

1 Duplex Ultrasound, Clinical Score, and D-Dimer to Rule in and
2 Out Deep Venous Thrombosis (DVT) and Postthrombotic
3 Syndrome (Pts): Bridging the Gap between DVT and Ptsin the
4 Primary Care and Hospital Setting

5 Dr. J. J. Michiels

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7

8 **Abstract**

9 First episodes of DVT in adults and elderly are elicited in two-thirds of cases by risk factors,
10 including varicose veins, cancer, pregnancy/postpartum, oral contraceptives below the age of
11 50 years, immobility or surgery. Pain and tenderness in the calf and popliteal fossa may occur
12 resulting from conditions labeled as alternative diagnosis (AD) including Baker's cyst,
13 hematoma, or muscle tears or pulls. The requirement for a safe diagnostic strategy of deep
14 vein thrombosis (DVT) should be based on an objective post-test incidence of venous
15 thromboembolism (VTE) of less than 0.1

16

17 **Index terms**— deep venous thrombosis, ultra sonography, post-thrombotic syndrome, elisa d-dimer, medical
18 elasticstockings, anticoagulation

19 **1 I. Introduction Deep Vein Thrombosis:**

20 Dvt irst-time episodes of deep vein thrombosis (DVT) are in two-thirds of cases caused by risk factors, including
21 varicosis, cancer, immobility, or surgery, oral contraceptives and thrombophilia (table 1) ??,2. Alterations
22 in blood coagulability with changes in blood flow and endothelial damage, are the precursors of intravenous
23 thrombosis. A number of other hereditary and acquired conditions that predispose to thrombosis (thrombophilia)
24 have been recognized. These include protein C and S deficiency, antithrombin III deficiency and activated protein
25 C resistance (which is usually associated with a factor V genetic abnormality 3 . Screening for these thrombophilia
26 and for anticardiolipin antibody, should only be performed in patients having familial, sporadic or recurrent
27 thrombosis.

28 Duplex Ultrasound, Clinical Score, and D-Dimer to Rule in and Out Deep Venous Thrombosis (DVT) and
29 Postthrombotic Syndrome (Pts): Bridging the Gap between DVT and Ptsin the Primary Care and Hospital
30 Setting A first DVT event in adults and elderly has a gradually increasing 20 to 30% DVT recurrence rate after
31 5 years followup. Research studies show that complete recanalization on DUS within 1 to 3 months and no
32 reflux is associated with with low recurrence of DVT (1.2% patient/years) and withno PTS obviating the need
33 of MECS and anticoagulation after 3 to 6 months post-DVT respectively. Delayed recanalization at 3 months
34 post-DVT and the presence of reflux due to valve destruction on DUS at 3 months post-DVT is associated with
35 a high risk of DVT recurrence as the cause of symptomatic PTS indicating the need to wear MECS and extend
36 anticoagulation.

37 **2 DVT**

38 The onset of a thrombosis is often 'silent' and may remain so. It commonly occurs at or about day 7 to 10 after
39 a surgical operation, parturition or the onset of an acute infection. Between one-third and two-thirds of patients
40 complain of some swelling and pain in the leg, usually in the calf ??1][2][3] . An iliac thrombosis should be
41 suspected if the whole leg is swollen and dusky. Direct pressure on the calf muscles or over the course of the deep
42 veins usually elicits direct tenderness. There may be a cyanotic hue to the leg and superficial venous dilatation.

5 COLLATERAL SUPERFICIAL VEINS (NONVARICOSE) 1

43 The temperature of the leg may be raised, and oedema of one ankle is an important physical sign. However, chest
44 pain or cardiac arrest from pulmonary embolism may be the first indications of a DVT. Pulmonary hypertension
45 may follow repeated small emboli, and is associated with the development of progressive dyspnoea.

46 Pain and tenderness in the calf and popliteal fossa may occur resulting from alternative diagnoses (AD)
47 like conditions such as a ruptured Baker's cyst, a torn plantaris tendon, a hematoma, or muscle tears or pulls.
48 Cutaneous infection (e.g. cellulitis), lymphoedema, venous reflux, peripheral arterial disease, and rheumatological
49 causes should also be differentiated from DVT.

50 As compared with phlebography (the reference gold standard to exclude and diagnose proximal DVT in
51 prospective management studies), the sensitivity of compression ultrasonography (CUS) is 97% for proximal
52 and 73% for distal vein thrombosis 4,5 . CUS has many advantages over phlebography. It is noninvasive, simple,
53 easy to repeat, relatively inexpensive, and free of complications. However, there are two main disadvantages
54 of CUS. First, calf vein thrombosis will be overlooked by CUS because it is safe to limit CUS estimation to
55 the subpopliteal, popliteal, and femoral veins for the diagnosis of symptomatic proximal DVT. Second, isolated
56 thrombi in the iliac and superficial femoral veins within the adductor canal are rare but difficult to detect and
57 therefore easily overlooked in symptomatic patients with suspected DVT (10).

58 Estimates of clinical score as low, moderate, and high for the probability of proximal DVT, based on medical
59 history and physical examination is the first step when DVT is suspected (Table ??) 4,5 . A score of 0
60 (asymptomatic) means a low probability, a score of 1 or 2 a moderate probability, and a score of 3 or more
61 a high probability for DVT.

62 3 Clinical feature Score

63 Active cancer treatment ongoing or within previous 6 months or palliative 1

64 Paralysis, paresis, or recent plaster immobilization of the lower leg(s) 1

65 Recent immobilization for more than 3 days or major surgery within last 4 weeks 1

66 Localized tenderness/pain along the distribution of the deep venous system 1

67 4 Entire leg swollen 1

68 Calf swelling by more than 2 cm when compared with the asymptomatic leg 1

69 (measured 10 cm below tibial tuberosity)

70 Pitting oedema greater in the symptomatic leg 1

71 5 Collateral superficial veins (nonvaricose) 1

72 Total Rotterdam DVT score 8 mat ity)

73 Tabel 2 : Clinical score list for predicting pretest probability for proximal DVT The Rotterdam modification
74 of the Wells' score 4,5 .

75 D-dimer is a degradation product of a crosslinked fibrin clot. It has gained a prominent role for ruling out DVT.
76 The prevalence of DVT after a negative first CUS is uniformly low, 2 to 3%, during a 3 months followup with
77 a NPV of 97 to 98% in large prospective management studies (figure ??)4. The combination of a negative first
78 CUS and a negative SimpliRed safely excludes DVT to zero or less than 1% (NPV > 99.3 to 100%) irrespective
79 of clinical score (figure ??) (11). This simple, safe and most effective strategy obviates the need of repeated CUS
80 on the basis of which anticoagulant therapy can safely be withheld and reduces the number of repeated CUS
81 testing from about 75% to 30% (figure 1) 6 .

82 Figure ?? : Safe exclusion and diagnosis of deep vein thrombosis by the sequential use of CUS and SimpliRed
83 test in the primary care setting or outpatient ward 6 The negativepredictivevalue of a normalqualitative D-
84 dimerSimpliRedtest is not high enoughfor the exclusion of DVT 4,5 . After a negativefirst CUS and a
85 negativeSimpliRed (Simplify) test DVT isexcludedwith anegativepredictivevalue of 99.0% with the needtorepeat
86 a second CUS when the D-dimer is positive (Figure ??) 6 .

87 The feasibility of a strategytoexclude DVT by a negativerapid ELISA VIDAS D-dimer test (<500 ng/ml) alone
88 without the need of CUS, on the basis of whichanticoagulant treatment is withhold, has been tested in the large
89 prospective management Geneva study (table3) 6 In thisGeneva study of 474 outpatientswithsuspected DVT,
90 the sensitivity and negativepredictivevalue(NPV) of a rapid ELISA D-dimer test forthrombosisexclusionwere 98.2
91 and 98.4% respectively (table 3). A negative CUS followedby a negative ELISA VIDAS D-Dimertest result (<500
92 ng/mL) exclude DVT and pulmonaryembolismwith a sensitivity, and NPV of 100% irrespective of clinical score
93 (table 3 left arm, Geneva Study) 7 .

94 Table ?? : Results of CUS and ELISA D-dimertesting in 593 patientswithsuspected DVT in the prospective
95 Geneva management study 7 .

96 We tested the sequential use of the sensitive quantitative ELISA VIDAS D-dimer test, clinical score, and
97 compression ultrasound (CUS) as a safe and costeffective diagnostic work-up of DVT in a large prospective
98 management study according to the diagnostic algorithm in figure 2A. According to figure 2A DVT is excluded
99 after a negative CUS and normal VIDAS D-Dimer (<500 n g/m L) with a sensitivity and NPV of 100%. If the
100 first CUS is negative and the VIDAS D-dimer increased (>500 n g/m L) a second CUS was performed within
101 one week.

102 Out of 865 outpatients with suspected DVT, a 1st CUS was negative in 675 , and positive in 190 (22%). In 249
103 outpatients with a normal ELISA VIDAS (<500 n g/m L) the CUS was true negative in 248 and false negative
104 in 1 (sensitivity 99.5%, figure 2B). The negative predictive value of a first CUS was 98.6% (662 out of 675) on
105 the basis of which a second CUS within one week should beper for med. A 2nd CUS was indicated in 427 and
106 performed in 382 because of increased ELISA VIDAS D-dimer (>500 n g/m L) and proved to be positive in 13
107 (1.9% of 381).

108 The overall prevalence of DVT in o rprospective management study was 190 plus 13 = 203 (23.4%, figure 2
109 B). The prevalence of DVT on CUS at increasing ELISA VIDAS cut off levels of 0 to 500 (N=249), 500 to 1000
110 (N=196) and above 1000 n g/m (N=374) was 0.5%, 5.1% and 19.5%. A normal ELISA VIDAS D-dimer test
111 (<500 ng/mL) aloneex cluded DVT at a sensitivity and NPV of 99.5% and a specificity of 37.5% (figure 2 B).

112 The sensitivit y for DVT exclusion of an ELISA VIDAS test result between 500 and 1000 n g/m L after a first
113 negative CUS was 99.6 as test edbyrepeated CUS. The combination of a first negative CUS and an ELISA VIDAS
114 test between 500 and 1000 n g/m L will exlude DVT with a NPV of 99.7% (figure 2B). From this prospective
115 management study we concluded that the combined use of a sensitive quantitative ELISA D-dimer test, clinical
116 score, and compression ultrasound (CUS) is a safe and costeffective diagnostic work-up to exclude and diagnose
117 according to the algorithm in figure 3. First, it is safe to exclude DVT and pulmonary embolism by a negative
118 CUS and normal ELISA D-Dimer test (<500 n g/ml, left arm) with a sensitivity and NPV of 100%. Second, it
119 is safe to exclude DVT by a first negative CUS and an ELISA VIDAS D-Dimer test result of <1000 n g/m L in
120 asymptomatic cases with a low clinical score of zero (middle arm) with a sensitivity and NPV of 99,6%. Third,
121 attentive clinicians should be aware that the combination of a negative first CUS and an ELISA D-Dimer test
122 above 500 n g/m L in patients with persistent complaints, signs and symptoms suspected for DVT are candidates
123 to perform a second CUS (right arm, figure 3). This new strategy in figure 3 is predicted to l reduce repeaedt
124 CUS testing by two-third, which has been tested in a large prospective management study of more than 2000
125 patients with suspected DVT between 2006 and 2013 (manuscript in preparation). The sensitivity of a normal
126 (<500 ng/ml) turbidimetric D-dimer assay Tinaquant (Roche Diagnostics, Marburg Germany) for the exclusion
127 of DVT in a large management studywas 97.7% at a specificity of 42% and a NPV 97% (figure 4)8. A normal
128 Tinaquant test result (<500 ng/ml) as a stand alone test appearstobe not sensitivenough for the exclusion of
129 DVT. The combination of a negative first CUS, a normal Tinaquant test result (<500 n g/ml) and a low clinical
130 score had a negative predictive value of 99.4% without the need of CUS testing and thusreduced the number of
131 CUS testingby 29% (Figure 4) 8 . Those patientsa first negative CUS, a Tinaquant around and above 500 n
132 g/m L and persistent symptom ssuspected for DVT (moderate/high clinical score) are candidate for CUS testing
133 within one week toexclude or diagnose DVT or analternative diagnosis in the primary care setting. 9 . To safely
134 exclude DVT, a high sensitivity and NPV are needed to limit missed DVT cases. At the 500 n g/m L threshold,
135 the ELISA VIDAS assay did meet this criterion (table ??A) in contrast to the Tinaquant. For the Tinaquant
136 D-Dimer assay lower threshold are preferred for excluding DVT in the primary care setting (table ??B). We
137 emphasize that DVT should be diagnosed and excluded based on a non-in vasie strategy with an objective post-
138 test incidence of venous throm boembolism (VTE) of lessthan 0.1% with a negative predictive value of 99.5% to
139 99.9% during 3 months follow-up 10 .

140 Modification of the Wells score bye limination of the "minus 2 points" for AD is mandatory and will improve
141 the diagnostic accuracy of DVT suspicion significantly in the primary care setting and outpatient ward 4,5,10 .
142 The sequentialuse of complete DUS first, followed by ELISA D-Dimer testing and modified clinical Wells' score
143 assessment is safe and effective for the exclusion and diagnosis of DVT and AD.

144 6 III.

145 7 Introduction Postthrombotic

146 Syndrome: PTS

147 The postthrombotic syndrome (PTS) is a chronic condition that affects the deep venous system, and may
148 also extend to the superficial venous system of the legs in patients with a documented history of deep vein
149 thrombosis (DVT) [11][12][13] . Clinical symptoms of PTS may vary considerably and range from scarcely visible
150 skin changes to changes in pigmentation, pain, discomfort, venous ectasia, oedema, and ulceration. Patients
151 experience pain, heaviness, swelling, cramps, itching or tingling in the affected limb. Symptoms may be present
152 in various combinations and may be persistent or intermittent. Typically, symptoms are aggravated by standing
153 or walking and improve with resting, leg elevation and lying down. Next to varicose veins, a specific sign of
154 early forms of venous incompetence is the so-called corona phlebectatica para plantaris (ankle flare). There are
155 telangiectases surrounding the malleoli of the ankle. Other signs are oedema, hyperpigmentation, and eczema.
156 Signs of more advanced disease are dermatoto-and liposclerosis, a localized induration of the skin and sometimes
157 of the underlying tissues, with fibrosis and inflammation. Through microthrombi, an area of whitened skin with
158 reddish spots may occur, called atrophie blanche or white atrophy. The most severe sign is the venous leg ulcer,
159 a chronic wound that fails to heal spontaneously or within the time range of normal healing of the skin.

160 DVT has a recurrence rate of about 20% to 30% after 5 years, but the rate varies depending on the presence of
161 risk factors for thrombosis recurrence and particularly increases after discontinuation of prolonged anticoagulation
162 11 .The only clear identified risk factor for overt PTS is recurrent or ipsilateral DVT, which increases the risk of

163 PTS several fold ??1-13. In a prospective study of 313 consecutive DVT patients, Prandoni et al have shown that
164 Residual Vein Thrombosis (RVT) at any time post-DVT is a risk factor for recurrent VTE. In this study, DUS of
165 the common femoral and popliteal veins was performed at 3, 6, 12 24 and 36 months post DVT. The cumulative
166 incidence of RVT was 61%, 42%, 31%, and 26% at 6, 12, 24 and 36 months (1/2, 1, 2 and 3 years) post DVT
167 respectively. Of 58 VTE recurrent episodes, 41 occurred at time of RVT. The hazard ratio for recurrent VTE was
168 ???.4 with persistent RVT versus those with earlier complete vein renatalization2. The post-DVT recanalisation
169 process in patients with acute proximal DVT is completed between 3 months to 2 years, depending on the severity
170 of DVT and the presence or absence of transient or persistent risk factors for thrombosis recurrence and PTS.
171 This observation is in favor to extend anticoagulation at 6 months and 1 year post-DVT when RVT on DUS is
172 present in symptomatic PTS patients during follow-up for about 2 to 3 years or even life-long post-DVT.

173 The CEAP (Clinical-Etiology-Anatomic-Pathophysiologic) (table 5) for PTS is the best known and widely
174 used by phlebologists but not by clinicians or vascular medicine specialists 3 . In 1992, Prandoni developed
175 an original standardized scale for the assessment of PTS in post-DVT legs. Each subjective sign and objective
176 symptom was scored as 0, 1, 2 or 3 based on subjective judgement 13 . The 5 signs and 7 symptoms of the
177 Prandoni score are taken over by PTS investigators as the Villalta in the literature exactly as first designed by
178 prandoni for use in clinical practice (table 6) 11 . The original Prandoni (subjective Villalta) score of signs and
179 symptoms has never been evaluated against the objective CEAP scoring system as we proposed in table ?? . It is
180 mandatory to validate both the Prandoni (Villalta) scoring of signs and symptoms of early PTS in the modern
181 setting of PTS evaluation against objective scoring system in table 3 at 1, 3, 6 and 12 months up to 2 years
182 post-DVT. This statement is of particular interest, since literature data are convincing in showing that PTS is
183 present in about 50% one year post-DVT using the Villalta score as compared, and does not increase in frequency
184 and severity when under continuous medical care. Conclusion: the Prandoni scoring system is an ordered use of
185 CEAP clinical symptoms and signs (C&S) by internist without expert dermatological evaluation and objective
186 testing with CUS. Moreover this scoring system should be used at 1, 3, 6, 9 months and 1 years pos-DVT for the
187 assessment of disappearance or persistence of DVT symptoms and the appearance of mild, moderate and severe
188 PTS symptoms

189 8 V. Normal Versus Abnormal DUS at 3 Months Post-DVT

190 The study of Prandoni et al 14 have clearly demonstrated that about half of the DVT patients do not develop
191 PTS in the control group, and that compression therapy using medical elastic compression stockings (MECS)
192 decreases this incidence with 50% (from circa 50 to 25% indicating an absolute reduction rate of 25%) during an
193 observation and treatment period of 2 years following DVT. Family doctors, phlebologists and internists usually
194 treat the acute phase of DVT with anticoagulants for at least 3 to 6 months 1-4 . Physicians with interest and
195 expertise in phlebology are usually confronted much later and frequently too late with overt post-thrombotic
196 complications of DVT [11][12][13][14] .

197 In the study of Siragusa et al 15 follow-up was 1.3% (95% CI, 1-7%, B in figure ??). The proportion of provoked
198 vs unprovoked DVT was 64% and 36% indicating that this distinction is artificial in terms of risk assessment.
199 The group of 180 DVT patients with residual venous thrombosis (with no or partial recanalization on DUS) were
200 randomized to stop anticoagulation at 3 months post-DVT (N=92) or to continue anticoagulant for 9 additional
201 months and discontinued 12 months post-DVT. During follow-up from the time of anticoagulation discontinuation
202 recurrent VTE events started to occur in 25 of 92 = 15, 2% person-years who discontinued anticoagulation at 3
203 months post-DVT (A1 in figure) and in 17 of 88 patients = 1.1% person-years who discontinued anticoagulation
204 at 12 months post-DVT (A2 in figure ??). Very interestingly, the proportion of provoked vs unprovoked DVT in
205 patient with RVO (incomplete recanalization) at 3 months post-DVT was 23% vs 77% again indicating that this
206 distinction is artificial in terms of risk on DVT recurrence.

207 Figure ?? : Discontinuation of anticoagulation at 3 months post-DVT in DVT patients with rapid
208 recanalization of leg veins within 90 days (3 months, N=78) is followed by a very low DVT recurrence rate
209 B). In patients with residual vein occlusion on DUS at 3 months post-DVT discontinuation of anticoagulation
210 at 3 months (A2, N=92) or at 12 months DVT (A1, N=88) is followed by increased VTE recurrence rate 15
211 These two prospective studies demonstrate that half of the patients with a first DVT do not need therapy with
212 MECS in cases with rapid complete recanalization and no PTS at 3 months post-DVT obviating the need of
213 anticoagulant treatment at 6 months post-DVT ??4,15. Early mobilisation of the patient, adequate anticoagulant
214 therapy and immediate compression treatment with MECS reduces the chance to develop PTS significantly. In
215 the prospective study of 313 consecutive DVT patients, the cumulative incidence of normal DUS (no RVT)
216 was 39%, 58%, 69% and 74% at 6, 12, 24 and 36 months post DVT respectively. About one quarter of DVT
217 patients had RVO at time point 3 years post-DVT 12 . Of 58 VTE recurrent episodes, 41 occurred at time of
218 RVT. The hazard ratio for recurrent VTE was 2.4 with persistent RVO versus those with earlier complete vein
219 renatalization 12 . In view of this, three subsequent yet unanswered questions in the treatment of DVT are 13
220 VI. Rapid Versus Delayed Recanalization Related to Reflux in Post-DVT Patients Predict PTS Phlebologists
221 generally distinguish two main types of PTS 13 . 1. The reflux type (circa 90%) 2. The obstruction type (circa
222 10%) In a substantial number of patients only partial re-canalisation (=residual venous occlusion: RVO) occurs
223 as opposed to complete obstruction or nearly complete obstruction. In the prospective study of Prandoni et al
224 the cumulative incidence of complete recanalization was 39%, 58%, 69%, and 74% at 6, 12, 24 and 36 months

225 (1/2, 1, 2 and 3 years) post DVT respectively 12 . Sequential DUS imaging can easily assess this. DVT patients
226 with complete re-canalisation (no RVO) can be divided in two groups 3 : 1. Those with functional (intact)
227 vein valves 2. Those with dysfunctional vein valves Dysfunctional vein valves result in reflux and ultimately
228 in increased venous pressure, which is the main hemodynamic determinant of symptomatic PTS in need for
229 MECS and extended anticoagulation. Asymptomatic post-DVT patients with complete recanalisation but with
230 no reflux or compensated reflux (low risk DVT recurrence) might be candidates for discontinuation of MECS
231 therapy within the period of 2 years 13 .

232 Meissner et al studied the relationship between time to complete recanalization post-DVT (lysis time) and the
233 development of reflux in patients with a first episode of DVT at 3 months interval during the first year (figure ??)
234 16 . Duplex criteria for complete occlusion were defined as the absence of detectable flow, either spontaneous or
235 with augmentation, in an incompressible venous segment. Partial occlusion was defined as normal or diminished
236 flow, either spontaneous or with augmentation, in an incompletely compressible venous segment. Complete
237 lysis (recanalization) was presumed to have occurred when spontaneous phasic flow returned and the vein was
238 completely compressible 16 . For the posterior tibial veins (PTV), flow detected after distal augmentation in
239 a completely compressible vein is accepted as evidence of complete recanalization (lysis). The median time
240 from DVT to complete recanalization (lysis time) was about 3 months (100 days) for patients without reflux
241 in all segments (figure 3). In contrast, the median time from DVT to complete recanalization (lysis time) of
242 all segments was about 9 to 12 months (more than 6 months) for DVT patients who developed reflux as the
243 main determinant of symptomatic PTS (figure ??). As shown in figure 2, loss of valve competence leading to
244 ambulatory venous hypertension (AVP) and diversion of venous flow through incompetent perforator veins appear
245 to play an important role in the development of late complications of PTS. In the study of 123 legs with DVT
246 (107 patients) by Markel et al about two third of the involved legs had developed valve incompetence (figure 7)
247 17 . The distribution of reflux at the end of the first year follow-up in this study was the following: popliteal vein,
248 58%, femoral vein, 37%, greater saphenous vein, 25% and posterior tibial vein, 18%. Reflux appeared to be more
249 frequent in the segments previously affected by DVT (figure 7) 17 . The data of the DVT-LYSIS reflux studies in
250 figures 3 and 4 will predict that discontinuation of anticoagulation at 3 months post-DVT in DVT patients with
251 rapid recanalization of leg veins within 90 days (3 months, N=78 figure ??) will be followed by a very low DVT
252 recurrence rate B). In patients with delayed recanalization at 6 to 12 months DVT discontinuation are at high
253 risk for reflux and PTS development and therefore candidates for continuation of MECS and anticoagulation for
254 at least 1 to 2 years. In the Maastricht study 18 , 125 consecutive DVT patients with confirmed proximal DVT
255 (22% had a history of previous VTE) were followed for 2 years using the Vilalta clinical scores on four consecutive
256 visits; 3, 6, 12, and 24 months post-DVT. After 6 months, patients with allowed to discontinue MECS therapy.
257 If reflux was discontinue MECS therapy. Accordingly, MECS therapy was discontinued in 17% of patients at 6
258 months, in 48% at 12 months, and in 50% at 24 months. Reflux on CUS was present in 74 of 101 (73.3%) tested
259 patients. Reflux alone was not determinative for the prediction of PTS. The cumulative incidence of PTS was
260 13.3% at 6 months, 17.0% at 12 months, and 21.1% at 24 months. Varicosis or venous insufficiency (present in
261 11% at baseline) was significantly associated with PTS; hazard ratio 3.2 (1.2-9.1). In this study patients with
262 a low probability for developing PTS can be identified as early as 6 months post-DVT ??9,20. Individualized
263 shortened duration of MECS therapy in post-DVT patients with no or asymptomatic reflux on Vilalta clinical
264 scores seems to be a safe management option. o Global Journal of DUS at 6 months post-DVT in unprovoked
265 DVT and DVT recurrence rate after discontinuation of anticoagulation is not predictive for DVT recurrence.

266 In a post-hoc analysis in a selected large group of 452 patients with unprovoked DVT (table ??), Le Gal et
267 al performed DUS at time point 6 months if the post-DVT patient had signs or symptoms at time point 5 to
268 7 months post-DVT when oral anticoagulation (OAT) was stopped19. In the study of Le Gal et al 184 of 452
269 (46%) had overt PTS with any hyperpigmentation (=CEAP >4), edema (CEAP >3) or redness in either leg
270 (table ??).

271 Recanalization on DUS was complete in 220 and abnormal in 231 with minimal wall thickening in 11, partial
272 thrombus resolution in 78 and minimal thrombus resolution (obstruction) in 23 and missing data in 67, but reflux
273 was not measured. During follow-up off OAT 45 of 231 with abnormal CUS (19.5%) and 32 out of 220 patients
274 (14.6%) with normal DUS (complete recanalization) had recurrent VTE (figure 8) 19 .

275 Table ?? : Baseline characteristic of 452 patients with unprovoked DVT at time point 6 months post-DVT at
276 time of discontinuation of anticoagulation 19 . D-dimer abpve the upper limit of normal after discontinuation
277 surely belong to the group of symptomatic post-DVT patients at high risk to develop PTS. In the prolong study,
278 extended anticoagulation in post-DVT patients with increased D-dimer reduced the risk of DVT recurrence from
279 11% patient/years to less than 2% patient/years, whereas the incidence of DVT recurrence was still increased,
280 4.4% patient/years, in post-DVT patients with a normal D-dimer on month after discontinuation of regular
281 anticoagulation 20 . This may implicate that DVT recurrence in those patients with either a normal or increased
282 D-dimer very likely do occur in those with incomplete or complete RVT after 6 months. Reflux was not measured
283 in this study.

284 As the extension of the PROLONG study Palareti performed the DULCIS (D-dimer and ultrasound in
285 combination Italian Study) to establish the optimal duration of anticoagulation for VTE in 988 evaluable DVT
286 patients with a first unprovoked DVT 21 . After at least 3 months of anticoagulation D-dimer was measured
287 and DUS performed to measure residual venous thrombosis (RVT <4 mm) and followed according two main

288 strategies. First, if the D-dimer level was below age and gender specific cut-off for each of the different D-dimer
289 assay used, anticoagulation was stopped and D-dimer levels were reassessed at 15, 30, 60 and 90 days. If at time
290 of at least 6 months post-DVT the D-dimer remained below the cut-off, anticoagulation was definitely stopped
291 and patients were followed up for 2 years. In 506 (51%) of the 988 analyzed patients all Ddimer were below the
292 cut-off in the 3 months (90 days) after stopping anticoagulation. The incidence of VTE was 2.8%, distal DVT
293 1.1% and superficial venous thrombosis (SVT) in 2.3% patient/years. Second, if one of the D-dimer levels was
294 above the cut-off in the period of 3 month (90 days) after discontinuation anticoagulation was resumed. This
295 cohort 373 patients with increased D-dimer levels above the age and gender adjusted cut-off levels received oral
296 anticoagulation for 2 years follow-up and only 4 VTE events (0.7% patient/years) were observed at the cost of
297 14 major bleedings (2.3% patients/years) 21 . In a third cohort 109 patients (11% patient/years) with at least
298 one D-dimer measurement above cut-off, who refused oral anticoagulation treatment the incidence of major VTE
299 was 8.8%, and distal DVT or SVT 2.3% patient/years.

300 9 VII.

301 10 DVT and PTS Bridging the Gap

302 In view of the proposed concept in figure ??, complete recanalization within 1 to 3 months and no reflux is
303 predicted to be associated with no PTS obviating the need of anticoagulation and MECS at 6 months post-DVT.
304 Delayed incomplete or complete recanalization at 6 to 12 months post-DVT is associated with a high risk of
305 DVY recurrence as the cause of PTS and usually complicated by reflux due to valve should be anticoagulated
306 for 2 years and are to be considered for extended or even life-long anticoagulation with VKA or NOAC 13 . As
307 prevention of DVT recurrence as the best option to prevent the occurrence and progression of PTS. Michiels
308 &Moosdorff started in 2012 a pilot study to test the feasibility of a multicenter prospective management and
309 safety outcome study to further improve the proposed concept in figures 9 and 10 in the primary care setting.
310 destruction, thereby indicating the need to extend anticoagulant treatment and wearing MECS. Patients with
311 delayed but complete recanalization with reflux or without RVT but no PTS at 6 to 12 months post-DVT while
312 wearing MECS are candidates for extended anticoagulation for about one year and to be reevaluated at time
point one year post-DVT according to the PROLONG and DULCIS strategy (figures 9 and 10) 13,20,21 ¹



Ultrasound

Figure 1: Duplex Ultrasound ,

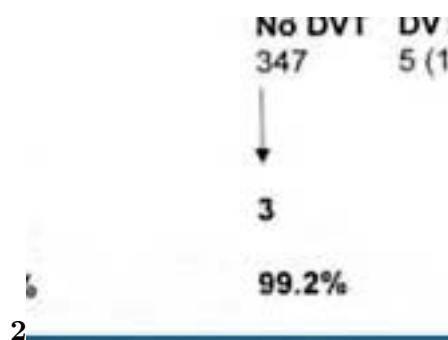


Figure 2: Figure 2 A

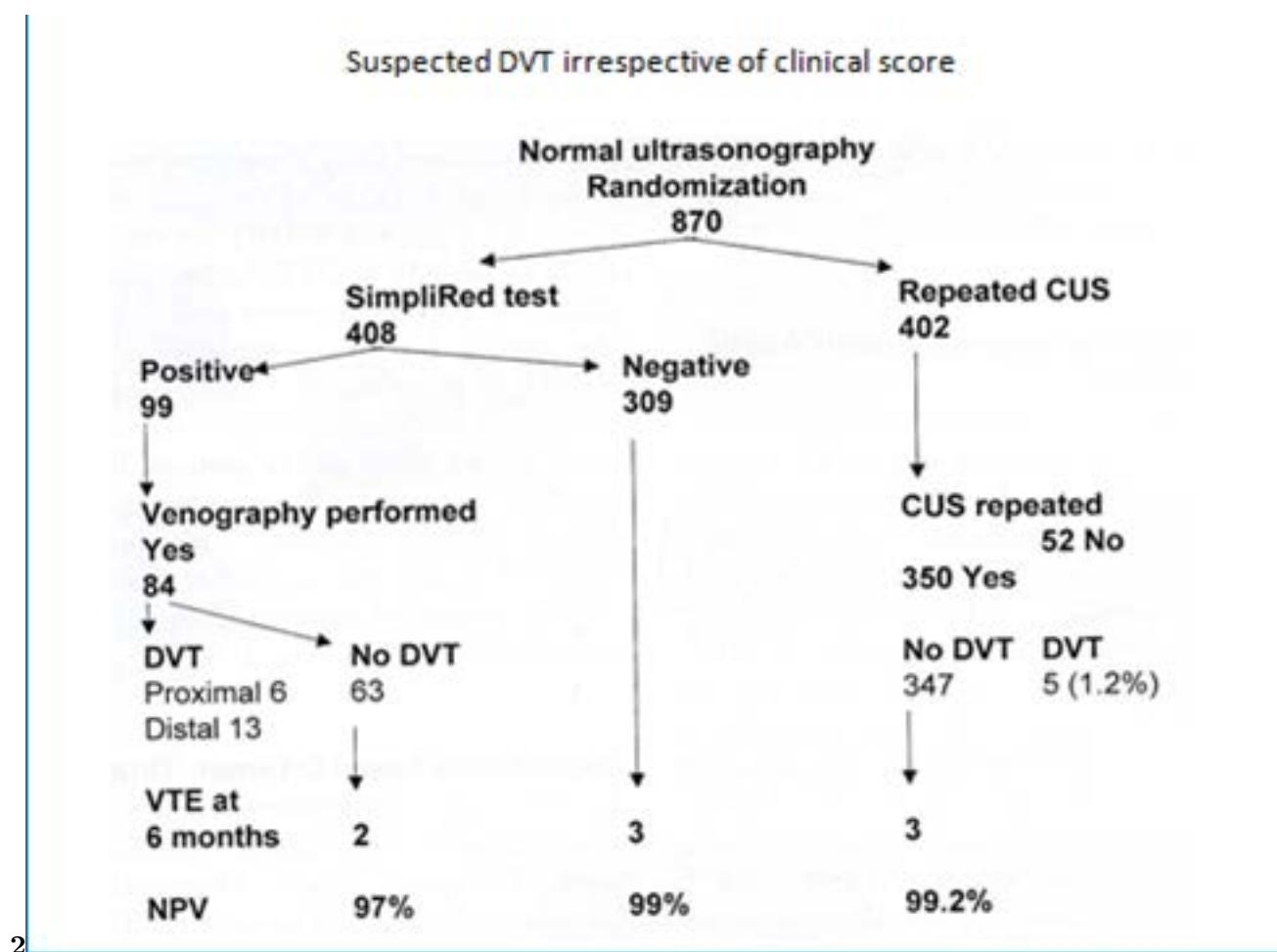


Figure 3: Figure 2 B

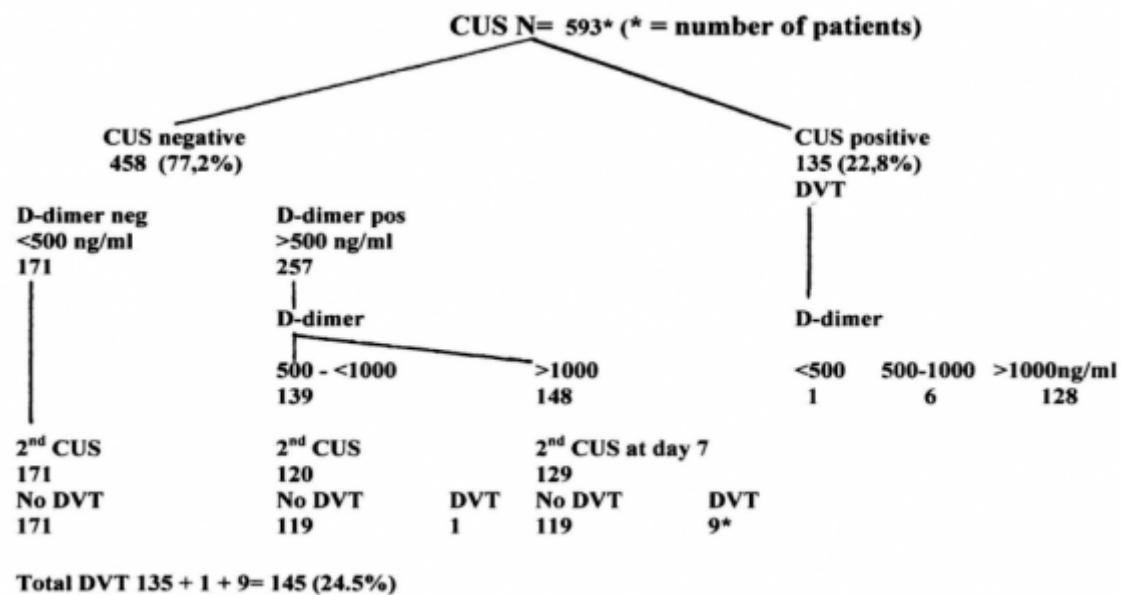
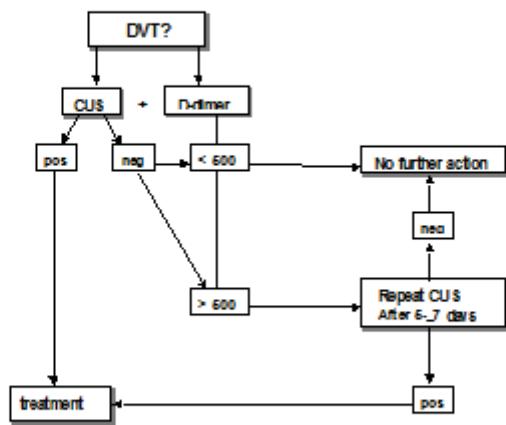


Figure 4: Figure 3 :

Diagnostic strategy: CUS and ELISAD-Dimer



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Figure 5: Figure 4 :

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Figure 6: Table 4 A

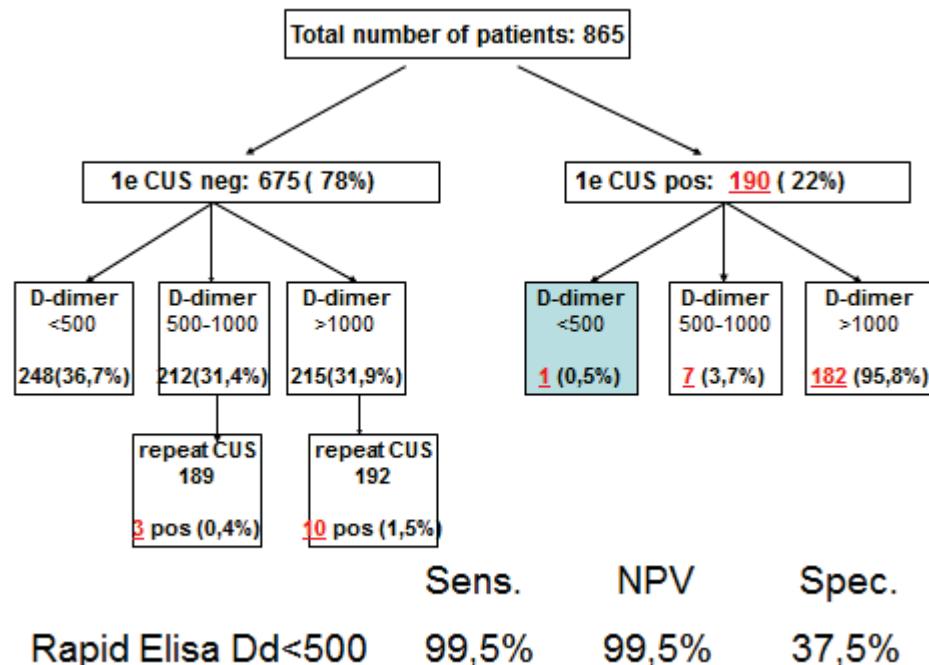


Figure 7:

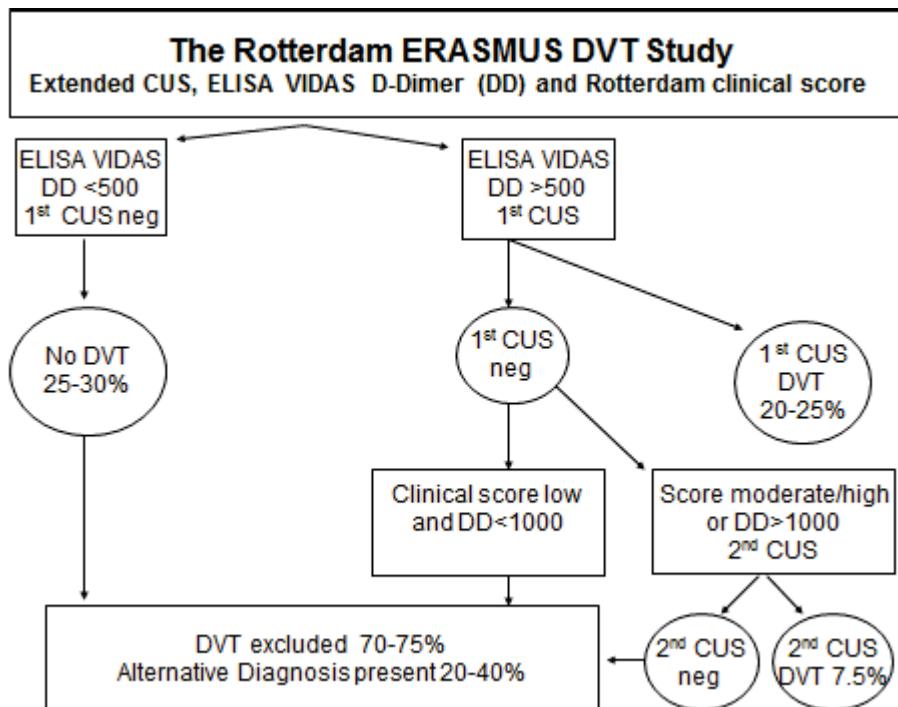


Figure 8:

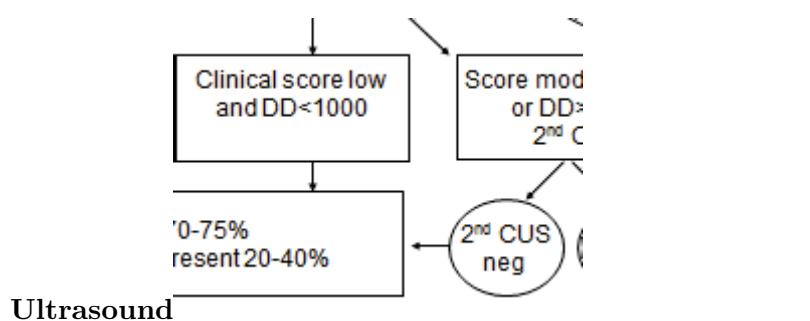
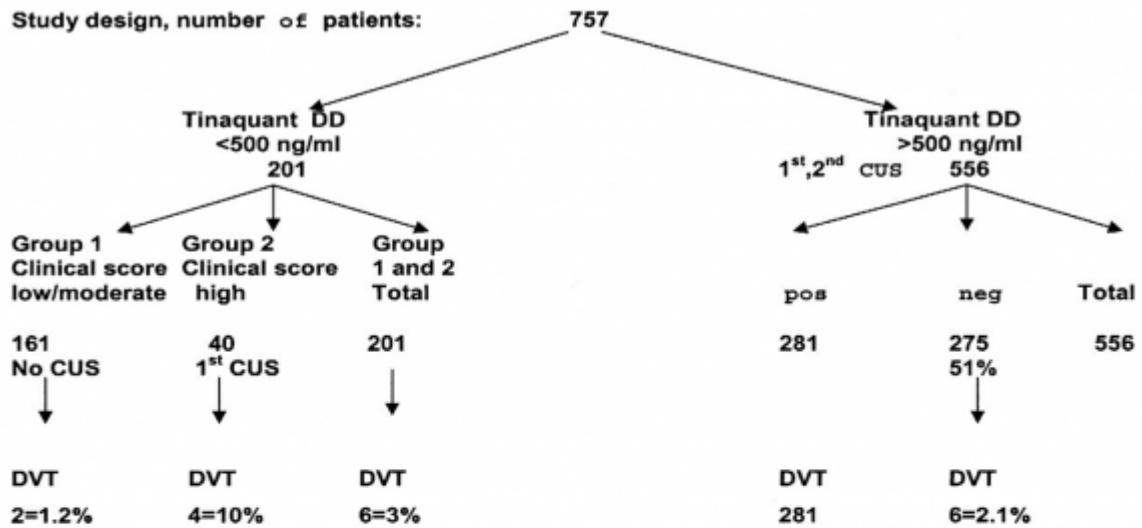


Figure 9: Duplex Ultrasound ,



Prevalence of DVT 39% (293/757).

Sensitivity of 97,8%, Specificity of 42% and a Negative Predictive Value of 97%, which is not high enough for the exclusion of DVT by a negative Tinaquant test alone.

Group 1 with low to moderate clinical score NPV 98.8% at a specificity of 28%.

Group 2 with high clinical score: 4 patients out of 40 had DVT at presentation (10%) and one pulmonary embolism was reported during follow-up.

Serial CUS negative predictive value 97.9%.

Ultrasound6

Figure 10: Duplex Ultrasound ,Figure 6 :

D-dimer cut-off value (ng/ml)	DVT absent*	DVT present*	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)
100	5	1	99	1	83
200	23	1	99 (96 - 100)	6 (4 - 9)	96 (79 - 100)
300	47	1	99 (96 - 100)	13 (10 - 17)	99 (89 - 100)
400	69	1	99 (96 - 100)	19 (15 - 23)	99 (92 - 100)
500	103	1	99 (96 - 100)	29 (24 - 34)	99 (95 - 100)
600	123	2	97	34	98
700	141	2	97	39	99
800	156	2	97 (93 - 100)	44 (38 - 49)	99 (96 - 100)
900	173	3	96	48	98
1000	199	8	88	56	96
1100	220	8	88	62	97
1200	241	9	87	67	96
1300	254	10	85	71	96
1400	264	10	85	74	96
1500	277	11	84	77	96
all patients	358	67			

7

Figure 11: Figure 7 :

D-dimer cut-off value (ng/ml)	DVT absent*	DVT present*	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)
100	24	1	99	7	96
200	68	2	98 (95 - 100)	21 (16 - 25)	97 (95 - 100)
300	109	5	95 (90 - 99)	33 (28 - 38)	96 (90 - 99)
400	136	6	94 (89 - 99)	41 (36 - 47)	96 (94 - 98)
500	167	9	91 (85 - 97)	51 (45 - 56)	95 (91 - 98)
600	189	11	89	57	95
700	202	12	88	61	94
800	216	14	84 (76 - 91)	65 (60 - 70)	93 (89 - 96)
900	220	19	80	67	92
1000	227	22	77	69	91
1100	230	23	76	70	91
1200	235	24	75	71	91
1300	244	27	72	74	90
1400	251	28	71	76	90
1500	258	29	70	78	90
Ultrasound all patients	330	97			

Figure 12: Duplex Ultrasound ,

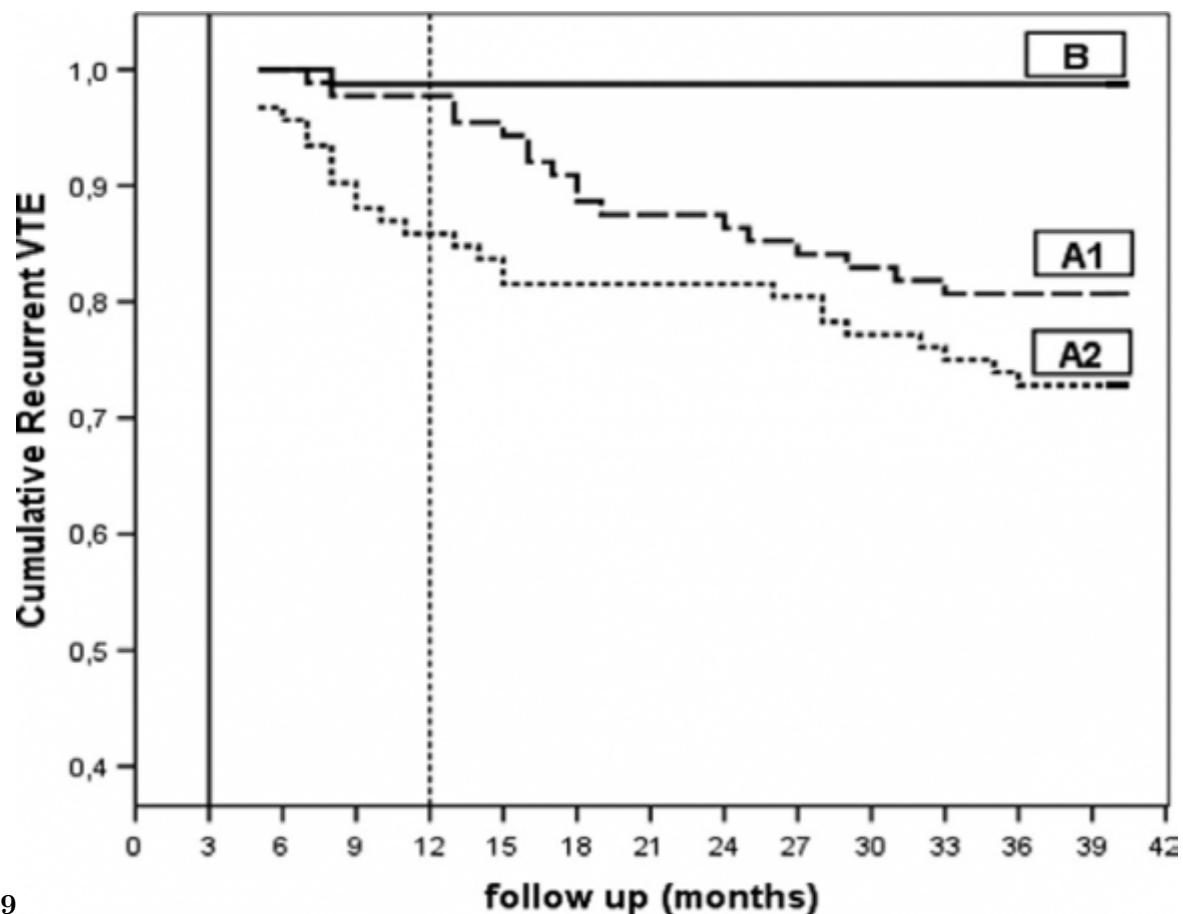
96	48	8
88	56	8
88	62	8
87	67	8
85	71	8
85	74	8
84	77	8

8

Figure 13: Figure 8 :

DVT absent*	DVT present*	Sensitivity (95% CI)
24	1	99
68	2	98 (95 - 100)
109	5	95 (90 - 99)
136	6	94 (89 - 99)
167	9	91 (85 - 97)
189	11	89
202	12	88

Figure 14: Duplex Ultrasound ,



9

Figure 15: Figure 9 :

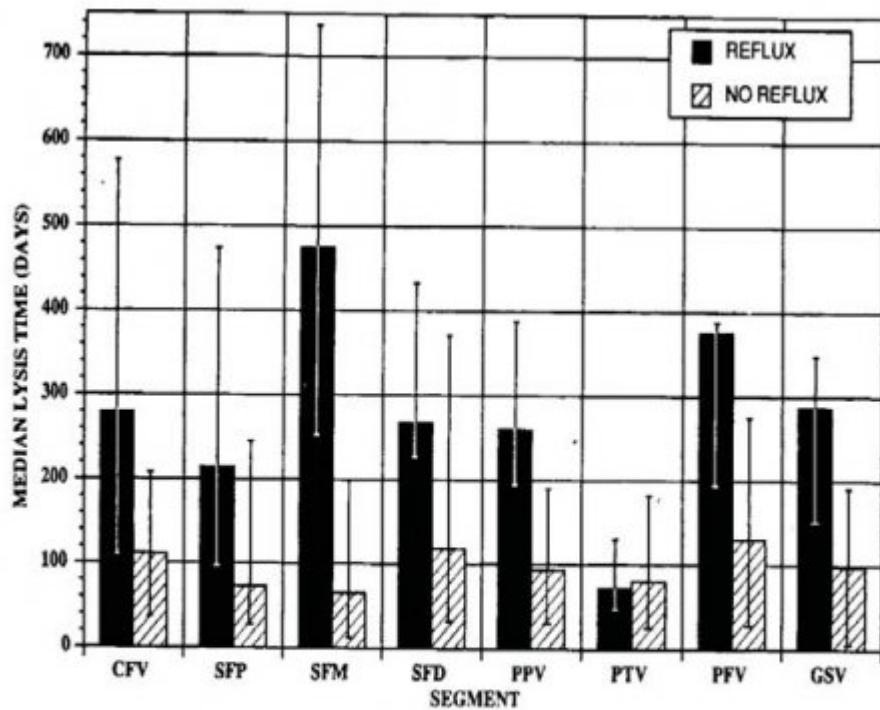


Fig. 1. Median time from thrombosis to recanalization for all segments (lysis time), grouped according to reflux status at last visit. *Error bars* show interquartile range (25th to 75th percentile).

10

Figure 16: Figure 10 :

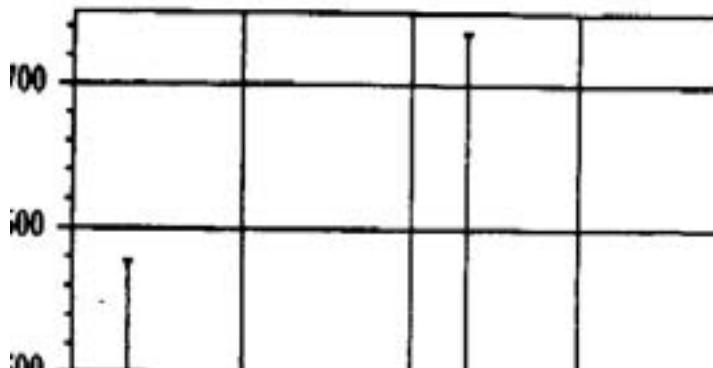


Figure 17:

1

Number	%
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Figure 18: Table 1 : Characteristics of 1668 patients with a first deep vein thrombosis (DVT) subdivided in calf vein 203 (17%), polpiteal vein 498 (41%) and femoral politieel 502 (42%) Search for new risk factors First DVT anno 2012 Tick et al JTH 2008 Main Characteristics: Risk factors for 1 st DVT

[Note: II. Clinical Features and Diagnosis of]

Figure 19: Thrombophilia FV Leiden & FII 20210 25 Conclusion from Tick et al JTH 2008;6:2075-2081 Change from Surgery, Malignancy & Immobilization (primary VTE prevention) to Minor Injury, Plaster Cast and OAC (no primary VTE prevention) as eliciting factors for 1 st DVT. Michiels 2012 Lecture World IUA Congress Prague

5

C Classification	Symptom
Clinical: C	
C0 asymptomatic	No visible varicose veins

Figure 20: Table 5 A

6

	months post-DVT up to 2 years post-DVT 13	All belong to
5 Subjective symptoms: Identical to S of CEAP 7 Objective sign :		
C of CEAP 15		
Heaviness of the foot/leg	Pretibial oedema	C3
Pain in calf/thigh	Induration of the skin	C4
Cramps in calf/thigh	Hyperpigmentation	C4
Pruritus	New venous ectasia	C2
Paraesthesia	Redness	
Pain during calf compression (post DVT)		
Ulceration of the skin	C5, C6	
sign or symptom is graded with as 1, 2, or 3. (1 = mild, 2 = moderate, 3 = severe). Ulceration of the skin 4 points		
The presence leg ulcer is a late complication of PTS consistent with severe CVI, CEAP 5, 6.		
Definition of clinical post-tromb ic syndrome according to Prandoni (Villalta)		
Absent:	score <5	
Mild-to-moderate:	score between 5 and 10 and 10 to 15 respectively	
Severe:	score >15 at 2 consecutive occasions	
Source: Pesavento R, Prandoni P. Phlebology Digest 2007;20:4-8		

Figure 21: Table 6 :

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