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SUMMARY TABLE

What is known on this topic

- PCDT did not prevent the post thrombotic syndrome in patients with acute deep vein thrombosis (DVT) in the ATTRACT trial but improved a number of short- and long-term secondary outcomes.
- It is uncertain if the benefit of PCDT in ATTRACT occurred in patients with femoral-popliteal DVT (defined as femoral DVT that did not involve the common femoral or the iliac veins).

What this paper adds

- Detailed analysis of a broad range of short- and long-term outcomes in 300 patients with femoral-popliteal DVT.
- PCDT did not improve any short- or long-term outcomes, but increased bleeding.
- PCDT should not be used as initial treatment of femoral-popliteal DVT.

Abstract

Background and Objectives: The ATTRACT trial reported that pharmacomechanical catheter-directed thrombolysis (PCDT) did not reduce postthrombotic syndrome (PTS), but reduced moderate-to-severe PTS and the severity of PTS symptoms. In this analysis, we examine the effect of PCDT in patients with femoral-popliteal DVT (without involvement of more proximal veins).

Patients/Methods: Within the ATTRACT trial, 300 patients had deep vein thrombosis (DVT) involving the femoral vein without involvement of the common femoral or iliac veins and were randomized to receive PCDT with anticoagulation or anticoagulation alone (No PCDT). Patients were followed for 24 months.

Results: From 6 to 24 months, between the PCDT vs. No PCDT arms, there was: no difference in any PTS (Villalta scale ≥5: Risk Ratio [RR]=0.97; 95% confidence interval [CI], 0.75 to 1.24); moderate-or-severe PTS (Villalta scale ≥10: RR=0.93; 95% CI, 0.57 to 1.52; severity of PTS scores; or general or disease-specific quality of life (p >0.5 for all comparisons). From baseline to both 10 days and 30 days, there was no difference in improvement of leg pain or-swelling between treatment arms. From baseline to 10 days, major bleeding occurred in three vs. none (p=0.06) and any bleeding occurred in eight vs. two (p=0.032) PCDT vs. No PCDT patients. Over 24 months, recurrent venous thromboembolism occurred in 16 PCDT and 12 No PCDT patients (p=0.24).

Conclusion: In patients with femoral-popliteal DVT, PCDT did not improve short- or long-term efficacy outcomes, but it increased bleeding. Therefore, PCDT should not be used as initial treatment of femoral-popliteal DVT. (NCT00790335).

Introduction

Pharmacomechanical catheter directed thrombolysis (PCDT), which refers to mechanical thrombus disruption in combination with thrombolytic therapy, rapidly removes thrombus and has the potential to improve both short- and long-term outcomes in patients with acute deep vein thrombosis (DVT). We recently reported the findings of the Acute Venous Thrombosis: Thrombus Removal with Adjunctive Catheter-Directed Thrombolysis (ATTRACT) Trial which compared PCDT with No PCDT (i.e. anticoagulation alone) in patients with acute DVT that involved the femoral or more proximal veins.(1;2) PCDT did not reduce the primary outcome of any post thrombotic syndrome (PTS) but reduced the secondary outcomes of moderate-or-severe PTS and the severity of PTS symptoms and signs. Acutely, PCDT also reduced leg pain and swelling but increased bleeding.

Among ATTRACT patients, there were important differences in the anatomic extent of DVT present at randomization, and these differences may have influenced the benefits and risks of PCDT. For example, patients with more extensive proximal DVT have a higher risk of recurrence, are more likely to develop PTS, and have more severe PTS than patients with less extensive DVT.(3;4) To minimize imbalances in the extent of DVT that was present in the PCDT and No PCDT treatment arms, randomization in ATTRACT was stratified according to the extent of DVT at diagnosis. In the current analyses, which were pre-planned, we explore the benefits and risks of PCDT in the subgroup of ATTRACT patients who had femoral-popliteal DVT without involvement of more proximal deep veins.

Methods

Study patients and clinical management

The design and main results of ATTRACT have previously been described.(1;2) In brief, patients 16 to 75 years old with symptomatic DVT that involved the femoral, common femoral, or iliac veins (with or without other involved veins) were enrolled provided they did not have symptoms for more than 14 days, high bleeding risk, active cancer, established PTS, or ipsilateral DVT in the previous 2 years. Patients were enrolled in community and university-based clinical centers in the US. The study was approved by the research ethics boards of participating institutions and all patients provided informed consent.

Patients' baseline characteristics, including whether they had iliofemoral or femoral-popliteal DVT, were assessed before randomization. To be included in the femoral-popliteal randomization stratum and, therefore, eligible for inclusion in the current analysis, patients were to have thrombus in the femoral (with or without involvement of the popliteal vein) but not the common femoral vein or the iliac vein.

Patients were randomized in a 1:1 ratio to PCDT or to No PCDT. In addition to stratification as "femoral-popliteal" and "iliofemoral" DVT, patients were also stratified by clinical center. Patients in both the PCDT and No PCDT arms received anticoagulant therapy and elastic compression stockings. PCDT was done using one of three methods. If the popliteal vein was occluded, patients initially received recombinant tissue plasminogen activator (rt-PA) infusion through a multi-sidehole catheter for ≤30 hours ("infusion-first" method). If the popliteal vein was patent, patients initially received rapid delivery of rt-PA through either the AngioJet Rheolytic Thrombectomy System (Boston Scientific, Marlborough, MA) or the Trellis

Peripheral Infusion System (Covidien, Inc., Mansfield, MA). After initial delivery of rt-PA, physicians could use balloon maceration, catheter aspiration, AngioJet or Trellis thrombectomy, percutaneous transluminal balloon venoplasty, stent placement (iliac or common femoral vein), continued rt-PA infusion through a multi-sidehole catheter, or a combination of procedures, to clear residual thrombus and treat obstructive lesions. Stenting of the iliac or common femoral vein was encouraged if there were obstructive lesions (e.g. extrinsic compression such as May-Thurner Syndrome) with ≥50% diameter narrowing, robust collateral filling, or a mean translesional pressure gradient >2 mmHg . Treatment was discontinued when there was at least 90% thrombus removal with restoration of flow, or a serious complication. The maximum allowable total dose of rt-PA for initial and follow-up procedures was 35 mg.

Follow-up and outcomes

Study outcomes were assessed at 10 and 30 days, and at 6, 12, 18, and 24 months post-randomization. The primary efficacy outcome was the presence of PTS, defined as a Villalta scale score ≥5 or an ulcer, in the leg with the index DVT, between the 6-month and the 24-month follow-up visits.(5;6) The Villalta scale rates the severity, from 0 to 3, of five patient-reported symptoms (pain, cramps, heaviness, pruritus, paresthesia) and six clinician-observed signs (edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression). Points for symptoms and signs are summed into a total score (range 0-33), and patients can be categorized as having no PTS (score 0-4), mild PTS (score 5-9), moderate PTS (score 10-14) or severe PTS (score >14, or presence of ulcer). Patients were also counted as having PTS if they had an unplanned endovascular procedure to treat severe venous symptoms

more than 6 months after randomization, unless there was a Villalta <5 in the preceding 4 weeks. Major non-PTS treatment failures were also assessed.(2)

Using the Villalta scale, the presence of moderate-or-severe PTS (Villalta scale score ≥10, or an ulcer), or severe PTS (Villalta scale score ≥15, or an ulcer) were assessed as secondary outcomes. Using the Venous Clinical Severity Score (VCSS; ranges from 0 to 27, with higher scores indicating more severe PTS), the presence of PTS (VCSS ≥4) or severe PTS (VCSS ≥8) were also assessed.(7) The proportion of patients with a Villalta scale score ≥5 and ≥10, and a VCSS ≥4 and ≥8 at each visit was recorded. The severity of PTS was evaluated at 6, 12, 18 and 24 months using the Villalta scale and the VCSS as continuous measurements. Leg pain and leg swelling were assessed at baseline, 10 days, and 30 days, using a 7-point Likert pain scale and by measuring calf circumference.

In the PCDT arm, thrombus removal was quantified using the proximal vein components of the Marder score (0 to 24, with 24 representing complete thrombosis) by independent central readers who scored venograms done before and after the procedure.(8)

Safety outcomes included bleeding, recurrent venous thromboembolism, and deaths, which were reported throughout follow-up and summarized through 10 days.

General health-related quality of life was assessed with the SF-36 Health Status Survey and venous disease-specific quality of life was assessed with the Venous Insufficiency Epidemiological and Economic Study (VEINES-QOL) measure.(9;10) Detailed definitions of trial outcomes have previously been reported.(1;2) Both the clinical personnel who administered efficacy outcome assessments and the central adjudicators were blinded to treatment allocation.

Sample Size

Sample size for the whole ATTRACT study was 692 patients based on the following assumptions: 30% of control patients would develop PTS between 6 and 24 months; PCDT would reduce PTS by at least 33%; 10% loss to follow-up; need to have 80% power to detect the hypothesized treatment effect; acceptance of a two-side α error of 0.05. We did not prespecify the proportion of enrolled patients who were expected to have femoral-popliteal DVT, nor did we require that a minimum number of femoral-popliteal DVT patients be included. A sample size of 300, corresponding to the number of patients in the current analysis, provides approximately 80% power to detect a 47% PTS reduction assuming a control proportion of 30%, and an effect size (i.e. mean difference divided by the standard deviation) of at least 0.32, assuming a two-sided α=0.05 with each type of analysis.

Statistical Analysis

Two types of analyses were performed: a modified intention-to-treat analysis (primary analysis) that included all randomized patients except those who did not have DVT at enrollment; and a per-protocol analysis (secondary analyses) that excluded patients who, within 7 days post-randomization, were randomized to PCDT but did not receive it, or who were randomized to control but had skin puncture for PCDT thrombolysis or any thrombolytic therapy.

Cumulative proportions were compared using the Cochran-Mantel-Haenszel test adjusted for clinical center. Treatment effects are summarized using stratum-adjusted risk ratios (RR) with their corresponding 95% confidence intervals (CI).

The mean Villalta and VCSS assessments at each visit were estimated using piece-wise linear regression growth curve models adjusting for clinical center and pre-specified baseline

covariates (age, sex, body mass index [BMI], race). Changes from baseline to 10 and 30 days for leg pain scores and calf circumferences, were compared between the two arms using linear regression, adjusted for clinical center.

Results

Baseline Characteristics

Of the 692 patients in ATTRACT, 300 (43%) had femoral-popliteal DVT of whom 140 were randomized to PCDT and 160 were randomized to No PCDT (Fig. 1). Median age was 53 years, 73% were male, the index DVT was in the left leg in 59% and symptoms were present for a median of 7 days. Baseline characteristics were well balanced between the two treatment arms (Table 1).

Protocol and Treatment Adherence

Within 7 days after randomization, 1 patient assigned to No PCDT had PCDT, and 5 patients assigned to PCDT did not have the procedure (Fig. 1). These patients were excluded from the per-protocol analysis. PCDT was performed a median of one day post-randomization. Initial anticoagulant therapy, which was usually low molecular weight heparin or unfractionated heparin, was similar in the PCDT and No PCDT arms (Table 2).

In PCDT patients, initial rt-PA delivery was with the "infusion-first" method in 66% (median total rt-PA dose of 22 mg), the AngioJet method in 21% (median total rt-PA dose of 21 mg), and the Trellis method in 9% (median total rt-PA dose of 14 mg); 5% did not recieve rt-PA (Table 2). After initial rt-PA delivery, additional endovascular methods were used in 85% of patients (summarized in Table 2). Mean percent thrombus removal, as assessed by pre- and post-PCDT venography, was 79% (95% CI, 74% to 83%). The mean pre- and post-lysis Marder

scores were 10.2 and 2.1 respectively (mean change was -8.1; 95% CI, -7.2 to -8.9; p<0.001). The mean duration of anticoagulation before first permanent cessation during follow-up, use of antiplatelet therapy, and use of compression stockings were similar in the PCDT and No PCDT arms (Table 2).

Primary Efficacy Outcome

PTS, as assessed by a Villalta scale score ≥5 or ulceration, developed in 61 (44%) patients assigned to PCDT and 71 (44%) patients assigned to No PCDT over 24 months (RR=0.97; 95% CI, 0.75 to 1.24; p=0.79; Table 3). The findings were similar in a per-protocol analysis (59 of 135 with PCDT vs. 70 of 159 with No PCDT, RR=0.97; 95% CI, 0.75 to 1.25; Supplementary Table S1). Results were similar in pre-specified subgroups, except for a suggestion that the treatment effect of PCDT may have been more favorable in patients with a major reversible risk factor when the DVT occurred compared to those without such a risk factor ($p_{interaction}$=0.04; Fig. 2).

Secondary Efficacy Outcomes

Moderate-or-severe PTS, as assessed by a Villalta scale score ≥10 or ulceration, developed in 24 (17%) patients assigned to PCDT and 29 (18%) patients assigned to No PCDT (RR=0.93; 95% CI, 0.57 to 1.52; p=0.77) (Table 3). The findings were similar in a per-protocol analysis (Supplementary Table S1). Results were similar in pre-specified subgroups except for a suggestion that the treatment effect of PCDT may have been more favorable in patients with higher baseline Villalta scores ($p_{interaction}$=0.03; Fig. 3).

Severe PTS, as assessed by a Villalta scale score ≥15 or ulceration, developed in 10 (7%) patients assigned to PCDT and 13 (8%) patients assigned to No PCDT (RR=0.84; 95% CI, 0.37 to 1.87; p=0.66; Table 3). Ulceration developed in 3 (2.1%) patients assigned to PCDT and 5

(3.1%) patients assigned to No PCDT (Table 3). The proportion of patients who had PTS, or moderate-or-severe PTS, as assessed by the Villalta scale, at each 6, 12, 18 and 24-month visit are shown in Table 3; these proportions did not differ between the PCDT vs. No PCDT arms at any of the follow-up visits. The above findings were similar in a per-protocol analysis (Supplementary Table S1).

PTS, as assessed by a VCSS ≥4, developed in 43 (31%) patients assigned to PCDT and 50 (31%) patients assigned to No PCDT (RR=0.99; 95% CI, 0.72 to 1.38; p=0.97; Table 3). Severe PTS, as assessed by a VCSS ≥8, developed in 9 (6%) patients assigned to PCDT and 14 (9%) patients assigned to No PCDT (RR=0.76; 95% CI, 0.35 to 1.65; p=0.49; Table 3). The findings for these two outcomes were similar in a per-protocol analysis (Supplementary Table S1).

There was no difference in PTS severity, as assessed by mean Villalta score and mean VCSS, between the PCDT and No PCDT arm from 6 to 24 months in the modified intention-to-treat (Table 4) nor the per-protocol analyses (Supplementary Table S2).

Mean change in leg pain from baseline for PCDT vs. No PCDT was -1.44 vs. -1.35 Likert points at 10 days (p=0.68), and -1.93 vs. -1.88 Likert points at 30 days (p=0.85). Mean change in leg circumference from baseline for PCDT vs. No PCDT was 0.45 cm vs. 0.37 cm at 10 days (p=0.81), and 0.08 cm vs. -0.41 cm at 30 days (p=0.14). The findings for these outcomes were similar in the per-protocol analyses (Supplementary Table S2).

Mean change in general quality of life and in disease-specific quality of life from baseline to 30 days and from baseline to 24 months did not differ between the PCDT vs. No PCDT arms (Table 4 for modified intention-to-treat analysis and Supplementary Table S2 for per-protocol analysis).

Safety Outcomes

Within 10 days, in PCDT vs. No PCDT patients, major bleeding occurred in 3 (2.1%) vs. no patients (p=0.063; none were fatal or intracranial), and any bleeding occurred in 8 (5.7%) vs. 2 (1.3%) patients (p=0.032; Table 3). Recurrent venous thromboembolism within 24 months occurred in 16 (11%) PCDT vs. 12 (8%) No PCDT patients (p=0.24) (none were fatal). Three deaths were observed during the study: one in the PCDT arm and 2 in the No PCDT arm. None occurred within 10 days post-randomization (Table 3).

Discussion

This analysis found that PCDT did not improve any prespecified short-term or long-term efficacy outcomes but increased bleeding in ATTRACT trial patients who had femoral-popliteal DVT. Within the femoral-popliteal subgroup of ATTRACT patients, there was a suggestion that PCDT may have reduced "any PTS" more in patients whose DVT was provoked by a major risk factor (e.g. recent surgery), and may have reduced moderate-or-severe PTS more in patients who had higher Villalta scores at baseline. However, as there were many subgroup comparisons and as the tests of interaction were not strongly statistically significant, it is likely that these two findings occurred by chance and that the treatment responses did not truly differ between these subgroups.(11;12) During follow-up, the prevalence of PTS of 44% in both treatment groups indicates that PTS remains a substantial problem in patients who have femoral-popliteal DVT.

Unlike in the overall study, PCDT did not appear to reduce early symptoms of leg pain or leg swelling or the occurrence of moderate-or-severe PTS in the femoral-popliteal DVT subgroup. This suggests that, as we have reported elsewhere, improvements in these outcomes with PCDT was confined to the iliofemoral DVT subgroup.(13)

The CAVENT (Catheter-Directed Venous Thrombolysis in Acute Iliofemoral Vein Thrombosis) trial, which evaluated 209 patients, reported that catheter-directed thrombolysis reduced the risk of PTS at 2 and 5 years but did not report findings separately for patients with femoral-popliteal (required involvement "above mid-thigh level") and iliofemoral DVT.(14;15) Our analysis has several limitations. As only 43% of ATTRACT trial patients had femoral-popliteal DVT, power to detect difference in outcomes with PCDT vs. No PCDT in the femoral-popliteal subgroup is substantially less than in the overall trial. Furthermore, in the absence of a statistically significant test of interaction to support a difference in the PCDT treatment effect between the femoral-popliteal and iliofemoral subgroups, the treatment effect estimate from the overall trial may be the most reliable estimate of the treatment effect in each of the femoral-popliteal and the iliofemoral subgroups.(11;12) However, as the risk of developing PTS is influenced by the extent of DVT, it is important to understand outcomes in the ATTRACT patients whose proximal DVT was confined to the femoral vein.(4) Another limitation is that more patients were lost to follow-up in the No PCDT arm (28% versus 16%) which has the potential to reduce the apparent efficacy of PCDT in our analysis. An additional sensitivity analysis for the primary outcome of any PTS, after using multiple imputation to replace missing data, found a risk ratio of 0.84 (95%CI, 0.67 to 1.04) for PCDT compared with control.

A strength of these analyses is that they were prespecified, and that the femoral-popliteal and iliofemoral subgroups were stratification factors in the randomization of patients to PCDT and No PCDT. An additional limitation is that differences in the occurrence of PTS between the treatment groups might emerge with longer than two years of follow-up.

In conclusion, whereas the overall findings of ATTRACT found ~~suggested~~ that PCDT reduced moderate-or-severe PTS, reduced the severity of PTS symptoms, and improved recovery of leg pain and swelling, the current analysis does not support such benefits in patients with femoral-popliteal DVT. As PCDT is associated with bleeding, early PCDT does not appear to be warranted in patients with femoral-popliteal DVT without involvement of more proximal veins.

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Conflict of Interests

Dr. Kearon reports receiving grant support and consulting fees from Bayer;

Dr. Goldhaber, receiving grant support from BiO2 Medical and grant support and consulting fees from Boehringer Ingelheim, BMS, Daiichi Sankyo, Janssen, Portola, Bayer, and BTG/Ekos;

Dr. Comerota, receiving consulting fees from Medtronic;

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Dr. Leung, receiving research support and consulting fees from Boston Scientific;

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No other potential conflict of interest relevant to this article was reported.

Table 1: Baseline Characteristics by Treatment Group

Baseline Characteristic	PCDT Arm n = 140	Control Arm n = 160	Total N = 300
Age, years: *median (IQR)*	53 (43, 60)	54 (44, 63)	53 (43, 62)
Male: *n (%)*	98 (70)	120 (75)	218 (73)
Race: *n (%)*			
White	107 (76)	128 (80)	235 (78)
Black/African-American	28 (20)	27 (17)	55 (18)
Other	5 (4)	5 (3)	10 (3)
Body mass index, kg/m^2: *median (IQR)*	30 (27, 35)	30 (26, 34)	30 (27, 35)
Symptom severity (Villalta[a]) class: *n (%)*[b]			
None or minimal (score 0-4)	33 (24)	38 (24)	71 (24)
Mild (score 5-9)	50 (36)	59 (37)	109 (36)
Moderate (score 10-14)	38 (27)	38 (24)	76 (25)
Severe (score ≥ 15)	19 (14)	24 (15)	43 (14)
Leg with index DVT, Left: *n (%)*	83 (59)	93 (58)	176 (59)
Previous DVT or PE: *n (%)*	35 (25)	42 (26)	77 (26)
Previous ipsilateral DVT: *n (%)*	2 (1)	4 (3)	6 (2)
DVT risk factors: *n (%)*[c]			
Major surgery	8 (6)	13 (8)	21 (7)
Hospitalization	9 (6)	9 (6)	18 (6)
Plaster cast immobilization	1 (1)	6 (4)	7 (2)
Outpatient: *n (%)*	112 (80)	144 (90)	256 (85)
Days from start of DVT symptoms to rand: *median (IQR)*	6 (4, 11)	7 (4, 10)	7 (4, 10)
eGFR, mL/min: *median (IQR)*	89 (73, 101)	83 (71, 99)	86 (72, 100)
Leg pain severity: *n (%)*			
0-2	26 (19)	38 (24)	64 (21)
3-4	60 (43)	55 (34)	115 (38)
5-7	53 (38)	65 (41)	118 (39)
Unknown	1 (1)	2 (1)	3 (1)

Between-leg circumference difference[d], cm: *median (IQR)*	2 (1, 3)	2 (1, 3)	2 (1, 3)
Pre-randomization AC[e] therapy: *n (%)*[c]	134 (96)	147 (92)	281 (94)
LMWH	79 (59)	95 (65)	174 (62)
UFH	38 (28)	39 (27)	77 (27)
Rivaroxaban	9 (7)	4 (3)	13 (5)
Warfarin	65 (49)	81 (55)	146 (52)
Other	7 (5)	9 (6)	16 (6)

IQR, inter-quartile range; DVT, deep vein thrombosis; PE, pulmonary embolism; rand, randomization; eGFR, estimated glomerular filtration rate; LMWH, low molecular weight heparin; UFH, unfractionated heparin

[a] **Villalta Scale**: 5 patient-reported signs (cramps, itching, pins & needles, leg heaviness, pain) and 6 blinded clinician-reported symptoms (pretibial edema, skin induration, hyperpigmentation, venous ectasia, redness, pain during calf compression) scored on a 4-point scale (0=none/minimal, 1=mild, 2=moderate, 3=severe) and summed into a total score, or the presence of an ulcer (score=15), for each leg

[b] One patient in the control arm were not assessed

[c] Subjects may fit into more than one category

[d] Circumference of leg with index DVT minus circumference of the other leg

[e] Anticoagulant (AC) therapy that was given after DVT diagnosis and before randomization

Table 2: Study Treatments Post Randomization

Treatment over Time	PCDT Arm n = 140	Control Arm n = 160
Initial AC [a] therapy: *n (%)*[b]	*n = 140*	*n = 160*
UFH	45 (32)	27 (17)
LMWH	82 (59)	95 (59)
Other	18 (13)	41 (26)
At 30 days: *n (%)*[b]	*n = 138*	*n = 149*
Any AC therapy	138 (100)	149 (100)
Antiplatelet therapy	17 (12)	17 (11)
Compression stockings used ≥ 3 days per week	110 (80)	116 (78)
At 6 months: *n (%)*[b]	*n = 121*	*n = 136*
Any AC therapy	91 (75)	120 (88)
Antiplatelet therapy	26 (21)	15 (11)
Compression stockings used ≥ 3 days per week	81 (67)	89 (65)
At 24 months: *n (%)*[b]	*n = 110*	*n = 106*
Any AC therapy	55 (50)	49 (46)
Antiplatelet therapy	28 (25)	23 (22)
Compression stockings used ≥ 3 days per week	61 (55)	56 (53)
Duration of AC therapy: *n (%)*	*n = 140*	*n = 160*
Never started	0	0
Not stopped during study period	71 (51)	90 (56)
Stopped during study period:	69 (49)	70 (44)
Days to stopping: *median (IQR)*	215 (184, 369)	223 (190, 300)
PCDT Procedure Details (PCDT Arm only)		
Initial rt-PA delivery method:		
Infusion-First: *n (%)*	92 (66)	
rt-PA total dose, mg: *median (IQR)*	22 (17, 25)	
rt-PA duration, hours: *% below 4h*, *mean (SD)* [c]	0%, 21 (5.4)	
AngioJet: *n (%)*	29 (21)	
rt-PA total dose, mg: *median (IQR)*	21 (10, 28)	
rt-PA duration, hours: *% below 4h*, *mean (SD‡*	41%, 20 (5.0)	
Trellis: *n (%)*	12 (9)	
rt-PA total dose, mg: *median (IQR)*	14 (11, 23)	
rt-PA duration, hours: *% below 4h*, *mean (SD)*[c]	75%, 18 (11.7)	
Other:[d] *n (%)*	7 (5)	

Additional endovascular methods used: *n (%)*		
None	21	(15)
1 or more	119	(85)
Type of additional method: *n (%)*[b]		
Balloon venoplasty	57	(48)
Balloon maceration	78	(66)
Rheolytic thrombectomy (AngioJet)	76	(64)
Stent placement	12	(10)[e]
Large-bore catheter aspiration	19	(16)
Isolated thrombolysis (Trellis)	3	(3)
Veins that were accessed: *n (%)*[b]	137	(98)
Ipsilateral popliteal vein	102	(74)
Ipsilateral tibial vein	39	(28)
Ipsilateral common femoral vein	3	(2)
Internal jugular vein	4	(3)
Other vein	9	(7)
Marder scores: *median (IQR)*		
Pre lysis	10	(7, 13)
Post lysis	1	(0, 3)

IQR, Inter-quartile range; rt-PA, recombinant tissue plasminogen activator; SD, standard deviation

[a] Anticoagulation (AC) therapy given post randomization

[b] Subjects may fit into more than one category

[c] Distributions are bimodal with spikes below 4 hours (means and SDs are for post 4-hour data)

[d] 4 PCDT procedures where there was no acute thrombus on venogram and 3 not attempted

[e] Stents were placed in the iliac vein in 11 patients (reasons: stenosis in 9, extrinsic compression in 4, not specified in 1) and in the femoral vein in 1 patient (reason: stenosis and residual thrombosis).

Table 3: Binary Study Outcomes by Treatment Group (Intention To Treat)

Outcome	PCDT Arm n = 140		Control Arm n = 160		Risk Ratio		P Value
	Events	(%)	Events	(%)	Estimate	95% CI	
PTS:[a]							
Ulcer (any assessment)	3	(2.1%)	5	(3.1%)			
Villalta ≥ 5 (without ulcer)	58	(41%)	66	(41%)			
Late endovascular procedure only	0	(0%)	0	(0%)			
Total	61	(44%)	71	(44%)	0.97[b]	0.75, 1.24	0.79
PTS: VCSS ≥ 4[a]	43	(31%)	50	(31%)	0.99[b]	0.72, 1.38	0.97
PTS incidence proportion:[c]							
At 6 months	28/122	(23%)	45/136	(33%)	0.69	0.46, 1.04	
At 12 months	34/117	(29%)	39/121	(32%)	0.90	0.61, 1.32	
At 18 months	39/106	(37%)	29/99	(29%)	1.26	0.85, 1.86	
At 24 months	31/113	(27%)	34/107	(32%)	0.86	0.57, 1.30	
Moderate-severe PTS (Villalta ≥ 10)[d]	24	(17%)	29	(18%)	0.93	0.57, 1.52	0.77
Moderate-severe PTS incidence proportion:[e]							
At 6 months	10/122	(8%)	14/136	(10%)	0.80	0.37, 1.73	
At 12 months	13/117	(11%)	9/121	(7%)	1.49	0.66, 3.36	
At 18 months	13/106	(12%)	11/99	(11%)	1.10	0.52, 2.35	
At 24 months	12/113	(11%)	15/107	(14%)	0.76	0.37, 1.54	
Severe PTS: Villalta ≥ 15[f]	10	(7.1%)	13	(8.1%)	0.84	0.37, 1.87	0.66
Severe PTS: VCSS ≥ 8[f]	9	(6.4%)	14	(8.8%)	0.76[b]	0.35, 1.65	0.49
Major non-PTS treatment failure	0	(0%)	2	(1.3%)	0.23	0.01, 4.72	0.19
Any treatment failure[g]	61	(44%)	73	(46%)	0.94[b]	0.73, 1.21	0.65
Major bleeding in first 10 days	3	(2.1%)	0	(0%)	7.99	0.42, 153	0.063
Any bleeding in first 10 days	8	(5.7%)	2	(1.3%)	4.57	0.99, 21.2	0.032
VTE:							
First 30 days	4	(2.9%)	2	(1.3%)	2.29	0.43, 12.3	0.32
Total over 24 months	16	(11%)	12	(8%)	1.52	0.75, 3.11	0.24
Death	1	(0.7%)	2	(1.3%)	0.57	0.05, 6.23	0.64

PTS, post-thrombotic syndrome; CI, confidence interval; VTE, venous thromboembolism

[a] Cumulative proportion of patients who developed PTS (ulcer, Villalta ≥ 5 or LEP) at any time between 6 and 24 months inclusive;

[b] Cochran-Mantel-Haenszel (CMH) test adjusted for center;

[c] At each visit, the proportion of patients with any PTS according to the Villalta scale among those who had an assessment performed (denominator);

[d] Cumulative proportion with moderate or severe PTS (pre-specified analysis);

[e] At each visit, the proportion of patients with any moderate or severe PTS according to the Villalta scale among those who had an assessment performed (denominator);

[f] Cumulative proportion with severe PTS;

[g] Composite of PTS or major non-PTS treatment failure. Villalta scores (0-33 range) – higher is worse; VCSS scores (0-27 range) – higher is worse.

Table 4: Continuous Study Outcomes by Treatment Group (Intention To Treat)

Outcome	PCDT Arm n = 140		Control Arm n = 160		PCDT – Control Difference	
	n	**mean** (SE)	**n**	**mean** (SE)	**Estimate** (SE)	**P-value**
Villalta mean score[a]**:** [(1)]						
At 6 months	122	2.75 (0.52)	136	3.34 (0.51)	-0.59 (0.44)	0.19
At 12 months	117	2.86 (0.51)	121	3.35 (0.50)	-0.50 (0.42)	0.24
At 18 months	106	2.97 (0.52)	99	3.37 (0.52)	-0.41 (0.45)	0.37
At 24 months	113	3.08 (0.55)	107	3.39 (0.55)	-0.32 (0.53)	0.55
VCSS mean score [bc] **:** [(2)]						
At 6 months	121	1.87 (0.16)	134	2.12 (0.16)	-0.26 (0.22)	0.25
At 12 months	114	b	119	b	b	b
At 18 months	105	b	94	b	b	b
At 24 months	103	b	93	b	b	b
SF-36 general Quality of Life[c]**:** [(3)]						
PCS: Change, baseline to 24 months	107	12.00 (0.97)	99	11.03 (0.96)	0.97 (1.22)	0.43
MCS: Change, baseline to 24 months	108	2.34 (0.67)	99	2.75 (0.67)	-0.41 (0.87)	0.63
VEINES disease-specific Quality of Life[c]**:** [(4)]						
Overall: Change, baseline to 24 months	108	27.27 (2.04)	99	25.90 (2.01)	1.37 (2.54)	0.59
Symptoms: Change, baseline to 24 months	108	20.60 (2.04)	99	20.14 (2.01)	0.46 (2.52)	0.86
Leg pain severity[§] (7-point scale)**:** [(5)]						
Change, baseline to Day 10	136	-1.44 (0.15)	148	-1.35 (0.15)	-0.09 (0.21)	0.68
Change, baseline to Day 30	136	-1.93 (0.15)	146	-1.88 (0.15)	-0.04 (0.22)	0.85
Index leg circumference[d] (cm)**:** [(6)]						
Change, baseline to Day 10	130	0.45 (0.24)	146	0.37 (0.23)	0.08 (0.33)	0.81
Change, baseline to Day 30	130	0.08 (0.25)	145	-0.41 (0.23)	0.50 (0.34)	0.14

[a] Mean scores, standard errors (SE) and treatment differences estimated using growth curve models and piece-wise linear regression adjusted for center, and baseline covariates (age, sex, BMI, race)

[b] Model estimates are unchanged over visit times due to the lack of a significant time trend

[c] Mean scores, standard errors (SE) and treatment differences estimated using growth curve models and piece-wise linear regression adjusted for center, and baseline covariates (age, sex, BMI, race, Villalta score)

[d] Mean change scores, SEs, and treatment differences estimated using multiple linear regression adjusted for center

[(1)] Villalta scores (0-33 range) – higher is worse;

[(2)] VCSS scores (0-27 range) – higher is worse;

[(3)] SF-36 major scales: physical component score (PCS, 0-100 range) and mental component score (MCS, 0-100 range) – higher is better, with a difference of 3 to 4 points considered clinically meaningful;

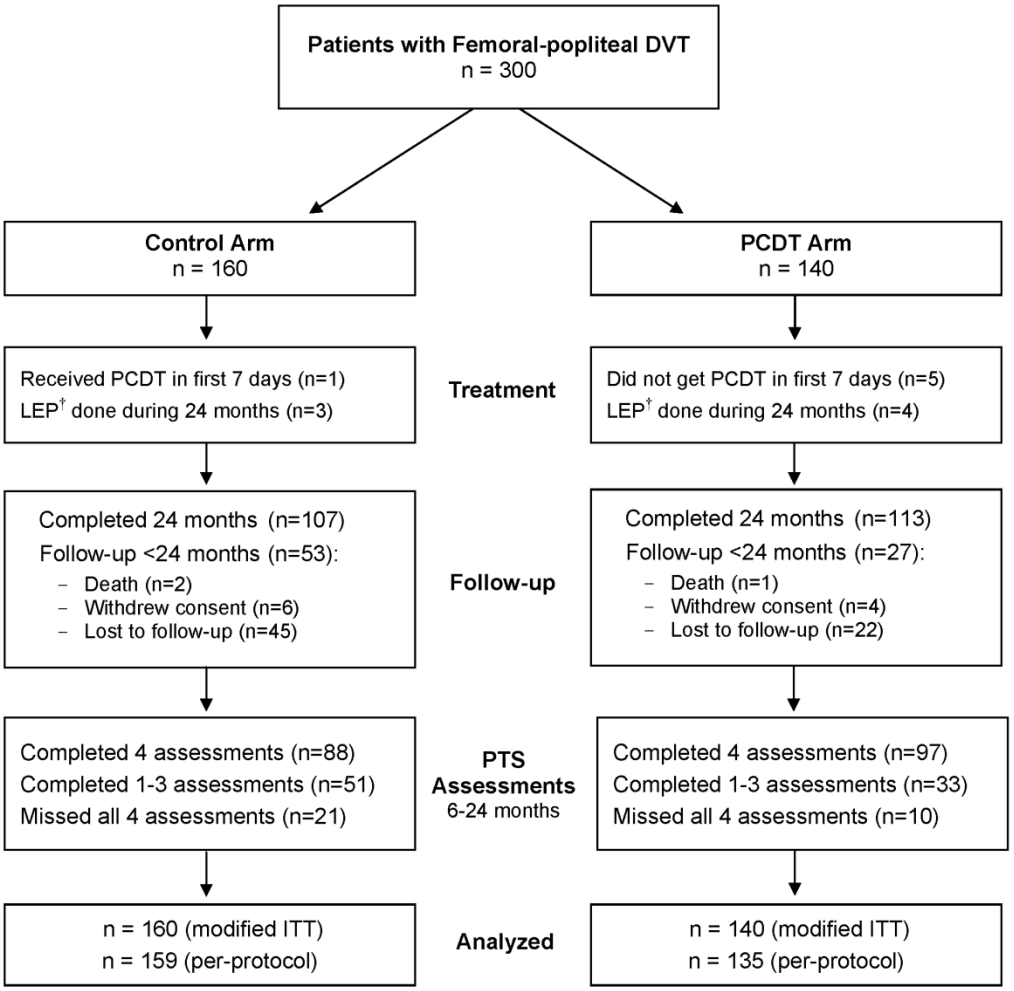
[4] VEINES overall score (0-100 range) and symptom specific score (0-100 range) – higher is better;

[5] patient-reported severity of pain in the index leg (0-7 range) – higher is worse;

[6] leg circumference measured at 10cm below tibial tuberosity of the index leg.

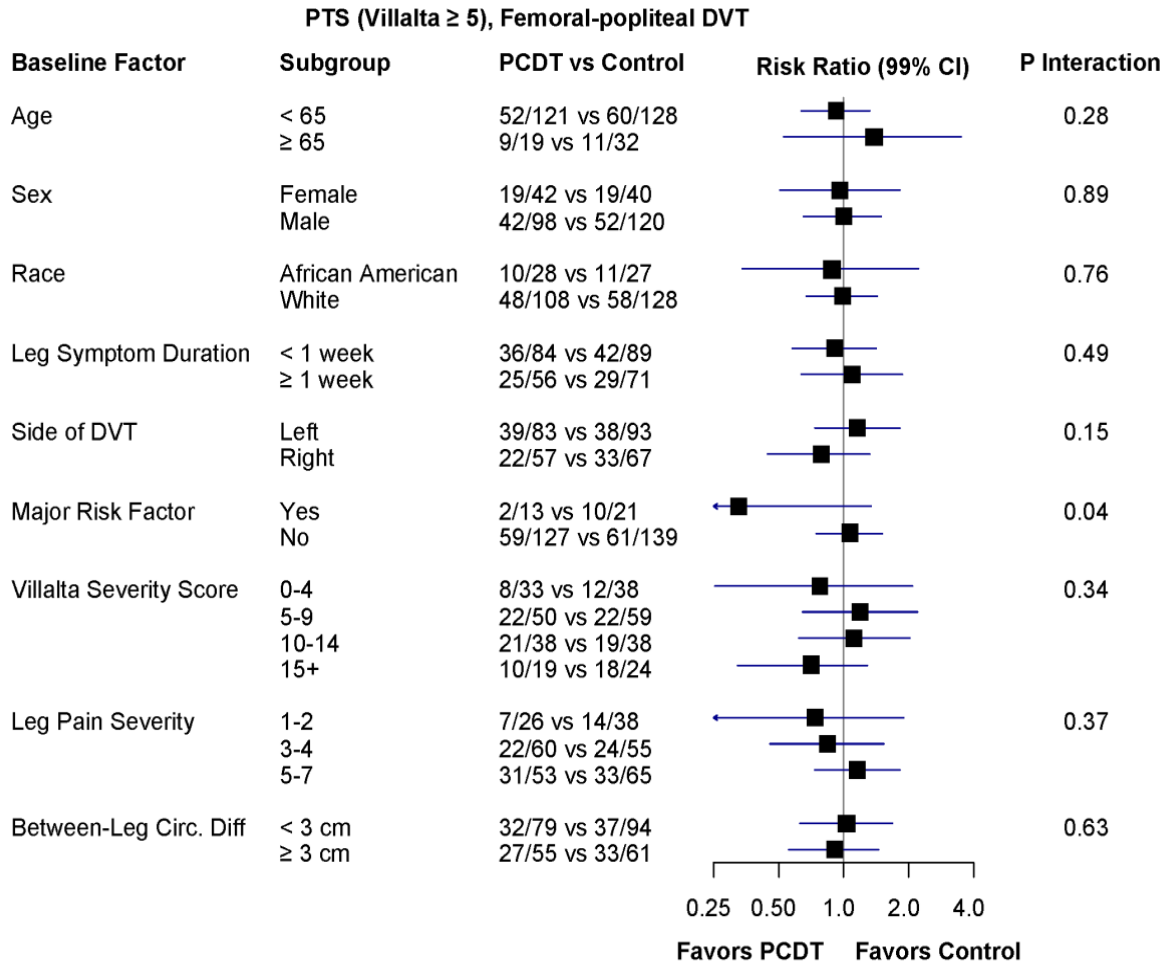
Figure Legends

Fig. 1. Patient flow diagram for patients with femoral-popliteal DVT.



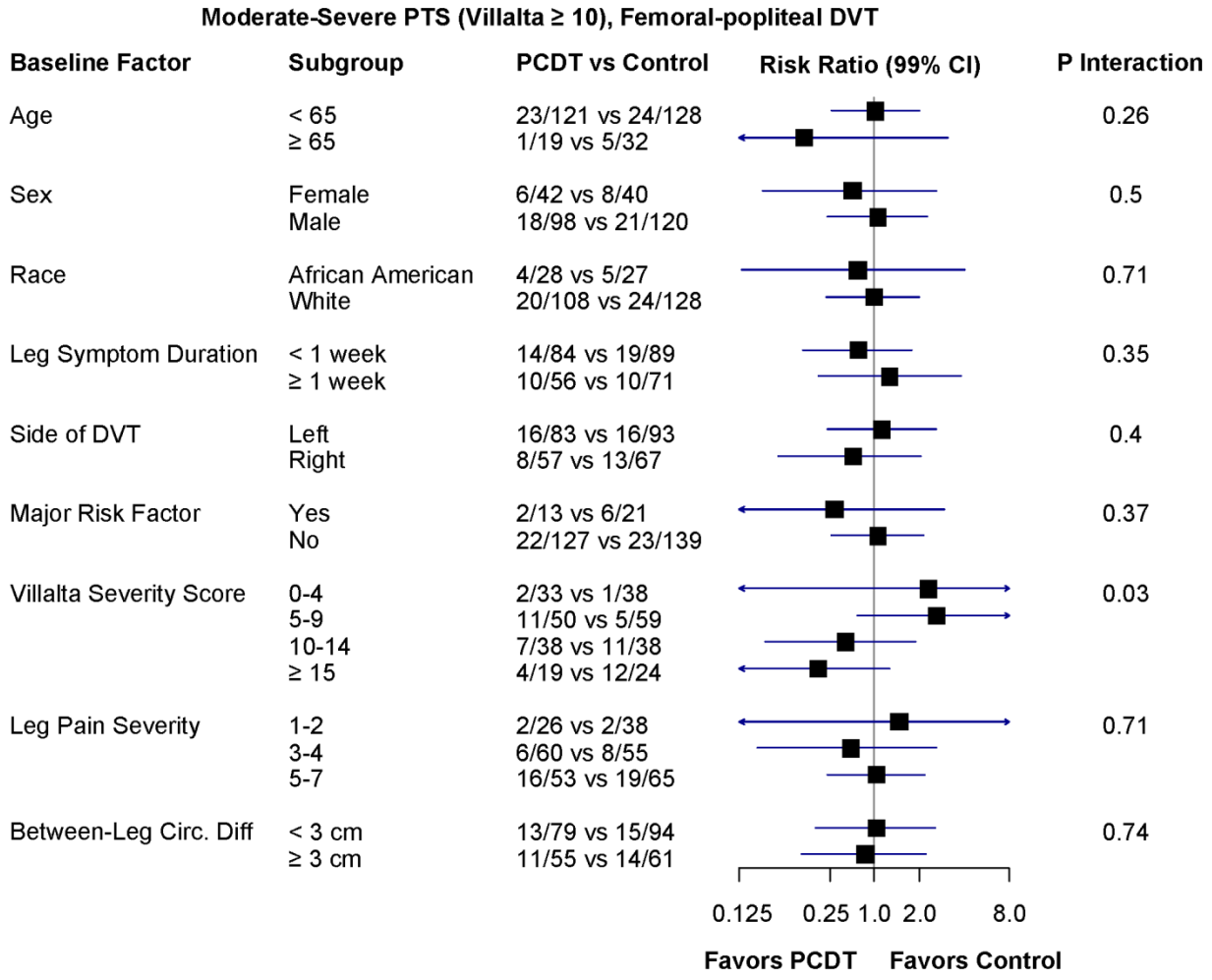
PCDT, pharmacomechanical catheter-directed thrombolysis; DVT, deep-vein thrombosis; LEP, Late Endovascular Procedure (not including inferior vena cava filter).

Fig. 2. Subgroup analysis of "any PTS" in patients with femoral-popliteal DVT.



Forest plot of risk ratios (PCDT vs. No PCDT) for the occurrence of PTS from 6 to 24 months among subgroups of patients. The horizontal lines represent 99% confidence intervals. PCDT, pharmacomechanical catheter-directed thrombolysis; DVT, deep vein thrombosis.

Fig. 3. Subgroup analysis of "moderate-or-severe PTS" in patients with femoral-popliteal DVT.



Forest plot of risk ratios (PCDT vs. No PCDT) for the occurrence of moderate-or-severe PTS from 6 to 24 months among subgroups of patients. The horizontal lines represent 99% confidence intervals.

PCDT, pharmacomechanical catheter-directed thrombolysis; DVT, deep vein thrombosis.

Reference List

(1) Vedantham S, Goldhaber SZ, Kahn SR, Julian J, Magnuson E, Jaff MR et al. Rationale and design of the ATTRACT Study: a multicenter randomized trial to evaluate pharmacomechanical catheter-directed thrombolysis for the prevention of postthrombotic syndrome in patients with proximal deep vein thrombosis. Am Heart J 2013; 165(4):523-530.

(2) Vedantham S, Goldhaber SZ, Julian JA, Kahn SR, Jaff MR, Cohen DJ et al. Pharmacomechanical Catheter-Directed Thrombolysis for Deep-Vein Thrombosis. N Engl J Med 2017; 377(23):2240-2252.

(3) Douketis JD, Crowther MA, Foster GA, Ginsberg JS. Does the location of thrombosis determine the risk of disease recurrence in patients with proximal deep vein thrombosis? Am J Med 2001; 110(7):515-519.

(4) Kahn SR, Shrier I, Julian JA, Ducruet T, Arsenault L, Miron MJ et al. Determinants and time course of the postthrombotic syndrome after acute deep venous thrombosis. Ann Intern Med 2008; 149(10):698-707.

(5) Kahn SR, Partsch H, Vedantham S, Prandoni P, Kearon C. Definition of post-thrombotic syndrome of the leg for use in clinical investigations: a recommendation for standardization. J Thromb Haemost 2009; 7(5):879-883.

(6) Kahn SR. Measurement properties of the Villalta scale to define and classify the severity of the post-thrombotic syndrome. J Thromb Haemost 2009; 7(5):884-888.

(7) Vasquez MA, Rabe E, McLafferty RB, Shortell CK, Marston WA, Gillespie D et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American Venous Forum Ad Hoc Outcomes Working Group. J Vasc Surg 2010; 52(5):1387-1396.

(8) Marder VJ, Soulen RL, Atichartakarn V, Budzynski AZ, Parulekar S, Kim JR et al. Quantitative venographic assessment of deep vein thrombosis in the evaluation of streptokinase and heparin therapy. J Lab Clin Med 1977; 89(5):1018-1029.

(9) Ware JE, Kosinski MA, Keller S. SF-36 physical and mental measures: A user's manual. The Health Institute, New England Medical Centre, 1994.

(10) Lamping DL, Schroter S, Kurz X, Kahn SR, Abenhaim L. Evaluation of outcomes in chronic venous disorders of the leg: development of a scientifically rigorous, patient-reported measure of symptoms and quality of life. J Vasc Surg 2003; 37(2):410-419.

(11) Wallach JD, Sullivan PG, Trepanowski JF, Sainani KL, Steyerberg EW, Ioannidis JP. Evaluation of Evidence of Statistical Support and Corroboration of Subgroup Claims in Randomized Clinical Trials. JAMA Intern Med 2017; 177(4):554-560.

(12) Sun X, Briel M, Busse JW, You JJ, Akl EA, Mejza F et al. Credibility of claims of subgroup effects in randomised controlled trials: systematic review. Br Med J 2012; 344:e1553.

(13) Comerota AJ, Kearon C, Gu CS, Julian JA, Goldhaber S Z, Kahn SR et al. Endovascular thrombus removal for acute iliofemoral deep vein thrombosis: Analysis from a Stratified

Multicenter Randomized Trial. Circulation 2018;Published ahead of print December4, 2018 (https://www.ahajournals.org/doi/abs/10.1161/CIRCULATIONAHA.118.037425).

(14) Enden T, Haig Y, Klow NE, Slagsvold CE, Sandvik L, Ghanima W et al. Long-term outcome after additional catheter-directed thrombolysis versus standard treatment for acute iliofemoral deep vein thrombosis (the CaVenT study): a randomised controlled trial. Lancet 2012; 379(9810):31-38.

(15) Haig Y, Enden T, Grotta O, Klow NE, Slagsvold CE, Ghanima W et al. Post-thrombotic syndrome after catheter-directed thrombolysis for deep vein thrombosis (CaVenT): 5-year follow-up results of an open-label, randomised controlled trial. Lancet Haematol 2016; 3(2):e64-e71.