Genetic and Nongenetic Implications of Racial Variation in Response to Antiplatelet Therapy

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Race has been identified as an independent risk factor for poor prognosis and an independent predictor of survival in coronary artery disease. Race-related dissimilarities have been identified in cardiovascular patients in terms of age of presentation, co-morbidities, socioeconomic status, and treatment approach as well as genetically driven race-related disparities in responsiveness to medications. Antiplatelet therapy represents a fundamental component of therapy in cardiovascular patients, especially in patients presenting with acute coronary syndromes. It has been argued that the different level of platelet reactivity and varying response to antiplatelet therapy among races may account in part for worse outcomes in certain populations. The purpose of this review is to describe genotypic and phenotypic race-related differences in platelet reactivity and responsiveness to cardiovascular treatment, focusing on antiplatelet therapy to highlight the need establish a more effective and targeted antithrombotic strategy. **(Am J Cardiol 2019;123:1878−1883)**

Cardiovascular disease (CVD) is the leading cause of death for all races, ethnicities, and socioeconomic classes in the United States; however, the burden of disease is greater among racial/ethnic minority groups. Despite improvements in narrowing the US mortality difference between blacks and whites, significant disparities in certain populations and communities remain.[1] The burden of coronary artery disease (CAD) is higher in blacks and minorities than in whites. This is related to genetic and nongenetic factors. In particular, disparities in genetic and nongenetic determinants of platelet function and/or responsiveness to antiplatelet therapy have been described with variable association to clinical outcomes [2,3] (Figure 1). Dual antiplatelet therapy is the mainstay pharmacotherapy after percutaneous coronary intervention (PCI). The decision-making process of type and duration of dual antiplatelet therapy is variable among patients, and race has been advocated as affecting the decision-making process in the choice of antithrombotic therapy.[2−4] The major limitation of randomized clinical trials is related to the heterogeneous patient population, limiting the ability of generalizing the findings to subgroups that are underrepresented in those clinical trials. Understanding specific racial differences in relation to antithrombotic therapy after PCI can potentially lead to optimization of therapy and consequent improved outcomes and decrease in disparities for the treatment of CVD. This review will focus on racial disparities in genetic and nongenetic differences in platelet function and antiplatelet therapy.

Genetic/Heritable Differences in Platelet Function

Variation in platelet function/reactivity is partially related to heritable factors. Moreover, Bray et al evaluated the contribution of inheritance to the variability in platelet function in unaffected individuals from white and black families with premature CAD.[5] Platelet reactivity was studied in the absence of antiplatelet agents in ∼700 whites and 320 blacks, showing moderate (in whites) and strong (in blacks) heritability related to epinephrine- and adenosine diphosphate-induced aggregation and heritability (in blacks only) for collagen-induced platelet aggregation in platelet-rich plasma.[5] A cross-sectional study from the Atherosclerosis Risk in Communities Study found that blacks have significantly higher levels of platelet activation markers assessed by flow cytometry, consistent with a proinflammatory profile.[6] One study evaluating maximum platelet-fibrin clot strength on thromboelastogram in 252 (63 blacks and 189 whites) subjects which underwent nonemergent coronary stenting showed that blacks (especially black women) had significantly higher maximum platelet-fibrin clot strength, a shorter time to platelet-fibrin clot formation, and worse clinical outcomes than whites had (cardiac ischemic events at 6 months: 22% in blacks and 14% in whites). Differences in the coagulation index also were observed, with the highest recordings in blacks, suggesting that ex vivo platelet-fibrin clot characteristics differ among races.[7] Edelstein et al[8] investigated platelet function among healthy white versus black participants and, in an elegant series of experiments, demonstrated race-related differences in platelet activation through enhanced activation of the

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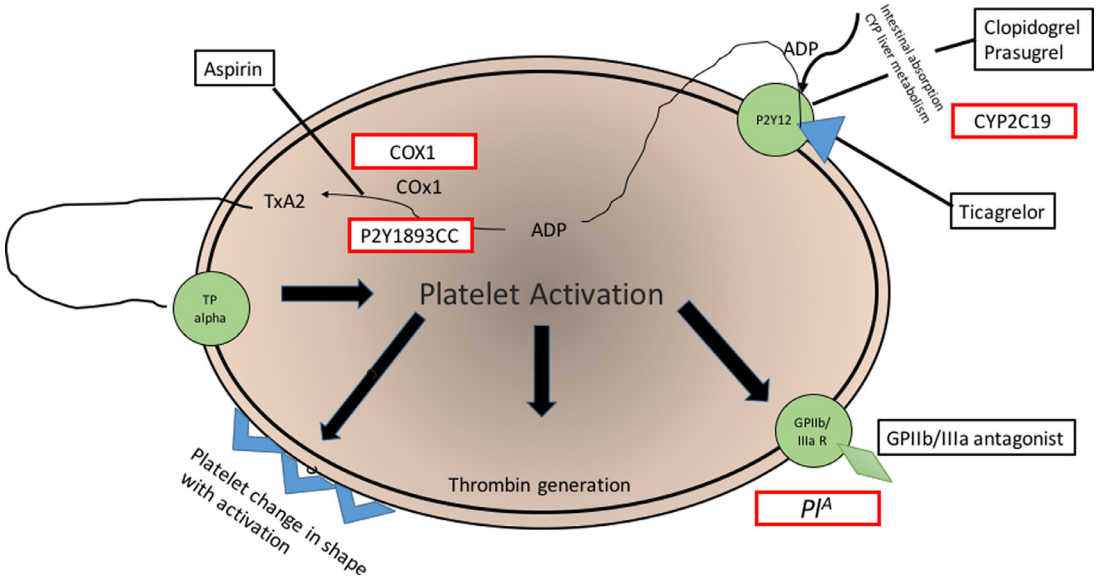

Figure 1. Adenosine diphosphate (ADP) promotes platelet activation by binding to the P2Y12 receptor; this leads to shape change, activation of the glycoprotein IIb/IIIa receptors, and platelet aggregation. Clopidogrel and prasugrel directly and irreversibly block ADP through the antagonism of the P2Y12 receptor. Ticagrelor binds at a separate site of the P2Y12 receptor and indirectly blocks ADP activation through reversible binding, leaving the receptor intact. Aspirin blocks cyclooxygenase-1, causing a decrease in thromboxane A2. Genetic mutations that affect race-related differences in platelet responsiveness to antiplatelet therapy are reported in red boxes.
ADP = adenosine diphosphate; COX1 = cyclooxygenase-1; GP = glycoprotein; TP = thromboxane A2 receptor; TxA2 = thromboxane A2. (Color version of figure is available online.)

thrombin receptor-protease activated receptor 4 in blacks although potentiation of the G_q pathway of platelets, thus determining platelet hyperactivity in this population compared with whites. Of note, this characteristic persisted in the presence of cyclooxygenase (COX) and P2Y12 receptor dual inhibition, suggesting that current antiplatelet therapy may provide less protection to blacks than whites in relation to this mechanism as well.[9] Interestingly, a recent genome-wide association study by Qayyum et al identified genetic loci related to adenosine diphosphate-induced platelet aggregation in black, but not in white, Americans associated with increased-activity platelet aggregation.[10] Hispanics have been reported to have increased platelet counts in a genome-wide study of over 12,000 Hispanics in which specific loci were identified and recognized as being associated with abnormal platelet count and hyperactivity.[11]

Nongenetic Considerations in Race-related Differences in Platelet Function

Investigators in the MESA cohort showed that blacks generally had the highest thrombogenic and dysfunctional endothelial profile, followed by Hispanic and whites and, finally, East Asian individuals.[12] Hispanics have been shown to have higher rates of cardiovascular risk factors, coronary heart disease, and stroke than those of whites.[13] Furthermore, South Asian and Filipinos have been shown to have greater proportionate mortality burden from CVD.[14] Studies of Hispanics and Asians, however, often do not account for the heterogeneity of the population. In MESA, Chinese participants (12% of the total) were 20% less likely than whites to have hyperlipidemia.[15] Race-related differences have been described in terms of expression of proinflammatory cytokine levels known to be associated with a proatherosclerotic phenotype (i.e., interleukin-6, fibrinogen, and C-reactive protein [CRP]) and hence playing a role in the higher likelihood of blacks developing atherosclerosis and experiencing more clinical events.[16] For instance, CRP levels measured in 2,749 subjects participating in the Dallas Heart Study were found to be significantly higher in blacks than in whites, with 40% and 58% of the black men and women having CRP levels >3 mg/L compared with 31% and 51% in white men and women, respectively.[17] Similarly, a cross-sectional observation of 3,154 individuals enrolled in the SWAN study including a multiethnic population revealed that the median CRP levels in blacks were highest at 3.2 mg/L, followed by Hispanics (2.3 mg/L), whites (1.5 mg/L), and East Asians (0.6 mg/L). These differences persisted after adjusting for body mass index (BMI). In contrast, East Asians have lower levels of inflammatory markers and are less thrombogenic than are whites.[18] Interestingly, a large cohort from MESA suggested that inflammatory biomarkers such as CRP, IL-6, or fibrinogen did not predict cardiovascular mortality in East Asians but did predict mortality in whites, blacks, and Hispanics.[19] Gorog et al observed that the time to create platelet-rich thrombi under shear was longer in Japanese subjects than in whites, suggesting a less prothrombotic profile in the Japanese population.[20] This favorable background seems to be counteracted by increased prevalence of some cardiovascular risk factors in this population.

Genetic Differences in Response to Antiplatelet Therapy

Aspirin resistance is defined as failure to prevent atherothrombotic events and/or inability to cause platelet

Table 1
Variant and allele frequencies in the human CYP2C19 family among various ethnicities

Allele	Defining variant	Allele frequencies in indicated populations %					Functional consequence
		EUR	AFR	EAS	SAS	AMR	
*1	None	59.2	44.5	60.5	51.9	77	Normal
*2	rs4244285	18.3	18.1	31.0	34.0	10.1	Inactive
*3	rs4986893	<0.1	<0.1	6.7	0.4	<0.1	Inactive
*4	rs28399504	0	<0.1	<0.1	<0.1	0.2	Inactive
*5	rs56337013	0	0	0	<0.1	0	Inactive
*6	rs72552267	0	0	<0.1	0	<0.1	Inactive
*7	rs72558186	0	0	0	<0.1	0	Inactive
*8	rs41291556	<0.1	<0.1	0	<0.1	<0.1	Inactive
*9	rs17884712	0	1.2	0	<0.1	<0.1	-
*10	rs6413438	0	0.4	<0.1	0	<0.1	Decreased
*12	rs55640102	0	<0.1	0	0	0	-
*13	rs17879685	0	1.6	0	<0.1	0.1	-
*15	rs17882687	0	2.0	0	<0.1	<0.1	-
*16	rs192154563	0	<0.1	0	<0.1	0	-
*17	rs12248560	22.4	23.5	1.5	13.6	12	Increased
*22	rs140278421	0	0.1	0	0	<0.1	-
*23	rs118203756	0	0	<0.1	0	0	-
*24	rs118203757	0	<0.1	0	<0.1	<0.1	-
*25	rs118203759	0	0	0	0	0	-
*27	Rs7902257	0.1	8.3	0.1	0	0.3	Decreased

Adapted from Zhou Y et al[51] used with permission of Creative Commons; copyright 2017.
AFR = Africans; AMR = admixed Americans; CYP = cytochrome P450; EAS = East Asians; EUR, Europeans; SAS = South Asians.

aggregation. Reduced responsiveness to aspirin has been shown to be associated with an increased incidence of major adverse cardiovascular events such as death, myocardial infarction, and stroke, as well as stent thrombosis after PCI.[21] Pharmacogenetic studies of aspirin responsiveness in the general population, however, have produced controversial results without clear evidence of clinical implications of such genetic variation. This is in part related to lack of consistency in the methods to assess platelet function in response to aspirin and lack of a clear definition of "aspirin resistance" among studies. Previous studies have, in fact, estimated that 5% to 45% of the population do not achieve an adequate antiplatelet effect from aspirin.[22] Furthermore, genetic studies are often small and lack clinical implications. Krasopoulos et al. published a meta-analysis of 20 studies on ~3,000 subjects and showed worse cardiovascular outcomes in patients deemed resistant to aspirin.[23] In another meta-analysis of 27 studies, Weng et al explored 4 candidate genes (*COX-1, COX-2, ITGA2B,* and *ITGA2A*) and reported that *COX-2* and *ITGA2* genetic defects increased the risk of aspirin resistance, especially in Chinese populations.[24]

There are considerable racial differences among the genetic polymorphisms that control the activity of CYP2C19 isoforms in relation to clopidogrel resistance. Incomplete response to clopidogrel is primarily related to genetic polymorphisms such as CYP2C19*2, which is most commonly associated with poor metabolism of the drug, increased platelet aggregation, and poorer cardiovascular outcome (Table 1).[25] Homozygosity for loss of function for the CYP2C19*2 has been described in 2% of whites, 4% of blacks, and 14% of East Asians, while heterozygosity was reported in 30% of whites, 40% of blacks, up to 50% of East Asians, and 18% of Mexican Americans.[26] The greater prevalence of the CYP2C19*2 among East Asians is associated with worse clinical response to clopidogrel in this population, despite East Asians having greater bleeding frequency than whites have.[27] Interestingly, a high prevalence of loss-of-function variants has been discovered in Vanuatu and Papua New Guinea, with allele frequencies of 70% (*2) and 13% (*3).[28] Black ethnicity has been shown to be an independent predictor of high on-treatment platelet reactivity (HTPR), implying that unique genetic characteristics in blacks determine clopidogrel response.[29] The CYP2C19*17 allele is associated with increased clopidogrel activity and has been associated with racial differences, with prevalence of <5% in East Asians and up to 30% in European and African populations.[30] Interestingly, higher allele frequencies for *9, *10, *13, *15, and *27, (1.2%, 0.4%, 1.6%, 2%, and 8.3%, respectively) are seen uniquely in the African population (Table 1). Moreover, a study of African descent showed a 12-fold increase in metabolic activity after clopidogrel administration that was not accounted by presence of the CYP2C19*17 variant, suggesting undiscovered genetic variants associated with this phenotype.[29] Finally, several other genes have been studied related to clopidogrel resistance but have not been found to be associated with outcomes in the general population. Of note, a genetic subanalysis of the TRITON-TIMI 38 study showed that CYP genetic variants did not affect metabolite levels, platelet aggregation, and outcomes in the 1,466 patients allocated to prasugrel therapy, supporting that there is less pharmacological variability than with clopidogrel.[25] The PLATO trial showed a 16% reduction in ischemic end points with the use of ticagrelor compared with clopidogrel in patients with acute coronary syndromes (ACS). A subgroup analysis of the PLATO trial showed a trend toward better outcomes with clopidogrel use versus ticagrelor for patients enrolled in North

America, but race unlikely had an impact in this result.[31] Pharmacogenetic studies of ticagrelor have not found significant associations with certain genotypes in the general population.[32] However, the degree of platelet inhibition with prasugrel and ticagrelor is higher in East Asian patients than in whites, and a genetic etiology has been advocated but not elucidated. Levels of the active metabolite of prasugrel were found to be ~40% higher in East Asians than in whites,[33] with the difference persisting after adjusting for BMI, thus suggesting a heritable etiology. Therefore, for prasugrel, a lower maintenance dose of 3.75 mg daily was used in clinical studies and approved for Japanese patients. Genetic polymorphisms might also account for the so-called "Asian paradox," which is characterized by the finding of a higher prevalence of HTPR in Asians than in whites treated with P2Y12 inhibitors but with similar thrombotic event rates after PCI. For example, factor V Leiden (G1691A) and prothrombin (G20210A) gene mutations are more common in whites than in Asians.[34]

Glycoprotein (GP) IIb/IIIa receptor antagonists (abciximab, tirofiban, and eptifibatide) block platelet aggregation by inhibiting the binding of fibrinogen to the GP IIb/IIIa receptors on activated platelets. Overall, data on race-specific differences with GP IIb/IIIa inhibitors are limited. The contribution of genetic factors in the general population specifically affecting the target of GP IIb/IIIa inhibitors has been investigated, but results are controversial.[35] Most studies have evaluated the role of the *PlA* polymorphism, but no race variability has been reported.[35] Race-related variability in GP IIb/IIIa receptor density or function has been described and could explain the variable response to GP IIb/IIIa among various populations (i.e., this may in part explain the higher rates of bleeding complications associated with the use of GP IIb/IIIa inhibitors in East Asians).[36]

Nongenetic Differences in Response to Antiplatelet Therapy

In a study with subjects from families with premature CAD, heritable factors accounted for the majority of the variance in platelet response to aspirin, although there was no difference between blacks and whites.[37] On the contrary, differential aspirin use may contribute to geographic/racial disparities in cardiovascular outcomes. Indeed, an important racial disparity exists in the use of aspirin, with blacks and Hispanics less likely to take aspirin than whites.[38] However, whether this disparity was related to less prescription versus lower adherence to prescribed medications is not known in these self-reported surveys. Similarly, a recent study of the Chinese Registry of Acute Coronary Events reported that only 34% to 39% of patients with diagnosed ACS used aspirin at study enrollment.[39]

The efficacy of clopidogrel has been reported in several randomized clinical trials (i.e., CURE,[40] CREDO,[41] CLARITY-TIMI 28,[42] COMMIT,[43] and CHARISMA[44]). However, few of these trials published data on ethnic-related differences in cardiovascular outcomes. The CHARISMA trial,[44] for example, showed that race was a predictor of increased cardiovascular and all-cause mortality (for blacks and Hispanics) and bleeding complications (blacks and Asians). Resistance to clopidogrel, other than genetically determined, is also related to a variety of factors, including cellular and clinical factors such as blood glucose level, diabetes, high systolic and diastolic blood pressure, dietary habits, and medication interactions; environmental factors also may further aggravate outcomes in populations with increased resistance to clopidogrel.[45] In a recent study by Pendyala et al, HTPR (defined as P2Y12 reaction unit >208) was present in 56% of blacks and 35% of whites in a patient population with the same CYP2C19 carrier status.[46] However, how much each factor influences clopidogrel resistance variability is unknown. Race-related differences also have been reported in terms of phenotypic differences in response to prasugrel or ticagrelor administration. In a recent report, the active metabolite of prasugrel was found to be ~40% higher in East Asians than in whites,[33] a difference not totally explained by BMI. Ticagrelor was also shown to be associated with a 16% reduction in the composite ischemic end point compared with clopidogrel in patients with ST-elevation myocardial infarction and patients with non-ST-elevation myocardial infarction before percutaneous intervention.[31] Ticagrelor has been shown in the PLATO trial to be more effective than clopidogrel among various populations recruited (from Asia/Australia, Central/South America, and Europe/Middle East/Africa) with no geographic variation but reported increased nonfatal bleeding.[31] Interestingly, a subgroup analysis of the PLATO trial comparing Asian (n = 1,106) to non-Asian (n = 17,515) patients showed no difference in bleeding events.[47] However, this subgroup analysis included patients from various Asian populations. Indeed, East Asians have been found to have higher levels of the active metabolite of ticagrelor and increased platelet inhibition after a load of ticagrelor than are present in whites.[48] The small representation of black subjects in the PLATO trial precluded the ability to draw conclusions on racial disparities. Waksman et al[4] showed in 2015 that ticagrelor had better antiplatelet action than clopidogrel did in 34 black subjects after elective PCI. Gaglia et al[3] in 2017 showed in a study of 29 black patients presenting with ACS and compared with a historical cohort of white patients that ticagrelor was effective in both whites and blacks. In this study, HTPR was absent in blacks with ACSs loaded with ticagrelor compared with whites. Thus, the variable responsiveness to clopidogrel in blacks and whites, related at least in part to genetic variability, is abolished with the use of ticagrelor.

Conclusions

There are still marked racial disparities/differences related to a complex network of socioeconomic and clinical factors. Racial disparities are complex, with socioeconomic implications that are not discussed in our review. With a growing multiethnic population in the United States, the US Food and Drug Administration encourages participation and data collection from various racial and ethnic groups and recommends analysis of the data for race effects. Recent evidence suggests the potential benefit of genotype-guided antiplatelet therapy after PCI, which might be helpful in directing therapy in patients with CYP loss of function allele.[49,50] However, despite the previously described

racial differences, current American and European guidelines do not recommend tailored therapy related to racial disparities. This is likely related to a lack of evidence and inclusion of minorities in large randomized clinical trials to support recommendations. Genetic variability in platelet reactivity and response to antithrombotic therapy plays a determinant role in patient outcomes after PCI. However currently, large randomized trials, mainly performed in whites, do not support genotype-guided therapy in patients with CVD. In the era of promotion of personalized medicine, one strategy is to focus research on disparities dependent on genetic or acquired differences to better care for our patients. With the identification of differences in metabolic pathways between races, it is important to consider generalizability while developing new antiplatelet drugs, and it is of paramount importance that genetic differences be recognized and understood by clinicians to optimally treat diverse populations.

Disclosure

Ron Waksman: Advisory Board: Abbott Vascular, Amgen, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., Cardioset; Consultant: Abbott Vascular, Amgen, Biosensors, Biotronik, Boston Scientific, Medtronic, Philips Volcano, Pi-Cardia Ltd., Cardioset; Grant Support: Abbott Vascular, AstraZeneca, Biosensors, Biotronik, Boston Scientific, Chiesi; Speakers Bureau: AstraZeneca, Chiesi; Investor: MedAlliance.

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