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SHORT COMMUNICATION

Clinical Utility of D-Dimer for Rule-Out or Rule-In of Venous Thromboembolism in Syncope

Patrick Badertscher[1,2] · Jeanne du Fay de Lavallaz[1,2] · Angelika Hammerer-Lercher[3] · Christian Mueller[1,2] · for the BASEL IX Investigators

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Syncopeis a common reason for patient presentation to the emergency department (ED). Its differential diagnosis often is challenging and includes benign vasovagal, but also acute life-threatening cardiovascular causes such as pulmonary embolism (PE) [1]. As syncope is a rather uncommon presentation of PE [1–3], it is largely unknown whether D-dimer concentrations, which are recommended in suspected PE and low-to-intermediate pre-test-probability [4], can also be applied in patients presenting with syncope.

We aimed to address these uncertainties in a large diagnostic multicenter study prospectively enrolling unselected patients presenting with syncope to the ED (NCT01548352) [1]. Patients were enrolled prospectively from May 2010 to February 2017. Patients with ongoing anticoagulation therapy and with missing blood samples were excluded. D-dimer was measured in a blinded fashion using two different assays in a central laboratory: Innovance® D-dimer [5]and Innovance® Loci-high-sensitivity D-dimer (Siemens Healthcare, New York, USA). The presence of venous thromboembolism (VTE=PE or venous thrombosis) at presentation and/or during 720 days follow-up was centrally adjudicated by independent cardiologists according to guidelines as described in detail elsewhere [4]. In brief, patients were determined to not have an index PE if none of three assessments provided evidence of VTE: (A) the initial clinical work-up possibly including computed-tomography pulmonary angiography or ventilation/perfusion-scanning; (B) the initial study-specific work-up including Wells score and D-dimer in all patients; (C) 720-day clinical follow-up. To maximize sensitivity for VTE, all VTE and all cardiovascular deaths without clear alternative causes occurring during 720-day follow-up were considered clinically missed VTE at index-presentation. Patients were excluded if on oral anticoagulation.

Three endpoints were evaluated: First, the diagnostic accuracy of D-dimers for PE if measured in unselected patients presenting with syncope to the ED. Second, the diagnostic performance of applying D-dimer within the three most widely used algorithms for the rule-out of PE: (a) 2-level Wells-score using age-adjusted, (b) fixed cutoffs, and (c) the YEARS-algorithm with only three items of the Wells-score (clinical signs of deep vein thrombosis, hemoptysis, PE the most likely diagnosis) and using a D-dimer threshold of 0.5 mg/L in presence, and 1.0 mg/L in absence of one of the YEARS-items (4). Third, the specificity for different D-dimer cutoffs to rule-in VTE.

Among 1396 eligible patients, mean age was 68 years, 42% were women, median duration of follow-up was 751 days (IQR, 722–873 days), and 19 patients were adjudicated to have VTE at index presentation and 31 patients (2.2% [95%CI 1.5–3.1%]) to have VTE at index or during follow-up. D-dimer concentration was higher in syncope due to VTE versus those from other causes (Innovance® 6.86 mg/l versus 0.78 mg/l, $p<0.001$). The diagnostic accuracy of D-dimer for VTE as quantified by the area under the receiver-operator-characteristics curve was high: Innovance® 0.85 (95%CI 0.80–0.91, Fig. 1). In these patients, when using a fixed cutoff of D-dimer concentration<0.5 mg/L, 32% of patients (n=450), and when using age-adjusted cutoffs, 44% of patients (n=612), could safely be ruled out

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Patrick Badertscher and Jeanne du Fay de Lavallaz contributed equally and should be considered first authors.

✉ Patrick Badertscher
Patrick.Badertscher@usb.ch

1 Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Petersgraben 4, CH-4031 Basel, Switzerland

2 GREAT Network, Basel, Switzerland

3 Department of Laboratory Medicine, Kantonsspital Aarau, Aarau, Switzerland

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(without missing any patients with VTE at the index presentation or during FU). When using the YEARS algorithm with pre-test-probability adapted cutoffs, 57% of patients (n=792) could be ruled-out, thereby missing 2 non-fatal PE cases (1 at Index presentation, 1 during FU after 55 days). Internal validation using a second D-dimer-assay (Innovance® Loci-high-sensitivity) confirmed these findings (Fig. 1A). Regarding VTE rule-in, the specificity for the diagnosis of VTE increased with increasing D-dimer concentrations (Fig. 1B). Using a cutoff of 8 mg/l, specificity for VTE was 95% (95%*CI* 93–96%).

Three insights of major clinical relevance evolved from these analyses. First, D-dimer concentrations were significantly higher in patients with syncope due to adjudicated VTE versus those with other causes, providing high diagnostic accuracy for VTE. Second, using D-dimer concentration within one of the three widely used PE rule-out algorithm with their established cutoffs provided high safety. Third, D-dimer concentrations of 8 mg/L or higher have a specificity of 95% and should be considered also as part of rule-in pathways for VTE.

A limitation of this study is that not all patients underwent definitive VTE-imaging during the index evaluation, but all patients underwent clinical follow-up for up to 720 days. We would expect clinically relevant PE accounting for syncope to manifest itself during 720-day FU period; thus, the diagnosis of PE was infrequently missed.

In conclusion, D-dimer provides high accuracy for the detection of VTE in unselected patients presenting with syncope to the ED, thereby providing high clinical utility for rapid rule-out with excellent safety as well as rule-in of VTE.

Additional BASEL IX Investigators and Contributors to be listed in PubMed [1]Cardiovascular Research Institute Basel (CRIB) and Department of Cardiology, University Hospital Basel, University of Basel, Switzerland
[2]Division of Cardiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia, Canada
[3]GREAT network
[4]Hospital Clinic, Barcelona, Catalonia, Spain
[5]Emergency Department, University Hospital Zürich, Zürich, Switzerland
[6]Servicio de Urgencias, Hospital Clínico San Carlos, Madrid, Spain
[7]Emergency Department, Kantonsspital Liestal, Switzerland
[8]Christchurch Hospital, Christchurch, New Zealand
[9]Emergency Department, Kantonsspital Luzern, Switzerland
[10]Royal Brisbane & Women's Hospital, Herston, Australia
[11]Emergency Medicine, Department of Medical-Surgery Sciences and Translational Medicine, University Sapienza Rome, Sant'Andrea Hospital, Italy
[12]Baylor College of Medicine, Department of Emergency Medicine, Houston, Texas, USA
[13]Instituto Cardiovascular de Buenos Aires, Buenos Aires, Argentina
[14]Department of Internal Medicine, Hospital of Lachen, Switzerland
[15]Laboratory Medicine, University Hospital Basel, Switzerland
[16]Laboratory Medicine, University Hospital Zürich, Switzerland
[17]Blood Transfusion Centre, Swiss Red Cross, Basel, Switzerland

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Declarations

Conflict of Interest The authors designed the study, gathered and analyzed the data, vouch for the data and analysis, wrote the paper, and decided to publish. Drs. Badertscher, du Fay de Lavallaz, and Mueller had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors have read and approved the manuscript. The sponsors had no role in designing or conducting the study and no role in gathering or analyzing the data or writing the manuscript. The manuscript and its contents have not been published previously and are not being considered for publications elsewhere in whole or in part in any language, including publicly accessible web sites or e-print servers. Professor Mueller has received research support from the Swiss National Science Foundation, the Swiss Heart Foundation, the European Union, the KTI, Abbott, Beckman Coulter, BRAHMS, Idorsia, Novartis, Quidel, Roche, Siemens, and Singulex, as well as speaker/consulting honoraria from Amgen, Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, Idorsia, Novartis, Osler, Roche, and Sanofi. Dr. Badertscher has received research funding from the "University of Basel," the "Stiftung für Herzschrittmacher und Elektrophysiologie," and the "Freiwillige Akademische Gesellschaft Basel." PD Dr. Hammerer-Lercher has received speaker honoraria from Abbott and Beckman Coulter outside the submitted work. All other authors declare that they have no conflict of interest with this study.

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