Acute deep vein thrombosis and endovascular techniques: It is time for a new aggiornamento!☆

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KEYWORDS
Acute iliofemoral deep vein thrombosis; In situ thrombolysis; Pharmacomechanical thrombectomy; Post-thrombotic syndrome; Chronic venous insufficiency

Abstract The stated aims of treating acute deep vein thrombosis (DVT) are to prevent a pulmonary embolism, stop the clot from spreading, reduce the risk of a recurrence; they are less concerned with the late morbidity associated with post-thrombotic syndrome (PTS). In accordance with the French (Afssaps, 2009) and North American (ACCP, 2008) recommendations, anticoagulants (LMWH, heparin, AVK) form the cornerstone for treating DVT. These treatments appear to be far less effective in preventing post-thrombotic syndrome (PTS), associated with venous hypertension, residual occlusion, and with reflux caused by valve incompetence. Given that, the new aim is to optimise the prevention of PTS, the ACCP guidelines, unlike those of Afssaps, ‘suggest’ for selected patients suffering from acute iliofemoral DVT, the use of both classic anticoagulants, and in situ percutaneous administration of thrombolytic drugs (recommendation grade 2B) and simultaneous correction of any underlying anatomical anomalies using angioplasty and stenting (recommendation 2C). Contemporary endovascular methods, referred to collectively as ‘facilitated’ thrombolysis, combine low doses of rtPa or Urokinase administered locally, and the removal of the clot using various mechanical, rotating, rheolytic systems, or using ultrasound. The results of non-randomised, heterogeneous studies objectivised a lysis rate of 80%, a 50% lower risk of haemorrhage complications compared with systemic thrombolysis (<4%), and a clear reduction in treatment time (one-shot methods possible for procedures lasting less than 2 hours). This data ties in with the modern ‘open vein’ concept which underpins the hope of an improvement in the late prognosis of acute DVT, through the removal of a clot, thereby improving permeability and valve integrity; this hypothesis is supported by the results at 24 months of a randomised CaVent objectifying absolute risk reduction of 15% in the thrombolysis in situ. The current randomised study (ATTRACT trial) comparing the combination of ‘facilitated thrombolysis’ in addition to the usual treatment with the traditional treatment alone for acute iliofemoral DVT, the statistical power of which has been established (600

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Overview of the situation

In France, the recommendations for good practice that govern the prevention and treatment of venous thromboembolic disease in medical practice, drawn up in 2009 by the working group of the French Health Products Safety Agency (Afsaps), stipulate that the use of thrombolytic drugs is not recommended as first-line treatment during the acute phase (grade B in the classification chosen by the French National Health Evaluation and Accreditation Agency (ANAES) and the French National Health Authority (HAS) or "scientific presumption") [1]. The arguments behind this negative position taken by the group of experts are based purely on the conclusions of a meta-analysis of randomised trials that assessed the effect of the systemic injection of thrombolytic drugs (versus usual antithrombotic treatment), published in 2004 by the Cochrane Agency [2]. This meta-analysis included 11 trials and 700 patients, the vast majority of whom were treated with high doses of Streptokinase or Urokinase. The analysis concluded that the scale of the adverse effects, mainly serious haemorrhaging complications (10%, with an increase in the relative risk of 73%), considerably outweighed the benefits observed (an increase in the relative risk of full lysis of the clot by 76%, and a reduction in the relative risk of a post-thrombotic syndrome of 33%) (Fig. 1).

The report by Afsaps was also of the opinion that given the current level of knowledge, there is no data available to suggest that one route of administration is better than another (local in situ, or systemic). It did however state that if a group of medical and surgical experts work together, thrombolytic drugs could be administered via the systemic venous route if the patient suffers a serious obstructive syndrome or phlegmatia caerulea dolens in order to prevent the condition turning into gangrene, or requiring amputation (grade C). These recommendations on the precise issues of indication and the route of administration for thrombolytic drugs are different from those laid down by the American College of Chest Physicians [3]. The recommendations are based not only on the Cochrane meta-analysis carried out in 2004, but also on the assessment of exhaustive documentation, prior to and after this date, from 19 trials [4–22], which were very heterogeneous (945 patients). These trials were not randomised but focussed on the use of modern local in situ fibrinolytic drugs at low doses (rtPa, Urokinase), which were combined with mechanical procedures to extract the clot in the most recent cases. This method revealed a lysis rate of 80%, with a reduction in haemorrhaging complications of 50% compared with the older studies, and a considerable fall in the time to carry out the interventional act (less than 2 hours with some techniques). So, as regards the treatment of acute deep vein thrombosis (DVT), the authors of the ACCP recommendations “suggest” that for the patients selected (Fig. 2), in situ thrombolysis may be used with a view to reducing the symptoms and post-thrombotic morbidity, if appropriate expertise and resources are available (recommendation “weak”, grade 2B). After effective thrombolysis, the authors “suggest” correcting underlying venous morphological anomalies, using balloon angioplasty and a stent (grade 2C). The same authors “suggest” that pharmomechanical thrombolysis — including mechanical procedures to break up/aspirate the clot — should be preferred to in situ thrombolysis alone, in order to reduce treatment time, if suitable expertise and resources are available (grade 2C). Finally, they put forward the suggestion that if local thrombolysis techniques are not accessible, systemic thrombolysis may be considered (grade 2C). So, it can be seen that there are differences of opinion either side of the Atlantic with regard to the treatment of acute DVT. This can be explained mainly by way of the different ideas held as to the aims of the treatment, in particular regarding the prevention of late morbidity.

Aims of the treatment of acute deep vein thrombosis

The usual issue raised by acute DVT, in clinical practice, is that of preventing early complications, such as pulmonary embolism, stopping the thrombus spreading, and preventing the recurrence of DVT. The main choice of treatment — anticoagulation drugs — relatively effectively fulfils clinical objectives, but does not appear to be totally effective in dissolving the thrombus, restoring permeability, and maintaining the anti-reflux function of the valves. Chronic venous insufficiency is a potential late complication that manifests itself through the occurrence of a post-thrombotic syndrome (PTS), with varying levels of clinical severity, which is associated with the gradual emergence of venous hypertension [23]. The clinical consequences are a change to subcutaneous tissue and the skin, through extravasation of macromolecules and cells [24]. The combination of a residual venous obstruction and valve incompetence is associated with the highest morbidity rate for PTS [25]. The incidence rate of PTS varies from 20 to 50%, 2 years after an acute deep vein thrombosis attack according to Tick et al. [26]. In principle, the frequency is falling, given that the definition is stricter, based on the Villalta scale (Fig. 3), also given that both its diagnostic and prevention, by wearing an elastic strap, systematically improved [27]. A natural history study of iliofemoral DVT treated with anticoagulants alone revealed 15% of patients suffered ulceration, 40% venous claudication, of which 15% had difficulty walking, and 100% suffered an impact on their quality of life after 5 years, and
Acute deep vein thrombosis and endovascular techniques

Figure 1. Randomised studies with systemic thrombolysis as reported by the Cochrane Agency 2004. From [2].

<table>
<thead>
<tr>
<th>Auteurs</th>
<th>N</th>
<th>Lyse complète</th>
<th>Syndrome post-thrombotique</th>
<th>Hémorragie majeure</th>
<th>Mortalité</th>
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<tr>
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<td>30</td>
<td>6/9</td>
<td>2/9</td>
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<td>2/10</td>
</tr>
<tr>
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<td>34</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Common, 1976</td>
<td>50</td>
<td>6/23</td>
<td>1/26</td>
<td>7/23</td>
<td>5/26</td>
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<tr>
<td>Arsnesen,</td>
<td>43</td>
<td>-</td>
<td>4/17</td>
<td>9/18</td>
<td>4/21</td>
</tr>
<tr>
<td>Kil, 1961</td>
<td>20</td>
<td>-</td>
<td>-</td>
<td>3/11</td>
<td>4/9</td>
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<tr>
<td>Schulman, 1969</td>
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<td>8/14</td>
<td>6/13</td>
<td>-</td>
<td>1/17</td>
</tr>
<tr>
<td>Verma, 1969</td>
<td>21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Goldhaber, 1990</td>
<td>64</td>
<td>3/53</td>
<td>0/12</td>
<td>2/53</td>
<td>0/12</td>
</tr>
<tr>
<td>Turk, 1990</td>
<td>83</td>
<td>-</td>
<td>-</td>
<td>5/41</td>
<td>2/42</td>
</tr>
<tr>
<td>Schweizer, 1996</td>
<td>69</td>
<td>-</td>
<td>-</td>
<td>25/44</td>
<td>17/22</td>
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<td>Schweizer, 2000</td>
<td>250</td>
<td>57/200</td>
<td>1/50</td>
<td>12/200</td>
<td>0/50</td>
</tr>
<tr>
<td>Esfarav, 2002</td>
<td>35</td>
<td>11/18</td>
<td>0/17</td>
<td>0/18</td>
<td>0/18</td>
</tr>
</tbody>
</table>

Mélas-analyse Li, Cochrane 2004: 11 essais, 701 patients

RR = 0.24 [0.07; 0.82] (P = 0.05)
RR = 0.68 [0.47; 0.94] (P = 0.03)
RR = 1.73 [1.04; 2.86] (P = 0.04)
RR = 0.84 [0.29; 2.42] (P = 0.70)

Figure 2. Recommendations by the American College of Chest Physicians (ACCP) for the treatment of deep vein thrombosis. From [4].
account for one of the major predictive factors for the late occurrence of a PTS, since the risk is multiplied by 2.6 versus femoropopliteal DVT [28]. New treatment paradigms have appeared in the United States that tie in with the recent attention paid to the harmful consequences of PTS. So in 2008, thanks to SK Galson [29], a "National Call Action on deep venous thrombosis and pulmonary embolism" was initiated. It was the seventh action of this kind in 11 years, and called for resources to carry out research into the causes, prevention and treatment of DVT and pulmonary embolisms, with priority given to a clinical assessment of new percutaneous systems for the thrombectomy procedure. It is justified in particular by the fact that some current prospective studies suggest that the concept of quality of life in the later stages of life associated with DVT needs to be considerably updated, stating that carrying out research into ways of attaining immediate therapeutic objectives alone is clearly insufficient to ensure optimal clinical efficacy in such patients. One of the strong messages conveyed by this more modern idea of thromboembolic disease is that some patients with extensive iliofemoral venous thrombosis have to be referred to a vascular surgeon or an interventional radiologist for a consultation in order for the long-term benefits of early treatment with endovascular thrombolysis to be assessed [30].

**The "open vein" concept**

The open vein concept is closely connected with an active strategy, the aim of which is to quickly remove the occlusive thrombus (through lysis or extraction). The result of this is that there is a reduction in the incidence rate of recurrence and PTS, by creating permeability and by keeping greater valve integrity. After a DVT attack, "natural" recanalisation occurs by way of spontaneous fibrinolysis; 6 months after a deep vein occlusion has been treated, there is a 60% chance that the segment will be totally reopened, and a 40% chance that it will be blocked or partially recanalised, and a 50% chance of valve insufficiency [31]. Six months after a DVT incident, Johnson et al. observe that there is both obstruction and reflux in 65% of cases. These two conditions occurring together is a serious concern, which multiplies the risk of a PTS by 3.5. The recanalisation rate depends on the location. It is much lower for iliofemoral thromboses than for popliteal or distal thromboses [32]. It would appear that conventional solutions are not perfectly suited to restoring permeability and valve function in patients who have suffered an acute attack of DVT. This gives strength to the intuitive principle that it is beneficial to facilitate and speed up recourse to lysis. Arguments that back up the "open vein" concept may now be found in studies on patients with DVT who were treated with anticoagulants alone. Prandoni et al. [33] show in patients who develop PTS after DVT, that the frequency of residual venous thrombosis or popliteal valve reflux is much higher after 6 months (47% versus 23%). Moreover, a randomised study comparing surgical thrombectomy with anticoagulation treatment, confirmed that there was greater venous permeability and a reduction in PTS with the "aggressive" option than with anticoagulation treatment alone [34]. This open vein hypothesis is also borne out by older trials with systemic thrombolysis: in the Cochrane group analysis of 12 randomised trials systemic thrombolysis versus anticoagulation, rate post-thrombotic syndrome was found significantly lower in patients in the first group (with a relative risk of 0.66). Similarly, studies reporting the results of the thrombolysis in situ are in line of this concept: the national venous registry determined that the degree of lysis was achieved predictive permeability to 1 year (79% for grade III or complete lysis, obtained in 31%, 58% for grade II or partial lysis 50–90%, obtained in 58% and 32% for grade I) as well as the overall rate of valvular reflux was 58%, it was 28% for patients with initial complete lysis was achieved [35].

Animal experiments, the natural history, and observational and randomised studies, have shown that the thrombus can be destroyed, permeability restored, and valve competence maintained. The crucial question is: can this be achieved without major risk, and is there also a real clinical difference in the long-term? In other words, is the risk/benefit analysis favourable?

"**Modern**" thrombolysis

**In situ thrombolysis**

The principle is to infuse a thrombolytic agent alone, in situ, in contact with the thrombus, via a closed-end, multi-hole catheter, over a great length, inserted percutaneously (Cragg-MacNamara type catheter). The theoretical benefit is firstly improved efficacy, thanks to the high concentration of medication being injected directly into the thrombus, and secondly, its safety, thanks to the reduced fibrinogenolytic systemic effects, which consequently potentially reduces the risk of haemorrhage. The molecule currently being used in most of contemporary studies is the plasminogen tissue activator, or rtPA (Actilyse®); Urokinase, withdrawn from the American market for a long time, is of rare use, while

<table>
<thead>
<tr>
<th>Villalta scale</th>
<th>CEAP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms:</td>
<td>Clinical:</td>
</tr>
<tr>
<td>Heaviness</td>
<td>0–None</td>
</tr>
<tr>
<td>Pain</td>
<td>1–Telangiectasis</td>
</tr>
<tr>
<td>Cramps</td>
<td>2–Varicosities</td>
</tr>
<tr>
<td>Pruritus</td>
<td>3–Edema</td>
</tr>
<tr>
<td>Parathesis</td>
<td>4–Pigmentation,</td>
</tr>
<tr>
<td>Signs:</td>
<td>lipodermatosclerosis</td>
</tr>
<tr>
<td>Pretribial edema</td>
<td>5–Healed ulceration</td>
</tr>
<tr>
<td>Induration</td>
<td>6–Ulcere</td>
</tr>
<tr>
<td>Hypopigmentation</td>
<td>Etiology</td>
</tr>
<tr>
<td>New venous ecstasis</td>
<td>Congenital/primary/secondary</td>
</tr>
<tr>
<td>Redness</td>
<td>Anatomical disconnection:</td>
</tr>
<tr>
<td>Pain of calf compression</td>
<td>Superficial, deep, perforator, or combination</td>
</tr>
<tr>
<td>(Ulceration receives a score of 15)</td>
<td>Pathophysiology:</td>
</tr>
<tr>
<td>Each factor is scored: 0 (none) to 3 (severe)</td>
<td>Reflux, obstruction, or</td>
</tr>
<tr>
<td>Mild: score 5-9</td>
<td>combination</td>
</tr>
<tr>
<td>Moderate: score 10-14</td>
<td>Severe:</td>
</tr>
<tr>
<td>Severe: score &gt;15</td>
<td>&gt; C4</td>
</tr>
</tbody>
</table>

Figure 3. Villalta scale and CEAP classification of post-thrombotic syndromes. From [27].
in France it has a marketing authorization for treatment with intravenous high dose (4000 to 5000IU/kg per hour) for venous occlusions caused by thrombus being formed or recently formed.

Based on thorough documentation of the scientific literature (19 trials, with quite similar designs), dedicated to this technique, the ACCP 2008 recommendations were drawn up. Significant lysis was reported in 79% of 945 patients treated using this method. Older trials, and in particular the prospective, multi-centre National Deep Venous Registry [35], used high doses of Urokinase. Of those 287 patients treated in 65 centres, serious cases of haemorrhage were observed in almost 10% of cases, most of which were located near the puncture point. In 16% of cases, the haemorrhaging was minor, and in 0.4% cerebrovascular accidents (CVA) were reported. More recent trials (after 2000), using low dose infusions of rtpA (0.5 to 1 mg/H) reported a low rate of major local haemorrhage in about 5% of patients (no CVA), amounting to a reduction of around 50% compared with the figures for thrombolysis in the 1990s [36]. This increased level of safety is in part connected with a likely improvement in the way indications were chosen, with an optimisation of the required dose, but it is even more likely it was connected with the use of a percutaneous micropuncture needle (21G needle), inserted popliteally, under ultrasound guidance, in a patient placed in a decubitus ventral position [37] (Fig. 4).

The results after 24 months of a randomised Norwegian study, which started in 2006 (CaVenT study) have just been published [38]. This aim of this study was to compare traditional treatment (LMWH and AVK) with in situ thrombolysis, using rtpA at a dose of 00.1 mg/kg/h, up to a maximum of 20 mg/24 h, combined with LMWH, without a vena cava filter, followed by angioplasty of any underlying lesions (at the discretion of the surgeon). At 24 months, 34 patients in the thrombolysis group (41% of the total 108 subjects) reached the primary endpoint of SPT versus 55 (56% of 101 control subjects), a reduction in absolute risk of developing PTS by 15%, associated better patency of the iliac vein (65% against 45%). The duration of thrombolytic therapy was 2/3 days with 88% lysis (total or between 50 and 90%), the price of 9% of bleeding complications (3% severe).

So, despite, undeniable progress in terms of the risk/benefit ratio, the technique has still not achieved very widespread use, mainly because it is time-consuming; infusion time, although shorter thanks to modern protocols, can be as high as 48 hours. To try to get around this major disadvantage, thrombolytic treatments are tending towards “facilitated” thrombolysis or pharmacomechanical thrombolysis.
Pharmacomechanical thrombolysis (PhMT)

There are two ideas for carrying out this interventional gesture, which, it must be remembered, has been attributed a grade 2C recommendation by the ACPP 2008, and should be used in preference to in situ thrombolysis (but always used in association with it): first generation methods combining percutaneous thrombectomy tools and traditional in situ thrombolysis infused locally, reduce the dose and the fibrinolytic treatment by around 50%, the main aim of which is to improve safety; while more recent methods referred to as "one-shot" methods aim to quickly disperse an intrathrombic bolus thrombolytic to ease full extraction of the thrombus in one short procedure lasting between 1 and 3 hours, thereby avoiding the need for a long secondary infusion. There are three types of tool available, which are generally inserted through the skin into the popliteal area [7,21,39,40–46]:

- rotating motorised systems that break up the thrombus using a helix (or a cage) revolving at high speed (Amplatz thrombectomy Device; Microvena, Arrow-Terotola percutaneous thrombolytic Device; Arrow, Cragg-Castaneda thrombolytic brush; Micro Therapeutics) or which disintegrate the thrombus with a sinusoidal Nitinol wire rotating at high speed (1,500 revs per minute) between two occlusion balloons, 15 to 30 cm apart, in a zone where the rTPA is injected (Trellis system; Bacchus vascular). The Trellis system (Fig. 5) is activated for periods of 15 minutes, interspersed with infusions of 5 to 10 mg of rTPA (1 mg/minute and up to 10 mg) followed by manual thromboaspiration using a Desilet or a traditional wide-cup catheter (10 F), and an auto-expanding stent is also inserted if any underlying anomalies are discovered. An optional vena cava filter is not systematically inserted (indicated in cases of pulmonary embolism or exten- sion associated cava), and it is removed after 3 months, and it is also advisable to apply intermittent pneumatic compression for 24 hours. The Galway Trellis Experience, reported by O’Sullivan, in 36 patients presenting with acute DVT, reported 100% technical success, effectiveness achieved in less than 2 hours, and primary permeability after 3 months of 85%. No haemorrhaging was observed in his experience [43];

- in addition to the rotating tools, so-called "rheolytic" instruments can also be used (AngioJet; Possis; Hydroliser; Cordis, Oasis Thrombectomy System; Boston Scientific): the thrombus is initially sprayed with fibrinolytic agent, and then very high speed jets (400 km/h) of saline are applied, thereby creating a depression by way of a Venturi effect, so that the fragmented thrombotic material can be aspirated (Fig. 6). The device did not come into contact with the wall, but there was a theoretical risk of haemolysis. The results of 160 patients from the PEARL register [44] showed that lysis was achieved in 93% of the segments treated, achieved in almost 100% of cases in under 48 hours, and in two thirds of the cases, in under 6 hours. Two relatively recent, non-randomised, retrospective cohorts compared the TPM with the AngioJet system and the traditional technique: the first study [18] observed that there was no difference in terms of the lysis rate achieved, but much quicker success with the AngioJet (76 minutes/18 hours). The second one [17] confirmed this clear reduction in interventional gestural time (26 hours/43 hours) and the quantity of Urokinase injected (2.7 million IU/5.6 millions IU);

- finally, a third type of tool is available, the concept of which is based on boosting the effectiveness of the thrombolytic drug with ultrasound (Ekos EndoWave; Ekos Corporation, Omniwave; OmniSonic Corp); it comes in the form of a triple lumen catheter with multiple ultrasound transducers which emit high frequency, low energy ultrasound which destroy the strands of fibrin of the thrombus, thereby helping to expose the plasminogen receptors to the locally-injected fibrinolytic drug [45]. There is no mechanical effect unlike the other systems, but the infusion time will probably be longer. The fibrinolytic drug used in the rare studies available is rTPA at a dose of 2 mg/H for 5 hours, then 1 mg/H up to a maximum of 20 mg. In the published studies, the interventional gesture is faster: 22 hours compared with 34 hours for traditional thrombolysis with full lysis of around 70% and
a low haemorrhagic complication rate of 3.8%, which is probably thanks to the lower infusion time [46].

It should be remembered that treating an associated anatomical lesion by way of angioplasty-stenting is a grade 2C recommendation. This situation is not rare, especially if there is left iliofemoral DVT in a young patient suffering from Cockett’s syndrome, in the form of stenosis which is often underestimated by the venogram, and which is caused by compression due to the pulsating of the right iliac artery; the proportion of patients who benefit from this extrasupport in the published series, during thrombolysis or stenting, is between 33 and 67% (56%). Stents are used almost systematically to counter the spring-back often observed when the balloon is inflated; Stents are used either auto-expanding steel models, or more recently models in Nitinol. A recent meta-analysis on the use of various mechanical percutaneous thrombectomy systems was reported [47] in the form of 16 retrospective series using rheolytic, rotating or ultrasound assisted systems, on a total of 481 patients. It should be pointed out that there are no randomised studies currently available. Technical success (grade II or III lysis) was observed in between 83 and 100% of patients, and the overall incidence rate for haemorrhagic complications requiring a transfusion came to 7.5%.

The Attract study [48], sponsored by the National Heart and Blood Institute is a randomised, double-blind phase III, multi-centre study with two parallel arms. This randomised trial is currently being carried out in 60 centres throughout North America on 692 patients suffering from symptomatic DVT. The patients receive either pharmacomechanical treatment combined with standard thrombectomy (anticoagulant and elastic compression) or the standard traditional treatment. Endovascular techniques use either rtpA alone, at a dose of 0.01 mg/kg per hour, up to a maximum of 24 hours with a maximum dose of 35 mg, or rtpA delivered in one-shot via a trellis system or an AngioJet, with up to a maximum of 25 mg administered. The statistical power of this study was weighted in order to ascertain whether using pharmacomechanical techniques might reduce the occurrence of a PTS by a third after 2 years of follow-up.

The PTS is assessed every 6 months against the Villalta scale, and to date over 100 patients have been recruited and the monthly inclusion rate continues to climb.

The results after 6 months of a randomised study (Torpedo study) have just been published [49]. This study was carried out in symptomatic patients suffering from acute proximal DVT, and has compared anticoagulants alone (81 patients), versus pharmacomechanical treatment: a combination of mechanical thrombectomy, angioplasty, stenting and rtpA (88 patients). Although this study did not use a validated measurement (such as the Villalta score) to define whether and to what extent the patient was suffering from PTS, it nonetheless revealed a significant reduction in the incidence of cases of weak or moderate post-thrombotic syndrome after 6 months, when compared with the traditional treatment (4%/25%), without an increase in the risk of haemorrhaging, estimated to be 2%.

Who should be treated?

Given that the clinical and biological phenotypes within the population presenting with DVT vary widely, it is essential for clinical decisions to be guided by thorough randomised studies. If they are currently underway, or not yet available, clinical common sense justifies these treatments being prescribed for those who are likely to benefit, with as low a risk as possible.

A number of factors may reasonably influence such decisions:

- an assessment of the risk of bleeding: this risk must be assessed by taking into account recent major surgery, trauma, pregnancy, cardiorespiratory arrest, other invasive procedures, lesions to the central nervous system, digestive system, or renal failure;
- the clinical severity of the deep vein thrombosis: urgent endovascular thrombolysis is indicated to save a limb, or in the case of other serious complications such as Phlegmatia Caeulea Dolens or extensive thrombosis of the vena cava, in particular if a suprarenal extension is in place—that might lead to a fatal pulmonary embolism or acute renal failure. The use of in situ thrombolytic in such situations is justified if there is no other effective treatment available. In other situations, it is advisable to use this measure, as non-urgent treatment, after strictly assessing the benefits in relation to the risks. In such cases, a lower threshold must be applied to exclude patients who would be at a greater risk of haemorrhaging if they underwent thrombolytic treatment;
- anatomical extension of deep vein thrombosis: patients with iliocavofemoral DVT have a greater risk of both PTS and thrombotic relapse. Although current studies entail some methodological limitations, it seems that these patients might benefit from endovascular treatment. For those patients who have a low risk of bleeding, a compromise between the risk and the possible benefits of non-urgent, first-line treatment should be discussed. Because of a lack of actual proof, a very low decision threshold should be applied in order to exclude patients if there is the slightest risk of bleeding. Patients with asymptomatic DVT and venous thrombosis of the legs should not be treated with thrombolysis, mainly because the risk of PTS is low. Finally, patients with chronic femoropopliteal thrombosis should not be given this type of treatment;
- assessment of life expectancy, functional status and comorbidity: patients who are chronically unable to walk, or who have a low life expectancy are unlikely to benefit from this type of treatment. However, young patients, who presumably have a low risk of bleeding are more suitable to receive this type of treatment;
- patient preference: the benefit-risk should be clearly explained to the patient to guide their choice.

A treatment algorithm of acute iliocavofemoral DVT, put forward by O’Sullivan [50], is shown in Fig. 7. Its adaptation to French patients faces for the moment the rule of Afssaps recommendations, lack of marketing authorizations for Actilyse (recall that the WMA has Urokinase, systemically in PST acute), the major extracost induced by the use of power tools or rotational rhéolytiques (which also are not all distributed in our country, and whose funding is not supported).
Figure 7. Treatment algorithm for deep vein thrombosis put forward by O’Sullivan [50].

Conclusion
An increasing number of arguments put forward by proof-based medicine give weight to the validity of open vein theory for the prevention of the post-thrombotic syndrome after iliofemoral deep vein thrombosis. It has been established that modern, pharmacomechanical methods have a risk/benefit ratio that appears to be positive for this precise sub-group, to whom honest information should be given on alternative treatments.

Disclosure of interest
The authors declare that they have no conflicts of interest concerning this article.

References
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