

# Deferral of Objective Assessment of Deep Vein Thrombosis and Pulmonary Embolism Without Increased Risk of Thrombosis

## *A Practical Approach Based on the Pretest Clinical Model, D-Dimer Testing, and the Use of Low-Molecular-Weight Heparins*

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**Background:** Treatment of patients with suspected deep vein thrombosis (DVT) or pulmonary embolism (PE) is problematic if diagnostic imaging is not immediately available. Pretest clinical probability (PCP) and D-dimer assessment can be used to identify patients for whom empirical protective anticoagulation is indicated. To evaluate whether PCP and D-dimer assessment, together with the use of low-molecular-weight heparins (LMWHs), allow objective appraisal of DVT and PE to be deferred for up to 72 hours, patients with suspected DVT and PE were prospectively examined.

**Methods:** Patients identified with a high PCP or a moderate PCP with positive D-dimer test results received a protective full-dose treatment of LMWH; the remaining patients were discharged without anticoagulant administration. However, all patients were scheduled to undergo objective tests for DVT or PE within 72 hours. Standard antithrombotic therapy was adminis-

tered when deferred diagnostic tests confirmed venous thromboembolism.

**Results:** In total, 409 consecutive patients with suspected DVT and 124 with suspected PE were included in this study. A total of 23.8% (95% confidence interval [CI], 20.3%-27.3%) of patients had confirmed venous thromboembolism. At the short-term follow-up (72 hours), only a single thromboembolic event (0.2%; upper 95% CI, 0.6%) had occurred, whereas at the 3-month follow-up, 5 events (1.2%; 95% CI, 0.2%-2.1%) had occurred in patients in whom diagnosis of DVT or PE had previously been ruled out. None of the patients had major bleeding events. Ninety percent of patients were treated as outpatients.

**Conclusion:** Our study demonstrates that this approach allows the safe deferral of diagnostic procedures for DVT and PE for up to 72 hours.

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**V**ENOUS THROMBOEMBOLISM (VTE) is a common and potentially fatal disease.<sup>1</sup> Standardized guidelines are now available for its diagnosis and therapy,<sup>2</sup> but little information is available for instances in which diagnostic tests for deep vein thrombosis (DVT) and pulmonary embolism (PE) cannot be performed because institutions are poorly equipped or because of night or weekend referral. In these cases, attending physicians have to decide whether to treat incompletely assessed patients or to hospitalize them until confirmatory tests can be performed. Therefore, an approach is required that allows patients to be categorized as being at high or low risk for thromboembolic complications so that

they can be treated with the least empirical and most risk-free treatments.

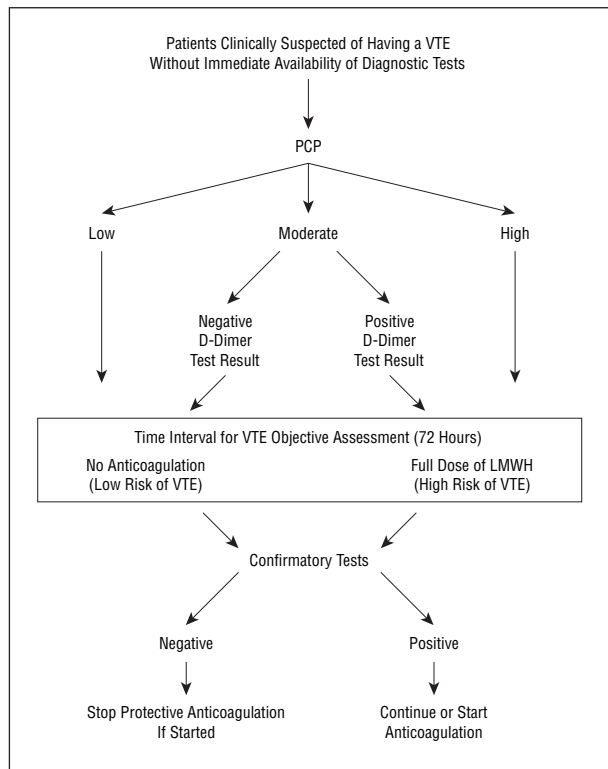
Although empirical protective anticoagulation is usually given to patients in such circumstances, no clear-cut information is available about dosage, duration, or type of anticoagulant or the time during which deferral of diagnostic procedures can be considered safe. Recent data suggest that a standardized clinical score can be used for this purpose. Anderson et al<sup>3</sup> showed that the use of a pretest clinical probability (PCP) assessment, together with the administration of unfractionated heparin, allowed safe deferral of diagnosis of patients with suspected DVT until objective assessment with compressive ultrasonography could be performed. However, the short half-life of un-

## CLINICAL ASSESSMENT

Patients with suspected DVT or PE were evaluated in the emergency department and treated according to the PCP score results. The PCP for DVT was assessed as previously described<sup>10</sup>; clinical probability for PE was assessed using a previously reported clinical model.<sup>11,12</sup> Before the beginning of the study, emergency department physicians participated in a short educational session on the PCP and the intervention algorithm. Before being discharged from the emergency department, all patients were informed about signs of PE and DVT progression and asked to return for immediate evaluation if any such symptoms developed.

## DIAGNOSTIC ASSESSMENT PROTOCOL

The following currently accepted criteria were used for the diagnosis of DVT. Patients were considered to have DVT when full noncompressibility of the lower limb veins (in the proximal or distal segments) was detected following compressive ultrasonography. In cases with a negative compressive ultrasonogram result but a positive D-dimer test result, an additional compressive ultrasonogram was scheduled for 1 week later.<sup>2</sup> Patients suspected of having PE were treated as described.<sup>11,12</sup> Briefly, physicians first used the clinical model to determine patients' PCP for developing a PE and then performed the D-dimer test. Patients with low PCP and a negative D-dimer test result had no further tests for PE, but bilateral deep venous ultrasonography was performed. All other patients underwent ventilation-perfusion (V/Q) lung scanning or lung computed tomography. If the scan was not diagnostic, bilateral deep venous ultrasonography was performed. Patients were diagnosed as having PE if they had a high-probability V/Q scan, an abnormal imaging result (ultrasonography, computed tomography, or angiography), or a venous thromboembolic event during the follow-up; this approach was applied to all of the risk categories. All diagnostic tests were performed by operators who were unaware of the D-dimer assay results or PCP assessment. Blood for the D-dimer assay was drawn at presentation, mixed with trisodium citrate (1 vol), and tested by technicians unaware of other test results. The assay (Dimertest; Dade Behring, Deerfield, Ill) was performed as described.<sup>13</sup> The results of the D-dimer test, a latex agglutination assay based on a monoclonal antibody that recognizes an epitope on the D-dimer fragment of cross-linked fibrin, were compared with an agglutination reference method; the correlation coefficient ( $r$ ) was 0.94. Intra-assay reproducibility was assessed (10 replicates of 3 samples with different levels), and results were equivalent for all replicates. Interassay reproducibility was determined using 10 plasma samples, with titers ranging from 1 to 16. In 10 runs, replicates did not vary by more than 1 titer. The  $r$  between the 2 methods was 0.91. The D-dimer test results were available in 30 minutes; PCP assessment lasted 10 to 15 minutes.



**Figure 1.** Study algorithm. VTE indicates venous thromboembolism; PCP, pretest clinical probability; and LMWH, low-molecular-weight heparin.

fractionated heparin<sup>4</sup> imposed a time limit of 24 hours between clinical assessment and diagnostic testing.

The introduction of low-molecular-weight heparins (LMWHs), drugs with a more favorable pharmacodynamic profile and a reduced association with major bleeding and mortality,<sup>4,5</sup> have made home treatment of patients with suspected VTE an attractive option.<sup>6</sup> The D-dimer test is widely used for the exclusion of VTE in low-risk patients,<sup>7,8</sup> but there are few data about its utility for confirming the classification of high-risk patients in emergency situations.<sup>9</sup> Critically, data are lacking to guide the treatment of patients clinically suspected of having a PE who cannot undergo immediate diagnostic imaging. We report a prospective clinical trial aimed at evaluating whether data derived from PCP and D-dimer testing, together with the use of LMWHs, permit safe treatment of patients with suspected DVT and PE when objective assessment is not immediately accessible.

## METHODS

### PATIENT POPULATION

Outpatients who presented with suspected acute VTE (DVT and/or PE) at the emergency department of the IRCCS Policlinico San Matteo were considered eligible for the study. Exclusion criteria included the following: (1) life-threatening conditions or serious comorbidities that required immediate hospitalization; (2) relapse of a previously documented PE or DVT in the same leg; (3) current use of oral anticoagulant therapy; (4) history of bleeding or any other contraindication to heparin; (5) age younger than 18 years; (6) life expectancy of less than 3 months; and (7) refusal to give informed consent.

### ALGORITHM OF INTERVENTION

**Figure 1** shows the study algorithm. Patients allocated to the low-PCP group (regardless of D-dimer test results) or the moderate-PCP group with a negative D-dimer test result were considered as being at low risk for VTE and discharged without anticoagulant therapy. Conversely, patients with moderate PCP with a positive D-dimer test result or high PCP (regardless of the D-dimer test result) were considered as being at high risk for VTE and received LMWHs as protective anticoagulation. First administration of LMWH was performed in the emer-

**Table 1. Patient Characteristics\***

Baseline Feature	Suspected DVT (n = 409)	Suspected PE (n = 124)	All Patients (N = 533)
Age, mean (range), y	60.8 (18-90)	59.3 (22-91)	60 (18-91)
Sex, M/F	171/238	55/69	226/307
Time since onset of symptoms, mean, d	9.2	3.7	6.4
Cancer	29 (7.1)	8 (6.4)	37 (6.9)
Prevalence of VTE	91 (22.2)	36 (29)	127 (23.8)
Proximal DVT	80 (88)	8 (22.2)	88 (69.2)
Distal isolated DVT	8 (8.7)	2 (5.5)	10 (7.8)
VTE at the femoral-saphenous cross junction†	3 (3.2)	1 (2.7)	4 (3.1)
Isolated PE‡	NA	25 (69.4)	25 (19.6)

Abbreviations: DVT, deep vein thrombosis; NA, not applicable; PE, pulmonary embolism; VTE, venous thromboembolism.

\*Data are presented as number (percentage) unless otherwise indicated.

†One patient had both proximal DVT at the cross junction and VTE.

‡No symptoms of concomitant venous thrombosis.

gency department, where patients were instructed in self-administration. The emergency department physicians had the option of admitting patients to the hospital irrespective of PCP and D-dimer test results. All patients underwent diagnostic imaging testing within 72 hours of PCP and D-dimer test assessment. In cases of a positive diagnostic imaging test result, LMWH therapy was continued and oral anticoagulant therapy was initiated<sup>2</sup>; in cases of negative diagnostic test results, LMWH treatment was withdrawn.

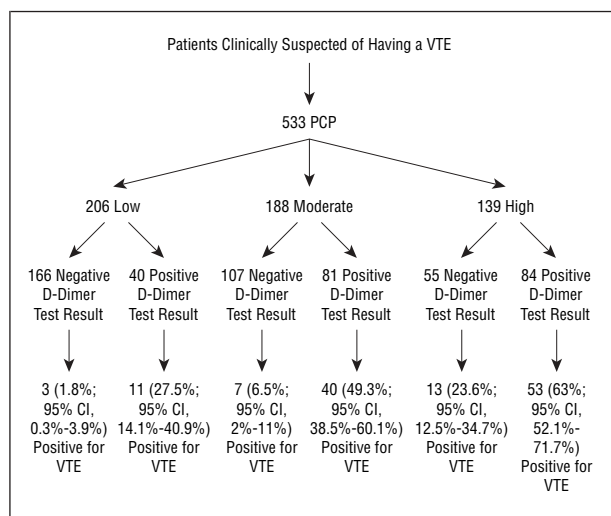
### FOLLOW-UP

Patients were monitored for 2 periods of follow-up: short-term and long-term. Short-term follow-up was defined as the time between patient referral and diagnostic testing (ie, ≤72 hours). Patients were asked to return or contact the emergency department physicians in case of (1) worsening of symptoms related to the affected leg or symptomatic PE in patients suspected of DVT; (2) worsening of respiratory symptoms in patients suspected of PE; (3) major and minor bleeding during protective anticoagulation; or (4) any other reason for hospitalization due to VTE-related symptoms. The long-term follow-up (3 months) was used to record the incidence of acute DVT or PE in patients for whom this diagnosis had previously been ruled out. At any follow-up time, in case of signs or symptoms suggestive of the aforementioned events, patients underwent objective assessment.

### STATISTIC ANALYSIS

Before initiating the study, we estimated that the primary event rate (DVT or PE and major bleeding) during the follow-up period would be less than 2%. We planned to include a sufficient number of patients to ensure that the upper limits of the 95% confidence intervals (CIs) were less than 2.5%. This resulted in a projected sample size of at least 500 patients.

The rate of occurrence of any thromboembolic event during the short- or long-term follow-up was determined, and 95% CIs were calculated. The proportion of patients who developed VTE in each PCP group and the relative 95% CIs were determined, as were the proportions of patients who developed events during long-term follow-up. Paired *t* and Pearson  $\chi^2$  tests were used as indicated; *P* < .05 (2-tailed) was considered statistically significant. Diagnostic accuracy of the D-dimer assessment was calculated in terms of sensitivity, specificity, and positive and negative predictive values with corresponding 95% CIs<sup>14</sup> after a follow-up of 3 months.



**Figure 2.** Incidence of venous thromboembolism (VTE) according to pretest clinical probability (PCP) and D-dimer test results. CI indicates confidence interval.

## RESULTS

### STUDY POPULATION

Of 678 consecutive patients referred to the emergency department during January 1999 to December 2001, 145 were excluded from the study for the following reasons: oral anticoagulant therapy (n = 34), untested for D-dimer (n = 29), untested for PCP (n = 3), untested for compressive ultrasonography (n = 14), no V/Q lung scanning (n = 19), recurrent VTE (n = 11), and refusal of informed consent (n = 35). In total, 533 patients proved eligible for study entry. Of these, 409 patients had suspected DVT and 124 had suspected PE.

**Table 1** shows the clinical characteristics of the patients. Of 533 patients, 206 (38.6%) had a low PCP, 188 (35.2%) had a moderate PCP, and 139 (26%) had a high PCP (**Figure 2**). The prevalence of VTE was 6.7% (95% CI, 3.5%-9.9%), 25.0% (95% CI, 18.9%-31.1%), and 47.4% (95% CI, 39.2%-55.6%) in the low, moderate, and high groups, respectively. In total, VTE was confirmed in 127

**Table 2. Short- and Long-term Follow-up Outcomes**

Patient Category	Short-term Follow-up Events, No. (%) [Upper 95% CI]	Long-term Follow-up Events, No. (%) [Upper 95% CI]
Low risk of VTE		
Low PCP (n = 206)	0 (0) [1.45]	0 (0) [1.36]
Moderate PCP with negative D-dimer test result (n = 107)	0 (0) [1.89]	1 (0.9) [2.68]
High risk of VTE		
Moderate PCP with positive D-dimer test result (n = 81)	1 (1.2) [3.5]	2 (2.4) [5.7]
High PCP (n = 139)	0 (0) [1.66]	2 (1.4) [2.7]

Abbreviations: CI, confidence interval; PCP, pretest clinical probability; VTE, venous thromboembolism.

(23.8%) of 533 patients (95% CI, 20.3%-27.3%). In 91 (22.2%) of 409 patients (95% CI, 18.4%-22.6%), DVT was present, and in 36 (29.2%) of 124 (95% CI, 21.2-37.2), PE was present. Prevalence of VTE according to D-dimer test results is shown in Figure 2.

### SHORT-TERM FOLLOW-UP OUTCOME

The median time of deferred tests was 51 hours 30 minutes; among those patients allocated to receive anticoagulation, the median administration duration was 42 hours 30 minutes. Patient compliance was excellent; only 8 (3.6%) failed to conduct the course of LMWH. Among those patients allocated not to receive protective anticoagulation, 6.8% in the low- and 6.5% in the moderate-PCP group had a confirmed VTE (3.9% of the entire population). Of those patients who received protective anticoagulation, approximately half (21.5% of the entire population) did not have VTE at the time of diagnosis (Figure 2).

No events occurred during the short-term follow-up (Table 2); 1 patient only, at high risk for VTE (moderate PCP and positive D-dimer test result), had a worsening of symptoms during anticoagulation, and a proximal DVT of the left leg was confirmed by compressive ultrasonography. None of the patients developed a bleeding complication, and none were lost to follow-up.

### LONG-TERM FOLLOW-UP OUTCOME

Five patients (1.2%; 95% CI, 0.2%-2.1%) developed recurrent VTE (Table 2). Among patients categorized as being at low risk for VTE, because of symptoms of PE 1 patient underwent a V/Q scan, the results of which classified the patient as low probability; he became symptomatic for distal DVT on day 61. Among patients considered as being at high risk of VTE, 2 patients suspected of DVT (0.5%) (who both previously tested negative for DVT by compressive ultrasonography) developed clinical symptoms of thromboembolism (proximal DVT on the 46th and 77th days). They belonged to the moderate- and high-PCP groups, and both had a positive D-dimer test result. Among patients suspected of PE, 2 (1.6%) with a previously negative

V/Q scan result developed symptomatic DVT (on the 34th and 61st days).

Five patients (0.9%) died. One patient treated for VTE had an ischemic stroke. Three patients died of malignancies diagnosed before the study entry, and 1 died of chronic renal insufficiency. None of these patients showed symptoms of VTE or bleeding. Two patients were lost to follow-up.

### DIAGNOSTIC ACCURACY OF D-DIMER TESTING AND ITS IMPACT ON THE DECISION TO HOSPITALIZE PATIENTS

The respective sensitivity, specificity, and positive and negative predictive values were as follows: 78% (95% CI, 56.9%-100.1%), 84.8% (95% CI, 79.7%-89.9%), 65% (95% CI, 50.3%-79.7%), and 98.1% (95% CI, 96.6%-99.6%) in the low-PCP group; 85.1% (95% CI, 74.9%-95.3%), 70.9% (95% CI, 63.5%-78.3%), 50.6% (95% CI, 39.8%-61.4%), and 93.4% (95% CI, 88.6%-98.2%) in the moderate-PCP group; and 80.3% (95% CI, 70.7%-89.9%), 57.5% (95% CI, 46.2%-68.8%), 63.1% (95% CI, 52.8%-73.4%), and 76.3% (95% CI, 65.1%-87.5%) in the high-PCP group. This analysis confirmed a high negative predictive value for D-dimer testing in patients with low and moderate PCP.<sup>8,9,15-17</sup>

In our study, emergency department physicians were given the option of hospitalizing patients regardless of PCP and D-dimer test results. Data from a separate analysis to evaluate whether D-dimer testing influenced the physician's choice are shown in Table 3. After excluding other causes of hospitalization (concomitant diseases), our results showed that there was a higher and statistically significant ( $P < .001$ ) prevalence of negative D-dimer test results in patients who were discharged after the initial visit compared with those admitted to the hospital.

### COMMENT

Because of the difficulties of clinical diagnosis, objective diagnostic assessment of DVT and PE is important. When this is not possible, VTE treatment of at-risk patients can prove highly unsatisfactory. Patients with minor signs or symptoms are frequently left untreated until diagnostic testing is performed, whereas physicians tend to hospitalize and/or treat patients with empirical anticoagulation irrespective of the actual risk of VTE. Despite the frequency of organizational problems that delay objective assessments, appropriate evidence-based data to support patient treatment has not been forthcoming. The only reported clinical trial data<sup>3</sup> recommend the use of a PCP scale and unfractionated heparin to treat patients but concedes that this treatment limits deferral of confirmatory diagnosis to 24 hours.

We propose that in addition to the use of PCP, the treatment of patients at high risk of developing VTE can be improved by introducing D-dimer testing in conjunction with the administration of LMWH as a protective anticoagulant. The rationale for this is that the high negative predictive value and sensitivity of the D-dimer as-

**Table 3. Patient Hospitalization According to PCP and D-Dimer Test Results After the Exclusion of Comorbid Conditions**

PCP	Patients With Positive D-Dimer Test Results, No. (%)		Patients With Negative D-Dimer Test Results, No. (%)	
	Total Patients	Patients With PE	Total Patients	Patients With PE
Low (n = 206 total patients; 51 patients with PE)	2/40 (5)	1	1/166 (0.6)	1
Moderate (n = 188 total patients; 37 patients with PE)	14/81 (17)	9	4/107 (3.7)	2
High (n = 139 total patients; 36 patients with PE)	23/84 (27)	14	9/55 (16)	5

Abbreviations: PCP, pretest clinical probability; PE, pulmonary embolism.

say may aid the identification of patients at low risk for VTE and that the administration of LMWHs to at-risk patients may allow deferral of objective assessment for VTE without significant risk of major bleeding.

In our investigation, we introduced a structured model composed of PCP, D-dimer testing, and LMWH administration for the treatment of patients with suspected acute VTE in whom diagnostic tests could not be performed for up to 72 hours. Our algorithm for intervention was based on a conservative and protective approach for patient treatment, with patients selected as being at risk for VTE receiving a therapeutic dose of LMWH. Although the administration of protective anticoagulation may appear to be a suboptimal treatment strategy, it nonetheless appears to be a safe option, since no thromboembolic events were recorded during the short-term follow-up period if one excludes a single case that was unresponsive to heparin.

The high negative predictive value of the D-dimer assay is considered useful for excluding patients with low or moderate clinical indication of DVT and/or PE.<sup>8,9,15-18</sup> In our study, a negative D-dimer test result was used to avoid unnecessary use of protective anticoagulation in the moderate-PCP group; previously, such patients had received a full dose of anticoagulants.<sup>3</sup> Hence, the use of D-dimer testing reduced the prescription of anticoagulant treatment to at least half of our patient population. We are aware that these results can be influenced by the D-dimer assay, since the diagnostic accuracy of this test strictly depends on the methods used. We performed a rapid D-dimer latex assay because results can be quickly obtained, its diagnostic accuracy is fairly good<sup>15</sup>, and results are highly comparable with those of other D-dimer tests.

The prevalence of VTE in the high-PCP group would have made the withholding of protective anticoagulation unsafe, even in the subgroup of patients with a negative D-dimer test result. Conversely, in those patients categorized as being at low risk, we chose to avoid administration of anticoagulation because of the reported low prevalence of VTE (3%-8%),<sup>8,9,15-18</sup> which was similar to the rate obtained in our study (6.7%).

It could be argued that the prevalence of VTE (at the time of diagnostic imaging) in low-risk patients was high enough to suggest the administration of a course of protective anticoagulation. This decision could be considered, especially for those with a positive D-dimer test result. However, in these patients no events occurred at the short-term follow-up, suggesting that our approach is safe.

One should also take into account that the high rate of false-positive D-dimer results would increase the rate of inappropriate use of anticoagulation, but the advantage of extending such an approach to patients with low PCP and a positive D-dimer test result should be evaluated prospectively.

Although we did not intend that D-dimer testing should influence the physician's decision to hospitalize patients, it did. Patients with a negative D-dimer test result were more frequently discharged from the emergency department than patients with a positive result; this was evident in all groups of patients regardless of PCP scores or clinical presentation (DVT or PE). Our study demonstrated that rates of hospitalization could be reduced. In fact, after exclusion of comorbidities as a reason for hospitalization, only 53 (9.9%) of 533 patients (Table 3) in the entire cohort were admitted to the hospital before undergoing confirmatory tests. In patients with DVT, the rate of hospitalization (5.1%, 21/409) has to be considered very low compared with the previously reported rate of 10%.<sup>3</sup> Likewise, the rate of hospitalization in patients with PE (25.8%, 32/124) is considered fairly low compared with our (and others') previous rate of almost 100% admission. These data are even more significant if the fact that most of the patients were allocated to the moderate- or high-PCP group is taken into account.

Another important element highlighted by this study is that most patients in whom a thrombotic event was detected could safely be treated at home regardless of their initial PCP and D-dimer test results or clinical presentation (DVT or PE). The lack of reports of bleeding or thrombotic events during the short-term follow-up interval before objective assessment suggests that our approach is effective and safe. By the 3-month follow-up, a small number of events had occurred, with an incidence of events similar to that reported in previous studies.<sup>3,8-10,16</sup>

What are the practical implications of the study data? The results of our investigations provide a tool for treating patients clinically suspected of having acute VTE mainly at home; in fact, only 5% of patients with DVT and 26% of patients with suspected PE were admitted to the hospital. Hence, most patients with confirmed VTE were treated at home during the entire course of their illness. In conclusion, our investigation demonstrates that this simple, integrated approach can allow a safe deferral of diagnostic imaging for up to 72 hours in patients who present with suspected acute VTE.

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