Thrombogenicity markers for early diagnosis and prognosis in COVID-19: a change from the current paradigm?

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Standard biomarkers have been widely used for COVID-19 diagnosis and prognosis. We hypothesize that thrombogenicity metrics measured by thromboelastography will provide better diagnostic and prognostic utility versus standard biomarkers in COVID-19 positive patients. In this observational prospective study, we included 119 hospitalized COVID-19 positive patients and 15 COVID-19 negative patients. On admission, we measured standard biomarkers and thrombogenicity using a novel thromboelastography assay (TEG-6s). In-hospital all-cause death and thrombotic occurrences (thromboembolism, myocardial infarction and stroke) were recorded. Most COVID-19 patients were African–Americans (68%). COVID-19 patients versus COVID-19 negative patients had higher platelet-fibrin clot strength (P-FCS), fibrin clot strength (FCS) and functional fibrinogen level (FLEV) ($P \leq 0.003$ for all). The presence of high TEG-6 s metrics better discriminated COVID-19 positive from negative patients. COVID-19 positive patients with sequential organ failure assessment (SOFA) score at least 3 had higher P-FCS, FCS and FLEV than patients with scores less than 3 ($P \leq 0.001$ for all comparisons). By multivariate analysis, the in-hospital composite endpoint occurrence of death and thrombotic events was independently associated with SOFA score more than 3 [odds ratio (OR) = 2.9, $P = 0.03$], diabetes (OR = 3.3, $P = 0.02$) and FCS > 40 mm (OR = 3.4, $P = 0.02$). This largest observational study suggested the early diagnostic and prognostic utility of thromboelastography to identify COVID-19 and should be considered hypothesis generating. Our results also support the recent FDA guidance regarding the importance of measurement of whole blood viscoelastic properties in COVID-19 patients. Our findings are consistent with the observation of higher hospitalization rates and poorer outcomes for African–Americans with COVID-19. *Blood Coagul Fibrinolysis* **32:544–549**

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Introduction

Coronavirus disease 2019 (COVID-19) is a thromboinflammatory disease. Coagulation abnormalities during COVID-19 are associated with a poor prognosis. Standard biomarkers, including D-dimer, C-reactive protein (CRP), lactate dehydrogenase, white blood cell count (WBC), procalcitonin, ferritin and troponin-I have been used to assess both management and prognosis of thromboembolic complications in COVID-19 patients [1,2]. Conventional thromboelastography (TEG) determined high platelet–fibrin clot strength (P-FCS) is associated with thrombotic event occurrences in patients undergoing coronary artery stenting [3,4]. Similarly, a hypercoagulable profile was identified in patients admitted with COVID-19 to critical care settings as compared to a normal reference population and was associated with thromboembolic complications [5–9]. We and others have shown inadequate response to anticoagulation in patients with COVID-19 as measured by TEG [10,11].

Our goals of this study were as follows. As prior studies compared thrombogenicity in COVID-19 to a healthy reference population, we compared thrombogenicity/hypercoagulability in patients with pneumonia but without COVID-19. We felt that these comparisons would provide a comparative perspective of the derangements in haemostasis in COVID-19. We measured thrombogenicity using a novel TEG assay (TEG-6 s, Haemonetics Corporation, Braintree, Massachusetts, USA) and compared them with standard biomarkers to determine which measurements provided earlier evaluation of COVID-19. As data are only emerging on the relation of early biomarker measurements to outcomes, we analysed the relation of thrombogenicity, and standard biomarkers measured on presentation to the Sequential Organ Failure Assessment (SOFA) score.

Materials and methods

We report an analysis of the ongoing The Evaluation of Hemostasis by Thromboelastography, Platelet Function

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Testing and Biomarker Analysis in Hospitalized COVID-19 Patients (TARGET-COVID) study (URL: https://www.clinicaltrials.gov; Unique identifier: NCT04493307). The study was performed in accordance with standard ethical principles and approved by the Institutional Review Board at Lifebridge Health, Baltimore. Written consent was obtained from all patients. The study was conducted following the 'Ethical Principles for Medical Research Involving Human Subjects' outlined in the Declaration of Helsinki.

Hospitalized patients with COVID-19 and suspected COVID-19

Patients hospitalized between 24 April 2020 and 10 December 2020 at the Sinai Hospital of Baltimore with at least one of the following were prospectively enrolled: a confirmed COVID-19 diagnosis by reverse transcription-PCR or immunoglobulin (Ig)M antibody assay before or during hospitalization, a negative reverse transcription-PCR assay but symptoms of COVID-19, an elevated D-dimer and imaging showing pneumonia or ground glass pulmonary opacity.

Blood and urine samples

Laboratory assessments in COVID-19 patients were obtained as soon as possible after hospital admission. Venous blood was collected into Vacutainer tubes (Becton-Dickinson, Franklin Lakes, New Jersey, USA) containing 3.2% trisodium citrate for the TEG-6 s assay.

Thromboelastography

The novel TEG-6 s is a microfluidic automated cartridge-based assay that can be used at the bedside [12]. The citrated multichannel assay measures platelet-fibrin clot strength or maximum amplitude (P-FCS or MA), reaction time (R, a measure of the enzymatic phase of coagulation), kinetics (K, a measure of the time to reach 20 mm of clot strength from R), angle (α, reflective of the velocity of clot strength generation), FCS (a measure of fibrin clot strength measured in the presence of tissue factor and glycoprotein IIb/IIIa inhibitor to isolate the contribution of fibrinogen during clot generation) and functional fibrinogen levels (FLEV, is extrapolated from the FCS) [12].

Standard biomarkers markers of COVID-19

These markers were analysed in the central pathology laboratory at the Sinai Hospital of Baltimore. Lactate dehydrogenase, CRP and ferritin were measured using Siemens Advia Chemistry XPT systems (Siemens Medical Solutions USA, Inc. Malvern, Pennsylvania, USA). Procalcitonin was measured using Abbott ARCHITECT B.R.A.H.M.S PCT assay (Abbott, Abbott Parks, Illinois, USA). Complete blood cell analysis was performed using Sysmex XN-1000 Hematology Analyser (Sysmex America Inc, Lincolnshire, Illinois, USA). Coagulation parameters were measured using STA Compact Max Analyser (Diagnostica Stago, Inc., Parsippany, New Jersey, USA).

Sequential organ failure assessment

The SOFA score is based on PaO_2, FiO_2, presence or absence of mechanical ventilation, platelet number, Glasgow coma scale, bilirubin, mean arterial pressure or administration of vasoactive agents and creatinine (https://www.mdcalc.com/sequential-organ-failure-assessment-sofa-score). Patients were categorized as SOFA score at least 3 and less than 3 for comparison of standard and TEG makers.

Clinical events

Patients were followed for in-hospital events, including all-cause death, thromboembolism (systemic or pulmonary), myocardial infarction (MI), transient ischemic attack and ischemic or haemorrhagic stroke.

Statistical analysis

Continuous values were shown as mean ± SD for normally distributed data and mean and confidence interval for not normally distributed data. The Shapiro–Wilk test was used to determine the normality of data. Categorical variables were shown as counts and percentages. A repeated measure of variance and unpaired *t*-test analyses were used for between-group comparisons for normally distributed data, while the Kruskal–Wallis test was used for comparing nonparametric data. High cutoff values for TEG and conventional biomarkers were based on the upper cut off values of the normal range for each parameter reported by the manufacturer. *P* value less than 0.05 was considered a significant difference between treatments (MedCalc Software Ltd, Ostend, Belgium). After dichotomization of continuous variables using the optimal cut-off, categorical variables were evaluated in a univariate analysis for predicting the presence of high TEG and standard COVID-19 markers. Variables with *P* value less than 0.1 were then entered into the multivariate analysis providing odds ratio (OR) and *P* value.

Results

Most COVID-19 patients were African–Americans (67%), obese (57 versus 24% in the COVID-19 negative group, $P = 0.01$) and receiving anticoagulants (94%), aspirin (31%), antibiotics (79%), antiviral agents (41%), convalescent plasma (37%) and corticosteroids (77%) (Tables 1 and 2). Standard biomarker values were above the upper normal reference levels but similar between groups ($P > 0.05$ for all comparisons) (Fig. 1). Overall, COVID-19 patients compared with COVID-19 negative patients had higher P-FCS ($P = 0.003$), FCS ($P = 0.002$) and FLEV ($P = 0.001$) (Table 3). Moreover, the presence of high TEG-6 s metrics better discriminated COVID-19 positive from COVID-19 negative patients. The prevalence of high levels of standard biomarkers did not differ

Table 1 Patient demographics

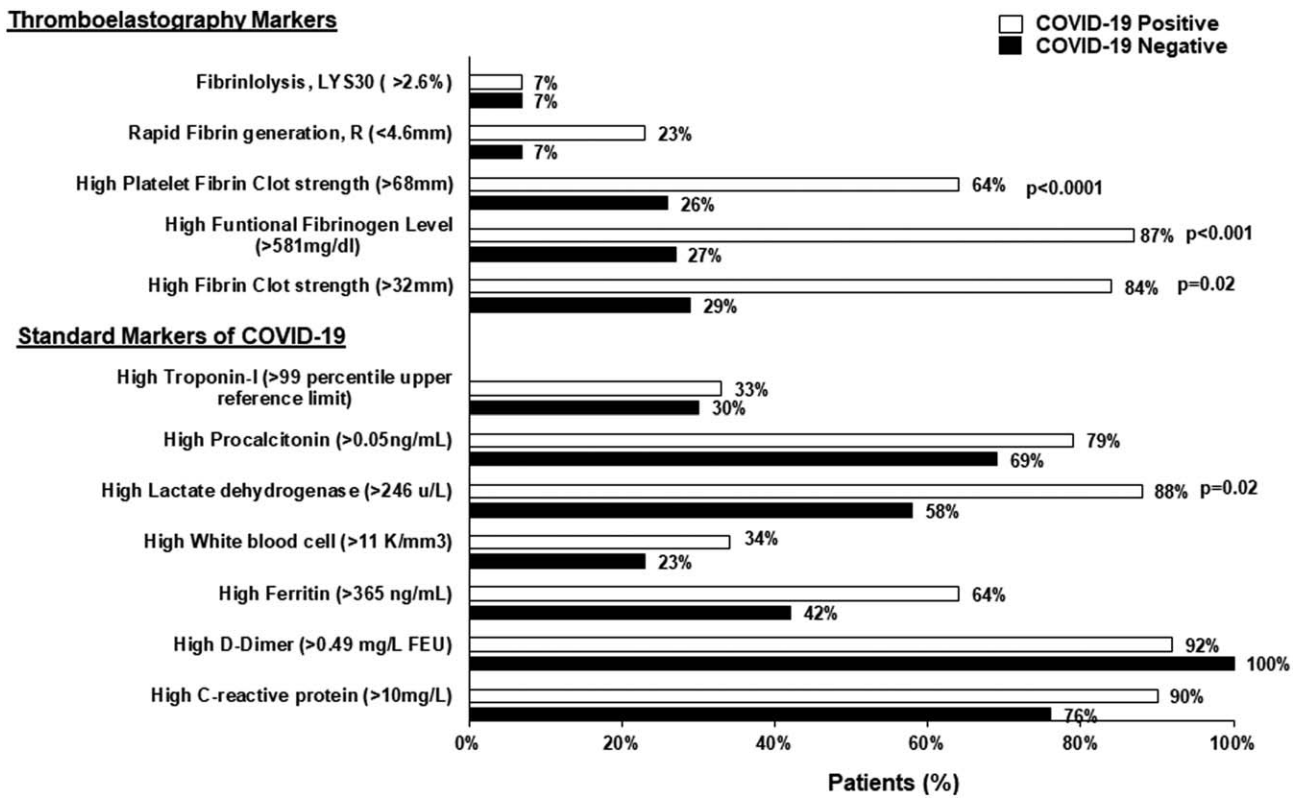
	COVID-19 negative patients ($n=18$)	COVID-19 positive patients ($n=119$)	*P*
Age (years)	63 ± 20	59 ± 18	0.42
Male, %	56	58	0.88
Race, %			
African–American	67	66	0.93
Hispanic	0	13	0.14
White	33	19	0.21
Asian	0	2	0.58
BMI (kg/m^2)	29.8 ± 15.0	34.0 ± 13.3	0.25
Co-Morbidities			
No. Co-morbidities (mean ± SD)	3.3 ± 2.2	3.7 ± 2.0	0.47
Hypertension, %	61	73	0.33
Hyperlipidaemia, %	41	35	0.63
Obesity, %	24	57	0.01
Diabetes mellitus, %	24	46	0.09
Cardiovascular disease, %	24	22	0.78
Respiratory disease, %	42	22	0.07
Neurological disease/mental illness	42	27	0.20
Renal or liver disease, %	7	23	0.15
Cancer/Autoimmunity, %	27	19	0.47
SOFA Score (mean ± SD)	2.1 ± 1.7	3.3 ± 3.1	0.14

Table 2 Medications in COVID-19 positive and negative patients

	COVID-19 negative ($n=18$)	COVID-19 positive ($n=119$)	*P*
Antiviral medications, %			
Remdesivir	0	32	–
Hydroxychloroquine	0	9	–
Convalescent plasma	0	37	–
Antithrombotic medications, %			
None	7	6	0.87
Enoxaparin prophylaxis	40	46	0.64
Heparin prophylaxis	13	25	0.28
Therapeutic Anticoagulation	40	22	0.11
Aspirin	38	31	0.41
$P2Y_{12}$ inhibitor	7	6	0.87
Antibiotic medications, %			
Ceftriaxone	44	53	0.48
Azithromycin	38	48	0.44
Vancomycin	31	9	0.008
Steroids	25	77	<0.001
Statins	44	35	0.47
Proton pump inhibitors/ Histamine-2 blockers	33	40	0.48

between groups except for higher lactate dehydrogenase in COVID-19 positive patients ($P=0.02$). COVID-19 positive patients had a much higher prevalence of high platelet-fibrin clot strength ($P<0.001$), functional fibrinogen levels ($P<0.001$) and fibrin clot strength ($P=0.02$) (Fig. 1). COVID-19 positive patients with SOFA score of at least 3 had higher platelet-fibrin clot strength, fibrin clot strength and functional fibrinogen levels than patients with scores less than 3 ($P\leq0.001$ for all comparisons). Among standard markers, age, D-dimer and white blood

Fig. 1



Thromboelastography and standard markers in COVID-19 positive and negative patients. FEU, fibrinogen equivalent units.

Table 3 Thromboelastography metrics and standard biomarkers

	COVID-19 positive patients ($n = 119$)	COVID-19 negative patients ($n = 18$)	*P*
Platelet-fibrin clot strength (mm)	68.4 ± 4.9	64.4 ± 6.6	0.003
Fibrinogen clot strength (mm)	42.0 ± 11.5	31.3 ± 12.9	0.002
Functional fibrinogen level (mg/dl)	773 ± 203	575 ± 221	0.001

COVD-19 positive patients

	SOFA score ≥3	SOFA score < 3	*P*
Platelet-fibrin clot strength (mm)	70 ± 5	67 ± 5	0.001
Fibrinogen clot strength (mm)	44 ± 13	36 ± 11	<0.001
Functional fibrinogen level (mg/dl)	848 ± 198	678 ± 201	<0.001
Age (years)	65 ± 15	55 ± 18	0.002
D-dimer (fibrinogen equivalent units)	3.7 ± 4.1	1.8 ± 3.1	0.004
White blood cells	10.6 ± 4.8	8.5 ± 4	0.006

Values are expressed as mean ± standard deviation. SOFA, sequential organ failure assessment.

cells were higher in patients with SOFA score of at least 3 ($P \leq 0.006$ for all comparisons) (Table 3). Whites have lower functional fibrinogen levels compared with African–Americans ($P = 0.035$) and there was an overall trend for higher values for P-FCS, FCS and FLEV among African–Americans and Hispanics compared with whites (Table 4). Patients who died ($n = 16$) were older (73 ± 11 versus 56 ± 18 years, $P = 0.001$), and had higher SOFA score (7.7 ± 4.5 versus 2.7 ± 2.1, $P < 0.001$), D-dimer (5.6 ± 5.5 versus 2.2 ± 3.1 mg/l fibrinogen equivalent units, $P = 0.003$), CRP (150 ± 105 versus 90 ± 78 mg/l, $P = 0.03$), ferritin (0.94 ± 0.25 versus 0.62 ± 0.49 ng/ml, $P = 0.03$), procalcitonin (6.4 ± 17.1 versus 0.7 ± 1.9 ng/ml, $P = 0.01$), fibrinogen clot strength (45 ± 12 versus 38 ± 12 mm, $P = 0.05$) and functional fibrinogen levels (871 ± 194 versus 736 ± 216 mg/dl, $P = 0.02$). By multivariate analysis, the in-hospital composite endpoint occurrence of death ($n = 16$) and thrombotic events (venous thrombosis = 1, pulmonary thromboembolism = 6, MI = 24 and stroke = 3) was independently associated with SOFA score more than 3 (OR = 2.9, $P = 0.03$), diabetes (OR = 3.3, $P = 0.02$) and fibrin clot strength more than 40 mm (OR = 3.4, $P = 0.02$).

Discussion

Our novel study using point-of-care TEG in COVID-19 demonstrated greater thrombogenicity in COVID-19 positive patients than COVID-19 negative patients with pneumonia as indicated by higher platelet-fibrin clot strength, fibrin clot strength and functional fibrinogen level and a greater incidence of high platelet-fibrin clot strength, fibrin clot strength and functional fibrinogen level. High TEG-6s metrics better discriminated COVID-19 positive patients from negative patients than elevated standard markers and fibrin clot strength and functional fibrinogen levels were associated with death and fibrin clot strength was independently associated with the composite endpoint occurrence of death and thrombotic events.

Earlier, haematological changes in COVID-19 were compared with disseminated intravascular coagulation (DIC) and anticoagulant therapy was suggested based on DIC. DIC-induced by sepsis, pneumonia and so on, is due to excessive activation of coagulation with the consumption of coagulation factors. The main characteristics of DIC are prolonged activated partial thromboplastin time/prothrombin time (aPTT/PT), thrombocytopenia, elevated d-dimer and microangiographic thrombosis. Although COVID-induced coagulopathy (CIC) is associated with elevated d-dimer and inflammation markers (CRP, interleukin-6, procalcitonin, ferritin), there are mild changes in aPTT/PT and platelet count and significantly higher fibrinogen is the hallmark observation in COVID-19. Thrombocytopenia has been reported mainly in critically ill COVID-19 patients. It has been suggested that elevated levels of factor VIII/ Von Willebrand factor

Table 4 Thromboelastography metrics in African–Americans, whites and Hispanics

	African–Americans ($n = 79$)	Whites ($n = 23$)	Hispanics ($n = 15$)
Platelet-fibrin clot strength (mm)	68.6 ± 4.9	67.1 ± 4.2	70 ± 5.9
Fibrinogen clot strength (mm)	41.7 ± 12.2	37.1 ± 10.6	41.1 ± 14.2
Functional fibrinogen level (mg/dl)	776 ± 209	674 ± 173*	824 ± 241

* $P = 0.035$ between African–Americans and whites.

(indicating dysfunctional endothelium) and elevated fibrinogen levels (indicating the acute phase response induced by interleukin-6/cytokine storm) most likely contribute to the prothrombotic state that may be confined to lungs.

In our study, patients with COVID-19 and patients admitted with pneumonia with high d-dimer levels have similar rate of high troponin, procalcitonin, lactate dehydrogenase, white blood cell count, ferritin and CRP. However, hypercoagulability markers such as high platelet-fibrin clot strength, fibrin clot strength and high fibrinogen levels are the main distinctive characteristics that differentiate COVID-19 patients from patients admitted with pneumonia. Thus far, elevated D-dimer levels have been attributed to high coagulation activity and used as a marker of breakdown of clot that may be highly present in lungs. On the basis of these observations, D-dimer levels have been used to personalize intensification of anticoagulant therapy. However, recent observations demonstrated that elevated levels of D-dimer are due to extravascular fibrin degradation and due to fibrinolytic breakdown of the pulmonary thrombi. In light of this recent observation and our study results, we suggest that intensification of anticoagulation may be more appropriate based on hypercoagulability characteristics measured by viscoelastic assay such as TEG6 s.

Haematological changes in COVID-19 were earlier compared with DIC, and anticoagulant therapy was suggested based on observations similar to DIC [13,14]. DIC induced by sepsis or pneumonia is associated with an excessive activation of coagulation with the consumption of coagulation factors. The main characteristics of DIC are prolonged aPTT/PT, thrombocytopenia, elevated d-dimer and microangiographic thrombosis [15]. Although CIC is associated with elevated d-dimer and inflammation markers (CRP, interleukin-6, procalcitonin, ferritin), there are mild changes in aPTT/PT and platelet count and significantly elevated fibrinogen level is the hallmark observation in COVID-19. Thrombocytopenia has been reported mainly in critically ill COVID-19 patients. It has been suggested that elevated levels of factor VIII/ Von Willebrand factor (indicating dysfunctional endothelium) and elevated fibrinogen levels (indicating the acute phase response induced by interleukin-6/cytokine storm) most likely contribute to the prothrombotic state in COVID-19 patients that may be confined to the lungs [16]. In the current study, patients with COVID-19 and patients admitted with pneumonia with high d-dimer levels have a similar rate of high troponin, procalcitonin, lactate dehydrogenase, white blood cell count, ferritin and CRP, whereas hypercoagulability markers such as high platelet-fibrin clot strength, fibrin clot strength and high fibrinogen levels are the main distinctive characteristics that differentiate COVID-19 patients from patients admitted with pneumonia. Thus far, elevated D-dimer levels have been attributed to high coagulation activity, used as a marker of the clot breakdown in the lungs and correlated with worst clinical outcomes. On the basis of these observations, D-dimer levels have been used to personalize the intensification of anticoagulant therapy [13,17]. However, recent studies suggest that elevated pulmonary inflammation during COVID-19 is associated with very high levels of fibrinogen that are leaked into systemic circulation and converted into fibrin and then degraded to d-dimer by proteolytic enzymes released from neutrophils [18]. Thus, high d-dimer levels observed during COVID-19 may indicate high degree (cytokine storm) of lung inflammation rather than in situ thrombus formation. Considering these recent observations and our study results, we suggest that intensification of anticoagulation may be more appropriate based on hypercoagulability characteristics measured by viscoelastic assays than D-dimer levels.

Limitations

A major limitation of this study is that the number of COVID-19 negative patients are low, both groups are not statistically comparable. Unlike most of the previous studies that compared the COVID-19 patients with healthy controls, we have included hospitalized patients with a negative reverse transcription-PCR assay, but symptoms of COVID-19, an elevated D-dimer and imaging showing pneumonia or ground glass pulmonary opacity. We felt that these comparisons would provide a comparative perspective of the derangements in haemostasis in COVID-19. Therefore, it was difficult to enrol a substantial number of hospitalized patients with pneumonia but without COVID-19. Secondly, the study population is mainly consisted of African–Americans and our findings are consistent with the observation of higher hospitalization rates and poorer outcomes for African–Americans with COVID-19. Extrapolation of our findings to other races and ethnicities will require a further study.

Due to limited number of patients, we could only demonstrate an overall trend for higher values for P-FCS, FCS and FLEV among African–Americans and Hispanics compared with whites.

Finally, this is also the largest observational study to assess the early diagnostic and prognostic utility of TEG versus standard biomarkers to identify COVID-19 and should be considered hypothesis generating. Point-of-care TEG may be more useful to rapidly discriminate patients with COVID-19 and provide important prognostic information including prediction of death at an early stage as compared to standard biomarkers. TEG-6 s metrics support an important role for fibrinogen in the thrombotic complication in COVID-19. Very recently, the United States Food and Drug Administration (FDA) published a guidance highlighting the importance of measurement of whole blood viscoelastic properties to facilitate patient management by healthcare providers during the COVID-19 public health emergency

[19]. The current study results support the above FDA guidance. The study population mainly consisted of African–Americans and our findings are consistent with the observation of higher hospitalization rates and poorer outcomes for African–Americans with COVID-19 [14]. Our evidence also provides a potential mechanistic explanation for racial disparities observed in COVID-19 and requires further investigation [20]. These findings are particularly relevant to ongoing studies of antithrombotic therapy in COVID-19, wherein personalization of therapy could be facilitated by the bedside assessment of specific TEG metrics.

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Conflicts of interest

Dr. Gurbel reports grants and personal fees from Bayer HealthCare LLC, Otitopic Inc, Amgen, Janssen, and US WorldMeds LLC; grants from Instrumentation Laboratory, Haemonetics, Medicure Inc, Idorsia Pharmaceuticals, and Hikari Dx; personal fees from UpToDate; Dr. Gurbel is a relator and expert witness in litigation involving clopidogrel; in addition, Dr. Gurbel has two patents, Detection of restenosis risk in patients issued and Assessment of cardiac health and thrombotic risk in a patient.

Dr. Levy serves on steering committees for Instrumentation Labs, Merck and Octapharma.

Dr. Tantry reports receiving honoraria from UptoDate and Aggredyne.

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