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Commentary

Race-Related disparities in COVID-19 thrombotic outcomes: Beyond social and economic explanations

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African Americans (AAs) have worse COVID-19-related outcomes than Caucasians and Asians, a disparity currently attributed to potential social and economic factors. In this commentary, we endeavor to examine important race-related differences in intrinsic thrombogenicity as another significant contributing factor and propose objective hemostasis assessments to address racial disparities in COVID-19 outcomes.

A prothrombotic state plays a central role in the prognosis of patients with COVID-19 with increased venous and arterial clotting commonly described. Severe COVID-19 is associated with high D-dimer, fibrinogen, and von Willebrand factor levels, and various levels have been reported to predict dosing strategies, mortality, and potential benefit from anticoagulation. A D-dimer >2600 ng/mL predicted venous thromboembolism (VTE) (area under the curve 0.760, 95% CI, 0.661–0.858; p 0.0001, sensitivity 89.7%, and specificity 59.5%) among American ICU patients [1]. Also, elevated acute phase reactants (C-reactive protein, fibrinogen, ferritin), and proinflammatory cytokines (tumor necrosis factor- α and interleukins-1 and -6) are COVID-19 hallmarks.

Racial disparities in thrombotic risk have been widely described in the pre-COVID-19 era. AAs have higher VTE rates than Caucasians, whereas Caucasians have higher rates than Asians/Pacific Islanders [2]. African Americans with coronary artery disease (CAD) have poorer cardiovascular outcomes, particularly death, than Caucasians and Asians. The highest ischemic event rate after elective

percutaneous coronary intervention (PCI) was reported in AA women. This group also had the highest platelet-fibrin clot strength as measured by thromboelastography, a marker independently predictive of ischemic events [3]. AA women had higher thrombin-induced platelet-fibrin clot strength than Caucasians and race was an independent predictor of high thrombin-induced platelet-fibrin clot strength by multivariate analysis in another CAD study [4]. Thromboelastography in age- and sex-matched East Asians and Caucasians (n=249 each) with stable CAD demonstrated delayed initiation of clot formation, lower clot strength, and greater clot lysis in the former race [5]. The disconnect between heightened platelet reactivity and lower post-PCI ischemic event rates, particularly stent thrombosis, and higher bleeding in East Asians (a phenomenon called the "East Asian Paradox"), further supports greater endogenous antithrombosis in East Asians [5].

Thrombotic outcome disparities have been attributed to specific hemostasis factors

(Table 1). Caucasians more often have prothrombotic factor V and prothrombin genetic mutations than Asians. AAs have the highest factor VIII, plasmin-antiplasmin complex, and von Willebrand factor levels versus intermediate levels in Caucasians and Hispanics and the lowest levels in Asians (Table 1). D-dimer is highest in AAs and lowest in Asians. Additionally, endothelial dysfunction is observed more often in AAs than Caucasians, and disparate regulation of the Gq pathway after protease-activated receptor-4 (PAR-4) stimulation associated with greater platelet activation has been reported (Table 1).

Caucasians also have higher CRP than Asians. After adjusting for age, socioeconomic status, BMI, and other risk factors, AA race was associated with increased CRP, and fibrinogen was higher in AAs than Caucasians despite demographic adjustments (Table 1). The totality of evidence supports that AAs have the most elevated inflammation and thrombosis biomarkers, followed by Caucasians (especially of European descent) and then Asians. The prothrombotic stimulus induced by COVID-19 combined with inherent greater thrombogenicity likely contributes to the disparity in clinical outcomes among

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Table 1
Race -related differences in intrinsic thrombogenicity and inflammation.

Factors	Race/Ethnicity effect	Interpretation
Factor V Leiden and G20210A mutation ^{a,b}	Caucasians > Asians	Prothrombotic
Fibrinogen, factor VII, factor VIII, Plasmin-antiplasmin complex and VWF levels ^{c,d}	African Americans > Caucasians > Asians	Prothrombotic
D-dimer levels ^{d,e}	African Americans > Caucasians > Asians	Prothrombotic
Efficient coagulation inactivation by APC or enhanced fibrinolysis ^f	Asians > Caucasians	Fibrinolytic
Longer occlusion time on Global Thrombosis Test ^g	Japanese > Westerners	Delayed clot initiation
Prolonged time of initiation of clot formation; lower level of clot strength; increased activity of clot lysis ^h	East Asians > Caucasians	Delayed clot initiation; Fibrinolytic
High on treatment platelet reactivity to clopidogrel; Increased prevalence of CYP2C19×2 allele carrier status ⁱ	African Americans > Caucasians	Prothrombotic
High maximum platelet-fibrin clot strength ^j	African Americans > Caucasians	Prothrombotic
Differential regulation of Gq pathway after PAR-4 stimulation ^{k,l}	Blacks > Whites	Prothrombotic
CRP elevation ^{m,n}	African Americans > Hispanic > Caucasians > Asians	Proinflammatory

VWF= von Willebrand Factor; APC = Activated Protein C; CRP=C-reactive protein.

^a Gregg JP, Yamane AJ, Grody WW. Prevalence of the factor V-Leiden mutation in four distinct American ethnic populations. *Am J Med Genet* 1997;73:334–6.

^b Ridker PM, Miletich JP, Hennekens CH, Buring JE. Ethnic distribution of factor V Leiden in 4047 men and women. Implications for venous thromboembolism screening. *JAMA* 1997;277:1305–7.

^c Iso H, Folsom AR, Wu KK, et al. Hemostatic variables in Japanese and Caucasian men. Plasma fibrinogen, factor VIIc, factor VIIIc, and von Willebrand factor and their relations to cardiovascular disease risk factors. *Am J Epidemiol* 1989;130:925–34.

^d Lutsey PL, Cushman M, Steffen LM, et al. Plasma hemostatic factors and endothelial markers in four racial/ethnic groups: the MESA study. *J Thromb Haemost* 2006;4:2629–35.

^e Weng LC, Tang W, Rich SS, et al. A genetic association study of D-dimer levels with 50 K SNPs from a candidate gene chip in four ethnic groups. *Thromb Res* 2014;134:462–7.

^f White RH. The epidemiology of venous thromboembolism. *Circulation* 2003;107:14–8.

^g Gorog DA, Yamamoto J, Saraf S, et al. First direct comparison of platelet reactivity and thrombolytic status between Japanese and Western volunteers: possible relationship to the "Japanese paradox". *Int J Cardiol* 2011;152:43–8.

^h Jeong YH, Kevin B, Ahn JH, et al. Viscoelastic properties of clot formation and their clinical impact in East Asian versus Caucasian patients with stable coronary artery disease: a COMPARE-RACE analysis. *J Thromb Thrombolysis* 2020 Aug 27. doi: 10.1007/s11239-020-02,240-2.

ⁱ Pendyala LK, Torguson R, Loh JP, et al. Racial disparity with on-treatment platelet reactivity in patients undergoing percutaneous coronary intervention. *Am Heart J* 2013;166:266–72.

^j Lev EI, Bliden KP, Jeong YH, et al. Influence of race and sex on thrombogenicity in a large cohort of coronary artery disease patients. *J Am Heart Assoc* 2014;3:e001167.

^k Tourdot BE, Conaway S, Niisuke K, Edelstein LC, Bray PF, Holinstat M. Mechanism of race-dependent platelet activation through the protease-activated receptor-4 and Gq signaling axis. *Arterioscler Thromb Vasc Biol* 2014;34:2644–50.

^l Edelstein LC, Simon LM, Lindsay CR, et al. Common variants in the human platelet PAR4 thrombin receptor alter platelet function and differ by race. *Blood* 2014;124:3450–8.

^m Gijssberts CM, den Ruijter HM, Asselbergs FW, Chan MY, de Kleijn DP, Hofer IE. Biomarkers of Coronary Artery Disease Differ Between Asians and Caucasians in the General Population. *Glob Heart* 2015;10:301–11 e11.

ⁿ Kelley-Hedgepeth A, Lloyd-Jones DM, Colvin A, et al. Ethnic differences in C-reactive protein concentrations. *Clin Chem* 2008;54:1027–37.

racial groups. The preliminary results confirming the hypothesis were recently reported by Zakeri et al. [6].

Currently, D-dimer is the most widely reported biomarker associated with COVID-19 severity and outcomes, with an escalation of antithrombotic therapy proposed in patients with very high levels [7,8]. However, there are several limitations of this biomarker to monitor thrombogenicity during COVID-19. Despite evidence of elevated D-dimer in patients with severe COVID-19, VTE was not evident in the majority. D-dimer, an acute phase reactant with low specificity in the critically ill with conditions associated with fibrin formation, is generated during fibrinolysis and reflects later stage clot formation and hemostatic processes. There is also considerable variation in D-dimer measurements and the reported units that has made pooling of the studies for interpretation unreliable. About 2–3% of plasma fibrinogen is physiologically converted to crosslinked fibrin and then degraded to D-dimer [9]. Thus, elevated levels of fibrinogen in COVID-19 patients, especially among AAs, likely contribute to higher D-dimer values without necessarily an associated increase in fibrinolytic activity. Hence, even if the fibrinolytic system is impaired, D-dimer values may be high. Finally, D-dimer does not provide quantitative information on platelet function, thrombin generation, and the kinetics of clot formation.

Some of these limitations can be addressed by global hemostasis assays such as thromboelastography or rotational thromboelastometry. Whereas high D-dimer in COVID-19 may be associated with a prothrombotic state, a hypofibrinolytic state, or both, viscoelastic measurements of clot provide greater insight into the dynamics of coagulation, platelet function and fibrinolysis. Viscoelastic measurements can quantitate the response to both anticoagulant and antiplatelet therapy [10]. Thromboelastography is a whole blood *ex vivo* assay that provides viscoelastic measurements of the evolving clot from the time of initial platelet-fibrin clot formation to clot

strengthening to clot lysis. It can be used to assess platelet function and coagulation, the response to antiplatelet and anticoagulant agents, and to quantify fibrinolysis. Among patients with COVID-19, determination of thrombogenicity phenotype and response to antithrombotic agents can help to personalize the antithrombotic regimen [10]. In an ongoing study, "The Evaluation of Hemostasis by Thromboelastography, Platelet Function Testing, and Biomarker Analysis in Hospitalized COVID-19 Patients (TARGET-COVID Study)" (NCT04493307) the influence of the early detection of hypercoagulability on COVID-19 outcomes is being investigated.

Racial disparities in the outcomes of COVID-19 are surely influenced by important social and economic factors. However, differences in mortality and thromboembolic event occurrences in COVID-19 may also be, in part, explained by important, but comparatively unrecognized, race-related disparities in intrinsic thrombogenicity. We hypothesize that a patient's hemostatic blueprint determines clinical outcomes in COVID-19 and that early viscoelastic analysis of clot may facilitate future efforts to personalize antithrombotic therapy [10]. Such personalization holds the promise of mitigating the relationship of race to COVID-19 related outcomes.

Declaration of Competing Interest

Dr. Kreutz has received consulting fees from Haemonetics. Dr. Jeong has received honoraria for lectures from AstraZeneca, Sanofi-Aventis, Daiichi Sankyo/Lilly, Haemonetics, Otsuka, Han-mi Pharmaceuticals and Yuhan Pharmaceuticals; and research grants or support from AstraZeneca, Korean Society of Interventional Cardiology, Han-mi Pharmaceuticals, Yuhan Pharmaceuticals, Otsuka and Haemonetics. Dr. Levy reports honoraria for advisory boards from Instrumentation Labs, Merck, Octapharma, and Janssen. Dr. Gurbel reports grants and personal fees from Bayer HealthCare LLC, Ottopic Inc,

Amgen, Janssen, and US WorldMeds LLC; grants from Instrumentation Laboratory, Haemonetics, Medicare 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 and Assessment of cardiac health and thrombotic risk in a patient. Other authors report no disclosure.

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References

- [1] Maatman TK, Jalali F, Feizpour C, et al. Routine venous thromboembolism prophylaxis may be inadequate in the hypercoagulable state of severe coronavirus disease 2019. *Crit Care Med* 2020;48:e783–e90.
- [2] White RH, Keenan CR. Effects of race and ethnicity on the incidence of venous thromboembolism. *Thromb Res* 2009;123(Suppl 4):S11–7.
- [3] Gurbel PA, Bliden KP, Cohen E, et al. Race and sex differences in thrombogenicity: risk of ischemic events following coronary stenting. *Blood Coagul Fibrinolysis* 2008;19:268–75.
- [4] Lev EI, Bliden KP, Jeong YH, et al. Influence of race and sex on thrombogenicity in a large cohort of coronary artery disease patients. *J Am Heart Assoc* 2014;3:e001167.
- [5] Jeong YH, Kevin B, Ahn JH, et al. Viscoelastic properties of clot formation and their clinical impact in East Asian versus Caucasian patients with stable coronary artery disease: a COMPARE-RACE analysis. *J Thromb Thrombolysis* 2020 Aug 27. doi: 10.1007/s11239-020-02240-2.
- [6] Zakeri R., Bendayan R., Ashworth M., et al. A case-control and cohort study to determine the relationship between ethnic background and severe COVID-19. *E Clinical Medicine*. <https://doi.org/10.1016/j.eclinm.2020.100574>
- [7] Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19. *Lancet Haematol* 2020;7:e438–e40.
- [8] Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation. *Blood* 2020;135:2033–40.
- [9] Nossel HL. Radioimmunoassay of fibrinopeptides in relation to intravascular coagulation and thrombosis. *N Engl J Med* 1976;295:428–32.
- [10] Chaudhary R, Kreutz RP, Bliden KP, Tantry US, Gurbel PA. Personalizing antithrombotic therapy in COVID-19: role of thromboelastography and thromboelastometry. *Thromb Haemost* 2020. doi: 10.1055/s-0040-1714217.