Relationships Between Race, Bleeding, and Mortality in Coronary Reperfusion

Running title: Giugliano; Race, bleeding and mortality

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There are several examples of therapies that have differential effects in specific racially or ethnically distinct subgroups of the US population. For example, persons of African heritage generally have a poorer blood pressure response to angiotensin-converting enzyme inhibitors and beta-blockers compared to Caucasians, but derive greater benefit in the prevention of heart failure from the combination of isosorbide dinitrate and hydralazine. Indeed, this latter finding led to the first drug approved to treat a disease in patients identified by race. The explanations for racial and ethnic differences in response may be related to genetic factors that determine drug exposure (i.e., differences in absorption, distribution, metabolism, elimination), intrinsic factors (e.g., age, gender, weight, renal and/or hepatic function), extrinsic influences (e.g., diet, concomitant medications and non-traditional therapies, environmental exposure, cultural factors), or a combination therein.

The US Food and Drug administration (FDA) has long recognized the importance of evaluating the safety and efficacy of new therapies in standardized racial and ethnic subgroups. In 1998 they published the Demographic Rule (CFR 314.50 d (5)) and followed this in 2005 with a guidance document that provided recommendations for the collection of race and ethnicity data in clinical trials. Specifically in patients with ST-elevation myocardial infarction (STEMI), the clinical review of tenecteplase by the FDA Medical Officer raised a concern regarding worse clinical outcomes among individuals of African descent. Since patients of African descent were underrepresented and there was no identification of Hispanic ethnicity were collected, the FDA reviewer recommended that such data should be obtained in phase 4 trials.
Although no dedicated large phase 4 trials of fibrinolytic therapy in these under-represented racial and ethnic subgroups have been performed to date, in this issue of Circulation, Mehta et al\textsuperscript{2} report an analysis of bleeding and mortality in 5,109 African-Americans participating in the National Registry of Myocardial Infarction-4 and -5 between 2000-6. Since the proportion of patients in the analysis who received fibrinolysis and primary percutaneous coronary intervention (PPCI) were nearly equal, and these two distinct methods of reperfusion vary in the distribution of bleeding sites (i.e., more intracranial bleeding with fibrinolysis, more access site bleeding with PPCI), the authors present analyses that appropriately separated the population by mode of reperfusion. The major focus was a comparison of moderate or major bleeding between African-Americans and Caucasians. Major bleeding was defined as bleeding that was intracranial, resulted in hemodynamic compromise requiring treatment, or was fatal. Moderate bleeding was defined as bleeding that required transfusion. Secondary analyses examined the association of race and bleeding (individually and together) on inhospital mortality. Multivariate logistic regression models were constructed to adjust for differences in baseline characteristics and treatments, center-level effects, and possible interaction of race by reperfusion mode (fibrinolysis vs PPCI).

The authors report three primary findings. First, adjusted bleeding rates were higher in African-American than in Caucasians, whether treated with fibrinolysis (OR\textsubscript{adj} 1.21) or PPCI (OR\textsubscript{adj} 1.33). Second, adjusted in-hospital mortality was similar between African American and Caucasians regardless of the method of reperfusion. Third, patients who had a moderate or major bleed (regardless of race or reperfusion type) were less likely to survive the index hospitalization.

Each of these observations deserves consideration. It has been known since the early
days of fibrinolytic mega-trials over 2 decades ago that African Americans have higher rates of bleeding with fibrinolytic therapy\(^3\), possibly related to a more pronounced fall in fibrinogen observed after 5 hours.\(^4\) The current analysis extends the prior\(^3\), and more contemporary\(^5\) findings from clinical trials to a broader registry population that, most importantly, also includes patients treated with PPCI. It should be noted, however, that in the analysis by Mehta: 1) the vast majority of bleeding events were associated with transfusion, 2) African Americans were transfused more frequently than Caucasians, and 3) no breakdown of major vs moderate bleeding or of each of the 3 components of major bleeding was provided. Furthermore, the authors appropriately caution that “unmeasured confounders may have accounted for some or all of the variations seen in bleeding”; this is particularly relevant since the definition of moderate bleeding was dependent upon the use of transfusion. Nevertheless, variation in the decision to transfuse patients cannot explain all of the findings, since African Americans treated with fibrinolytics experienced a >50% higher rate of intracranial hemorrhage (\(p = 0.011\)) compared with Caucasians, despite being 6 years younger on average. Therefore, the reasons why African Americans with STEMI treated with reperfusion therapy have higher rates of bleeding are likely complex and multifactorial. To get to the next level of understanding, more details on the types of bleeding, analysis of alternative bleeding definitions\(^6\), and collection of additional potential confounding factors that are known to be associated with bleeding (e.g., combination antithrombotic therapy, excess dosing of antithrombotics, baseline hemoglobin, and presence of peripheral vascular disease)\(^7\) are needed.

The second major finding confirmed prior analyses from clinical trials spanning the prior 4 decades\(^4, 8, 9\) that there is no difference in adjusted short-term mortality between African Americans and Caucasians, once adjustment is introduced for baseline characteristics. Data are
conflicting regarding the independent contribution of race to longer-term mortality.\textsuperscript{4, 8, 10} An important contribution from the analysis by Mehta et al\textsuperscript{2} is to extended the prior findings of similar adjusted short-term mortality between these two racial groups now to registry patients treated with PPCI in the modern era.

The final set of analyses explored the relationships between bleeding and mortality -- overall and stratified by race. The major risk factors for bleeding among patients receiving fibrinolytic therapy were described in the early mega-trials\textsuperscript{11, 12}, with more recent research focusing on the development of quantitative risk scores\textsuperscript{13} and risk mitigation.\textsuperscript{14} African-Americans and Caucasians in NRMI-4 and -5 who experienced a moderate or severe bleed had higher mortality than those of the same race who did not bleed, with no evidence of modification in the effect due to race. This then raises the question, why if African Americans had more bleeding, and bleeding was associated with a significant increase in mortality, shouldn’t we expect a higher mortality in African Americans?

Determining the extent (if any) of a causal relationship between two post-baseline clinical events in a registry dataset is fraught with confounding and bias. Then, incorporating yet another variable (race) that itself demonstrates significant variation in baseline characteristics that are associated with a potential cause (bleeding), as well as the measured effect (mortality), makes any analysis treacherous. The nature of the relationship between bleeding and mortality is controversial, with some analyses concluding that this represents an \textit{association} highly confounded by comorbidities,\textsuperscript{15} while others report a strong independent relationship.\textsuperscript{13} To further muddle matters, transfusion itself has been associated with increased mortality in patients with acute coronary syndromes,\textsuperscript{16} and specifically in patients with STEMI undergoing PPCI,\textsuperscript{17} with several possible mechanisms proposed.\textsuperscript{18} The role played by transfusion is particularly relevant
in the work by Mehta et al.,\textsuperscript{2} since the majority of bleeding events were managed with transfusion. The relationship between bleeding and mortality is also complicated by the marked differences in fatality rates dependent upon the location of the bleed (intracranial vs non-intracranial)\textsuperscript{19}, which varied 10-fold between patients receiving fibrinolysis and those undergoing PPCI in NRMI-4 and -5. Additional considerations include the occurrence of other intervening medical events that themselves may lead to bleeding and death (e.g., cardiogenic shock), and the biologic plausibility of the relationship given the reported cause(s) of death.\textsuperscript{19}

Unfortunately, similar to Operation Market Garden\textsuperscript{20} in which overstretched Allied forces failed to hold positions crossing over the River Rhine thereby coining the infamous phrase “a bridge too far”, the authors have overextended their data, speculating that higher rates of bleeding in African Americans may explain higher long-term mortality observed in other datasets. In fact, temporal analyses of bleeding and mortality demonstrate a waning of the strength of the association as the time interval increases\textsuperscript{21}, with no significant effect after 40 days.\textsuperscript{21} In addition, a landmark analyses from the ExTRACT-TIMI 25 trial showed no independent relationship between either non-intracranial TIMI major bleeding in hospital and death at 31-365 days, or TIMI minor bleeding in hospital and death at 31-365 days, once baseline characteristics were included in multivariate models.\textsuperscript{19}

Nevertheless, reducing bleeding is \textit{ipso facto} desirable, and position statements\textsuperscript{22} have endorsed attempts to reduce bleeding in patients with acute coronary syndromes. Several promising strategies, such as use of radial arterial access\textsuperscript{23} and safer anticoagulants\textsuperscript{24} are rapidly being implemented, contributing to a recent decline in bleeding rates.\textsuperscript{25} In the meantime, specific focus on the cause and prevention of bleeding in high risk groups, including African Americans, should be a priority.
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