Deep vein thrombosis : diagnostic and prognostic challenges

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Disease prevalence dependent failure rate in diagnostic management studies in suspected deep vein thrombosis: communication from the SSC of the ISTH

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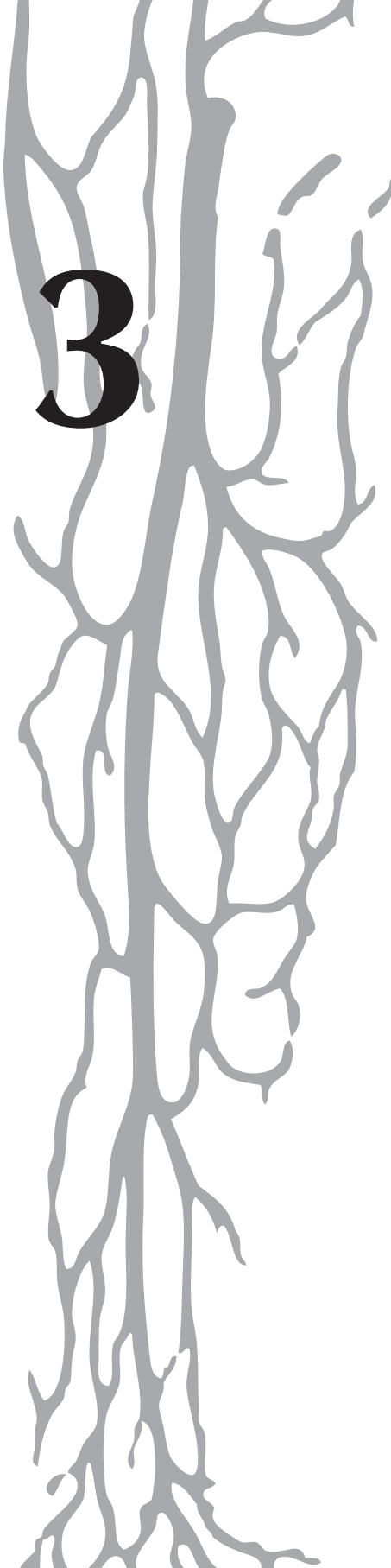

INTRODUCTION

Objective diagnosis of deep vein thrombosis (DVT) is important, because untreated DVT is associated with a high risk of acute pulmonary embolism and post-thrombotic syndrome. As it is impossible to diagnose DVT on the basis of clinical symptoms or laboratory tests alone, objective imaging testing is needed to confirm or refute the diagnosis. The favoured strategy for the diagnostic management of suspected first DVT is the combination of pre-test probability assessment, D-dimer testing and (serial) compression ultrasound (CUS).[1] Recently, several new diagnostic tests have been suggested, such as a higher D-dimer threshold of <1.0 µg/ml if there is a low clinical probability, computed tomography-venography if it is impossible to perform CUS, and magnetic resonance direct thrombus imaging (MRDTI) for the diagnosis of ipsilateral recurrent DVT.[2]

Notably, because contrast venography is still the reference for diagnosing DVT, current guidelines state that the standard against which all DVT diagnostic management studies should be evaluated is the percentage of patients with a venous thromboembolism (VTE) during 3 months of follow-up despite a normal venography finding, to ensure that new diagnostic tests or algorithms are tested against the reference standard.[1] This failure rate has been shown to be 1.3% (upper limit 95% confidence interval [CI] 4.4%) in a study evaluating 160 consecutive patients with suspected acute DVT and a negative venography finding.[3] Importantly, the threshold for doctors to suspect DVT and initiate diagnostic testing has lowered over the past few years. This trend is probably attributable to better awareness of the disease, and the availability of non-invasive CUS as an alternative to venography. This trend has been shown for suspected PE as well.[4] This lower diagnostic threshold has led to a sharp decrease in DVT prevalence in examined patients in recent studies, to even below 10%.[5] Bayes' theorem states that disease prevalence (the pre-test probability of having the disease) and failure rate (the post-test probability of having the disease) are related. This implies that, because the disease prevalence has decreased over the past few years, the diagnostic standard of diagnostic management studies should be changed accordingly.[6] In analogy to the SSC communication entitled: 'Towards a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: communication from the SSC of the ISTH,[4] the purpose of this ISTH SSC communication was to evaluate the association of DVT prevalence and diagnostic failure rate in published studies on diagnosis of DVT, in order to propose a new diagnostic safety threshold for future studies on the diagnostic management of suspected DVT.

METHODS

This systematic review and meta-analysis was performed in accordance with the PRISMA criteria.[7] All parts of the systematic review were performed by two independent reviewers (C.D. and Y.E.), disagreements were resolved by an additional reviewer (F.K.). A literature search of Pubmed, Embase, Web of Science, Cochrane and Cohchrane central register of controlled trials (central) was performed on 29 February 2016 with the aim to find all high-quality diagnostic studies in acute DVT from 1990 on. First, all references were screened by title and abstract. After exclusion of non-relevant studies, full-text articles were analysed for eligibility before final study selection. Study selection criteria were: 1) prospective study design, 2) pre-specified study protocol, 3) clear description of inclusion and exclusion criteria, 4) inclusion of >100 consecutive patients, 5) at least 3 months of follow-up, 6) <5% lost to follow-up, and 7) use of an appropriate diagnostic standard. The last of these was defined as: (an algorithm consisting of) a validated clinical decision rule combined with a highly sensitive D-dimer test, venography, and whole leg CUS or serial proximal CUS. In both CUS strategies, the lack of compressibility of a venous segment under the ultrasound probe was diagnostic for DVT. In case of suspected recurrent DVT, a non-compressible previously normalized vein or the enlargement of a residual thrombus diameter of ≥2 mm as compared with the previous CUS assessment was diagnostic for recurrent DVT.[8] To avoid risk of bias, only studies meeting all criteria were included in this meta-analysis. From each selected study, the following information was extracted: 1) year of publication, 2) total number of included patients, 3) diagnostic test or algorithm, 4) focus on proximal DVT only or also distal DVT 5) DVT prevalence at baseline and 6) failure rate defined by the incidence of patients with VTE despite a negative test during 3-month follow-up. Two graphs were plotted: one with year of publication versus DVT prevalence, the second with DVT prevalence versus failure rate. Reference lines with 95% confidence intervals, adjusted for number of patients included in the studies were calculated by the use of least squares linear regression analysis. The formula of this reference line was predefined as being the most accurate safety threshold for future studies. Primary analysis was based on studies with a 3-month follow-up period. A sensitivity analysis was performed that included studies with longer follow-up periods and studies restricted to proximal DVT. Statistical analyses were performed using SPSS version 23 (IBM, Armonk, NY, USA) and Stata 14.0 (Stata Corp., college Station, TX, USA).

FINDINGS

After the literature search, 1034 potentially relevant studies were identified and screened for eligibility. Seven hundred and nineteen studies were excluded after title and abstract screening, leaving 315 studies for full text evaluation. Finally, 51 studies were included, of which 46 had a follow-up period of exactly 3 months and were selected for the primary analysis. Study selection flowchart and reasons for exclusion are shown in **Appendix I**. Study characteristics and extracted information is summarized in **Appendix II**. The selected studies included a total of 28.145 patients, with a mean baseline DVT prevalence of 20% (95%CI 19.9-20.1, range 5.7-47%) and a failure rate of 0.80% (95%CI 0.79-0.81, range 0-2.8%). The reference line of the graph plotting DVT prevalence versus year of publication showed a decrease in DVT prevalence over the years, with a 2.65% decrease per 5 years, according to the formula: Y=27.95-0.53*x (R^2 0.066, p<0.001; **Fig.1a**). The second graph demonstrates that the mean failure rate increased with higher disease prevalence in individual studies with an absolute 1.0% higher DVT prevalence leading to a mean 0.026 percentage points increase in failure rate per 1% increase in prevalence, according to the formula 0.28 + 0.026*x (R^2 0.195, p<0.001; **Fig.1b**). The number 0.28 in this formula indicates the 3-month VTE incidence in a virtual, extrapolated study with 0% DVT prevalence at baseline (which is the cross-point of the reference line with the y-axis). The upper limit of the 95% CI of this regression line resulted in the formula: 1.25 + 0.026*x. The sensitivity analysis, including five additional studies with follow-up beyond the first 3 months and the one limited to studies analysing proximal DVT only, indicated comparable study outcomes (formulas 0.45 +0.02*x and 0.46+0.02*x respectively).

RECOMMENDATIONS

A DVT prevalence-dependent, diagnostic safety threshold should be considered for future diagnostic studies. Our systematic review and meta-analysis of high-quality DVT diagnostic management studies shows that the failure rate increases with 0.03 points per percentage point higher disease prevalence. We suggest that the formula with this regression coefficient of 0.03 combined with a baseline DVT prevalence of 1.25% should be used as diagnostic standard, based on the upper limit of the 95% confidence interval of our pooled analysis. We suggest that all future studies incorporate this formula in their power-analysis to prevent new diagnostic tests being evaluated in underpowered studies that do not allow for sufficient validation. For a power calculation example, we refer to our previous SSC communication.[4]

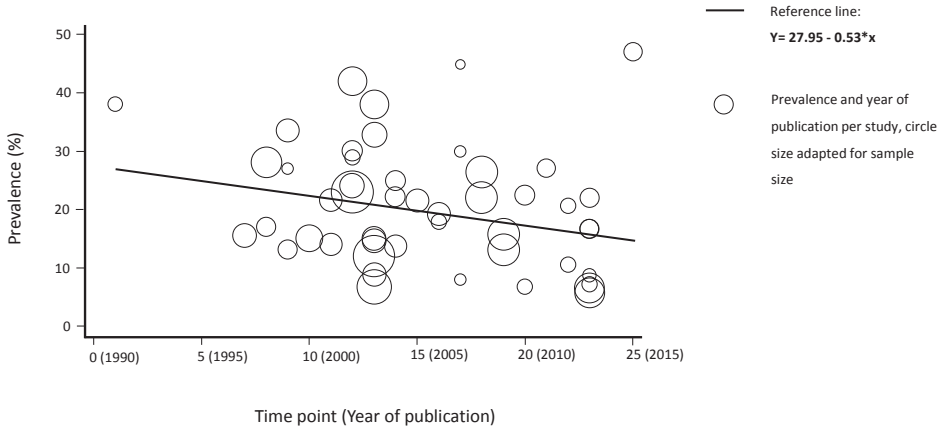

Figure 1a. Decrease of disease prevalence over the last years

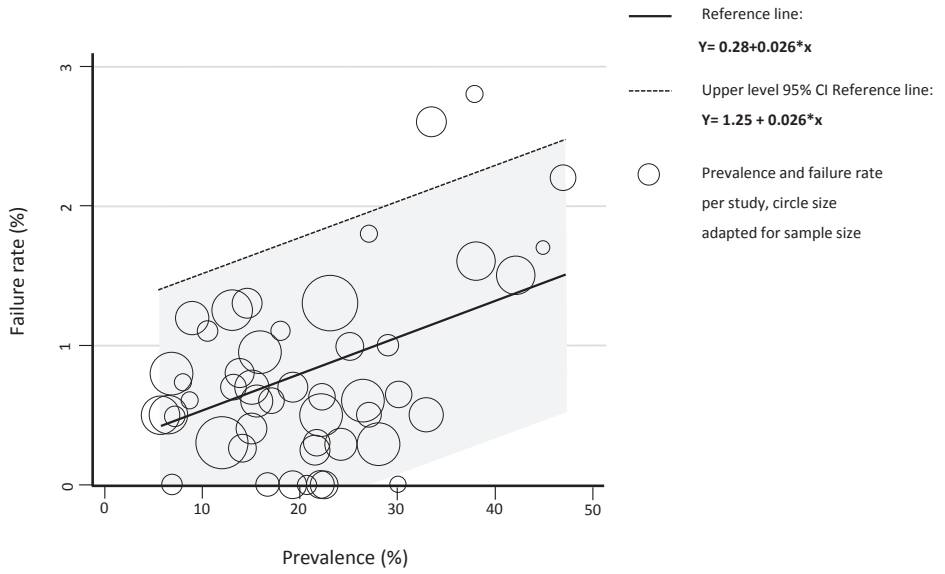

Figure 1b. Prevalence versus failure rate in high quality deep vein thrombosis diagnostic management studies. Grey area depicts the 95% confidence interval of the reference line.

DISCUSSION

This study confirms the decreasing baseline disease prevalence of DVT diagnostic management studies over the last years. We suggest incorporation of the DVT prevalence-dependent diagnostic safety threshold in all future diagnostic studies. The formula is, for example, also applicable to studies including patients with a higher a-priori risk of VTE, such as patients with cancer or previous VTE, mainly due to the fact that these patients

were well represented in the studies included in the meta-analysis and the adaptation of the accepted failure rate to this higher a-priori risk. Of note, the proposed diagnostic safety threshold in this study is not meant to be used in clinical practice, but merely as guidance for planning of future diagnostic studies. Notably, when using diagnostic tests in clinical practice, it is important to keep in mind that the diagnostic indices of tests may differ in specific patient groups. It was, for instance, shown that both sensitivity and specificity of the Wells rule variables differ in patients with cancer, which can lead to a higher rate of false negative test results in such patients.[9] Ideally, this phenomenon should be acknowledged in the design and reporting of (future) diagnostic studies by investigating diagnostic accuracy across different subgroups, where appropriate. Besides a proper safety threshold, it is also important to take the lower costs and/or lower risk of potential harms of a new test into account before its implementation. Even so, a relevant loss of sensitivity of a new diagnostic test does not easily weigh up against potential economic benefits. In conclusion, we propose a new diagnostic safety threshold for future DVT diagnostic management studies, in which the threshold is adjusted for the expected disease prevalence of the study population.

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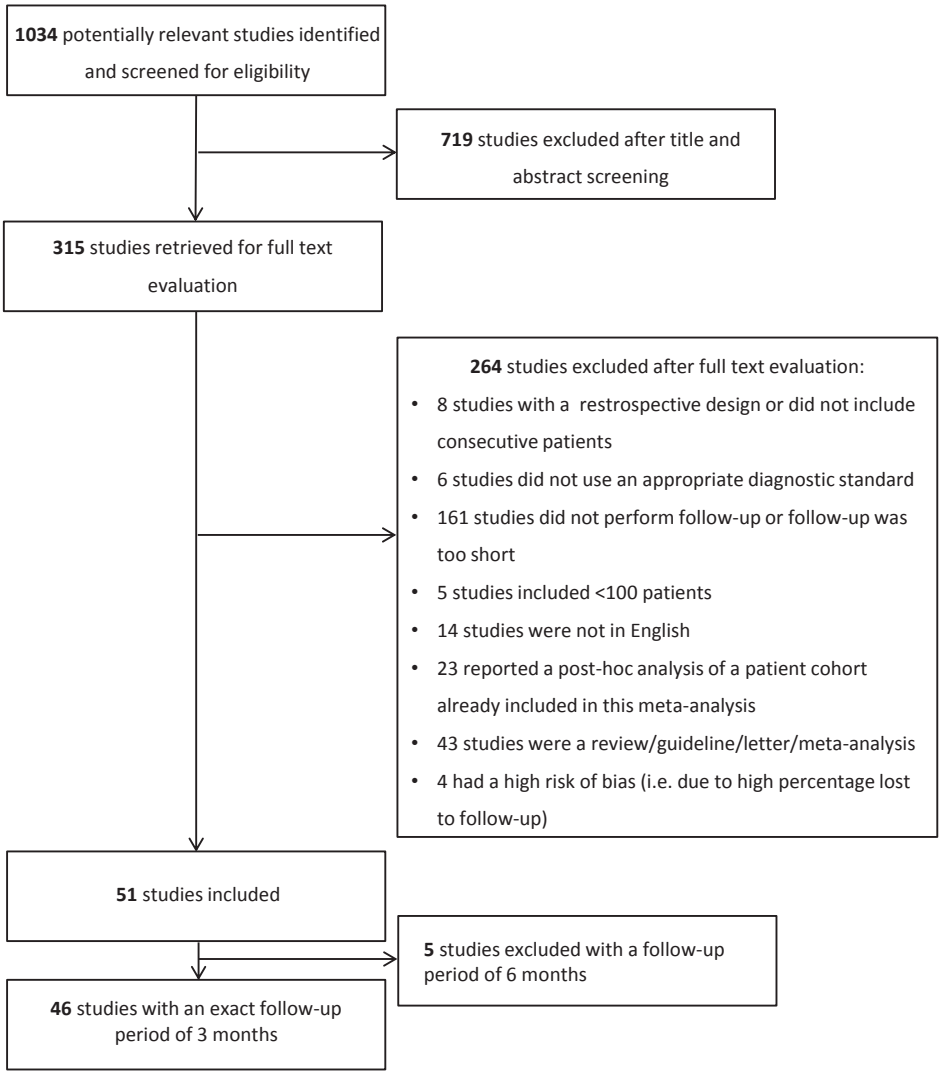

Appendix I. Flowchart of study selection

Appendix II.

Author	Year of publication	Diagnostic tests/ algorithm	Only proximal thrombosis	Follow-up (months)	Number of patients	Disease prevalence at baseline (%)	Failure rate (%)
Aguilar[1]	2007	Wells rule, D-dimer, (serial) proximal CUS	yes	3	105	44.8	1.7
Anderson[2]	1999	CDR, (serial)proximal CUS, venography	no	3	344	13.1	0.7
Anderson[3]	2003	CDR, (serial) proximal CUS, venography	no	3	1109	17.9	0.79
Bates[4]	2003	Wells rule, D-dimer, (serial) proximal CUS	yes	3	556	8.9	1.2
Bernardi[5]	1998	CUS, D-dimer test=> positive: serial proximal CUS	yes	3	946	28	0.4
Bernardi[6]	2008	Randomisation between D-dimer + serial proximal CUS and whole leg CUS	no	3	2098 (1045/1053)	22.1/26.4	0.9/1.2
Birdwell [7]	1998	(Serial) proximal CUS + venography to confirm DVT	no	3	405	17	0.6
Birdwell[8]	2000	(Serial) proximal CUS + venography to confirm DVT	no	3	709	15	0.7
Büller[9]	2009	CDR, D-dimer, US	yes	3	1002	13	1.25
Chan[10]	2007	(Serial) CUS	no	3	149	8	0.73
Chan[11]	2010	(Serial)CUS	no	3	249	6.8	0
Chan[12]	2013	(Serial)CUS	no	3	221	7.2	0.49
Cini[13]	2014	Wells rule, D-dimer, (Serial) proximal CUS	yes	3	326	16.6	0
Cogo[14]	1998	(Serial) CUS	no	6	1702	24	0.7
Cornuz[15]	2002	Wells rule, D-dimer,	no	3	278	29	1.0
Elias[16]	2003	Whole leg CUS	no	3	623	32.8	0.5
Engelberger[17]	2011	Wells rule, D-dimer, whole leg CUS	no	3	298	27	0.5
Gibson[18]	2009	Wells rule, D-dimer, serial proximal CUS/ whole leg CUS	no	3	1002	15.8	0.95
Heijboer[19]	1993	(Serial) CUS + venography to confirm DVT	no	6	490	19	1.5
Hogg[20]	2012	Wells rule, D-dimer (serial) CUS	no	3	199	20.6	0
Imberti[21]	2006	Wells rule, D-dimer (serial) proximal CUS	yes	3	534	19.2	0.7

Appendix II. (continued)

Author	Year of publication	Diagnostic tests/ algorithm	Only proximal thrombosis	Follow-up (months)	Number of patients	Disease prevalence at baseline (%)	Failure rate (%)
Janes[22]	2001	Wells rule, D-dimer, US	no	3	431	21.6	0.3
Kahn[23]	2001	Contrast venography	no	6	159	32	0.9
Kearon[24]	2001	Wells rule, D-dimer, serial US/impedence plethysmography + venography	no	3	445	14	0.26
Kearon[25]	2005	Randomisation between D-dimer +venography/serial CUS	no	6	408/402	4.7/1.2	2.1/0.75
Kraaijenhagen[26]	2002	CDR, D-dimer, (serial) CUS	no	3	1756	23	1.3
Le Gal[27]	2012	Whole leg CUS	no	3	210	10.5	4
Legnani[28]	2010	Wells rule, D-dimer, serial US	no	3	401	22.4	0
Linkins[29]	2013	Wells rule, Randomisation between testing D-dimer in all patients/ selective testing dependent on Wells rule, CUS	yes	3	863/860	6.5/5.7	0.5/0.5
Noren[30]	2002	Duplex US, venography is patients with equivocal US results	no	3	580	24	0.29
Penaloza[31]	2006	Wells rule, D-dimer, (serial) proximal CUS	yes	3	214	18	1.1
Perrier[32]	1999	Wells rule, D-dimer, CUS, venography	no	3	474	33.5	2.6
Prandoni[33]	2002	(serial)CUS + venography for all patients with positive CUS	yes	6	205	27	1.3
Prandoni[34]	2007	Proximal CUS, serial CUS when D-dimer positive	yes	3	146	30	0
Robinson[35]	2002	D-dimer + CUS	no	3	437	30	0.65
Ruiz-Gimenez[36]	2004	Wells rule, d-dimer (serial) proximal CUS	yes	3	401	25	0.99
Schellong[37]	2003	Whole leg CUS	no	3	1646	12	0.3
Schouten[38]	2015	Oudega rule, d-dimer, CUS	no	3	348	47	2.2

Appendix II. (continued)

Author	Year of publication	Diagnostic tests/ algorithm	Only proximal thrombosis	Follow-up (months)	Number of patients	Disease prevalence at baseline (%)	Failure rate (%)
Schutgens[39]	2003	Wells rule, D-dimer, CUS, serial CUS when D-dimer positive	yes	3	812	38	1.6
Siragusa[40]	2004	Wells rule, D-dimer, serial US	no	3	409	22.2	0.63
Sluzewski[41]	1991	(serial) proximal CUS	yes	3	174	38	2.8
Stevens[42]	2004	CUS	no	3	445	13.7	0.8
Stevens[43]	2013	Wells rule, whole leg CUS	no	3	183	8.7	0.6
Subramaniam[44]	2005	Whole leg CUS	no	3	526	21.5	0.24
Subramaniam[45]	2006	Whole leg CUS	no	3	453	19.2	0
ten Wolde[46]	2002	D-dimer+ (serial) CUS	no	3	1739	23	1.3
Tick[47]	2002	Wells rule, D-dimer, single CUS/(serial)CUS	no	3	811	42	1.5
van der Hulle[48]	2013	Wells rule, D-dimer, (serial) CUS	yes	3	389	22	0
Wells[49]	1997	Wells rule, (serial) CUS, venography	yes	3	593	15.5	0.6
Wells[50]	1999	Wells rule, (serial) CUS	yes	3	150	27	1.8
Wells[51]	2003	Wells rule, unlikely probability group: randomisation between first US or D-dimer	yes	3	566/530	15/14.5	0.4/1.3

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