients with suspected HIT who were positive by FCA but negative by SRA. For the authors, the fact that the dense granule release requires a stronger stimulus than that required for the release of α-granule constituents could represent a plausible explanation for this discrepancy (39). Moreover, the detection of platelet activation marker P selectin (CD62p) by FCA could distinguish HIT from HIT with thrombosis (21). For clinical hemostasis laboratories, the FCA that does not require radioactive products is more practical than SRA, and would represent an attractive alternative test for HIT diagnosis. Like SRA in our model, the FCA might have a positive medical impact and could offer a significant informative value.

POLICY IMPLICATIONS

Hemostasis laboratories should consider replacing the PAT by the SRA in patients with a high risk of thrombosis who are being treated by LMWH. Other tests such as the flow cytometric assay also should be evaluated since they may have a positive medico-economical impact on public health.

REFERENCES

1. Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. *Thromb Haemost*. 1992;68:95-96.
2. Barnes RW, Brand RA, Clarke W, et al. Efficacy of graded compression antembolism stockings in patients undergoing total hip arthroplasty. *Clin Orthop*. 1978;132:61-77.
3. Belch JJF, Meek DR, Lowe GDO, et al. Subcutaneous ancrod in prevention of deep venous thrombosis after hip replacement surgery. *Thromb Res*. 1982;25:23.
4. Boshkov LK, Warkentin TE, Hayward CPM, et al. Heparin induced thrombocytopenia and thrombosis: Clinical and laboratory studies. *Br J Haematol*. 1993;84:322-328.
5. Brieger DB, Mak KH, Marchant K, et al. Heparin-induced thrombocytopenia. *J Am Coll Cardiol*. 1998;31:1449-1459.
6. Chong BH, Burgess J, Ismail F. The clinical usefulness of the platelet aggregation test for the diagnosis of heparin-induced thrombocytopenia. *Thromb Haemost*. 1993;69:344-350.
7. Chong BH, Ismail F, Gallus AS, et al. Heparin induced thrombocytopenia: Studies with a new low molecular weight heparinoid, Org 10172. *Blood*. 1989;73:1592-1596.
8. Chong BH, Magnani HN. Orgaran in heparin induced thrombocytopenia. *Haemostasis*. 1992;22:85-91.
9. Clagett GP, Anderson FA, Levine MN, et al. Prevention of venous thromboembolism. *Chest*. 1992;102(Suppl 4):391-407.
10. Colin C, Vergnon P, Jullien AM, et al. Cost-effectiveness of screening blood donors for hepatitis C and non-A, non-B, non-C hepatitis. *Eur J Clin Microbiol Infect Dis*. 1997;16:220-227.
11. Dechavanne M, Ville D, Berruyer M, et al. A randomized trial of a low molecular weight heparin (Kabi 2165) versus adjusted dose subcutaneous standard heparin in the prophylaxis of deep vein thrombosis after elective hip surgery. *Haemostasis*. 1989;1:5-12.
12. Drummond MF, O'Brien BJ, Stoddart GL, Torrance GW, eds. *Méthodes d'évaluation économique des programmes de santé*. Paris: Economica; 1999.
13. Evarts CM, Feil EJ. Prevention of thromboembolic disease after elective surgery of the hip. *J Bone Joint*. 1971;53:1271-1280.
14. Fabris F, Ahmad S, Cella G, et al. Pathophysiology of heparin-induced thrombocytopenia: Clinical and diagnostic implications—A review. *Arch Pathol Lab Med*. 2000;124:1657-1666.
15. Gallus A, Raman K, Darby T.Venous thrombosis after elective hip replacement: The influence of preventive intermittent calf compression and surgical technique. *Br J Surg*. 1983;70:17-19.
16. Gouault-Heilmann M, Huet Y, Adnot S. Low molecular weight heparin fractions as an alternative therapy in heparin induced thrombocytopenia. *Haemostasis*. 1987;17:134-140.

17. Greinacher A, Michels I, Kiefel V, et al. A rapid and sensitive test for diagnostic heparin-associated thrombocytopenia. *Thromb Haemost*. 1991;66:734-736.
18. Harris WH, Salzman EW, Athanasoulis CA, et al. Aspirin prophylaxis of venous thromboembolism after total hip replacement. *N Engl J Med*. 1977;297:1246-1249.
19. Hoek J, Nurmohamen MT, ten Cate H, et al. Prevention of deep vein thrombosis following total hip replacement by a low molecular weight heparinoid (Org 10172). *Thromb Haemost*. 1989;62(Suppl 1):1637.
20. Ishak M, Morley KD. Deep venous thrombosis after total hip arthroplasty: A prospective study to determine the prophylactic effect of graded pressure stockings. *Br J Surg*. 1981;68:429-432.
21. Jy W, Mao WW, Horstman LL, et al. A flow cytometric assay of platelet activation marker P-selectin (CD62P) distinguishes heparin induced thrombocytopenia (HIT) from HIT with thrombosis (HITT). *Thromb Haemost*. 1999;82:1255-1259.
22. Kikta MJ, Keller MP, Humphrey PW, et al. Can low molecular weight heparins and heparinoids be safely given to patients with heparin-induced thrombocytopenia syndrome? *Surgery*. 1993;114:705-710.
23. King DJ, Kelton JG. Heparin associated thrombocytopenia. *Ann Intern Med*. 1984;100:535-540.
24. Lassen ML, Borris LC, Christiansen HM, et al. Low molecular weight heparin in the prevention of thromboembolism in elective hip replacement. *Thromb Haemost*. 1989;62(Suppl 1):398.
25. Leyvraz PF, Bachmann F, Hoek J, et al. Prevention of deep vein thrombosis after hip replacement: Randomized comparison between unfractionated heparin and low molecular weight heparin. *BMJ*. 1991;303:543-548.
26. Lindhoff-Last E, Eichler P, Stein M, et al. A prospective study on the incidence and clinical relevance of heparin-induced antibodies in patients after vascular surgery. *Thromb Res*. 2000;6:387-393.
27. Moskovitz PA, Ellenberg SS, Feffer HL, et al. Low dose heparin for the prevention of venous thromboembolism in total hip arthroplasty and surgical repair of hip fractures. *J Bone Joint Surg*. 1978;60:1065-1070.
28. Nguyen P, De Maistre E, Cornillet Lefebvre P, et al. Heparin induced thrombocytopenia in France: 1980-1998. *Semin Thromb Hemost*. 1999;25(Suppl 1):9-15.
29. Ortel TL, Eisbacher M, Chong BH, et al. Heparin induced thrombocytopenia state of the art. *Semin Hematol*. 1998;35(Suppl 5).
30. Paiement GD, Wessinger SJ, Harris WH. Survey of prophylaxis against venous thromboembolism in adults undergoing hip surgery. *Clin Orthop*. 1987;223:188-193.
31. Pauker SG, Kassirer JP. Therapeutic decision making: A cost-benefit analysis. *N Engl J Med*. 1975;293:229-234.
32. Pauker SG, Kassirer JP. The threshold approach to clinical decision making. *N Engl J Med*. 1980;302:1109-1117.
33. Planes A, Vochelle N, Mazas F, et al. Prevention of postoperative venous thrombosis: A randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement. *Thromb Haemost*. 1988;60:407-410.
34. Pouplard C, Amiral J, Borg JY, et al. Decision analysis for use of platelet aggregation test, carbon 14-serotonin release assay and heparin-platelet factor 4 enzyme-linked immunosorbent assay for diagnosis of heparin-induced thrombocytopenia. *Am J Clin Pathol*. 1999;111:700-706.
35. Rogers PH, Walsh PN, Marder VJ, et al. Controlled trial of low dose heparin and sulfinpyrazone to prevent venous thromboembolism after operation of the hip. *J Bone Joint Surg*. 1978;60:758-762.
36. Sheridan D, Carter C, Kelton JG. A diagnostic test for heparin induced thrombocytopenia. *Blood*. 1986;67:27-30.
37. Soreff J, Johnsson H, Diener L, et al. Acetyl salicylic acid in trial to diminish thromboembolic complications after elective hip surgery. *Acta Orthop Scand*. 1975;46:246-255.
38. Tomer A. A sensitive and specific functional flow cytometric assay for the diagnosis of heparin-induced thrombocytopenia. *Br J Haematol*. 1997;98:648-656.
39. Tomer A, Masalunga C, Abshire TC. Determination of heparin-induced thrombocytopenia: A rapid flow cytometric assay for direct demonstration of antibody-mediated platelet activation. *Am J Hematol*. 1999;61:53-61.

40. Trois exigences de l'exploitation séquentielle de plusieurs tests. In: Grenier B, ed. *Evaluation de la décision médicale: Introduction à l'analyse médico-économique*. Paris: Masson; 1999:137-141.
41. Trossaert M, Gaillard A, Commin PL, et al. High incidence of anti-heparin/platelet factor 4 antibodies after cardiopulmonary bypass surgery. *Br J Haematol*. 1998;101:653-655.
42. Turpie AG, Levine MN, Hirsh J, et al. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep vein thrombosis in patients undergoing elective hip surgery. *N Engl J Med*. 1986;315:925-929.
43. Vun CM, Evans S, Chong BH. Cross-reactivity study of low-molecular-weight heparins and heparinoid in heparin-induced thrombocytopenia. *Thromb Res*. 1996;81:525-532.
44. Wallis DE, Workman DL, Lewis BE, et al. Failure of early heparin cessation as treatment for heparin induced thrombocytopenia. *Am J Med*. 1999;6:629-635.
45. Warkentin TE, Kelton JG. A 14 year-study of heparin-induced thrombocytopenia. *Am J Med*. 1996;101:502-507.
46. Warkentin TE, Levine MN, Hirsh J, et al. Heparin induced thrombocytopenia in patients treated with low molecular-weight heparin or unfractionated heparin. *N Engl J Med*. 1995;332:1330-1335.