Clinical epidemiology of venous thromboembolic disease

Results of a French Multicentre Registry

E. Ferrari, M. Baudouy, P. Cerboni, T. Tibi, A. Guigner, J. Leonetti, M. Bory, P. Morand, on behalf of the French Multicentre Registry

Objective

Between July 1992 and December 1994, 16 French hospital centres, mainly cardiological, participated in a non-controlled observational study on venous thromboembolic disease. The objective of this survey was to collect data concerning the current status of pulmonary embolism and deep venous thrombosis.

Patients

During this period, 547 patients were included: 446 with deep venous thrombosis and 387 with pulmonary embolisms.

Results

Mean age of patients was 63 ± 21 years. There were no significant differences between the sexes. Pulmonary embolism and deep venous thrombosis tended to occur more frequently during the autumn and winter. In 30% of cases, prior deep venous thrombosis or pulmonary embolism was noted. No cause was found for the condition in 47% of cases. Ultrasound (echocardiography and/or venous ultrasound) was the most frequently requested investigation. Intravenous heparin remains the most widely used treatment (76%). Oral anticoagulation was begun before day 3 in less than 31% of cases. Thrombolytic treatment was used in 20% of pulmonary embolism cases, but was rarely prescribed for deep venous thrombosis (2.2%). The hospital recurrence rate (12/547 cases) was fairly low. The search for occult malignancy, performed in 48% of cases, seems to remain one of the major concerns of physicians. The combined pulmonary embolism and deep venous thrombosis mortality rate was 4.4%, while the death rate for pulmonary embolism alone was 6.2%.

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Key Words: Pulmonary embolism, deep venous thrombosis, epidemiology, thromboembolism, clinical diagnosis, cost effectiveness.

Introduction

Venous thromboembolic disease is now managed by new diagnostic techniques and new methods of cure and prevention. Nevertheless, much of the fundamental epidemiology of this disorder has not been adequately described. Although there are agreed methods of diagnosis and treatment, it is not known how they are applied in everyday practice.

In 16 French hospitals over a 30 month period an epidemiological registry was opened for patients hospitalized with pulmonary embolism and/or deep venous thrombosis. The aim of this prospective, non-controlled observational study was to collect data concerning the current status of venous thromboembolic disease. In particular, the following questions were addressed: what are the circumstances surrounding the onset of this disease? what diagnostic methods are available for the assessment of patients affected? what therapeutic attitudes have been adopted? what are the results of such management?

Methods

Sixteen French centres participated in a survey (REMATEV: REgistre sur la MALadie Thrombo Embolie Veineuse) into venous thromboembolic disease, starting in July 1992. All cases of deep venous thrombosis and/or pulmonary embolism with confirmed diagnosis (see below for inclusion criteria) were included. All pulmonary embolisms were included whatever the diagnostic criteria used.

The survey involved a checklist of 305 questions, with the possibility of some open answers. The checklist took into account all aspects of venous thromboembolic disease: thromboembolic history, circumstances of onset, risk factors, clinical findings, investigations and
their results, treatment options, results of actiological studies, immediate outcome and hospital mortality.

The checklist was filled out by a physician during the patient's hospitalization and updated later if necessary. The investigators were asked to include all cases of pulmonary embolism or deep venous thrombosis encountered in their centre during the period of the survey. No suggestions regarding management strategies were made to the physicians at the participating centres before the survey.

Results

Sixteen centres participated in the study: 13 cardiology centres, two respiratory disease centres and one internal medicine centre. (The initial number of centres involved was eight.)

Patients and seasonal distribution

Between July 1992 and December 1994, 547 patients (267 men and 280 women) were included. All had confirmed recent pulmonary embolism or deep venous thrombosis of the lower limbs. Mean age was 63 ± 21 years (range: 17 to 98).

Age distribution is shown in Fig. 1. More than half the patients were aged between 65 and 85 years, while fewer than 5% were under 24 and more than 11% over 85.

Seasonal distribution, obtained by adding together then averaging cases by month of the year, revealed that 144 (25%), 101 (19%), 116 (22%) and 181 cases (34%) occurred, respectively, during the 1st, 2nd, 3rd and 4th quarters of the year. Sixty-nine percent of cases of venous thromboembolic disease occurred during the autumn and winter: cf. Fig. 2. Thus, cases of pulmonary embolism or deep venous thrombosis are significantly higher during the first and fourth trimester ($\chi^2=27.4; P<0.01$).

Distribution of pulmonary embolism and deep venous thrombosis and past history

Among the 547 patients, 278 were hospitalized for pulmonary embolism. During their stay in hospital, 64% of them (n=177) were diagnosed for deep venous thrombosis. Two hundred and sixty-nine patients were admitted with deep venous thrombosis, of whom 109 were diagnosed as having pulmonary embolism. In all, 446 cases of deep venous thrombosis and 387 of pulmonary embolism were included. In 165 cases (30%), there was a history of venous thromboembolic disease in the form of: pulmonary embolism in 37 (7%); deep venous thrombosis of the lower limbs in 119 patients (21%); deep venous thrombosis other than of lower limbs in 9 (1.5%). Thirteen patients already had a vena cava filter.

Time lapse between first symptoms and management of disease

In 71% of cases of deep venous thrombosis (317/446), history revealed the existence of symptoms prior to diagnosis. In 33% (147 cases), these symptoms had been present for less than 3 days. In 46 cases (11%), they had been present for more than 3 days but less than 5 days. In the remaining cases, deep venous thrombosis symptoms had been present for more than 5 days.

Sixty-six percent of pulmonary embolism cases (257/387) were preceded by symptoms. These symptoms
were present for less than 3 days in 116 cases (30% of patients hospitalized for pulmonary embolism), for 3 to 5 days in 35 cases (9%) and for more than 5 days in the remaining 104 cases (41%).

Circumstances of onset

A probable cause of the onset of pulmonary embolism and/or deep venous thrombosis was found in 53% (289 cases); in the remaining 258 cases (47%), no cause was found. The most common initiator was prolonged bed rest and/or immobilization of a limb (n=129; 24%). In 90 cases (16-5% of all patients), neoplasia, which was usually being treated, was held responsible. Among such neoplasms in our series, prostate cancer treated by hormone therapy was the commonest aetiology (56% of malignant causes) followed by leukemias and lymphomas (25% of malignant causes). Postoperative pulmonary embolism or deep venous thrombosis was the third acknowledged aetiology: n = 86 (16% of all patients).

Risk factors

History of clinical examination revealed 'risk factors' or situations considered to be such in 258 cases (47%). These risk factors, taken alone, were not considered to constitute an aetiology likely to explain the venous thromboembolic event. They are as follows: varicose veins n=108; obesity n=107; heart failure or atrial fibrillation n = 73; journeys lasting more than 4 h within the 2 previous months n=40; contraceptive pill n = 13.

Current anticoagulant treatment

In 17% of cases (93 patients), anticoagulant treatment, most often in the form of low molecular weight heparin, was under way prior to diagnosed pulmonary embolism and/or deep venous thrombosis. These anticoagulants were prescribed at preventive doses in 43% of cases, but as a treatment for suspected deep venous thrombosis in 57%. In none of these cases was the diagnosis of deep venous thrombosis confirmed prior to treatment. Among patients treated with low molecular weight heparin for clinical symptoms of deep venous thrombosis, 50 received treatment for less than 10 days without subsequent anticoagulant regimen.

Clinical symptomatology

For deep venous thrombosis, oedema and calf pain were the most frequent symptoms (54% and 50% respectively), followed by changes affecting the skin or superficial veins (15% and 12% respectively) and fever (14%). For pulmonary embolism, patient history showed the presence of dyspnoea to be the commonest symptom (87%). Chest pain, tachycardia, syncope and collapse were noted in 46%, 40%, 14% and 7-6% of cases, respectively. Haemoptysis was rare, being present in only 25 cases of pulmonary embolism, i.e. less than 9% of patients.

Results of investigations requested: Table 1

<table>
<thead>
<tr>
<th>Investigation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest radiography</td>
<td>320</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>256</td>
</tr>
<tr>
<td>Pulmonary angiography</td>
<td>284</td>
</tr>
<tr>
<td>Isotope lung scan</td>
<td>174</td>
</tr>
</tbody>
</table>

*In some patients several of these investigations were performed.

Angiography is the method of investigation used most often. Echocardiography is prescribed more often than isotope lung scan.

Table 1 (b) Investigations ordered for diagnosis of deep venous thrombosis

<table>
<thead>
<tr>
<th>Investigation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous ultrasonography</td>
<td>372</td>
</tr>
<tr>
<td>Phlebography</td>
<td>221</td>
</tr>
</tbody>
</table>

*In some cases both investigations were performed.

Ultrasound is the most frequently ordered investigation (372 vs 221 phlebography).

Table 1 (a) Investigations ordered for diagnosis of pulmonary embolism

<table>
<thead>
<tr>
<th>Investigation</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary angiography</td>
<td>308</td>
</tr>
<tr>
<td>Echocardiography</td>
<td>248</td>
</tr>
<tr>
<td>Isotope lung scan</td>
<td>158</td>
</tr>
</tbody>
</table>

*In some patients several of these investigations were performed.

Chest radiography in pulmonary embolism patients

An chest X-ray was prescribed in all cases. The following radiological signs were described: atelectasis 23%, elevated hemidiaphragm 22%, pleural effusion 18%, over-inflation 9%, pulmonary infarction 7%. The initial chest X-ray was considered non-diagnostic in 57% of cases.

ECG results in pulmonary embolism patients

An ECG was performed in all cases of pulmonary embolism. The commonest ECG abnormality described was sinus tachycardia >100/min seen in 139 cases (36%). Repolarization abnormalities, in particular with negative T waves from V1 to V4 and sometimes to V5 were noted in 135 cases (35%). An S,Q3 or a complete or incomplete right bundle branch block was noted in 85 cases (22%).

Echocardiography

Echocardiography was performed diagnostically in 248 cases (64%) of pulmonary embolism. It revealed dilatation of the right heart cavities and measurable systolic pulmonary hypertension >40 mmHg in 58% of cases. A thrombus was seen in the right heart cavities in 10 cases (4%). In 57 cases, echocardiographic results were
estimated sufficient to allow a treatment strategy to be adopted with no need for angiography or scintigraphy before treatment.

In some of these patients, another examination, most often an isotope lung scan, was subsequently used to check the course of the disease.

**Isotope lung scan**

An isotope lung scan was used to diagnose pulmonary embolism in 158 cases. This involved a ventilation/perfusion scan in 96 cases and a perfusion scan in 62. Pulmonary embolism was confirmed using angiography in 103 of these cases.

**Pulmonary angiogram**

A pulmonary angiogram was used to diagnose or confirm pulmonary embolism in 308 cases. Some of these patients already presented with a high probability of pulmonary embolism. Severe side effects occurred in two patients: death was probably precipitated by angiographical investigation in one patient presenting with a very serious pulmonary embolism, with a Miller index >80% and a mean pulmonary artery pressure of 48 mmHg. In another case, renal failure, caused by the contrast medium and requiring haemodialysis, also hastened the course of the disease in a patient presenting with serious pulmonary embolism.

**Others**

In 60 patients, pulmonary embolism diagnosis was established in the absence of an angiographic, echocardiographic or scintigraphic examination. In other words, the diagnosis of pulmonary embolism was reached using clinical or radiological data. In all these cases, however, a recent deep venous thrombosis was identified and was an argument for the diagnosis of pulmonary embolism.

A chest computed tomography scan, set up to investigate the pericardium in one case, and a suspected dissecting aortic aneurysm in three, revealed thrombus in a proximal pulmonary artery and provided the diagnosis of pulmonary embolism in four cases.

Finally pulmonary embolism was diagnosed by means of clinical and/or radiological and/or ECG signs (in the presence of confirmed deep venous thrombosis) in 60 patients, by clot visualization by computed tomography scan in four patients, by echocardiographic signs in 17 patients, by isotope lung scan in 55 patients, and by angiography in 251 patients.

**Location of deep venous thrombosis**

By taking into account the upper extremity of the venous clot, the location of the deep venous thrombosis was correctly determined in 430 cases by venous ultrasonography and/or phlebography. It revealed 69 cases of calf deep venous thrombosis, 52 of popliteal deep venous thrombosis, 202 of femoral deep venous thrombosis, 95 of iliac deep venous thrombosis and 12 of inferior vena cava deep venous thrombosis. In all, 186 cases of deep venous thrombosis were found in the right lower limb, 232 in the left lower limb and 12 in the inferior vena cava: Table 2.

**Hospital recurrence**

Hospital recurrence or occurrence of pulmonary embolism in patients admitted for deep venous thrombosis was reported in 12 cases. In the majority of instances, this diagnosis was based upon clinical findings only and did not lead to further investigations (n = 9). Five recurrences were reported to have caused the death of the patient (three were confirmed at autopsy).

**Treatment**

In 392 cases (68%), the physician initiated anticoagulant treatment before diagnostic confirmation of deep venous thrombosis. Intravenous heparin was prescribed in 76% of cases while low molecular weight heparin was prescribed as the initial treatment in the remaining 24% of cases. Thrombolytic treatment was administered in 87 cases (15%), for deep venous thrombosis in 10 (i.e. 2-2% of the deep venous thrombosis cases) and pulmonary embolism in 77 cases (i.e. 20% of the pulmonary embolism cases). Drugs used were: streptokinase in 44 cases, tPA in 32 cases (in France this drug was only approved for use in pulmonary embolism in late 1994) and urokinase in eight cases. Mechanical thrombolysis was performed in three patients.

Among patients receiving thrombolytic treatment, there were two deaths from severe haemorrhagic complications (2-5%), five episodes of bleeding requiring transfusion (6%) and seven haematomas at the injection site not requiring a surgical procedure (8-6%). Early maintenance treatment with oral anticoagulants (initiated before the end of the 3rd day) was prescribed in 173 cases (31%).

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Table 2 **Location of deep venous thrombosis**

<table>
<thead>
<tr>
<th>Right</th>
<th>Deep venous thrombosis site</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Calf</td>
<td>37</td>
</tr>
<tr>
<td>23</td>
<td>Popliteal</td>
<td>29</td>
</tr>
<tr>
<td>95</td>
<td>Femoral</td>
<td>107</td>
</tr>
<tr>
<td>47</td>
<td>Low femoral**</td>
<td>43</td>
</tr>
<tr>
<td>48</td>
<td>High femoral***</td>
<td>64</td>
</tr>
<tr>
<td>36</td>
<td>Iliac</td>
<td>59</td>
</tr>
<tr>
<td></td>
<td>Vena cava</td>
<td></td>
</tr>
<tr>
<td>n=12</td>
<td></td>
<td>186</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>232</td>
</tr>
</tbody>
</table>

*From results of 430 cases of vein ultrasound and phlebography; **Lower half of femoral vein. ***Upper half of femoral vein.

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An inferior vena cava filter was indicated in 72 cases (16% of the deep venous thrombosis cases but 13% of all the venous thromboembolic disease cases). These involved a temporary filter in nine cases (12.5% of those with an inferior vena cava filter) and a permanent filter in 63 (87.5% of those with an inferior vena cava filter). All were inserted percutaneously. There were two malpositions of the inferior vena cava filter (excentric or above the renal veins). Anticoagulant treatment, mainly oral was continued after insertion of a permanent filter in 55 cases (87%).

Follow-up

Follow-up is reported only for the period of hospitalization. There were 24 deaths during the hospital phase, i.e. a 4.4% hospital mortality rate for the entire population included in the register and 6.2% for pulmonary embolism. Mean age of patients who died was 69.8 ± 15 years, differing significantly (P<0.05 using t-test) from that of the total group.

Pulmonary embolism was the main cause of death in 19 cases (79%), of which five were caused by recurrence of pulmonary embolism during the hospital stay. In the remaining cases, pulmonary embolism with concomitant disease contributed to the unfavourable outcome in very frail patients (cancer in two, Pseudomonas septicaemia in one bedridden state in one). Acute renal failure (after severe pulmonary embolism and angiography) was responsible for one death.

Aetiological evaluation

Investigations to seek a cause, when clinical examination and initial routine studies, i.e. complete blood count, chest X-ray, had suggested no aetiology, were undertaken in 279 cases (48%). These investigations sought a clotting anomaly, in particular a deficiency of C protein, S protein, or ATIII and the presence of circulating anticoagulant (activated protein C resistance was not known at the time of the study) and/or a possible occult malignancy. This latter investigation included assay of biochemical markers of malignant tumours in 183 cases, biochemical markers of malignant tumours in 183 cases, biochemical markers of malignant tumours in 183 cases, biochemical markers of malignant tumours in 183 cases, biochemical markers of malignant tumours in 183 cases, biochemical markers of malignant tumours in 183 cases.

Our register is not a comprehensive report of venous thromboembolic disease at a given moment in France. Nevertheless, it supplies precise information regarding cases of deep venous thrombosis and pulmonary embolism in hospital departments, mainly in cardiological centres. The mean age of our cohort, the absence of a gender ratio and the presence of a history of venous thromboembolic disease in almost one third of cases are in agreement with classical findings in the literature.

The low incidence of patients who had had symptoms for less than 3 days (30%) confirms the poor awareness and recognition of this disease process by patients and/or physicians. This lack of hospitalization and/or early management of the disease during its initial stages is one reason for its poor prognosis. Almost one in two cases of pulmonary embolism or deep venous thrombosis occurred in the absence of a classical predisposing context. This lack of an acknowledged cause is one of the novel aspects of venous thromboembolic disease aetiology in our registry. This fundamental concept differs from existing data, according to which 80% of deep venous thrombosis or pulmonary embolism occur in well-recognized circumstances. However, this trend has already been shown in another recent medical series.

Series mainly involving departments of medicine are more likely to include cases of pulmonary embolism or deep venous thrombosis diagnosed at home, in which the proportion of secondary venous thromboembolic disease is low. Better prevention in classical high-risk situations could also explain the decrease in 'secondary' venous thromboembolic disease. Finally, on account of their reduced physical activity and the coexistence of other morbidity factors, elderly patients, of which there were many in our series, are a well-known high-risk population for 'idiopathic' deep venous thrombosis.

While improved prevention may help to reduce secondary pulmonary embolism and deep venous thrombosis, prolonged immobilization remains the main recognized aetiology and points to the shortcomings of such prevention. It should be noted that 93 cases of pulmonary embolism or deep venous thrombosis occurred despite ongoing prevention, most often by low molecular weight heparin. Given the recognized efficacy of these heparins when properly prescribed, the question arises as to their application. Moreover, there is a particularly unfortunate tendency, when deep venous thrombosis is suspected clinically, to prescribe short courses of treatment and to stop administration of heparin as soon as clinical symptoms regress or disappear (50 cases in our registry). This finding casts no doubt on the efficacy of low molecular weight heparin. However, it shows that the easy administration of these anticoagulants (i.e. single daily dose, no need for biological controls) could lead to their being used too readily and even inappropriately.

With regard to special investigations, echocardiography (usually performed with venous echo-Doppler) is acknowledged to be a simple, non-invasive tool, widely used by cardiologists to diagnose pulmonary embolism (64% of cases). When asked 'what is the investigation which you feel has most contributed
to your diagnosis and evaluation of deep venous thrombosis or pulmonary embolism — one of the 305 questions in our survey — more than 80% of physicians answered: 'venous Doppler ultrasonography and/or echocardiography'.

In contrast, the isotope lung scan is seldom used. This is because cardiology departments tend to use angiography, often available on site, in particular when pulmonary embolism appears to be severe.

In the majority of cases, anticoagulant treatment is started as soon as the diagnosis is suspected. Intravenous heparin remains the most frequently prescribed treatment. Early maintenance therapy using oral anticoagulants is used in less than one third of patients.

For many physicians, the strategy of searching for the origin of a suspected pulmonary embolism, as suggested by several authors, is sufficient since proximal deep venous thrombosis will require the same anticoagulant treatment. Thus, diagnosis of deep venous thrombosis allows appropriate treatment for pulmonary embolism without explicit diagnosis of the latter. The high mean age (74 years ± 8) of patients in whom such a strategy was used was probably a factor in the adoption of this non-invasive strategy.

Despite the lack of clear proof showing the benefits of thrombolysis in pulmonary embolism in terms of survival, one pulmonary embolism in five received such treatment (while only a very small proportion of deep venous thrombosis were thrombolysed). This high incidence of thrombolytic treatment is because cardiology departments are familiar with it and deal with a large proportion of serious forms of pulmonary embolism.

A vena cava filter is inserted in more than 15% of deep venous thrombosis cases. Contraindication to anticoagulant treatment does not seem to be the main reason for the adoption of a vena cava filter since, in 87% of cases anticoagulants are continued, although at less than full dose. The indication for a vena cava filter seems to be widely influenced by the aspect of the clot.

The 6.2% pulmonary embolism hospital mortality rate is entirely consistent with results reported some years ago by other authors. The improved mortality rate which might have been expected from better management may have been offset by the increased number of severely ill patients with more extensive concomitant disease. It is likely that early recognition of the disease, although very poor (30% of pulmonary embolism hospitalized on day 1), leads to the hospitalization of more seriously ill patients, among whom mortality is highest.

Aetiological evaluation and, more specifically, the search for a subclinical cause to explain venous disease have been discussed in the literature. This problem appears to be even more crucial when the proportion of idiopathic venous thromboembolic disease is high, as in our series.

This evaluation led to the discovery in our series of 13 haematological disorders and five cancers. The search for clotting anomalies is less costly when the patient's initial work-up includes collection of the required samples (approximately $400 per patient). This is not the case with the search for subclinical malignancies. Taking the average time required for work-up (computed tomography scan, colonoscopy, gastric fibroscopy) as three additional days, the cost per patient would be 3 days × $500 = $1500, i.e. a total estimated cost of $350,000.

Given this cost and the very low yield of these investigations (five cancers were found, with very limited treatment potential in all five), we would conclude that a routine search for occult malignancy in cases of idiopathic deep venous thrombosis is not advisable.

**Conclusion**

Our survey, performed between 1992 to 1994, and involving 16 French hospitals, showed that in almost half the cases of venous thromboembolic disease seen in medical departments, no obvious cause or contributing factor was found. Although prevention has been widely adopted, it has not always been implemented in the most effective manner. The significant number of cases of pulmonary embolism or deep venous thrombosis which occur, despite low molecular weight heparin treatment, raises the question of how rigorously their indication is determined. In particular, when confronted with clinically suspected deep venous thrombosis, physicians often tend to prescribe a 'prophylactic' low molecular weight heparin regimen. This treatment is administered for only a few days and is frequently not followed by oral anticoagulant treatment or by conclusive proof of deep venous thrombosis. This trend is probably accounted for by the problems involved in performing specific examinations in outpatients, in order to confirm diagnosis. Furthermore, short courses of treatment, when interrupted prematurely, might be responsible for delayed diagnosis or aggravation of certain forms of venous thromboembolic disease.

With regard to diagnosis, non-invasive techniques and, in particular, venous ultrasonography and echocardiography, have assumed a major role. Cardiologists, above all, feel that this investigation often provides an answer to their questions. This new trend will probably have to be considered in the drafting of new guidelines. Despite relatively aggressive management of this disease (early heparin treatment, thrombolysis in one in five of pulmonary embolism cases), the mortality rate remains unchanged. The recurrence rate during hospitalization is relatively low (12 cases). Finally aetiological assessment, though very costly and of little practical use, is frequently requested.

**References**

Appendix 1

Clinical centers in order of Number of Patients enrolled

Hôpital Pasteur Nice: Cardiology department: Principal investigator: Emile Ferrari, MD. Co-investigators: Eric Drai MD, Alain Mihoubi, MD, Anne Tallbode, MD. Alain Imbert MD, Marcel Baudouy MD, Philippe Morand, MD.

Hôpital La Fontaine Antibes: Cardiology department: Investigators: Jean Leonetti MD, Pierre Cerboni, MD; Jean Philippe Darmon, MD; Alain Proton, MD.

Hôpital de Draguignan: Cardiology department: Alexandre Guigner, MD.

Hôpital de Cannes: Cardiology department: Thierry Tibi, MD.

Hôpital la Timone: Cardiology department: Investigators: Michel Bory MD, Serge Yvorra MD.

Hôpital la Fontaine Antibes: Respiratory disease center: Investigator: Christine Rotomondo MD; Jean Michel Chavaillon MD.

Hôpital de Menton: Cardiology department: Investigator: Jean Michel Bayada, MD.

Hôpital de Chimon: Cardiology department: Investigator: Gérard Doll MD.

Hôpital Pasteur Nice: Respiratory disease center: Investigators: Christophe Perrin MD, Franck Lemoigne MD, Fernand Maccone MD, Bruno Blaive MD, Michel Poudens MD.

Hôpital Sainte Marguerite Marseille: Cardiology department: Investigator: Pierre Djiane MD.

Hôpital Pasteur: Internal medicine department: Investigators: Jean Francois Roballon MD; Pierre Freychet MD.

Hôpital Gabriel Montpieu Clermond Ferrand: Cardiology department: Investigator: Jean Ponsonaille MD.

Hôpital Gilles de Corbiel: Corbiel-Estiones Paris: Cardiology department: Investigator: Hervé Lardoux MD.

Hôpital Rangueil Toulouse: Cardiology department: Principal investigator: Jean Paul Bouchoure MD.

Hôpital Montpellier: Cardiology department: Investigator: Robert Groleau-Raoux MD.

Hôpital Purpan Toulouse: Cardiology department: Investigators: Pierre Bernadet MD, Jacques Puel MD.

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