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Righini, Marc Philip; De Moerloose, Philippe; Reber, Guido; Bounameaux, Henri; Perrier, Arnaud

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# Potential role of D-dimer to rule in pulmonary embolism: a rebuttal

M. RIGHINI, P. DE MOERLOOSE, G. REBER, H. BOUNAMEAUX and A. PERRIER*
*Division of Angiology and Haemostasis and *Medical Clinic 1, Geneva University Hospital, Geneva, Switzerland*

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We read with great interest the recently published work by Kucher *et al*. [1], concerning the positive diagnosis of pulmonary embolism (PE) by a D-dimer/fibrinogen ratio >1000.

ELISA D-dimer assays have a high sensitivity which allows exclusion of PE or deep vein thrombosis (DVT) in about 30% of outpatients clinically suspected of having the disease [2–4]. In contrast, at the usual cut-off value, poor specificity precludes using D-dimer to rule in venous thromboembolism.

In their recently published work [1] based on a cohort of 191 outpatients with suspected PE, Kucher *et al*. tested the hypothesis that patients with PE have lower fibrinogen and higher D-dimer values than patients in whom the diagnosis is suspected but safely excluded. They found that a D-dimer/fibrinogen ratio >1000 allowed one to rule in PE in 26% (49/191) of patients with a positive predictive value of 100% [95% CI: 93–100]. As a D-dimer below 500 $\mu g\,L^{-1}$ was found in 29.3% of their patients, the association of D-dimer <500 $\mu g\,L^{-1}$ to exclude PE and a D-dimer/fibrinogen ratio >1000 to rule in PE allowed a definite diagnosis in 55% of patients. Moreover, the D-dimer/fibrinogen ratio was >1000 in 49 of 85 (58%, 95% CI: 47–68) patients with PE.

One main limitation of this study is the rather small sample size, as highlighted by the wide confidence interval for the positive predictive value (100%, 95% CI: 93–100). Furthermore, we are surprised that the authors obtained a 100% negative predictive value (NPV) at 780 $\mu g\,L^{-1}$. At that threshold, the NPV was only 97% (95% CI: 95–99) in a larger database including 874 outpatients clinically suspected of PE, as discussed below [2,5]. This suggests that the results could have been different in a larger sample. Another potential limitation could be the median fibrinogen value reported by the authors, which seems unusually low (median 2.7 $g\,L^{-1}$, range 0.4–5.2 $g\,L^{-1}$). Moreover, if standardization of D-dimer dosage has been difficult in the past, this may be the same for fibrinogen dosage. Therefore, in the absence of a well-admitted standardization of fibrinogen dosage [6], the described D-dimer/fibrinogen ratio may not be reproducible and widely useful.

We calculated the diagnostic performances of a D-dimer/fibrinogen ratio >1000 in a subset of 156 randomly selected patients suspected of PE for whom some plasma was left from two previously published studies [2,5]. Specificity was 95% (95% CI: 89–98) but positive predictive value was only 75% (95% CI: 51–91), which does not support the use of the D-dimer/fibrinogen ratio to rule in PE.

Previous studies have tried to assess the possibility of using elevated D-dimer thresholds to rule in PE. In a management study including 671 outpatients suspected of PE, Perrier *et al*. showed that at a cut-off of 4000 $\mu g\,L^{-1}$ the specificity of the test was 93.1% [7]. Posterior analysis of these data [8] suggested that an outpatient clinically suspected of PE who presents with a D-dimer level >4000 $\mu g\,L^{-1}$ has a likelihood ratio of 5 of having PE, which may be sufficient to initiate anticoagulant treatment before objective confirmation of the disease, at least in patients with intermediate clinical probability of PE.

To our knowledge, there is no other study based on a large cohort that could confirm the fact that a very elevated D-dimer value can predict the disease. Therefore, we retrospectively analyzed the data of two prospective studies including outpatients with suspected PE to assess whether adopting high D-dimer thresholds might allow to obtain a positive predictive value as high as that described by Kucher *et al*. using the D-dimer/fibrinogen ratio. We also evaluated the specificity and positive predictive value of high D-dimer thresholds in the subgroup of high clinical probability patients. The original studies [2,5] took place in Angers, Lausanne, Montreal and Geneva and included 1409 patients. However, as both studies used a 500 $\mu g\,L^{-1}$ cut-off to exclude venous thromboembolism, quantitative results of D-dimer >1000 $\mu g\,L^{-1}$ were available only in Montreal and Geneva, which reduced the available data for analysis to 874 patients. All patients underwent a sequential diagnostic work-up including clinical probability assessment, a rapid quantitative ELISA D-dimer test, and venous compression ultrasonography of the lower limbs if the D-dimer level was above 500 $\mu g\,L^{-1}$. Further tests were carried out when ultrasonography did not show a proximal DVT: ventilation-perfusion lung scan in the first study, helical computed tomography scan in the second study. Finally, pulmonary angiography was performed only if the non-invasive work-up was inconclusive in high clinical probability patients.

Correspondence: Marc Righini, Division of Angiology and Hemostasis, Geneva University Hospital, 24 Rue Micheli-du-Crest, 1211 Geneva 14, Switzerland.
Tel.: +41 22 372 9294; e-mail: marc.righini@hcuge.ch

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**Table 1** Effect of varying the D-dimer cut-off value on the test's characteristics in 874 patients

| D-dimer cut-off value ($\mu g\,L^{-1}$) | Specificity, % (95% CI) | Positive predictive value, % (95% CI) | False positive D-dimer, *n* | D-dimer above cut-off value, *n* (%) |
|---|---|---|---|---|
| 1000 | 70 (67–73) | 46 (42–52) | 205 | 372 (43) |
| 2000 | 88 (86–91) | 61 (54–67) | 80 | 205 (24) |
| 3000 | 93 (91–95) | 68 (60–75) | 49 | 152 (17) |
| 4000 | 96 (94–97) | 72 (63–80) | 29 | 103 (12) |
| 5000 | 97 (97–99) | 76 (66–84) | 20 | 84 (10) |
| 6000 | 98 (98–99) | 80 (68–88) | 12 | 60 (7) |
| 7000 | 99 (98–99) | 81 (68–91) | 8 | 44 (5) |
| 8000 | 99 (98–100) | 81 (66–91) | 7 | 37 (4) |
| 9000 | 99 (99–100) | 78 (61–89) | 7 | 32 (4) |
| 10 000 | 99 (99–100) | 75 (61–91) | 5 | 25 (3) |

The prevalence of PE was 22% (192/874). Patients were categorized as low clinical probability (526/874, 60%) intermediate clinical probability (284/874, 33%) and high clinical probability (64/874, 7%). Specificity and positive predictive value are shown in Table 1. These results are disappointing: even if increasing the cut-off of D-dimer progressively increases specificity, the positive predictive value reaches 81% in the best of cases. Moreover, in this cohort, although the specificity of D-dimer for a cut-off value of 7000 $\mu g\,L^{-1}$ is 99% (95% CI: 98–99), the positive predictive value is only 80% (95% CI: 68–88). Moreover, the proportion of patients with D-dimer level above that threshold is low (5% of all patients), limiting the clinical usefulness of such a diagnostic criterion. Therefore, ruling in PE by elevated D-dimer levels is inaccurate and of limited clinical usefulness, as few patients have such high D-dimer values. Moreover, clinicians may feel quite uncomfortable in ruling in PE without using any imaging technique.

Combining elevated D-dimer levels and high clinical probability should theoretically improve both specificity and positive predictive value of the test [9]. This is confirmed by our data as, in this subgroup of patients, a 100% (95% CI: 83–100) value of specificity and a 100% (95% CI: 87–100) value of positive predictive value are reached at the much lower cut-off level of 4000 $\mu g\,L^{-1}$. However, owing to the small number of patients, 95% confidence intervals are quite large and do not allow firm recommendations. Moreover, high clinical probability patients represent only 7.2% of our cohort and only 26 such patients (3%) have D-dimer levels $>4000\,\mu g\,L^{-1}$.

In conclusion, using a higher D-dimer threshold to rule in PE is inaccurate and cannot be recommended, even in patients with a high clinical probability of having the disease. In our hands, the D-dimer/fibrinogen ratio described by Kucher *et al*. did not fulfil its promise and its value should be confirmed in a larger patient population before being used in routine diagnostic algorithms.

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# Potential role of D-dimer to rule in pulmonary embolism: reply to a rebuttal

N. KUCHER,* H-P. KOHLER,† T. DOERNHOEFER,‡ D. WALLMANN§ and B. LAEMMLE¶

*Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA; †Emergency Department, University Hospital, Bern, Switzerland; ‡Radiology, University Hospital, Bern, Switzerland; §Cardiology, University Hospital, Bern, Switzerland; ¶Hematology, University Hospital, Bern, Switzerland*

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We agree with several comments by Righini and colleagues regarding our study to validate D-dimer/fibrinogen (D/F) ratio as a 'rule-in' test for patients with suspected pulmonary embolism (PE) [1]. The main limitation was the small sample size, causing wide confidence intervals of predictive values for PE diagnosis. We also agree that a D/F ratio $>1000$ should not be used as a 'stand-alone' test to rule in PE.

The diagnostic accuracy of the D/F ratio to predict PE may vary significantly with various laboratory assays, diagnostic reference methods, and patient populations. We measured plasma fibrinogen using the method by Clauss [2], while Righini and colleagues used an automated fibrinogen assay. The diagnostic strategy in our study was different in that contrast-enhanced spiral chest computed tomography (CT) was used as the principal imaging test. In addition, echocardiography was performed to screen for the presence of right ventricular (RV) dysfunction within 4 h of admission. Among consecutive patients with acute PE, approximately 30% of patients present with RV dysfunction and are at increased risk of adverse clinical outcomes [3,4]. Therefore, echocardiography has emerged as the principal tool for risk stratification of patients with acute PE [5–7]. Potentially live-saving interventions, such as thrombolysis or embolectomy, may be considered in high-risk patients based on rapid PE diagnosis by chest CT and confirmation of severe RV dysfunction by echocardiography [8]. In our study, the diagnostic approach with chest CT and echocardiography allowed for consecutive enrollment of hemodynamically unstable patients with suspected PE. A diagnostic strategy with venous leg ultrasound and ventilation perfusion scan as principal imaging tests, as used in the study by Righini and colleagues, does possibly not allow for inclusion of consecutive high-risk patients.

Correspondence: Nils Kucher, Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, 75 Francis Street, Boston, MA 02115, USA.
Tel.: +1 617 732 6986; fax: +1 617 738 7652; e-mail: nkucher@partners.org

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In our study [1], fibrinogen levels were inversely correlated with pulmonary occlusion rate as assessed by chest CT. Among 34 patients with a high pulmonary occlusion rate (modified Miller index [9] $>80\%$), median fibrinogen was $2.7\,g\,L^{-1}$ and median D/F ratio was 2740. Ten of the 34 patients had massive PE (cardiogenic shock), 16 had submassive PE (preserved arterial systolic pressure but severe RV dysfunction), and eight had non-massive PE (normal RV function). In the 31 patients with intermediate pulmonary occlusion (30–80%), median fibrinogen was $3.9\,g\,L^{-1}$ and median D/F ratio was 1010. One of the 31 patients had massive PE, two had submassive PE, and 28 had non-massive PE. In the 20 patients with a pulmonary occlusion rate $<30\%$, median fibrinogen was $4.4\,g\,L^{-1}$ and median D/F ratio was 420. None of the 20 patients had massive PE, one had submassive PE, and 19 had non-massive PE. Thus, D/F ratio $>1000$ may be of particular interest to identify high-risk patients with acute PE. Furthermore, high D-dimer plus low fibrinogen levels are associated with decreased factor XIII A-subunit levels, confirming significant consumption coagulopathy in PE patients with large clot burden [10].

In conclusion, the results from the study of Righini and coworkers and our study are not necessarily contradictory, since different laboratory assays, patient populations, and diagnostic reference methods were used. While D/F ratio is particularly increased in high-risk patients with submassive and massive PE due to consumption of clotting factors, further studies are needed to confirm its diagnostic accuracy in the entire population of patients with suspected PE.

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# Rebuttal to: Clinical manifestations of the prothrombin G20210A mutation in children

A. GREENWAY and P. MONAGLE
*Division of Laboratory Services, Royal Children's Hospital, Parkville, Victoria, Australia*

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We write with respect to the report of the clinical manifestations of the prothrombin G20210A (PT) mutation in a retrospective cohort of children with thrombosis [1]. The authors suggest this mutation is an important risk factor for thrombosis with 10% of their population positive for this mutation. The authors also report the significance of the increased likelihood of arterial clot and a predilection in the group identified to carry the PT mutation for CNS thrombosis.

As a control group was not considered in this cohort study the wider clinical implications of the PT mutation in other children without thrombosis remain unknown. Further, cases for this study were ascertained from 'a database or by memory', suggesting a high likelihood of selection bias.

Moreover, these studies fail to demonstrate a causative link between the presence of the PT mutation and thrombosis, therefore clinical treatment decisions based on the prevalence of such genetic markers remain difficult. This is particularly the case in the subgroup with venous thrombosis, where 92% of children had additional risk factors noted. The conclusion that PROG 'appears to be an important risk factor for thrombosis in children' is unsubstantiated by the data presented.

Correspondence: Anthea Greenway, 9th Floor, Div. of Laboratory Services, Royal Children's Hospital, Flemington Road, Parkville, VIC 3052, Australia.
Tel.: +61 3 9345 5914; fax: +61 3 9349 1819; e-mail: anthea.greenway@wch.org.au

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Whilst the exact mechanism of increased thrombotic risk in adults with PT mutation is unknown, increased plasma concentrations of prothrombin (up to 30% higher in heterozygous carriers) in those affected has been documented in adults. Similar studies in the pediatric population have failed to demonstrate this relationship. Balasa *et al*. measured prothrombin levels in 187 children, 4% of whom were heterozygote for the PT G20210A mutation [2]. The authors concluded that increased prothrombin concentration was not associated with this mutation, therefore the mechanism by which the mutation would increase the risk of thrombosis in childhood remains unknown. Studies of developmental hemostasis in childhood reveal that plasma prothrombin concentrations are significantly reduced in neonates and remain 10–20% reduced below adult levels until late teenage years [3]. Unfortunately, due to the retrospective nature of the current study prothrombin levels were not established in the cohort. It would be interesting to determine if the levels detected in this group were reduced as expected relative to the adult range, or if in fact there is any effect due to the presence of the mutation.

Other groups have retrospectively compared the frequency of risk factors such as the PT G20210A mutation in children with venous (though not arterial) thrombosis and suggested a similar trend. Junker *et al*. reported an increased frequency of PT mutation in their cohort of 4.2% vs. 1.1% controls with an odds ratio 4.1 [4]. However, the clinical relevance of these retrospective studies when compared with well-designed prospective studies, which have found no increased prevalence of the PT mutation in children with venous thrombosis [5], is questionable.