

# Toward a tailored diagnostic standard for future diagnostic studies in pulmonary embolism: Communication from the SSC of the ISTH

Dear Editor,

Over the past 20 years, there has been a shift in diagnostic strategies for diagnosing venous thromboembolism. Diagnostic tests for suspected acute pulmonary embolism (PE) have evolved from pulmonary angiography, which was the only available diagnostic test up to 30 years ago, to ventilation perfusion scintigraphy, computed tomography pulmonary angiography and combinations of a D-dimer test and clinical decision rules to determine the pretest probability of having PE.<sup>1</sup> The current diagnostic standard is an integrated algorithm starting with pretest probability assessment and a D-dimer test, only followed by radiological imaging in case of high pretest probability and/or a D-dimer test result above the applicable threshold.<sup>2</sup> Because of the less invasive character and more widespread availability of diagnostic tests for acute PE, the threshold for testing for PE has considerably decreased, which translated to a lower disease prevalence in study populations.<sup>3,4</sup> Nonetheless, the accepted failure rate (i.e., the 3-month incidence of symptomatic venous thromboembolism in patients in whom PE was considered absent and were left untreated) in diagnostic management studies remained the upper limit of the 95% confidence interval (95% CI) of the failure rate of conventional pulmonary angiography (2.7%).<sup>5</sup> Because, according to the theorem of Bayes the diagnostic failure rate (posttest probability) is associated with the disease prevalence (pretest probability) in a study population, the SSC proposed a new safety threshold dependent on disease prevalence to prevent that unsafe strategies would get accepted as accurate. To provide guidance on how to evaluate new diagnostic strategies, or existing strategies in various health care settings with corresponding higher or lower disease prevalence, we proposed a varying safety threshold, modeled on a linear regression analysis of disease prevalence and failure rate in pooled data from published high-quality diagnostic management studies. Application of this new safety threshold will lead to a stricter safety threshold in study populations with a sporadic disease prevalence.

Freund et al.<sup>6</sup> raise an interesting comment to the SSC of the ISTH communication paper published in 2017, which proposed a new diagnostic safety threshold for future diagnostic studies in patients with suspected acute PE.<sup>4</sup> They discuss that the definition of failure rate should be calculated only in patients in whom the new diagnostic strategy actually affected the diagnostic workup (i.e., in whom imaging was avoided) rather than the complete population. We agree with this comment. However, in our view, this latter group are all patients in whom PE is ruled

out without imaging test and not the small subgroup of patients where the study strategy was effectively applied (i.e., in whom the D-dimer threshold was changed compared to the “standard” algorithm). We agree that reporting the failure rate in the subgroup of patients affected by the change in algorithm is important to enable a comprehensive appraisal of the new algorithm. However, determining an acceptable failure rate in such a subgroup was outside the scope of this SSC guidance.

In their interpretation of the SSC communication, Freund and colleagues<sup>6</sup> slightly misinterpreted the application of the formula to calculate an appropriate safety threshold ( $1.82 + 0.0053 \times \text{prevalence}$ ). This formula does not determine the upper limit of the CI of the acceptable safety threshold, but the maximum acceptable “point estimate” of the failure rate. Considering this, the point estimate of the failure rate of the pregnancy-adjusted YEARS algorithm observed in the Artemis study (0.51; 95% CI, 0.09–2.9) is well below the *post hoc* calculated safety threshold ( $1.82 + 0.0053 \times 4 = 1.84\%$ ) for avoiding computed tomography pulmonary angiography.<sup>7</sup> Hence, according to the SSC communication, the diagnostic algorithm should be considered safe, even despite the low baseline PE prevalence.

In the second example discussed, a “heads and tails” strategy is applied to a virtual study population with a disease prevalence of 2.5%. The failure rate with “the toss of a coin” in a population of 4000 patients, of whom 2000 would have a negative test result, would be  $50/2000 = 2.5\%$ . The accepted failure rate according to the SSC formula would be 1.83%, however. Besides the question if it is reasonable to perform any test in a study population with such a low disease prevalence, the heads and tails strategy does not match the safety threshold as proposed by the SSC, confirming its relevance.

We therefore conclude that the proposed new way of determining the safety threshold for PE and DVT diagnostic studies as proposed by the SSC remains valid and appropriate.<sup>3,4</sup>

## KEYWORDS


clinical decision rules, D-dimer, diagnosis, pulmonary embolism, safety

## CONFLICT OF INTEREST

None.

## AUTHOR CONTRIBUTIONS

Charlotte E. A. Dronkers and Frederikus A. Klok wrote the first draft of the manuscript. Tom van der Hulle, Grégoire Le Gal, Paul A. Kyrle, Menno V. Huisman, and Suzanne C. Cannegieter critically revised the paper for important intellectual content.

Charlotte E. A. Dronkers<sup>1</sup>  
 Tom van der Hulle<sup>1</sup>  
 Grégoire Le Gal<sup>2</sup>  
 Paul A. Kyrle<sup>3,4</sup>  
 Menno V. Huisman<sup>1</sup>  
 Suzanne C. Cannegieter<sup>5</sup>   
 Frederikus A. Klok<sup>1</sup>

<sup>1</sup>Department of Medicine – Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, the Netherlands

<sup>2</sup>Department of Medicine and Ottawa Hospital Research Institute, University of Ottawa, Ottawa, ON, Canada

<sup>3</sup>Department of Medicine I, Medical University of Vienna, Vienna, Austria

<sup>4</sup>Karl Landsteiner Institute of Clinical Thrombosis Research, Vienna, Austria

<sup>5</sup>Department of Clinical Epidemiology, Leiden University Medical Center, Leiden, the Netherlands

#### Correspondence

Charlotte E. A. Dronkers, Department of Thrombosis and Hemostasis, LUMC, Albinusdreef 2, PO Box 9600, 2300 RC Leiden, the Netherlands.  
 Email: c.e.a.dronkers@lumc.nl

#### ORCID

Suzanne C. Cannegieter  <https://orcid.org/0000-0003-4707-2303>

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## The chromogenic Bethesda assay and the Nijmegen-Bethesda assay for factor VIII inhibitors in hemophilia A patients: Are they equivalent?

We previously described in this journal a modified Nijmegen-Bethesda assay (NBA) for factor VIII (FVIII) inhibitors in hemophilia A (HA) that uses preanalytical heat inactivation of infused or endogenous FVIII to allow inhibitor measurement postinfusion<sup>1</sup> and compared that assay with a chromogenic Bethesda assay (CBA) that is identical except for use of an FVIII chromogenic substrate assay (CSA) rather than a one-stage assay (OSA) as the endpoint for inhibitor detection.<sup>2</sup> Our primary focus was on use of the CBA as a confirmatory test for low positive NBA results. Introduction of the non-FVIII treatment product emicizumab (Hemlibra) has brought increased interest in inhibitor assays using CSA because emicizumab interferes with the OSA and

thus with Bethesda assays for FVIII inhibitors using the OSA.<sup>3-5</sup> CSA for FVIII that use bovine factor X (FX) are insensitive to emicizumab,<sup>5</sup> and a CBA using such CSA has been successfully used for inhibitor testing in its presence.<sup>6,7</sup> Clinical laboratories providing inhibitor testing have the option of maintaining two inhibitor assays and choosing the correct one for each patient depending on the product used or switching to a CBA to accommodate testing on all patients. Clinical adoption of a new assay methodology requires demonstration that the new method is equivalent to the old. Recent reexamination of the dataset of paired NBA and CBA results from our original paper<sup>2</sup> revealed differences that may influence such comparisons and that, if not considered, could hinder validation of the CBA for clinical use.

The results reexamined were from 1005 specimens collected from subjects with congenital HA enrolled in the Hemophilia