The Conundrum Surrounding Racial Differences on Ischaemic and Bleeding Risk with Dual Anti-Platelet Therapy

Antonio Greco[1] Davide Capodanno[1] Dominick J. Angiolillo[2]

[1] Division of Cardiology, CAST, P.O. "Rodolico," Azienda Ospedaliero-Universitaria "Policlinico-Vittorio Emanuele," University of Catania, Catania, Italy
[2] Division of Cardiology, University of Florida College of Medicine, Jacksonville, Florida, United States

Address for correspondence Dominick J. Angiolillo, MD, PhD, University of Florida College of Medicine–Jacksonville, 655 West 8th Street, Jacksonville, FL 32209, United States (e-mail: dominick.angiolillo@jax.ufl.edu).

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Dual anti-platelet therapy (DAPT), consisting of aspirin in combination with a platelet $P2Y_{12}$ inhibitor, is the mainstay of adjunctive pharmacotherapy after percutaneous coronary intervention (PCI) in both the elective and emergent setting.[1,2] The main drawback of DAPT is the increased risk of haemorrhagic complications, which sets the rationale for recent and on-going studies on how to appropriately risk stratify such patients[3–5] and investigations of strategies designed to minimize out-of-hospital bleeding, such as shortening DAPT duration, de-escalating DAPT or withdrawing aspirin.[6–8]

In recent years, the optimal duration of DAPT has been one of the most investigated topics in the field of PCI pharmacotherapy, with some debate over the long-term benefit beyond 12 months.[9,10] Several trials performed across the globe informed current guidelines issued by cardiovascular societies in Europe and the United States, which now generally recommend DAPT for 6 months after an elective PCI and 12 months after PCI in the context of an acute coronary syndrome.[1] As opposed to the classic 'one-size-fits-all' paradigm, a currently endorsed approach is to evaluate on a case-by-case basis whether those default DAPT durations should be shortened or prolonged based on the demographic and clinical circumstances of ischaemic and bleeding risk.[11]

Among individual factors that enter decision-making for DAPT duration in PCI practice, race has been advocated as a treatment modifier.[12] In particular, East Asian patients are known to experience more bleeding and less ischaemic complications after PCI as compared with Western patients.[12,13] However, the current European and United States focused updates on DAPT do not provide specific recommendations based on race,[1] which may explain their limited acceptance and applicability in certain areas of the world. Interestingly, trials of DAPT duration conducted in East Asia mostly explored the efficacy and safety of shorter versus longer DAPT regimens, in line with local bleeding concern (►**Table 1**).[14–17] Conversely, in Western countries where the ischaemic risk is higher, several trials of longer DAPT have been conducted in parallel with trials of shorter DAPT.[10,18–21] In global trials that included both Western and non-Western patients, data on sub-group analyses based on ethnicity are scant. On this background, it remains uncertain whether racial factors affect clinical outcomes of DAPT duration.

In this issue of *Thrombosis and Haemostasis*, the patient-level landmark meta-analysis by Kang et al is a meaningful asset to understand whether racial differences truly exist in the net benefit of DAPT.[22] Seven trials were included encompassing 16,518 patients (8,605 East Asians, 7,913 non-East Asians). The period of interest was the landmark between discontinuation of DAPT in the shorter DAPT arm and a mean follow-up of 500 days, reflecting a comparison of DAPT with single anti-platelet therapy. Notably, the two examined cohorts (i.e. East Asians and non-East Asians) greatly differed in their baseline risk profiles in a way that may impact ischaemic and bleeding outcomes, but statistical adjustment was performed to minimize confounding. In line with prior literature, East Asians were confirmed to experience a lower adjusted risk of ischaemic events (hazard ratio [HR]: 0.487, $p < 0.001$) and a higher adjusted risk of major bleedings (HR: 2.262, $p = 0.01$) as compared with non-East Asian patients. DAPT significantly increased the adjusted risk of major bleeding in East Asian patients (HR: 2.843, $p = 0.002$) but not in non-East Asian patients (HR: 1.375, $p = 0.523$), thus resulting in a smaller number needed to harm (186 vs. 424). Interestingly, the authors introduced a novel parameter called '*probability risk ratio*', representing the risk ratio of major bleeding to ischaemia. East Asians displayed a higher median probability risk ratio (0.66 vs. 0.15) and a significantly larger proportion of patients with higher probability

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Table 1 Randomized controlled trials comparing different DAPT durations

Trial	Year	Nation	DAPT duration	Patients	Primary endpoint	Bleeding definition	Findings
EXCELLENT	2012	Republic of Korea	6 vs. 12 months	1,443 (722 vs. 721)	Cardiac death, MI, TVR	TIMI	6 months DAPT non-inferior
PRODIGY	2012	Italy	6 vs. 24 months	1,501 (751 vs. 750)	All-cause death, MMI, stroke	TIMI, BleedScore, BARC	24 months DAPT non-superior
RESET	2012	Republic of Korea	3 vs. 12 months	2,117 (1,059 vs. 1,058)	Cardiac death, MI, stent thrombosis, TVR, major bleeding	TIMI	3 months DAPT non-inferior
OPTIMIZE	2013	Brazil	3 vs. 12 months	3,119 (1,563 vs. 1,556)	All-cause death, MI, stroke, major bleeding	REPLACE-2, GUSTO	3 months DAPT non-inferior
DES-LATE	2014	Republic of Korea	12 vs. 36 months	5,045 (2,514 vs. 2,531)	Cardiac death, MI, stroke	TIMI	Prolonged DAPT non-superior
ARCTIC-Interruption	2014	France	12 vs. 24 months	1,259 (624 vs. 635)	All-cause death, MI, stent thrombosis, stroke, urgent revascularization	STEEPLE	No benefits but instead harms from prolonged DAPT
SECURITY	2014	Italy	6 vs. 12 months	2,399 (682 vs. 1717)	Cardiac death, MI, stent thrombosis, stroke, major bleeding	BARC	6 months DAPT non-inferior
DAPT	2014	Australia, Europe, United States	12 vs. 30 months	9,961 (4,941 vs, 5,020)	Stent thrombosis, MACCEs (death, MI, stroke) and moderate to severe bleedings	GUSTO, BARC	Superiority of 30 months DAPT
ITALIC	2015	France	6 vs. 24 months	1,894 (953 vs, 941)	Death, MI, urgent TVR, stroke, major bleeding	TIMI	6 months DAPT non-inferior
ISAR-SAFE	2015	Asia, Europe, United States	6 vs. 12 months	4,000 (1,997 vs, 2,003)	Death, MI, stent thrombosis, stroke, major bleeding	TIMI	6 months DAPT non-inferior
OPTIDUAL	2016	France	12 vs. 48 months	1,385 (690 vs, 695)	All-cause death, MI, stroke, major bleeding	ISTH	Extended DAPT non-superior
I-LOVE-IT-2	2016	China	6 vs. 12 months	1,829 (909 vs, 920)	Cardiac death, TVMI, clinically indicated TLR	BARC	6 months DAPT non-inferior
IVUS-XPL	2016	Republic of Korea	6 vs. 12 months	1,400 (699 vs, 701)	Cardiac death, MI, stroke, major bleeding	TIMI	6 months DAPT non-inferior
NIPPON	2017	Japan	6 vs. 12 months	1,443 (722 vs, 721)	All-cause death, MI, stroke, major bleeding	REPLACE-2, BARC	6 months DAPT non-inferior
COBRA-REDUCE	2020 (estimated)	Europe, United States	14 days vs. 3–6 months	996	All-cause death, MI, stent thrombosis, stroke and bleeding	BARC	On-going
MASTER DAPT	2019 (estimated)	Worldwide	1 vs. 6–12 months	4,300 (2,150 vs, 2,150)	All-cause death, MI, stroke, major bleeding	BARC	On-going
XIENCE Short	2020 (estimated)	United States	3 months vs. standard for site	2,000	All-cause death and MI	BARC	On-going

Abbreviations: BARC, Bleeding Academic Research Consortium; DAPT, dual anti-platelet therapy; GUSTO, Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; ISTH, International Society on Thrombosis and Haemostasis; MACCEs, major adverse cardiovascular and cerebrovascular events; MI, myocardial infarction; REPLACE-2, Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events; STEEPLE, Safety and Efficacy of Enoxaparin in Percutaneous Coronary Intervention Patients; TIMI, thrombolysis in myocardial infarction; TLR, target lesion revascularization; TVMI, target vessel myocardial infarction; TVR, target vessel revascularization.

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of bleeding than ischaemia (32.3% vs. 0.4%, $p < 0.001$) as compared with non-East Asians.

The authors should be commended for their efforts in this delicate field which has several worthy aspects. In fact, this meta-analysis encompassed a large number of subjects, including a sizeable proportion of East Asian individuals. One of the key benefits of conducting a patient-level rather than a study-level meta-analysis is the possibility to control for potential confounders with multivariable statistical adjustment, which is indeed advantageous. Moreover, the study was intended as a landmark meta-analysis with censoring of events occurring before DAPT discontinuation in each trial, therefore shifting the focus from the optimal duration of DAPT to the ischaemia/bleeding risk trade-off of DAPT continuation.

However, there are some points of concerns that need to be mentioned. Some relevant trials were excluded for several reasons, including failure to obtain individual patient data from the original investigators. Ethnicity was defined only based on the countries participating in the enrolment process and the non-East Asian group was heterogeneous. The included trials differed with respect to randomization time points, adjudication processes and especially bleeding definitions. Clopidogrel was the mostly used drug in combination with aspirin, which makes the results not applicable to DAPT regimens using other $P2Y_{12}$ inhibitors. The variability of stents among different countries and populations (e.g. first-generation drug-eluting stents were mostly used in East Asian patients compared with their counterpart) acts as a major confounder, which is difficult to control adequately even with multivariable adjustment when ischaemic outcomes are assessed. Another theoretical concern is the lack of as-treated analysis owing to the missing data about protocol violations, namely, crossover rates or early DAPT discontinuation. Finally, the 'probability risk ratio' introduces a novel statistical parameter which is intuitive but not immune from criticism. In fact, the same ratio can be theoretically obtained in high ischaemic and high bleeding risk patients (high/high, e.g. $2/2 = 1$) and in the low ischaemic and low bleeding risk patients (low/low, e.g. $0.5/0.5 = 1$), in which the implication of DAPT may not be the same.

The underlying pathophysiologic mechanisms of racial disparities in the field of anti-thrombotic pharmacotherapy response have been widely examined over the years.[13,23–25] One reason for such conundrum in East Asians is the higher prevalence of CYP2C19 single nucleotide polymorphisms (mostly CYP2C19*2) diminishing the activity of clopidogrel and responsible for higher rates of on-treatment high platelet reactivity. Such 'East Asian paradox' (e.g. high platelet reactivity in the context of lower ischaemic events) suggests that Westerners' cut-off values for high platelet reactivity are hardly applicable to East Asian patients, which probably entail a different 'sweet spot' in terms of platelet inhibition.[26–28] East Asians also experience a greater exposure to prasugrel and ticagrelor compared with Caucasians, even after adjustment for body weight, thus suggesting that the optimal dose of the newer generation $P2Y_{12}$ inhibitors should be reduced.[29–32] Thrombogenicity is also quite variable among races, with substantial differences in coagulation, fibrinolysis, levels of haemostatic factors, plasma endothelial activation markers, genetic polymorphisms and inflammation processes.[33–35] Obesity is also associated with a pro-thrombotic status and appears to be less prevalent among East Asians.[36] In addition, minor reasons accounting for the observed racial differences could be the different lifestyle and the higher prevalence of *Helicobacter pylori* infection among East Asians, which could be more susceptible to gastrointestinal ulceration and bleedings, especially during anti-thrombotic treatments.[37] Finally, even the identification of high bleeding/ischaemic risk patients could be troublesome among East Asians. In fact, commonly used risk scores have been developed and validated in Westerners and may not be suitable for Easterners.[11] The need for a race-specific scoring system is powerfully emerging to help clinicians making the right choices for each patient.

Moving forward, how can we integrate the information from the important meta-analysis of Kang et al in our daily decision-making for patients of different ethnicity? First, after a global patient evaluation, thrombotic and bleeding risks should be assessed for every individual patient and 'one-size-fits-all' strategies should be avoided. Second, even if the results are consistent in showing that East Asian patients are more vulnerable to bleeding than ischaemia, a high bleeding risk should not be translated automatically into a shorter DAPT duration because a higher bleeding risk does not exclude a concurrent high thrombotic risk. The key to account for this overlap seems to be a careful appraisal of the relative bleeding/ischaemia risk trade-off. Third, patients on DAPT have to be followed-up strictly and DAPT dosages or duration should be modified promptly if severe adverse events occur. An important research question is how to improve current tools for decision-making, leading to the development of standardized definitions, race-specific risk scores, bleeding/ischaemia risk trade-off tools and guidelines to align clinical practice to patient's needs.

In conclusion, East Asian patients on DAPT suffer from more bleeding events compared with their Western counterpart. Current evidence on risk prediction and optimal DAPT regimens among the large and growing East Asian population is scarce, making management of these patients a tricky issue undermined by many pitfalls. Whereas further race-specific trials, dedicated risk prediction tools and regional or national guidelines are warranted and expected, the best strategy at present seems to personalize DAPT choices, dosages and duration in the attempt to minimize both ischaemic and bleeding complications.

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