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RECOMMENDATIONS AND GUIDELINES

Disease prevalence dependent failure rate in diagnostic management studies on 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 favored strategy for the diagnostic management of suspected first DVT is the combination of pretest 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^{-1} if there is a low clinical probability, computed tomography–venography if it is impossible to perform CUS, and magnetic resonance direct thrombus imaging 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 pulmonary embolism 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 pretest 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 the diagnosis of DVT, in order to propose a new diagnostic safety threshold for future studies on the diagnostic management of suspected DVT.

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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.), and disagreements were

resolved by an additional reviewer (F.K.). A literature search of PubMed, Embase, Web of Science, Cochrane Library and Cochrane central register of controlled trials (central) was performed on 29 February 2016, with the aim of finding all high-quality diagnostic studies in acute DVT from 1990 onwards (the search strategy is shown in Data S1). First, all references were screened by title and abstract. After exclusion of non-relevant studies, full-text articles were analyzed for eligibility before final study selection. Study selection criteria were: (i) prospective study design; (ii) prespecified study protocol; (iii) clear description of inclusion and exclusion criteria; (iv) inclusion of > 100 consecutive patients; (v) at least 3 months of follow-up; (vi) < 5% lost to follow-up; and (vii) 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 cases 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: (i) year of publication; (ii) total number of included patients; (iii) diagnostic test or algorithm; (iv) focus on proximal DVT only or also distal DVT; (v) DVT prevalence at baseline; and (vi) failure rate defined by the incidence of patients with VTE despite a negative test result during 3 months of follow-up. Two graphs were plotted: one with year of publication versus DVT prevalence, and the second with DVT prevalence versus failure rate. Reference lines with 95% CIs, 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 with 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. The study selection flowchart and reasons for exclusion are shown in Fig. S1. Study characteristics and extracted information are summarized in Table S1. 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: $Y = 27.95–0.53 \times x$ ($R^2 = 0.066$, $P < 0.001$; 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 $0.28 + 0.026 \times x$ ($R^2 = 0.195$, $P < 0.001$; 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: $1.25 + 0.026 \times x$. The sensitivity analysis, including five additional studies with follow-up beyond the first 3 months and the one limited to studies analyzing proximal DVT only, indicated comparable study outcomes (formulas $0.45 + 0.02 \times x$ and $0.46 + 0.02 \times x$, 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 by 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 a diagnostic standard, based on the upper limit of the 95% CI 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, see our previous SSC communication [4].

Discussion

This study confirms the decreasing baseline disease prevalence in DVT diagnostic management studies over the last few 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 because that these patients were well represented in

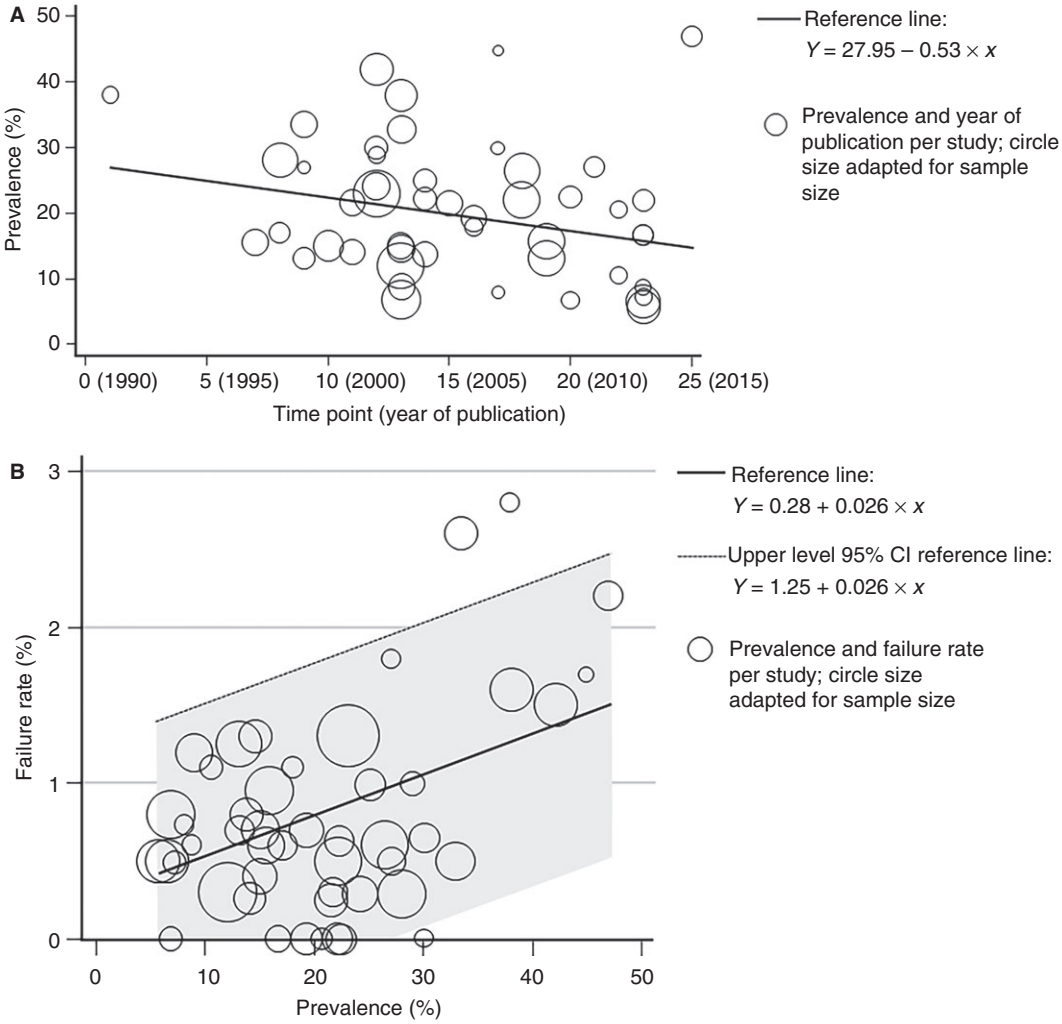

Fig. 1. Scatter plots with reference lines using least squares linear regression analysis (A) Decrease in disease prevalence over the last years. (B) Prevalence versus failure rate in high-quality deep vein thrombosis diagnostic management studies. The gray area depicts the 95% confidence interval (CI) of the reference line.

the studies included in the meta-analysis and the adaptation of the accepted failure rate to this higher *a priori* risk. Note that 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 diagnostic tests are used 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 the sensitivity and the 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.

Addendum

C. E. A. Dronkers and Y. M. Ende-Verhaar performed the literature search. C. E. A. Dronkers and Y. M. Ende-Verhaar performed the study selection and data extraction. C. E. A. Dronkers and F. A. Klok performed the analysis and drafted the paper. Y. M. Ende-Verhaar, P. Kyrle, M. Righini, S. C. Cannegieter, and M. V. Huisman critically revised the paper for important intellectual content. All authors designed the study and approved final publication.

Disclosure of Conflict of Interests

F. A. Klok reports receiving grants from Bayer, Bristol-Meyers Squibb, and Boehringer-Ingelheim; and non-financial support from Daiichi-Sankyo, outside the submitted work. The other authors state that they have no conflict of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Study characteristics and extracted information.
Data S1. Literature search strategy.
Fig. S1. Flowchart of study selection.

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