The Ecology of Stent Thrombosis: A View from a Sociobiological Perspective

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The introduction of drug-eluting stents (DES) into clinical practice in 2003 ushered in a new era for the mechanical treatment of coronary artery disease (CAD). Along with advancements in antiplatelet therapy and the more widespread use of cholesterol and inflammation lowering statin drugs, the need for repeat percutaneous coronary interventions after an index procedure has been dramatically reduced at the expense of the relatively small but potentially deadly risk of stent thrombosis (ST). Risk factors for this highly morbid complication of DES implantation include technical procedural issues, certain comorbidities such as diabetes mellitus and renal failure, incomplete endothelialization, acquired incomplete apposition, lesion characteristics, and premature discontinuation of dual antiplatelet therapy.1–3 The latter risk factor represents a common cause of late ST in a majority of patients, a factor that is likely influenced by medical and social parameters such that the evaluation of the effect of sociodemographic characteristics on what is thought of as a classic biological event merits closer examination.

In this issue of Circulation, Collins and colleagues report that black race independently predicted DES thrombosis despite similar compliance with clopidogrel therapy between black and nonblack patients, while accounting for socioeconomic status (SES) in their analyses.4 In their article, “Does Black Ethnicity Influence the Development of Stent Thrombosis in the Drug-Eluting Stent Era?,” the authors examined the determinants of stent thrombosis among patients undergoing DES implantation at a large volume single center. The study included 1594 black patients and 5642 nonblack patients. During a follow-up period of up to 3 years, 108 patients were identified with ST utilizing the Academic Research Consortium criteria. Multivariable analyses revealed that among patients who underwent percutaneous coronary interventions and DES implantation, early ST occurred at a rate of 0.83%, while late and very late ST were associated with rates of 1.11% and up to 1.76% respectively. In their analyses, compared to nonblacks, black patients persistently experienced higher rates of ST over time, such that after accounting for their measured confounders, black race independently predicted ST. These findings are intriguing and share consistency with previous sparse work in this arena, as well as with United States morbidity and mortality statistics demonstrating that black men and women have greater cardiovascular morbidity and mortality than most other races.5,6

One approach to discussing the findings by Collins et al4 is to ask and attempt to answer several questions, including (1) Is there support for any association between racial phenotype and the biology of de novo coronary atherosclerosis (ie, do we really think that blacks and nonblacks have different CAD pathophysiology)? (2) Does any link between race and the pathophysiology of CAD extend to stent thrombosis? (3) Do social and developmental influences of disease affect the biology of stent thrombosis? And (4) Are there potential genetic explanations for these findings?

Longstanding data indicate that blacks experience significantly higher rates of premature cardiovascular disease (CVD) and sudden cardiac death than nonblacks. However, few studies examined the epidemiology of apparent disease aggression in black patients outside of the context of access to care, health insurance coverage, or other financial disparities.6–8 Relatively little attention has been devoted to biochemical characteristics that might influence atherosclerosis, hemostasis, or thrombosis according to race. Skeptics of race-based statistics will often correctly point out the disproportionate burden of CVD risk factors in blacks compared to other groups, the well-documented larger differences in genetic substructure among blacks than between blacks and nonblacks, and the role of SES as explanations of why genetic explanations for these findings?

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The opinions expressed in this article are not necessarily those of the editors or of the American Heart Association.

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Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.110.973727
In addition, molecular biomarkers associated with CAD risk such as C-reactive protein, fibrinogen, intercellular adhesion molecule, and tissue plasminogen activator, among others, tend to be significantly more elevated in blacks compared to whites, even after taking into account traditional risk factors of CAD.\textsuperscript{15,16} Together with the finding that nondiabetic blacks have lipoprotein levels that are generally similar to those of whites, these observations raise the question of whether the molecular milieu involving an interplay between lipid, inflammatory, hormonal, hemostatic, and oxidative stress markers is patterned in such a way that the CAD phenotype is exaggerated in blacks, resulting in poorer outcomes.

However, what does the molecular milieu have to do with stent thrombosis and SES? While the hallmark of ST is clotting, the cellular and molecular processes involved in this thrombotic cascade are potentially heavily influenced by stressors to our biological allostasis. These stressors include but are not limited to typical socioeconomic measures such as poverty, unemployment or underemployment, unstable familial units, neighborhood environment, and discrimination. Stressors such as these propagate the up-regulation of inflammatory, sympathetic, and neurohormonal factors from birth which then dictate the pathogenesis of more aggressive coronary- and stent-related pathological processes such as thrombotic occlusion. The observation by Collins et al\textsuperscript{4} that race persistently predicted ST over time in part supports this ecology.

In addition to the limitations highlighted in the manuscript, Collins et al’s report\textsuperscript{4} of this single center, unrestricted analysis of ST has other limitations based on ecological, medical, and statistical grounds. First, the use of median income by zip code as a measure of SES is a crude estimate of SES that is less robust than, for example, education level or other indices such as neighborhood environment, which although heterogeneously defined provide more complete and stable assessments of SES. For example, it is uncertain whether median household income accounted for the number of people residing in the household. Moreover, because the mean age of the population studied was at least 60 years old, many patients could be retired or disabled, factors that would negatively impact income but not necessarily SES in a more general sense. As the authors noted, because compliance with antiplatelet therapy was similar in blacks and nonblacks, it attenuates the impact of this particular risk factor in the development of late and very late ST in these patients. However, while the authors appropriately highlight the need for genetic studies related to the utility of clopidogrel therapy by race, no data were presented about the use of typical concomitant medications such as aspirin, renin-angiotensin inhibitors, and statins, which could affect the molecular pathogenesis of ST. Similarly, whether patients used dual antiplatelet therapy daily or every few days (i.e., how compliance was measured as well as the frequency or adequacy of outpatient cardiovascular follow-up care) is unknown. Likewise, information about left ventricular function at the time of the procedure and at follow-up, infarct characteristics, the type of stent used during the index procedure, lesion complexity/number, use of thrombectomy or brachytherapy, and episodes of bleeding while undergoing dual antiplatelet therapy would be useful as they are potential confounders of any relationship between the interaction of race and DES on CVD and non-CVD outcomes. Of clinical importance as well is the type of index CVD event (eg, whether or not the patient experienced an ST elevation myocardial infarction), as the inciting event for DES implantation, because there is some suggestion that DES insertion in the context of thrombotic occlusions results in heightened risk of ST.\textsuperscript{3}

From a statistical viewpoint, the authors used Cox-proportional hazards models to determine the impact of race on time to stent thrombosis. Because this is a nonrandomized analysis of blacks and nonblacks, and the number of ST events was small, other analytic approaches (such as a matched propensity score analysis) could have been more efficient in minimizing bias and the impact of multiple confounders.\textsuperscript{2} With only 108 outcome events, the number of such variables that could be included in the Cox model is limited. Even this technique, however, could not adjust for potential confounders that remained unmeasured. In this particular analysis, there was also no documentation of formal interaction testing to examine the effect of race and DES on outcome (eg, stent thrombosis, CVD death, or all-cause mortality).

Besides additional work replicating Collins et al’s findings\textsuperscript{4} utilizing other databases, future work should also assess the determinants of ST within race (eg, among blacks), because such analyses will be critical toward understanding preventive and therapeutic approaches that might only become evident from within group analyses. Nevertheless, if replicated, the findings of the current study are of clinical importance because of the evident two-fold increase in cumulative ST rates in blacks compared to nonblacks, a statistic that should be considered quite high and would call for close examination of the risk/benefit ratio of DES in this population. Thus, this work by Collins et al\textsuperscript{4} adds to a growing body of evidence indicating that self-reported race might play a role in differential long term outcome after percutaneous revascularization and stenting.

Disclosures

None.

References


Key Words: Editorials • percutaneous transluminal coronary angioplasty • race • stent thrombosis
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_Circulation_. 2010;122:1053-1055; originally published online August 30, 2010; doi: 10.1161/CIRCULATIONAHA.110.973727

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/122/11/1053

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