

## EFFECT OF TICLOPIDINE ON THE LONG-TERM PATENCY OF SAPHENOUS-VEIN BYPASS GRAFTS IN THE LEGS

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### ABSTRACT

**Background** Optimal therapy to prevent late occlusion of arterial bypass grafts in the legs has not been determined. We assessed the effect of ticlopidine, an inhibitor of platelet aggregation, on the long-term patency of saphenous-vein bypass grafts for the treatment of peripheral vascular disease.

**Methods** A total of 243 patients with femoropopliteal or femorotibial saphenous-vein bypass grafts were randomly assigned to receive either ticlopidine (250 mg twice a day) or matching placebo for two years. The primary end point was graft patency at two years, as assessed by physical examination, measurement of the ankle brachial index, and duplex ultrasonography or arteriography. The incidence of death and major ischemic events was also analyzed in the two groups.

**Results** After two years, 66.4 percent of the patients were alive with a patent graft in the ticlopidine group, as compared with 51.2 percent in the placebo group (95 percent confidence interval for the difference between the two groups, 2.9 to 27.4 percent;  $P=0.02$ ). The two-year cumulative patency rate was 82 percent in the ticlopidine group and 63 percent in the placebo group ( $P=0.002$ ). There was no significant difference between groups in overall mortality or major ischemic events.

**Conclusions** Ticlopidine significantly improved the long-term patency of saphenous-vein bypass grafts in the legs. Since the drug was well tolerated, its use can be recommended after peripheral-vein bypass surgery. (N Engl J Med 1997;337:1726-31.)

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**A**UTOLOGOUS saphenous veins are the first choice of graft material for infringuinal arterial bypass surgery. Without adjunctive therapy, the patency rates can be as low as 50 percent at two years for femoropopliteal or femorotibial (i.e., below the knee) bypass grafts.<sup>1</sup> There are several causes of graft failure. Early occlusions are thrombotic, sometimes because of hypercoagulability but more usually because of incomplete ablation of venous valves, a defect in the anastomosis, or a kinked or compressed graft. Good operative technique, careful clinical monitoring, and proper perioperative anticoagulation therapy can prevent most of these events.

Late graft failures are mainly due to progressive stenosis of the arteries on either side of the bypass

or to deterioration of the graft itself. Stenosis is generally due to the development of fibrous intimal hyperplasia, which thickens the vessel wall, reducing the effective size and compliance of the lumen,<sup>2</sup> or to the progression of atherosclerosis. The mechanisms of endothelial hyperplasia are complex and not fully understood, but the adhesion of platelets to the damaged endothelial cell layer and their subsequent activities may play a part. Treatment with platelet-inhibiting drugs, especially aspirin, has been investigated as a way of improving the patency of saphenous-vein grafts. Multicenter randomized trials have shown that aspirin with or without dipyridamole increased the immediate and long-term patency of aortocoronary saphenous-vein grafts.<sup>3-6</sup> However, clinical studies have failed to establish the efficacy of aspirin, with or without dipyridamole, or of oral anticoagulation in femoropopliteal bypass with autologous-vein grafts.<sup>7-11</sup> Therapy with ticlopidine, an inhibitor of platelet aggregation, increases the distance that patients are able to walk<sup>12</sup>; reduces the rate of death, myocardial infarction, and stroke; and reduces the need for reconstructive arterial surgery of the leg in patients with intermittent claudication.<sup>13-16</sup> Moreover, as compared with placebo, ticlopidine increases the immediate and one-year patency of aortocoronary bypass grafts.<sup>17,18</sup> We undertook the present study to determine whether ticlopidine could reduce the rate of late occlusion of saphenous-vein grafts below the knee.

### METHODS

This multicenter, double-blind trial was carried out by members of the Association Universitaire de Recherche en Chirurgie. The study, which was designed and conducted in accordance with the European Guidelines for Good Clinical Practice for Research and the Declaration of Helsinki, was approved by the ethics committee of the Centre Hospitalier Universitaire Henri Mondor, Créteil, France. All patients provided written informed consent.

The main aim of the study was to compare prospectively the patency at two years of femoropopliteal or femorotibial saphenous-vein bypass grafts used in situ or reversed in two parallel groups of patients randomly assigned to receive 250 mg of ticlopidine (Ticlid, Sanofi Recherche, Montpellier, France) twice a day or placebo.

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\*The investigators and centers involved in the study are listed in the Appendix.

## Patients

All patients 18 to 80 years of age who required a femoropopliteal or femorotibial bypass graft for atheromatous occlusive disease and who had a saphenous vein suitable for grafting were considered for the study. The following were all reasons for exclusion: acute ischemia or aneurysm, marked stenosis in the ipsilateral iliac artery, previous arterial surgery on the same limb, reduced life expectancy, pregnancy, inability to comply with the protocol, associated conditions requiring treatment with platelet-inhibiting drugs or anticoagulants, and abnormalities of hemostasis. Randomization took place between the 3rd and 14th day after bypass surgery in patients with a patent graft (day 0). The randomization was not stratified.

## Randomization, Treatments, and Compliance

Treatment bottles containing a one-month supply of ticlopidine (250-mg tablets) or matching placebo were prepared by Sanofi and labeled according to a predetermined randomization list of numbers balanced in blocks of four. Boxes containing a 6-month supply were dispensed on day 0 and at 6, 12, and 18 months. The patients were instructed to take one tablet twice a day for the 24 months of the study. They were given a list of anticoagulants and drugs with antiplatelet effects and told to avoid taking these drugs during the study. In order to assess compliance, patients returned treatment packs at the end of each period so that unused pills could be counted.

## Definitions and End Points

Patients were evaluated at 1, 3, 6, 12, 18, and 24 months. At each point, patency was assessed by the same means used to demonstrate patency at entry: clinical examination, including checking for a pulse in the graft and the leg; measurement of the ankle brachial index; and duplex ultrasonography or arteriography. A graft was considered patent when pulses were present, the ankle brachial index had not decreased, and the scan or arteriogram showed no stenosis or occlusion of the graft itself or of the anastomoses. Primary patency was defined as the presence of a patent graft without any additional intervention. Secondary patency was defined as the presence of a patent graft with or without additional intervention such as surgical treatment of short stenoses, transluminal angioplasty, thrombectomy, or thrombolysis. Indications for reintervention were left to the physicians in charge of the patients' care.

The main end point was primary patency at two years among surviving patients. The secondary end points were secondary patency at two years among surviving patients and the occurrence of major clinical events, defined as death from any cause, nonfatal myocardial infarction, nonfatal stroke, ischemia of the limb, mesenteric infarct, or amputation of a leg or thigh. All records concerning graft patency were reviewed by a validation committee that was unaware of the patients' treatment assignments. The clinical events were reviewed and adjudicated blindly by an independent panel consisting of a cardiologist, a hematologist, and a vascular surgeon.

## Safety Monitoring

Records of clinical symptoms and laboratory tests were periodically reviewed by an independent safety committee. Particular attention was paid to gastrointestinal, hemorrhagic, allergic, and hematologic disturbances. The occurrence of fever, sore throat, or mouth ulcers prompted an immediate blood count. Full hematologic profiling, including erythrocyte, leukocyte, and platelet counts, was performed every 15 days for the first 3 months; blood biochemical profiling was performed at 1 month; and both were done 3, 6, 12, 18, and 24 months after randomization.

## Statistical Analysis

The results were expressed in two ways: by a crude calculation at 24 months and by a life-table analysis. In the crude calculation,

graft failure was considered to have occurred if the patients had an occluded graft, missed the evaluation at 24 months, or died before the 24-month follow-up (without prior graft failure). In the life-table analysis, patency of the grafts was assessed through each patient's last examination. The intention-to-treat analysis included all patients who entered the study. The per-protocol analysis included only events that occurred while the patients were taking the study drugs. Categorical data were compared by chi-square test. The log-rank test was used for the life-table analysis. The 95 percent confidence intervals for the differences in incidence used the normal approximation. All P values were two-tailed.

## RESULTS

### Patients

From 1989 to 1992, 243 patients (mean age, 67.4 years; range, 40 to 85) who had undergone a below-the-knee saphenous-vein bypass were enrolled in the study; 77.4 percent were men. A total of 122 patients were assigned to receive ticlopidine, and 121 to receive placebo. Minor deviations from the protocol were recorded for 11 patients (6 in the ticlopidine group and 5 in the placebo group): 5 were related to age, 2 to excessive delays between surgery and randomization, 2 to the fact that bypass had been performed previously in the same leg, 1 to a concurrent medical condition, and 1 to the placement of a prosthetic graft.

There were no significant differences in sex, age (mean [ $\pm$ SE], 67.1 $\pm$ 0.8 years in the ticlopidine group and 67.7 $\pm$ 0.8 years in the placebo group), or preoperative risk factors between the treatment groups (Table 1). The preoperative and postoperative ankle brachial indexes did not differ significantly between the two groups; the mean values for the group as a whole were 0.44 $\pm$ 0.02 preoperatively and 0.90 $\pm$ 0.02 postoperatively (0.92 $\pm$ 0.02 in the ticlopidine group and 0.88 $\pm$ 0.02 in the placebo group). There were no significant differences between groups with respect to the leg that was operated on (right or left), the site of proximal anastomosis, runoff (defined as the number of patent tibial arteries), and immediate graft patency. However, there was an unexpected significant difference ( $P=0.03$ ) between the two groups in the site of distal anastomosis (Table 1), with more tibial anastomoses in the ticlopidine group. The imbalance in the distribution occurred by chance.

### Treatment

The mean duration of therapy was not significantly different between groups: 468 days in the ticlopidine group and 421 days in the placebo group. The frequency of and reasons for the discontinuation of treatment (Table 2) differed significantly between groups. Discontinuation because of graft failure was approximately three times as common in the placebo group, whereas discontinuation because of nonhemorrhagic gastrointestinal side effects was more common in the ticlopidine group.

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.**

CHARACTERISTIC	TICLOPIDINE (N = 122)	PLACEBO (N = 121)
	no. (%)	
Male sex	96 (78.7)	92 (76.0)
Current angina pectoris or previous myocardial infarction	25 (20.5)	30 (24.8)
Impaired left ventricular function	13 (10.7)	9 (7.4)
Arrhythmia	11 (9.0)	19 (15.7)
Carotid stenosis*	27 (22.1)	26 (21.5)
Hypertension	59 (48.4)	65 (53.7)
Current smoker	31 (25.4)	23 (19.0)
Diabetes	33 (27.0)	26 (21.5)
Hyperlipidemia	29 (23.8)	31 (25.6)
Leriche-Fontaine stage of disease†		
IIb	33 (27.0)	27 (22.3)
III	37 (30.3)	50 (41.3)
IV	52 (42.6)	44 (36.4)
Previous vascular surgery	40 (32.8)	37 (30.6)
Site of distal anastomosis		
Popliteal	66 (54.1)	82 (67.8)
Tibial‡	56 (45.9)	39 (32.2)

\*Patients with carotid stenosis were included whether or not they had symptoms.

†In the Leriche-Fontaine staging system, stage IIb indicates claudication and an ability to walk less than 150 m, stage III pain at rest, and stage IV gangrene or ulcer.

‡P=0.03 for the difference between groups.

**TABLE 2. REASONS FOR DISCONTINUATION OF TREATMENT.**

REASON	TICLOPIDINE (N = 122)	PLACEBO (N = 121)	P VALUE
	no. (%)		
Graft failure	11 (9.0)	30 (24.8)	0.001
Death or ischemic event	15 (12.3)	18 (14.9)	0.56
Hemorrhage	0	2 (1.7)	0.15
Diarrhea	10 (8.2)	0	0.001
Gastritis	2 (1.6)	2 (1.7)	0.99
Skin disorder	2 (1.6)	2 (1.7)	0.99
Abnormal hepatic function	3 (2.5)	1 (0.8)	0.32
Withdrawal of consent	8 (6.6)	10 (8.3)	0.61
Other	7 (5.7)	9 (7.4)	0.59
Total	58 (47.5)	74 (61.2)	0.03

Two patients in the placebo group discontinued treatment because of hemorrhage.

**Study Outcomes**

At 24 months, bypass patency was assessed in 192 patients according to the protocol (171 by duplex ultrasonography and 21 by angiography). In 12 additional patients (8 in the ticlopidine group and 4 in the placebo group), patency at 24 months was assessed on the basis of clinical evaluation alone, and the results were confirmed by the validation committee. All 12 had patent grafts. Patency was not evaluated in the remaining 39 patients: 28 of these patients had died, and 11 did not attend the follow-up evaluation at 24 months. All 39 patients had had patent grafts at their last clinical and ultrasonographic examinations.

Table 3 shows the results of the intention-to-treat analysis. At 24 months, more patients were alive with a primary patent graft in the ticlopidine group than in the placebo group (66.4 percent vs. 51.2 percent; 95 percent confidence interval for the difference, 2.9 to 27.4 percent; P=0.02). The percentage of patients who were alive with secondary patent grafts was also greater in the ticlopidine group (68.9 percent vs. 55.4 percent, P=0.03).

Life-table analysis (Fig. 1) showed a two-year cumulative patency rate of 82±4 percent in the ticlopidine group and 63±5 percent in the placebo group (P=0.002). Logistic-regression analysis of the rate of primary patency at 24 months did not show any significant influence of the treatment group, type of vein construction (reversed or in situ), and risk factors such as diabetes, smoking habits, hypertension, history of ischemic events, and stage of arteriopathy on patency and confirmed the efficacy of ticlopidine treatment (P=0.01). When the percentage of primary patent grafts was analyzed according to the site of the lower anastomosis, the rate was 62 percent for grafts with below-the-knee popliteal anastomoses in the ticlopidine group, as compared with 55 percent in the placebo group, and 71 percent for grafts with tibial anastomoses in the ticlopidine group, as compared with 44 percent in the placebo group (P=0.11 by the Breslow-Day test).<sup>19</sup>

For the per-protocol analysis, 91 patients were excluded (47 patients in the ticlopidine group and 44 patients in the placebo group). The two-year cumulative patency rate was 81±5 percent in the ticlopidine group and 57±6 percent in the placebo group (P=0.001).

**Adverse Events**

Thirty-six patients died during the study (14.8 percent of the study group; 18 patients in each group). There was no significant difference between the two groups with respect to major adverse events (Table 4).

Sixty-nine patients in the ticlopidine group re-

**TABLE 3.** OUTCOMES AT 24 MONTHS AFTER RANDOMIZATION, ACCORDING TO THE INTENTION-TO-TREAT ANALYSIS.

OUTCOME*	TICLOPIDINE (N = 122)	PLACEBO (N = 121)	P VALUE
	no. (%)		
Primary patency	81 (66.4)	62 (51.2)	0.02
Proved graft failure	20 (16.4)	41 (33.9)	
Missed 24-mo evaluation	6 (4.9)	5 (4.1)	
Death (not preceded by graft failure)	15 (12.3)	13 (10.7)	
Secondary patency	84 (68.9)	67 (55.4)	0.03
Graft replaced	2 (1.6)	11 (9.1)	0.01

\*Primary patency was defined as the presence of a patent graft without any additional intervention, and secondary patency as the presence of a patent graft with or without additional intervention, such as surgical treatment of short stenoses, transluminal angioplasty, thrombectomy, or thrombolysis.

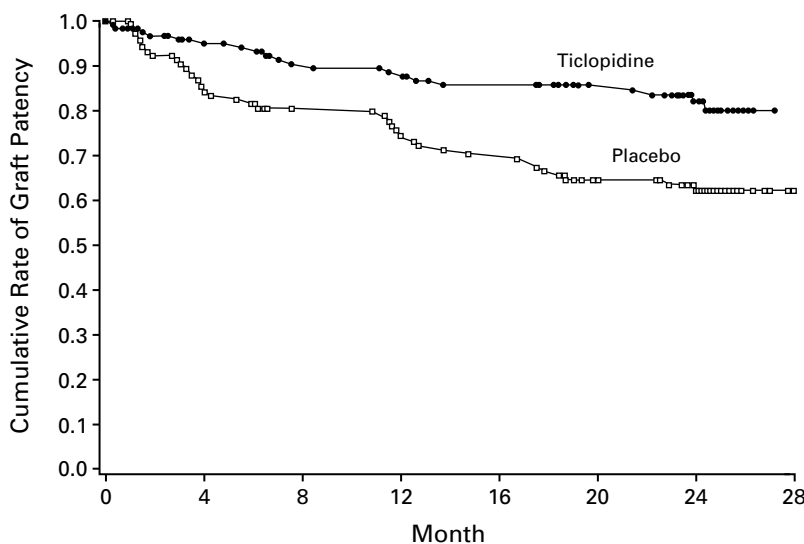
ported a total of 107 nonischemic adverse events, as compared with 47 patients in the placebo group reporting a total of 68 events ( $P=0.006$ ). The difference was almost entirely accounted for by gastrointestinal disorders (34 patients vs. 19 patients), chiefly diarrhea (20 patients vs. 4 patients). Six patients reported hemorrhagic events (two in the ticlopidine group and four in the placebo group). Attempted drainage of a subdural hematoma in an 85-year-old woman in the ticlopidine group eventually led to death (reported as fatal stroke in Table 4). Ocular and gastrointestinal hemorrhages led to the discontinuation of treatment in two patients in the

placebo group, whereas treatment was continued despite gastrointestinal hemorrhage in another patient in the placebo group. Early postoperative hematomas of the surgical wound in one patient in each group were surgically drained without the need to discontinue therapy. Three patients (two in the ticlopidine group and one in the placebo group) had hepatic-enzyme abnormalities, which eventually resolved after the discontinuation of treatment. Four patients (1 in the ticlopidine group and 3 in the placebo group) had mild neutropenia (polymorphonuclear neutrophil count, 1200 to 1700 per cubic millimeter), and 12 (5 in the ticlopidine group and 7 in the placebo group) had mild thrombocytopenia (platelet count, 80,000 to 150,000 per cubic millimeter), which was discovered by routine testing. Since there was no clinical consequence, treatment was continued in every case with no adverse effect.

## DISCUSSION

This prospective, double-blind, randomized study compared the effect of ticlopidine and placebo in patients who underwent a below-the-knee saphenous-vein bypass for ischemia of the lower limb. At two years, ticlopidine was associated with a significantly higher percentage of primary patent grafts among surviving patients (66.4 percent, as compared with 51.2 percent in the placebo group), as well as a higher cumulative patency rate (82 percent vs. 63 percent). There were also fewer major amputations in the ticlopidine group.

Even technically correct arterial reconstructions may become occluded. There is general consensus that adjuvant therapy is needed to improve patency.



**Figure 1.** Cumulative Rates of Graft Patency According to the Intention-to-Treat Analysis. There was a significant difference between groups ( $P=0.002$  by the log-rank test).

TABLE 4. INCIDENCE OF MAJOR ADVERSE EVENTS.\*

EVENT	TICLOPIDINE	PLACEBO	P VALUE
	(N=122)	(N=121)	
	no. (%)		
Death	18 (14.8)	18 (14.9)	0.98
Fatal stroke	1 (0.8)	0	0.32
Fatal myocardial infarction	5 (4.1)	4 (3.3)	0.74
Sudden death	3 (2.5)	3 (2.5)	0.99
Mesenteric infarction	1 (0.8)	1 (0.8)	0.99
Noncardiac causes	8 (6.6)	10 (8.3)	0.61
Nonfatal ischemic events	30 (24.6)	39 (32.2)	0.24
Nonfatal stroke	4 (3.3)	4 (3.3)	0.99
Transient ischemic attack	6 (4.9)	6 (5.0)	0.99
Nonfatal myocardial infarction	0	3 (2.5)	0.08
New angina pectoris	2 (1.6)	1 (0.8)	0.57
Ischemia of the limb	16 (13.1)	17 (14.0)	0.83
Ipsilateral amputation	2 (1.6)	8 (6.6)	0.05

\*All major events were recorded. Adverse events occurred in 40 patients in the ticlopidine group and 50 in the placebo group.

Heparins may prevent early occlusion<sup>20</sup> but are not considered practical for long-term use because of the need for parenteral administration. Oral anticoagulants may also have a role, but they require laboratory monitoring, they carry a risk of hemorrhage, and their efficacy is not yet fully established. In a retrospective study<sup>10</sup> comparing the effects of aspirin plus dipyridamole, warfarin, and no adjuvant therapy in 406 patients with various types of femoropopliteal or femorotibial reconstruction, patients who took warfarin or aspirin plus dipyridamole had a better patency rate irrespective of the graft material used. A prospective, randomized study of 71 patients followed for 18 months showed that at 12 and 18 months, the respective cumulative patency rates were 90 percent and 82 percent in the group treated with warfarin, as compared with 72 percent ( $P=0.04$ ) and 67 percent ( $P=0.07$ ) in the group with no adjuvant therapy.<sup>11</sup> However, these results may have been biased by the unequal distribution of distal anastomoses — there were more tibial anastomoses in the group with no adjuvant therapy.

Aspirin has been widely investigated.<sup>21,22</sup> Kohler et al.,<sup>7</sup> in a prospective, randomized study of infrainguinal saphenous-vein grafts (including above-the-knee and below-the-knee anastomoses), reported a two-year patency rate of 58 percent among 44 patients assigned to receive aspirin plus dipyridamole, as compared with a rate of 73 percent among 44 patients assigned to placebo. In a study of 549 patients with infrainguinal grafts, McCollum et al.<sup>8</sup> also failed to find a statistically significant benefit in terms of patency with aspirin plus dipyridamole as compared with placebo. On the other hand, Sheehan et al.<sup>9</sup> reported that aspirin plus dipyridamole had a beneficial effect in patients with infrainguinal prosthetic grafts.

Ticlopidine has been shown to reduce cerebrovas-

cular and cardiovascular ischemic events,<sup>23,24</sup> to increase the distance that patients with claudication were able to walk,<sup>12,16</sup> and to increase the patency of aortocoronary bypasses with the internal thoracic artery or the saphenous vein.<sup>17,18</sup> In a study of patients with intermittent claudication, Bergqvist et al.<sup>15</sup> found that ticlopidine reduced the need for reconstructive vascular surgery by about half, irrespective of whether the patients had previously undergone vascular surgery. The need for minor reinterventions was also reduced, but data on the long-term patency of the grafts were not provided. Currently, antiplatelet agents are prescribed to prevent major vascular ischemic events in patients with peripheral arterial disease.<sup>21</sup> However, at the time our study was initiated (1988), there was no convincing evidence of their efficacy either in reducing peripheral-graft occlusion or in preventing ischemic vascular events in patients with lower-limb ischemia.

Our study was limited to saphenous-vein bypass grafts in order to maintain the homogeneity of the study.<sup>1</sup> The graft could be used in situ or reversed, since a previous study had shown that there was no substantive difference in patency rates between the two techniques.<sup>25</sup> The patency rate in our study was also similar with the two techniques. Although there was a good balance with respect to the site of the proximal anastomosis, there were more tibial anastomoses in the ticlopidine group than in the placebo group. This appears to have occurred by chance, since there were no deviations from the randomization procedure. Statistical analysis did not show a significant interaction between the site of distal anastomosis and treatment. Femorotibial grafts may have a lower patency rate than femoropopliteal grafts.<sup>1</sup> This was confirmed in our study: the placebo group had a patency rate of 55 percent for popliteal anastomoses and 44 percent for tibial anastomoses. The greater number of tibial anastomoses in the ticlopidine group would be expected to bias the results against finding a treatment effect.

Ticlopidine has been shown to reduce the incidence of ischemic events unrelated to the graft, such as myocardial infarction, stroke, or vascular death, in patients with peripheral vascular disease in three previous studies.<sup>13,14,16</sup> Our study was too small to detect such a beneficial effect or the side effects associated with ticlopidine, such as severe neutropenia, which may occur in about 0.8 percent of patients.<sup>26</sup>

This study showed that ticlopidine therapy produced a significant and clinically meaningful improvement in the long-term patency of saphenous-vein grafts in the legs. Since the drug was well tolerated, its use can be recommended after femoropopliteal or femorotibial saphenous-vein bypass grafting.

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## APPENDIX

The following centers and investigators participated in the study: Study coordinator — J. Becquemin; Steering committee — A. Castaigne, J. Fiessinger, M. Samama, J. Arcan; Study monitoring — S. Fontecave, L. Sagnard, V. Vajou, D. Wozniak (Sanofi Recherche); Statistical analysis — S. Claudel (Sanofi Recherche), C. Gomeni (Simed); Participating centers and investigators — Centre Hospitalier Régional Universitaire, Hôpital Charles Nicolle, Rouen (26 patients): J. Testart, J. Watelet; Centre Hospitalier Régional Universitaire, Hôpital Laennec, Nantes (20): P. Patra, P. Chaillon; Clinique Poirier, Chambéry (19): B. Habozit; Centre Hospitalier Universitaire Henri Mondor, Créteil (16): J. Becquemin; Hôpital Nord, Saint Priest en Jarez (16): X. Barral; Centre Hospitalier Universitaire, Hôpital Jean Minjoz, Besançon (15): G. Camelot, J. Buniet, J. Besancenot; Hôpital de la Timone, Marseilles (13): P. Piquet; Hôpital Sud, Sainte Marguerite, Marseilles (14): A. Branchereau, P. Magnan; Centre Hospitalier Régional Universitaire, Hôpital République, Nice (11): M. Batt; Centre Hospitalier Régional Universitaire Nord, Grenoble (10): H. Guidicelli, J. Magne, I. Farah; Centre Hospitalier Universitaire, Hôpital Jean Bernard, Poitiers (10): J. Ricco; Hôpital Erasme, Brussels (9): J. Dereume, J. Ferreira; Centre Hospitalier Saint Phillipbert, Lomme (9): P. Puppink; Centre Hospitalier Régional et Universitaire, Hôpital Purpan, Toulouse (8): A. Barret; Centre Hospitalier Régional Universitaire, Hôpital Brabois, Vandoeuvre-lès-Nancy (8): G. Fieffe; Centre Hospitalier Régional Universitaire, Hôpital Civil, Strasbourg (8): J. Kretz, N. Chakfé; Centre Hospitalier Régional Universitaire, Angers (7): B. Enon, J. Chevalier; Centre Hospitalier Régional Universitaire, Hôpital Arnaud de Villeneuve, Montpellier (7): H. Mary; Centre Hospitalier Général Pasteur, Langon (6): P. Plagnol; Hôpital Beaujon, Clichy (4): B. Andreassian, G. Leseche; Centre Hospitalier Régional Universitaire, Hôpital du Bocage, Dijon (3): M. David, F. Becker; Hôpital Saint Michel, Paris (1): P. Lagneau, J. Launay; Centre Hospitalier Régional Universitaire, Hôpital Côte de Nacre, Caen (1): D. Maiza; Hôpital André Mignot, Le Chesnay (1): J. Tricot; Clinique Labrouste, Paris (1): C. Petitjean.

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