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Evaluation of the diagnostic performance of three D-dimer assays in patients with suspected deep vein thrombosis: STA-Liatest D-Di plus, Tina-quant D-dimer Gen. 2, and INNOVANCE D-dimer

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ABSTRACT

Introduction: D-dimer is a crucial test to exclude deep vein thrombosis (DVT). We aimed to evaluate the performance of three D-dimer assays: STA-Liatest D-Di Plus (Diagnostica Stago), Tina-quant D-Dimer Gen. 2 (Roche Diagnostics), and INNOVANCE D-Dimer (Siemens Healthineers Diagnostics) in the exclusion of DVT.

Methods: Samples (n = 1032) and clinical data were acquired from a prospective outcome study (Rivaroxaban for Scheduled Work-up of Deep Vein Thrombosis – the Ri-Schedule study), which included patients referred to the emergency department with suspected lower-limb DVT. D-dimer was determined with STA-Liatest, and only patients with positive D-dimer values (≥0.5 μg/mL) as stand-alone, were referred for compression ultrasonography to confirm or exclude DVT. Patients were followed up 90 days after inclusion. Samples were also analyzed with Tina-quant Gen. 2, and INNOVANCE assays. The diagnostic performances of the three assays were investigated.

Results: Positive D-dimer (≥0.5 μg/mL) was found in 733 patients (71%) with STA-Liatest, 691 patients (67%) with Tina-quant Gen. 2, and 766 (74%) with INNOVANCE. DVT was confirmed by compression ultrasonography in 196 patients (27%) with positive D-dimer with STA-Liatest. Of those, six (3%) had negative D-dimer (<0.5 μg/mL) with at least one of the three assays yielding a failure rate of 0.7% with STA-Liatest, 2% with Tina-quant Gen. 2, and 2% with INNOVANCE. The sensitivity and negative predictive value (NPV) for STA-Liatest were 99.0% (95% CI 96.4–99.9) and 99.3% (95% CI 97.4–99.8), for Tina-quant Gen. 2 97.5% (95% CI 94.1–99.2) and 98.5% (95% CI 96.6–99.4), and for INNOVANCE 98.0% (95% CI 94.9–99.0) and 98.5% (95% CI 96.1–99.4) respectively. The efficiency to exclude DVT based on D-dimer as a stand-alone test was 29% (95% CI 26–33) for STA-Liatest, 33% (95% CI 30–37) for Tina-quant Gen. 2, and 26% (95% CI 23–29) for INNOVANCE.

Conclusion: STA-Liatest, Tina-quant Gen. 2, and INNOVANCE showed good performances with sensitivity ≥97% and NPV ≥98%. The efficiency to exclude DVT varied and was highest for Tina-quant Gen. 2, whereas the failure rate was lowest for STA-Liatest.

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1. Introduction

D-dimer is a product of intravascular and extravascular fibrin proteolysis [1,2]. The formation of cross-linked fibrin requires activation of the coagulation system with the resultant generation of thrombin that converts fibrinogen into fibrin monomers. The fibrin monomers polymerize to form fibrin polymers that are cross-linked by activated factor XIII [2]. D-dimer serves as a valuable biomarker of coagulation activation and fibrinolysis and is a crucial test to exclude deep vein thrombosis (DVT). In addition, D-dimer has been evaluated for determining the optimal duration of anticoagulation therapy in DVT patients, for diagnosing and monitoring disseminated intravascular coagulation, and recently as a prognostic marker for Corona virus disease 2019 (Covid-19) [3].

Several assays are available for the measurement of D-dimer. However, D-dimer assays are not standardized, and due to the lack of reference material, numerical results vary among the different assays [4]. The main causes of variation in D-dimer assays are differences in specificity of the monoclonal antibodies used, differences in sizes of the degradation products presenting the D-dimer antigen, and differences in assay methodology, assay calibration standards, and instrumentation [2]. Most D-dimer assays reporting in fibrinogen equivalent units have a fixed cut-off of 0.5 μg/mL for a positive test in an attempt to harmonize the analyses across methods and countries. Furthermore, some institutions use age-adjusted D-dimer cut-off. Age-adjusted cut-off for D-dimer when diagnosing pulmonary embolism is widely recommended, as it increases specificity of the test and therefore its applicability [5]. Recent studies and meta-analyses also argue that this should be applied in the work-up of suspected DVT [6]. A cut-off of (age x 0.01) μg/mL of those patients ≥50 years is recommended and is the most widely used [7].

In this study we evaluated three D-dimer assays by comparing their diagnostic performance, using the cut-off of 0.5 μg/mL and the age-adjusted cut-off, in patients referred to the emergency department with suspected lower-limb DVT.

2. Material and methods

2.1. Study population and design

In the study, three D-dimer assays in three hospitals in South-Eastern Norway were compared: The STA-Liatest D-Di Plus assay (Diagnostica Stago, Asnières-sur-Seine, France) at Østfold Hospital, the Tina-quant D-Dimer Gen.2 (Roche Diagnostics, Mannheim, Germany) at Akershus University Hospital, and the INNOVANCE D-Dimer assay (Siemens Healthineers Diagnostics, Marburg, Germany) at Oslo University Hospital using blood samples and clinical data form the Ri-Schedule study. The Ri-Schedule study (Rivaroxaban for Scheduled Work-up of Deep Vein Thrombosis; NCT 02486445) was a prospective outcome study conducted at Østfold Hospital, Norway, performed between February 2015 and November 2018 [8–10]. Patients ≥18 years of age referred from primary care to the Emergency Department with suspicion of first or recurrent lower-limb DVT were included after acquisition of a written consent. Exclusion criteria were failure to consent, missing D-dimer result at baseline, and previous inclusion in the study within the past 3 months. Included patients underwent clinical probability evaluation (Wells score) and blood testing including D-dimer.

In the Ri-Schedule study, patients with positive D-dimer (≥0.5 μg/mL) performed by the STA-Liatest assay were referred for a whole-leg compression ultrasonography where all veins were assessed for compressibility. Patients with D-dimer <0.5 μg/mL were considered not to have DVT and did not undergo compression ultrasonography unless indicated to rule out other conditions. Patients were followed up 90 days after inclusion to determine the occurrence of symptomatic venous thromboembolism (VTE) [8,9]. The Ri-Schedule study enrolled 1653 patients, however, in our study, we included 1032 Ri-Schedule patients in whom frozen citrated plasma samples were available. None of these patients were on permanent anticoagulation at the time of inclusion. In this study, the main aim was to evaluate the performance of the three D-dimer assays using a fixed cut-off (≥0.5 μg/mL). However, we also assessed the age-adjusted D-dimer cut-off for the three methods since D-dimer levels increase with age. The age-adjusted cut-off was calculated using the following formula: (age x 0.01) μg/mL of those patients ≥50 years.

2.2. Collection of samples and D-dimer analysis

At inclusion, blood samples were collected in 3.2% sodium citrate tubes (Greiner Bio-One, Kremsmünster, Austria). Plasma was obtained by 15 min centrifugation at 2500 G, and D-dimer was measured by STA-Liatest D-Di Plus (Diagnostica Stago, Asnières-sur-Seine, France) on STA-R (Stago). Citrated plasma was aliquoted into Nunc Cryotubes within 2 h after venepuncture and then stored at −80 °C. In this study, obtained aliquots were thawed for 15 min at 37 °C and analyzed within 1 h by the Tina-quant D-Dimer Gen. 2 assay (Roche Diagnostics, Mannheim, Germany) on Cobas t711 (Roche) at Akershus University Hospital, and by the INNOVANCE D-Dimer assay (Siemens Healthineers Diagnostics, Marburg, Germany) on Sysmex CS-5100 (Siemens) at Oslo University Hospital according to the manufacturer's instructions. The three assays are based on an automated particle-enhanced

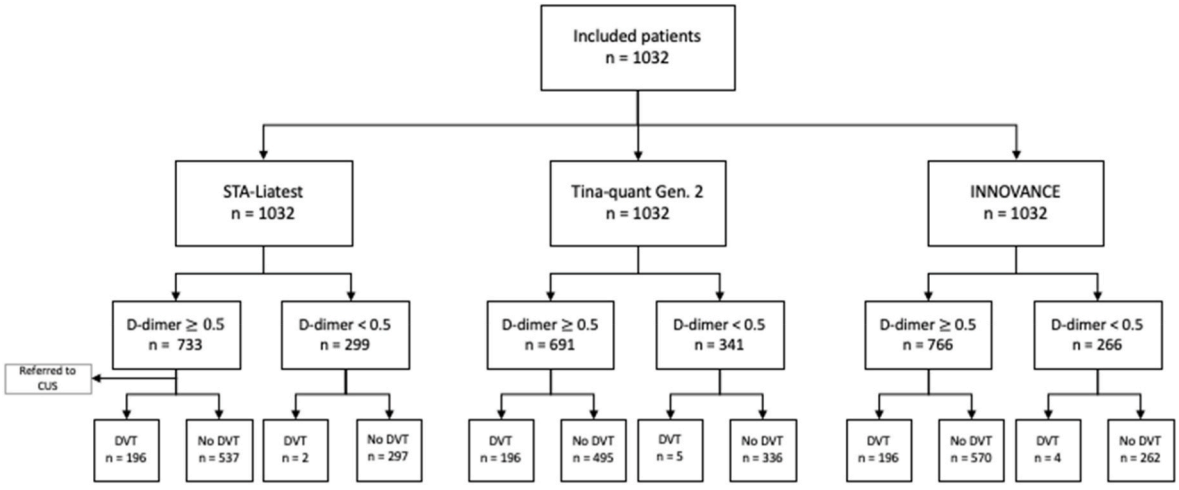

Fig. 1. Flowchart of study flow and outcomes at baseline based on fixed D-dimer cut-off. CUS = compression ultrasonography.

immunoturbidimetric method where monoclonal antibodies bound to latex beads detect and bind to plasma D-dimer and report D-dimer results in fibrinogen equivalent units. The reportable ranges of the assays varied and were 0.40–20 μg/mL for the STA-Liatest, 0.20–21 μg/mL for the Tina-quant Gen. 2, and 0.19–35 μg/mL for the INNOVANCE assay. The assays were calibrated according to the manufacturer's instructions, and their performances were regularly monitored by external quality control.

2.3. Pre-test probability score and compression ultrasonography

All patients included in the Ri-Schedule study underwent a clinical pre-test probability assessment of DVT using the three-tier Wells score [8,9]. The three-tier Wells score consists of eight parameters, and ranges between −2 and 8 points. It categorizes patients into low-risk (≤0 points), moderate-risk (1–2 points), and high-risk (≥3 points) of having DVT [11]. According to the Wells score, patients in the high-risk group should be referred for compression ultrasonography without D-dimer testing. However, in the Ri-Schedule study, all patients who had a D-dimer ≥0.5 μg/mL were referred for compression ultrasonography; patients with a D-dimer <0.5 μg/mL did not undergo this examination, regardless of their Wells score, with the exception of those in whom compression ultrasonography was needed to confirm or exclude other diagnosis [9] (see Fig. 1).

2.4. Statistical analyses

Median D-dimer concentrations were calculated per assay and values were expressed by median and interquartile range (IQR). Sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), efficiency, and failure rate were calculated with their 95% confidence interval (95% CI) for each assay using IBM SPSS Statistics for Windows, Version 26, Microsoft Excel, and MedCalc calculator [12]. Efficiency was defined as the proportion of patients in whom DVT had been ruled out based on D-dimer testing without compression ultrasonography. Failure rate was defined as the proportion of patients with negative D-dimer, but who were nevertheless diagnosed with DVT with compression ultrasonography either at baseline or within the 90 days follow-up period.

We used the STARD checklist to report our findings from this study [13].

3. Results

The mean age of the 1032 patients was 59 years (range 18–95). Median D-dimer values were 0.80 μg/mL (IQR 0.4–1.8) with STA-Liatest, 0.70 μg/mL (0.3–1.5) with Tina-quant Gen. 2, and 0.96 μg/mL (0.5–2.1) with INNOVANCE. Of the 1032 patients, 733 patients (71%) had a positive D-dimer with the STA-Liatest, 691 patients (67%) with the Tina-quant Gen. 2, and 766 (74%) with the INNOVANCE assay.

DVT was confirmed by compression ultrasonography examination in 196 patients (27%) with positive and 2 (0.7%) with negative D-dimer results with STA-Liatest, 196 patients (28%) with positive and 5 (2%) with negative D-dimer with Tina-quant Gen. 2, and 196 (26%) with positive and 4 patients (2%) with negative D-dimer with INNOVANCE. In total, six patients (3%) had DVT confirmed by compression ultrasonography examination but had a D-dimer result <0.5 μg/mL (false negative) with at least one of the three assays: two with STA-Liatest giving a failure rate of 0.7% (95% CI 0.1–2), five with the Tina-quant Gen. 2 resulting in a failure rate of 2% (95% CI 0.5–3), and four with the INNOVANCE assay yielding a failure rate of 2% (95% CI 0.4–4) (Table 1).

One patient out of the six had a false negative D-dimer with all the three assays. The false negative blood samples were reanalyzed and no discordant differences in the results were found for the STA-Liatest and Tina-quant Gen. 2. However, for the INNOVANCE assay one of the false negative D-dimer results became positive (Supplementary Table, patient number 2), and one of the true positive results became false negative (Supplementary Table, patient number 6), thus an unchanged total result.

By using a fixed D-dimer cut-off as stand alone, STA-Liatest had the highest sensitivity of 99.0% (95% CI 96.4–99.9), and Tina-quant Gen. 2 the highest specificity of 41% (95% CI 37–44). STA-Liatest had the highest NPV 99.3% (95% CI 97.4–99.8), and Tina-quant Gen. 2 the highest PPV 28% (95% CI 27–29) (Table 2). The application of age adjusted cut-off resulted in slightly lower sensitivity and NPV, and slightly higher specificity and PPV for all three assays (Table 2).

The efficiency of the assays, defined as the number of patients in whom DVT could be excluded based on a fixed D-dimer cut-off <0.5 μg/mL alone was 29% (95% CI 26–33) for STA-Liatest, 33% (95% CI 30–37) for Tina-quant Gen. 2, and 26% (95% CI 23–29) for INNOVANCE. The addition of Wells score <3 to the fixed D-dimer cut-off (Wells score was available for 993 of the patients) yielded a lower efficiency, but still highest for Tina-quant Gen. 2 with 30% (95% CI 26–33) (Table 1). The efficiency of the assays based on age-adjusted D-dimer as stand-alone was 40% (95% CI 37–45) for STA-Liatest, 44% (95% CI 40–49) for Tina-quant Gen. 2, and 35% (95% CI 31–38) for INNOVANCE, and with the addition of Wells score <3 became slightly lower (Table 1).

4. Discussion

This study showed good diagnostic performance for the three the D-dimer assays STA-Liatest, Tina-quant Gen. 2, and INNOVANCE in the exclusion of DVT. The failure rate was lowest with STA-Liatest (0.7%), and the efficiency of the assays to exclude DVT was highest for Tina-quant Gen. 2 (33%) (Table 1). By using fixed D-dimer cut-off as a stand-alone test, all three assays had a sensitivity ≥97% and NPV ≥98%. Applying age-adjusted cut-off as a stand-alone test resulted in lower sensitivity and NPV, but higher efficiency, i.e. less ultrasonographic examinations required, at the cost of a failure rate of ≥2% for all the three assays. This increase in the failure rate was less pronounced for the INNOVANCE assay which could be attributed to the fact that the D-dimer results were generally higher by this assay than the other two assays; therefore, fixed cut-off is more correct for STA-Liatest and Tina-

Table 1
Efficiency and failure rate with or without Wells score.

	Fixed cut-off			Age-adjusted cut-off		
	STA-Liatest	Tina-quant	INNOVANCE	STA-Liatest	Tina-quant	INNOVANCE
Efficiency (%)						
Without Wells score	29% (26–33)	33% (30–37)	26% (23–29)	40% (37–45)	44% (40–49)	35% (31–38)
With Wells score	26% (23–29)	30% (26–33)	24% (21–27)	36% (32–40)	38% (35–42)	32% (29–36)
Failure rate (%)						
Without Wells score	0.7% (0.1–2)	2% (0.5–3)	2% (0.4–4)	3% (1–50)	3% (2–5)	2% (0.8–4)
With Wells score	0.8% (0.1–3)	1% (0.4–4)	1% (0.3–4)	2% (1–40)	3% (1–5)	2% (0.9–5)

Efficiency: the proportion of patients in whom DVT had been ruled out based on D-dimer testing without compression ultrasonography. Failure rate: the proportion of patients with negative D-dimer, who were diagnosed with DVT with compression ultrasonography.

Table 2
Diagnostic performance of the three D-dimer assays.

	Fixed cut-off			Age-adjusted cut-off		
	STA-Liatest	Tina-quant	INNOVANCE	STA-Liatest	Tina-quant	INNOVANCE
Sensitivity	99.0% (96.4–99.9)	97.5% (94.1–99.2)	98.0% (94.9–99.0)	94.4% (90.2–97.2)	93.4% (89–96.4)	96.4% (92.8–98.6)
Specificity	36% (33–39)	41% (37–44)	32% (29–35)	49% (45–52)	53% (50–57)	42% (38–45)
NPV	99.3% (97.4–99.8)	98.5% (96.6–99.4)	98.5% (96.1–99.4)	97.3% (95.3–98.5)	97.1% (95.2–98.3)	98.0% (95.9–99.0)
PPV	27% (26–28)	28% (27–29)	26% (25–26)	30% (29–32)	32% (30–34)	28% (27–30)

quant Gen. 2. The addition of Wells score to the fixed D-Dimer cut-off and to the age-adjusted D-Dimer cut-off showed lower efficiencies for the three assays.

According to the Clinical and Laboratory Standards Institute (CLSI) guidelines, the recommended assay characteristics when testing patients with low or intermediate pre-test probability of VTE are a sensitivity of ≥97% with lower limit of the one-sided CI to ≥ 90%, and a NPV of ≥98% with lower limit of the one-sided CI of ≥95% [14]. All the three assays fulfilled the CLSI recommended characteristics for both the sensitivity and NPV.

Other studies evaluating the performance of and comparing different D-dimer assays such as INNOVANCE, Tina-quant, AxSYM, Quantia D-dimer (both Abbott Diagnostics), Auto Dimer (Trinity Biotech), D-Dimer HS (Intrumentation Laboratory), and D-Dimer Plus (Siemens), have found similar results for the sensitivity and NPV for D-dimer assays [15, 16]. A recent study by Hamer et al. also found a slightly higher NPV and sensitivity for STA-Liatest and INNOVANCE than Tina-quant, and that Tina-quant had a higher specificity in the exclusion of pulmonary embolism [17].

To our knowledge, two studies have validated the clinical performance of the Tina-quant D-Dimer Gen. 2 assay on the relatively new Cobas t711 analyzer for evaluation of patients with suspected DVT [18, 19]. These studies found slightly higher sensitivity than our study of 99.3% (95% CI 96.0–100.0) and 100.0% (95% CI 93.9–100.0), and NPV of 100% (95% CI 99.7–100.0). However, unlike the Ri-Schedule study, both of these studies excluded patients with symptoms for more than seven days, distal DVT, and patients with previous DVT and/or pulmonary embolism. Age-adjusted cut-off was investigated in one of these studies showing only a small reduction in sensitivity and NPV [19].

When applying age-adjusted cut-off to our data, the specificity increased, while both the sensitivity and the NPV decreased (Table 2). Only the INNOVANCE assay met the CLSI requirements for the NPV, and none for the sensitivity. However, regulatory requirements vary, and the Food and Drug Administration (FDA) in the USA has set the requirements for a D-dimer assay to exclude VTE together with the pre-test probability-score, to have a NPV ≥97% and sensitivity ≥95%. For the age-adjusted values, all assays met the FDA requirements for the NPV, but only INNOVANCE met the sensitivity requirements. The center participating in our study that is using the INNOVANCE assay, is applying age-adjusted cut-off. If age-adjusted cut-off would have been implemented for Tina-quant Gen. 2 and STA-Liatest, it would have resulted in a considerable decrease in sensitivity and NPV.

In a previous study by Fronas et al. where 1397 patients from the Ri-Schedule study were included, and STA-Liatest D-dimer with fixed cut-off was used together with whole-leg ultrasonography to rule out VTE, a failure rate for their strategy of 2% with an upper limit of the 95% confidence interval of 4% was accepted [9]. This failure rate was based on the rate of symptomatic VTE within 3 months of a negative venography (1.2%, 95% CI 0.2–4.4), which is the reference standard diagnostic management studies of DVT are typically evaluated against [9, 20]. Using fixed D-dimer cut-off as stand-alone resulted in 299 fewer compression ultrasonography examinations with STA-Liatest, 341 with Tina-quant Gen. 2, and 266 with INNOVANCE, rather than examining all patients with a suspected DVT with compression ultrasonography. With fixed D-dimer all the assays had a failure rate of ≤2% (Table 1). When applying Wells score to the fixed D-dimer, the failure rate decreased to 1% for Tina-quant Gen.2 and INNOVANCE, and just slightly increased with STA-Liatest, but the highest upper limit of the 95% CI remained ≤4%. By implementing age-adjusted D-dimer as a stand-alone test the efficiency increased, and this would have resulted in 417 fewer compression ultrasonography examinations with STA-Liatest, 457 with Tina-quant Gen. 2, and 356 with INNOVANCE, compared to examining all patients with a suspected DVT, at the cost of a higher failure rate of ≥2% for all assays. Applying Wells score <3 in combination with age-adjusted cut-off lowered the efficiency and more compression ultrasonography examinations would have been required.

In this study, six patients were confirmed to have DVT by compression ultrasonography but had D-dimer results <0.5 μg/mL with at least one of the three assays. Although D-dimer levels could decrease with time following thrombus formation, the symptom duration for these patients was less than 7 days. The Wells score for these patients varied between −1 and 3. When applying age-adjusted cut-off to these six patients, two more patients would have been missed with the STA-Liatest. All except one patient have had either DVT previously or other risk factors for VTE. Two of the six had a proximal DVT, two had distal DVT, and two had muscle vein thromboses. One patient with muscle vein thrombosis had negative D-dimer results with all assays. D-dimer could be less sensitive and have a lower NPV regarding distal DVT compared to proximal DVT [21]. Furthermore, there is no consensus regarding treatment of muscle vein thrombosis, and the evidence is not conclusive whether the benefit of treatment with anticoagulant therapy outweighs the risk of adverse effects [22]. However, more recent studies have shown that anticoagulant therapy for these patient were not superior to placebo [21].

The main limitation of the study is that the samples were analyzed retrospectively at two different laboratories and were not reanalyzed by the assay that they were originally analyzed with (STA-Liatest). Another limitation of the study is that we did not analyze markers of fibrinolysis, hence, defective fibrinolysis might have affected our D-dimer results. Although frozen samples were used in this study, it has been shown that D-dimer is stable in frozen samples up to three years at −60 °C [23]. The strength of our study is the large study population of 1032 patients, which included patients with both proximal and distal DVT and those with previous thromboembolism, and that all patients with suspected DVT were included regardless of symptom duration.

5. Conclusion

STA-Liatest, Tina-quant Gen. 2, and INNOVANCE showed good diagnostic performances with sensitivity ≥97% and NPV ≥98% when using fixed D-dimer cut-off. The efficiency to exclude DVT varied and was highest for Tina-quant Gen. 2, whereas the failure rate was lowest for STA-Liatest. Age-adjusted cut-off resulted in lower sensitivity and NPV, but higher efficiency and failure rate for the three assays; however, the increase in the failure rate was less pronounced for the INNOVANCE assay.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Lamya Garabet reports a relationship with Grifols Inc that includes: speaking and lecture fees. Waleed Ghanima reports a relationship with Amgen Inc that includes: consulting or advisory and speaking and lecture fees. Waleed Ghanima reports a relationship with Novartis Pharmaceuticals Corporation that includes: consulting or advisory and speaking and lecture fees. Waleed Ghanima reports a relationship with Pfizer that includes: consulting or advisory and speaking and lecture fees. Waleed Ghanima reports a relationship with Principia BioPharma Inc that includes: consulting or advisory. Waleed Ghanima reports a relationship with Sanofi that includes: consulting or advisory and speaking and lecture fees. Waleed Ghanima reports a relationship with SOBI (France) that includes: consulting or advisory and speaking and lecture fees. Waleed Ghanima reports a relationship with Grifols Therapeutics Inc that includes: consulting or advisory and speaking and lecture fees. Waleed Ghanima reports a relationship with UCB Inc that includes: consulting or advisory. Waleed Ghanima reports a relationship with argenx nv that includes: consulting or advisory. Waleed Ghanima reports a relationship with Cellphire Inc that includes: consulting or advisory. Waleed Ghanima reports a relationship with Bristol Myers Squibb Co that includes: speaking and lecture fees. Waleed Ghanima reports a relationship with Bayer Corporation that includes: speaking and lecture fees. Camilla Tovik Jorgensen reports a relationship with Bayer AG that includes: speaking and lecture fees.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tru.2023.100147.

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