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REVIEW

Racial and ethnic differences in pharmacotherapy to prevent coronary artery disease and thrombotic events

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Awareness of racial/ethnic disparities represents a key challenge for healthcare systems that attempt to provide effective healthcare and to reduce existing inequalities in the use of and adherence to guideline-recommended cardiovascular drugs to improve clinical outcomes for cardiovascular disease (CVD). In this review, we describe important racial/ethnic differences between and within ethnic groups in the prevalence, risk factors, haemostatic factors, anti-inflammatory and endothelial markers, recurrence, and outcomes of CVD.

We discuss important differences in the selection, doses, and response [efficacy and adverse drug reactions (ADRs)] in ethnically diverse patients treated with antithrombotics or lipid-lowering drugs. Differences in drug response are mainly related to racial/ethnic differences in the frequency of polymorphisms in genes encoding drug-metabolizing enzymes (DMEs) and drug transporters. These polymorphisms markedly influence the pharmacokinetics, dose requirements, and safety of warfarin, clopidogrel, and statins. This review aims to support a better understanding of the genetic differences between and among populations to identify patients who may experience an ADR or a lack of drug response, thus optimizing therapy and improving outcomes. The greater the understanding of the differences in the genetic variants of DMEs and transporters that determine the differences in the exposure, efficacy, and safety of cardiovascular drugs between races/ethnicities, the greater the probability that personalized medicine will become a reality.

Keywords Cardiovascular disease • Dual antiplatelet therapy • Racial/ethnic disparities • Adverse drug reaction • Drug-metabolizing enzymes

Introduction

The burden of cardiovascular disease (CVD) continues to increase globally.[1] It remains the leading cause of death and a major contributor to disability in virtually all ethnic groups. Epidemiological studies have demonstrated marked variations in the prevalence and natural history, risk factors (age, sex, hypertension, diabetes mellitus, obesity, dyslipidaemia, physical inactivity, and smoking), and outcomes of CVD between different races and ethnicities and within racial/ethnic groups.[1] Although race and ethnicity are terms that are frequently used interchangeably, each term denotes a different attribute. Race refers to a person's physical traits, whereas ethnicity refers to a person's racial ancestry plus genetic and cultural differences (e.g. language, history, traditions, and beliefs).[2] Furthermore, the efficacy and safety of cardiovascular drugs may differ between ethnicities, leading to geographical differences in the doses of approved drugs, drugs of choice, and drug labels.[2,3]

The precision medicine approach to CVD prophylaxis and treatment considers individual gene variability, drug pharmacokinetics (drug concentration over time), pharmacodynamics (relationship between drug concentration at the site of action and effect), demographic and environmental data (e.g. diet, age, lifestyle, exposure to drugs and toxins, and socioeconomic factors), and risk profiles with the aim of maximizing efficacy while minimizing or avoiding

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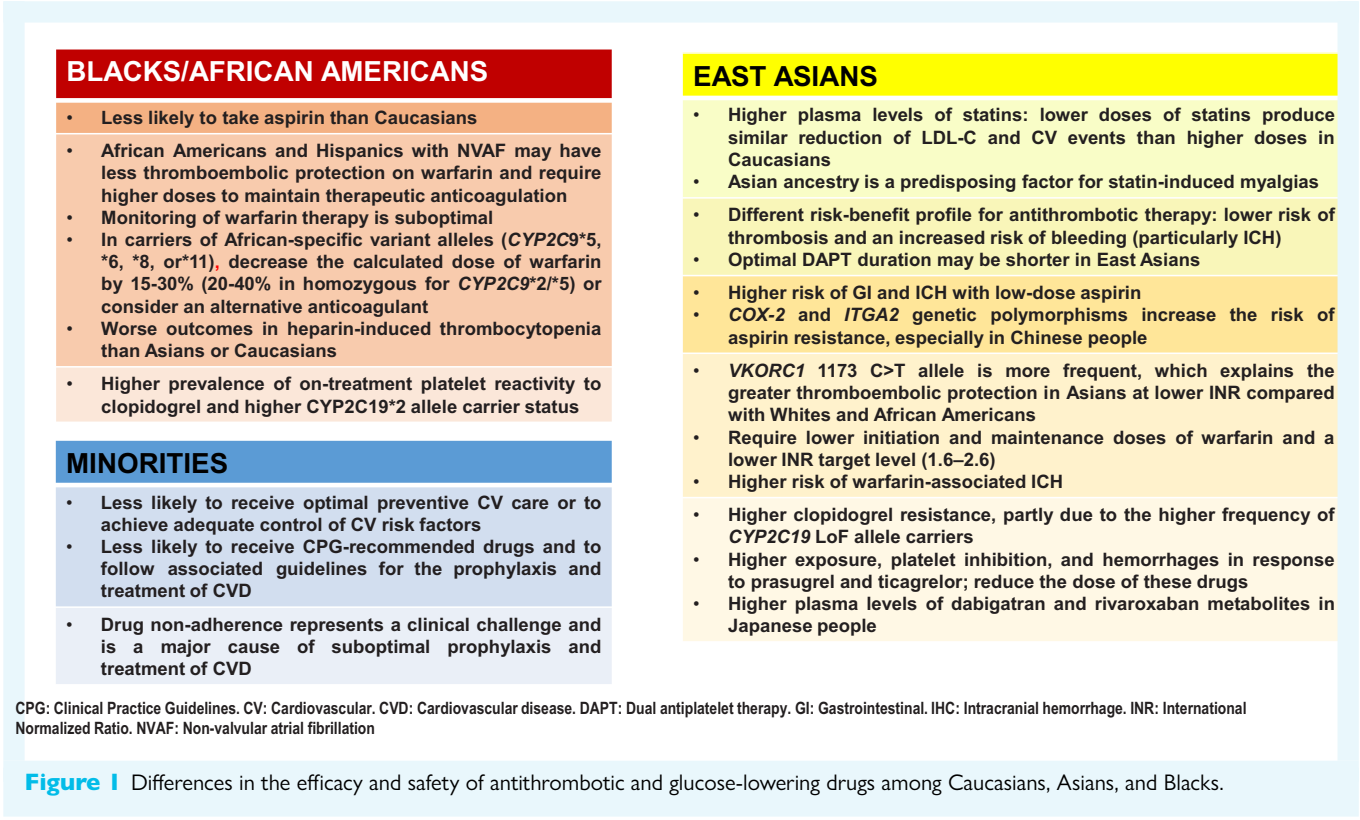

Figure 1 Differences in the efficacy and safety of antithrombotic and glucose-lowering drugs among Caucasians, Asians, and Blacks.

adverse drug reactions (ADRs).[2,3] Interestingly, many differences in drug pharmacokinetics and pharmacodynamics are driven by genetic variations that determine the expression and/or functional activity of drug-metabolizing enzymes (DMEs), transporters, and/or targets (receptors, enzymes, ion channels, and proteins involved in signal transduction).[4] Precision medicine has focused on cytochrome P450 isoforms (*CYP2D6, CYP2C9, CYP2C19*, and *CYP3A4*), which are responsible for the biotransformation of approximately 70% of clinically prescribed cardiovascular drugs. Multiallelic genetic polymorphisms in DMEs, which differ markedly in frequency between different ethnicities and regions, represent a major source of variability in drug pharmacokinetics and lead to distinct phenotypes termed as normal, poor [two loss-of-function (LoF) alleles], intermediate (one LoF allele), extensive, and ultrarapid (duplication or amplification of an active gene) metabolizers.[4] Awareness of variations in the frequency of DME-related genetic polymorphisms is important for identifying differences in drug response (excessive or subtherapeutic drug exposure leading to potential ADRs or lack of response, respectively), optimizing drug selection and dosing, and reducing disparities in the prophylaxis and treatment of CVD between different racial/ethnic groups.[4]

In this review, we describe important racial/ethnic differences in (a) the prevalence, risk factors, and outcomes of CVD (*Table 1*) and (b) efficacy, dose requirements, adherence, and/or ADRs of drugs used for the treatment of dyslipidaemia and thromboembolic events (*Tables 2–5*), which in many cases are related to differences in allelic variations in genes encoding DMEs (*CYP2C9, CYP2C19*, and *VKORC1*) and transporters (*ABCG2 and VKORC1*) among major ethnic groups (*Table 6*). Oral antithrombotic therapy (antiplatelet therapy and anticoagulation therapy) is a key element of pharmacotherapy in patients with CVD. Several reports have suggested that there may be possible differences in optimal therapeutic regimes of antithrombotic therapy among races and ethnics (*Tables 3* and *4*). Blacks exhibit a pro-inflammatory status and the highest thrombogenic and dysfunctional endothelial profiles, followed by Caucasians (*Table 1*). On the other hand, East Asian individuals show an inactive inflammatory status and the lowest risk of atherothrombotic events among different ethnic groups. Further, East Asians exhibit higher bleeding risk and a higher prevalence of intracranial haemorrhage (ICH) compared with Caucasians. This review supports a better understanding of the intrinsic differences among races and ethnicities to optimize anti-thrombotic pharmacotherapy for better outcomes. *Figure 1* summarizes the main differences in cardiovascular drug requirements and ADRs among Caucasian, Asian, and Black populations.

Do sex and ethnicity influence pharmacotherapy for angina pectoris?

Epidemiology of coronary artery disease

Understanding ethnic and geographical differences in the incidence, prevalence, pathophysiology, investigation, and management of coronary artery disease (CAD) and angina has been of great scientific interest for decades (*Table 1*). Data from the Global Burden of Disease Study[5] suggest that CAD is the second greatest contributor to disability-adjusted life-years worldwide. The global prevalence of CAD was estimated to be 197 million in 2019. However, the prevalence varies significantly between continents. Europe has a prevalence of 3547 per 100 000 in comparison to 1440 per 100 000 observed in Asia and Australasia, 1990 per 100 000 in the Americas, and 880 per 100 000 in Africa.[6] Even within European Society of Cardiology member states, there is great variation in the age-standardized incidence between and within ethnic groups and sexes, ranging from 44 per 100 000 female individuals in Portugal to 557 per 100 000 male individuals in Egypt.[7] When looking at data within, as opposed to between countries, ethnicity remains associated with differing rates of CAD, reiterating that factors independent of those directly related to the country of residence remain influential. The

Table 1 Racial/ethnic differences in risk factors and cardiovascular disease among different ethnic groups

Population	Cardiovascular diseases
African Americans (AA)	Higher prevalence of CV risk factors, including HTN, insulin resistance, T2DM, and obesity (particularly in women) than Whites, which explain the earlier age of onset and the higher rate of CVD [1–6].
	HTN is more severe and resistant, develops at an earlier age, and leads to higher rates of target organ damage (HF, stroke, MI, and end-stage renal disease) and mortality than in Caucasinas, Asians, and Hispanic Americans [2, 5–9].
	Similar LDL-C (with less atherogenic distribution of lipoprotein particles), higher HDL-C and PCSK9, lower triglycerides and higher Lp(a) levels compared with non-Hispanic Whites or Mexican Americans [10–13].
	AA with ASCVD had the highest rate of CV events, all-cause and cardiovascular death compared with other ethnic/racial groups worldwide, which could be explained by elevated risk factors [12, 14–17].
	Higher rates of IHD events (including MI), functional impairment, and death from ACS compared with other ethnic groups [2, 6, 9, 11,18–20].
	Black race predicts stent thrombosis (ST) after drug-eluting stent implantation [21].
	Lower prevalence and severity of coronary artery calcium than in Whites and Hispanics [12, 22].
	HF appears at an earlier age and presents an accelerated clinical course and poorer prognosis compared with Whites [2, 6].
	Higher risk of stroke and stroke-related mortality than White patients [2, 7, 11, 19, 20].
	VTE events are significantly higher among AA than in Caucasians, Hispanics, and Asians/Pacific Islanders [2, 23–25].
	Despite some risk factors for AF are more prevalent among AA, they present a lower prevalence and incidence of AF compared with Whites [26, 27].
	Higher thrombogenic, proinflammatory, and dysfunctional endothelial profile than Hispanic Americans and Whites [28–33].
	AA women have a higher platelet count than Caucasians and are less responsive to cyclooxygenase and P2Y12 receptor inhibitors [34].
	Two loci associated with ADP-induced aggregation (rs11202221 and rs6566765) may affect platelet function in AA but not in European Americans [35].
Blacks	HTN affects AA disproportionally to those from rural Caribbean or continental Africa [8].
	People of African or Caribbean heritage have a higher prevalence of T2DM and CVD recurrence compared with other ethnic groups [36, 37].
	Lower age-sex adjusted hazard ratios for initial lifetime presentation of all the coronary disease diagnoses than Whites [20].
	Lower rates of overall CVD [2].
American–Caucasians	The prevalence of conventional CV risk factors is generally greater in non-Caucasian ethnic groups. Whites had the lowest rates of diabetes mellitus and hypertension as compared with other ethnic groups [14].
	Non-Hispanic White women have the highest rates of elevated total cholesterol and LDL-C levels [12].
	More thrombogenic and dysfunctional endothelial profiles and proinflammatory cytokines than in East Asians [28, 38].
	The risk for AF is higher, but Caucasians are less vulnerable to AF-associated morbidity and mortality compared with other ethnic groups (the so-called AF ethnical paradox) [27].
	Higher prevalence of cardiometabolic abnormalities among normal weight people in all racial/ethnic minority populations than in Whites [39].
	The G1691A variant of the factor V (Leiden) gene and the G20210A variant of the prothrombin gene are more common in populations of European origin as compared with those of African, but is virtually absent in Asians [24, 40].
American Indians	High rates of CVD mortality are largely driven by the high prevalence of IHD, HTN, T2DM, CKD, obesity, smoking, and physical inactivity as compared with non-Hispanic Whites [3, 10].
	Native American/Alaskan populations have high rates of risk factors for ASCVD compared with non-Hispanic Whites [41].
	Lower total cholesterol, LDL-C, HDL-C, and Lp(a) levels as compared with non-Hispanic Whites [3, 10, 12].
Hispanic/Latino Americans	Lower CVD mortality than non-Hispanic Whites and Asians [2, 6, 9, 12].
	Rates of HF, stroke, and PAD are higher than for non-Hispanic Whites [2, 14, 18, 42, 43].
	Lower HDL-C, higher total cholesterol, LDL-C (more elevated small, dense particles) and triglyceride levels and similar Lp(a) levels, compared with non-Hispanic Whites [2, 6,10, 12, 44–47].
	Higher prevalence of HTN, T2DM, central obesity, and metabolic syndrome in non-Hispanic Whites [10, 43–49]. Mexican Americans have the highest prevalence of HTN, T2DM, obesity, and metabolic syndrome compared with other race/ethnic groups [2, 10].
Asians	Higher prevalence of CVD, DM, and metabolic syndrome with lower body mass index and smaller waist circumference compared with non-Asian patients [39, 48, 49].

Table 1 ***Continued***

Population	Cardiovascular diseases
	Lower prevalence of HTN, IHD, stroke, non-fatal MI, and both all-cause and cardiovascular mortality than in Blacks, Whites, or Hispanics [14, 16, 50–52].
	Higher prevalence of LDL-C among Asian Indians, Filipinos, Japanese, and Vietnamese than among Whites. Higher TG levels in all Asian American subgroups [12].
	Higher mortality burden of hypertensive heart disease compared with non-Hispanic Whites [53].
	Higher incidence of intracerebral or subarachnoid haemorrhages than Caucasians [50, 54, 55].
	In patients hospitalized with AF, the risk of ICH is 4-times greater among Asians as compared with Whites, even having a similar INR range [54, 56]. Thus, many Asian clinicians adopt a lower INR target range [33].
	Asian patients undergoing PCI had a lower adjusted risk for the composite end point of death, MI, and repeat revascularization than Whites [57].
	The incidence of AMI is lower than that in USA and Europe [58]. Asian patients with STEMI had a higher risk of major in-hospital bleeding compared with Caucasians [19, 59, 60].
	Low rates of PAD [14].
	Lower prevalence of VTE in Asians/Pacific Islanders than in Caucasians and much lower than in AA [24, 61].
	Asians achieved higher ACT levels compared with other racial groups [62].
	Lower thrombogenic, proinflammatory, and dysfunctional endothelial profile than Hispanic Americans and Whites [28–33, 38, 63].
East Asians (China, Japan, Korea)	Lower levels of LDL-C, HDL-C, triglycerides, and Lp(a) compared with non-Asians [9, 64].
	Higher prevalence of coronary vasospasm [65].
	Lower incidence of IHD and a decreased risk of post-PCI atherothrombotic complications compared with Caucasians [6, 33, 66].
	Unlike in Western countries, the reported prevalence of STEMI in East Asian countries is higher than that of non-STEMI [66, 67].
	The risk of bleeding and ischaemic events increases among East Asian patients with ACS [48].
	Despite a lower platelet inhibitory response to clopidogrel, they show a similar or lower risk of atherothrombotic events post-PCI but a higher risk of bleeding events during antithrombotic therapy compared with Westerners ('East Asian paradox') [33, 54, 57, 58, 68–74].
	This paradox might be related to a higher frequency of the *CYP2C19* LoF alleles in East Asian than in Whites (~65% vs. ~30%) [75, 76].
	Higher prevalence of ICH (and lacunar strokes) compared with ischemic stroke (30% and 70%, respectively) in comparison with Whites (15% and 85%, respectively) [52].
	Factor V Leiden allele is almost absent (5% of Caucasians) and prothrombin *G20210A* mutation is rare in East Asians (2–4% of Caucasians) [33, 77].
	East Asians patients with stable IHD have a lower level of platelet–fibrin clot strength, a major determinant of ischemic event occurrence, than Caucasian patients [78].
	Because East Asians have lower hypercoagulability than Caucasians, their optimal potency and achieved risk–benefit ratio during antithrombotic treatment would be relatively different compared with the Western population [78, 79].
South Asians (Bangladesh, Bhutan, India, Maldives, Nepal, Pakistan, Sri Lanka)	Higher prevalence of HTN, insulin resistance, T2DM, IHD, abdominal obesity, metabolic syndrome, and physical inactivity and a lower prevalence of AF than other ethnicities [2, 10, 14, 37, 77–81]. South Asian ancestry is a CV risk factor.
	Higher triglyceride and Lp(a), lower HDL-C levels, and similar mean LDL-C levels (but particle size are smaller and more atherogenic) compared with Whites [9, 82, 83].
	South Asian men have similarly high coronary artery calcium burden as White men, but higher than other racial/ethnic groups [77, 84, 85].
	Earlier onset and higher incidence and mortality rates from ASCVD compared with East Asians and non-Hispanic Whites [16, 37, 77].
	Higher rates of premature IHD (stable angina, MI) and mortality from IHD compared with other Asian ethnic groups and Whites [2, 12, 14, 20, 75, 85, 86].
	Higher risk of CVD recurrence compared with Europeans, possibly related to baseline risk vascular factors [37].
	Similar prevalence of hypertension to White populations, but south Asians may have increased indices of arterial stiffness compared with Whites [10, 20].
	Lower rates of PAD compared with other ethnic groups [14, 85].

References for this table will appear in Supplementary material online, *Table S1*.

AA, African Americans; ACT, activated clotting time; ACS, acute coronary syndrome; AF, atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CKD, chronic kidney disease; HDL-C, high-density lipoprotein cholesterol; HF, heart failure; HTN, hypertension; ICH, intracranial haemorrhage; IHD, ischemic heart disease; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein(a); MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; STEMI, ST-Elevation Myocardial Infarction; T2DM, type 2 diabetes mellitus; TG, triglycerides; VTE, venous thromboembolism.

Table 2 Racial/ethnic differences in the pharmacodynamics/pharmacokinetics of drugs used for the treatment of dyslipidemia between ethnic groups

Drugs	Racial/ethnic differences in response to drug therapy
Statins	There are differences in the efficacy, pharmacokinetics, and adverse effects of statins between East Asians and Caucasians, most likely related to genetic variations in genes encoding DMEs, drug transporters, and drug targets [1–3].
	Statin pharmacokinetics and safety are strongly influenced by polymorphisms in *SLCO1B1* and *ABCG2 genes*; the effects of genetic polymorphisms differ between statins [4–6].
	Higher plasma levels of statins are reached in Asians compared with Caucasians [2].
	In Japanese patients, lower doses of statins produce similar reductions in LDL-C and cardiovascular events than higher doses in Westerners and other ethnic groups [7–13].
	Maximum approved doses of atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin are 40, 60, 20, 20, and 20 mg in the USA and 80, 80, 80, 40, and 80 mg in Japan, respectively [6].
	Treatment with a low dose of pravastatin reduces the risk of IHD in Japan by the same amount as higher doses have been shown in Europe and the USA [1].
	For regressing coronary atherosclerotic plaque in patients with IHD, Asians need lower dosage of statins or lower intensity LDL-C lowering therapy than Westerners [12].
	Systemic exposure of rosuvastatin is 1.7–2-fold higher in Asians as compared with Caucasians [1, 7, 14–18]. Reduce the starting dose (5 mg) in Asian patients (not for other racial/ethnic groups) and increase the dose up to 20 mg/day [2, 14, 19–21].
	The required duration of rosuvastatin or atorvastatin administration for LDL-C lowering was longer in Westerners than in the Asian population (22–24 and 7.8–10.3 months, respectively) [7, 22].
	Systemic exposure to atorvastatin and simvastatin acid is greater in East Asians than in American Caucasians [23]. In adults of East Asian descent, other statins should be used preferentially over simvastatin [24].
	The frequency of *SLCO1B1* haplotypes among different races might explain the differences in response to statins [7, 25–28] (*Table 6*). The transport activity of hepatic cells is upregulated in people with SLCO1B1*1b and downregulated in people with SLCO1B1*5.
	Some polymorphisms (*SLCO1B1* c.521T > C and *ABCG2* c.421C > A) are more common in Asians than in Caucasians, which may explain the higher systemic exposure and the lower doses of statins needed in Asians compared with Caucasians [6, 7, 14, 26–33].
	ABCG2 c.421 variant influences the pharmacokinetics of atorvastatin, fluvastatin rosuvastatin, and simvastatin [4, 5, 34].
	The *SLCO1B1*1B* (c.388G-c.521T) haplotype, the predominant allele in East Asians, is associated with enhanced hepatic uptake and decreased plasma concentrations of atorvastatin, but not of rosuvastatin, in Caucasians [30].
	AA may have a less robust LDL-C response to lovastatin and simvastatin compared with Whites [7, 35, 36]. Two *HMGCR* gene polymorphisms, more prevalent in AA, are associated with the reduced LDL-C response to simvastatin [36].
Evolocumab	Similar reduction in LDL-C levels across racial/ethnic groups; among those with DM, Asian participants had greater LDL-C reduction [37].

References for this table will appear in Supplementary material online, *Table S2*.
AA, African–Americans; ABCG2, adenosine triphosphate (ATP)-binding cassette G2 intestinal and liver efflux transporter; ACEIs, angiotensin-converting enzyme inhibitors; BP, blood pressure; CCBs, calcium channel blockers; DPP4, dipeptidyl peptidase; FDC-I/H, fixed dose combination isosorbide dinitrate-hydralazine; GLP-1, glucagon-like peptide **1** receptor; GNB3, guanine nucleotide binding protein beta polypeptide 3 subunit; HF, heart failure; IHD, ischemic heart disease; LDL-C, low density lipoprotein-cholesterol; LoF, loss-of-function; LVI, left ventricular hypertrophy; MI, myocardial infarction; RAASIs, renin–angiotensin–aldosterone system inhibitors; SBP, systolic blood pressure; SLCO1B1, soluble organic anion—transporting polypeptide 1B.

increased relative rates of CAD in the South Asian community have been replicated in numerous large-scale epidemiological studies both within the United Kingdom and worldwide (*Table 1*). Of course, a significant proportion of the differing rates and severity of disease can be attributed to socioeconomic and income-related factors.[5]

Sex and ethnic differences in in-hospital outcomes

The most shocking observational data relate not to sex and ethnic differences in the prevalence of CAD but rather to differences in management decisions and patient outcomes. Despite the relatively a higher prevalence of CAD in male individuals, female individuals experience disproportionately worse outcomes.[2] In a large-scale prospective cohort study conducted in the USA, there was a drastic difference in in-hospital complications between ethnic subgroups. Large-scale observational data suggest that a great proportion of these differences may not be related to pathophysiological differences but rather due to differences in care provision, with up to 69% of sex-mortality disparities attributed to suboptimal care provision.[8]

Racial differences in coronary vasospasm

Data regarding the epidemiology of rare conditions, such as coronary spasm, are less widely available. However, there also appears to be

Table 3 Racial/ethnic differences in the pharmacodynamics/pharmacokinetics of anticoagulant drugs

Drug	Racial/ethnic differences in response to drug therapy
Anticoagulants	East Asians have lower hypercoagulability than Whites and, therefore, may have a different risk-benefit profile for antithrombotic therapy (antiplatelet and anticoagulation therapy), namely a lower risk of thrombosis and an increased risk of bleeding [1, 2].
Warfarin (VKAs)	Warfarin metabolism (S-warfarin is mainly metabolized by CYP2C9), dosage requirements to achieve goal INR and anticoagulation response vary across ethnic groups, but may be lower in Asians [3–5].
	Asians present a greater thromboembolic protection at lower INR compared with Whites and a higher risk of major bleeding (including ICH) at INR levels within the therapeutic range [4, 6–13].
	Asian patients may require lower initiation and maintenance doses of warfarin [1, 2].
	The adjusted mean weekly warfarin doses to maintain a therapeutic INR were 24, 31, 36, and 43 mg for Asian Americans, Hispanics, Whites, and AA, respectively [4–7].
	In patients with AF on warfarin, mean time in the therapeutic INR range (2–3) was lower in individuals from Asia or Africa (32–40%) than in White Americans (50.9%) and Westerners (62.4%) [14–17].
	Conflicting data regarding the optimal target INR in East Asian patients with AF. A lower INR (1.6–2.6 instead of 2–3) may be more adequate in East Asians than in Westerners (INR 2–3) [8, 12, 17–22]. Japanese guidelines recommend a reduced INR target level (1.6–2.6) in patients with AF aged $\geq$ 70 years [17, 21–23].
	In the USA individuals with AF, warfarin-associated ICH was significantly higher in Asians, Blacks, and Hispanics than in Whites, despite a similar INR range [8, 12, 14, 20].
	AA and Hispanics with NVAF may have less thromboembolic protection on warfarin and require higher warfarin doses to maintain therapeutic anticoagulation intensity compared with Whites [24, 25].
	AA spent less time within the therapeutic INR range compared with Whites, Asians, and Hispanics; AA and Hispanics have a significantly higher risk of bleeding from warfarin than Whites [8, 26–29].
	Lower concentrations of proteins C and S may explain the decreased response to warfarin among Blacks [29, 30].
	Genetic variants in CYP2C9 (*CYP2C9**2 and *CYP2C9**3), VKORC1 (3673G > A), *CYP4F2*, and the CYP2C cluster (e.g. rs12777823) are major factors responsible for the substantial interindividual variability in warfarin dose requirements and risk of bleeding between ethnicities [4, 6, 24–38].
	Carriers of *CYP2C9**2 or *3 LoF variants and/or VKORC1 1639G > A were more likely to have an INR $\geq$ 4 and of bleeding complications [3, 23, 24, 30, 39–41]. A lower dose of warfarin or an alternative oral anticoagulant might be considered.
	VKORC1 1173 C > T allele is more frequent in Japanese (89.1%) than Caucasians (42.2%) and AA (8.6%) [6], which can explain the greater thromboembolic protection in Asians at lower INRs compared with Whites and AA [3–5, 22, 27, 32].
	Although *VKORC1* variants are associated with a dose decrease, the proportional decrease is higher among European Americans than in AA [29].
	If African-specific variant alleles (*CYP2C9**5, *6, *8, or*11) are detected, decrease the calculated dose by 15–30% (20–40% in patients homozygous for variant alleles, i.e. *CYP2C9**2/*5) or consider an alternative agent [3, 24, 42, 43].
	Other variants in *VKORC1* (rs61162043) and in *CYP2C* (rs7089580) might be associated with the higher warfarin dose requirements in AA patients [3, 44].
	CYP2C9*2 is associated with lower dose requirements in European Americans but not in AA, and rs12777823, located upstream of CYP2C18, only among AA [29, 43].
	If the *CYP4F2**3 (i.e. c.1297A) allele is detected, increase the dose by 5–10% [3].
	AA carriers of the rs12777823G > A polymorphism in the *CYP2C* gene cluster requires a dose reduction of ~7 or 9 mg/week, respectively [31, 36, 37, 45].
DOACs	There are different pharmacokinetic profiles according to ethnicity [46–48], but race does not appear to influence primary efficacy and safety outcomes in pivotal trials in patients with AF or VTE [35, 49–61].
	The plasma levels of the metabolites of dabigatran and rivaroxaban were higher (20–30%) in Japanese than in Caucasians [62, 63]; apixaban showed similar exposure [64]; the trough concentration and anti-factor Xa activity during edoxaban therapy were 20–25% lower in Asians than in Caucasians [21, 48].
	Compared with VKAs, standard-dose NOACs significantly reduced S/SE in Asians than in non-Asians and were safer (less major bleeding and haemorrhagic stroke) in Asians than in non-Asians; gastrointestinal bleeding significantly increased in non-Asians [65, 66].
	Low-dose NOACs were similarly effective as VKAs in prevention against S/SE for both Asian and non-Asian patients, but might not be as effective for protection against ischemic stroke [65].
	Asian patients sustain more major bleeding events and ICH with relatively lower DOAC doses compared with non-Asians [21, 48]. Thus, the optimal use of DOACs in Asian patients remains to be settled [67].
	Western guidelines recommend the full dose of DOAC in AF patients undergoing PCI, while PCI-treated Asian patients with AF are mostly prescribed reduced-dose DOACs [68].
	In patients with NVAF, the ICH risk in Asian patients still appeared to be relatively higher compared with non-Asian patients [21, 48, 67].

Table 3 *Continued*

Drug	Racial/ethnic differences in response to drug therapy
Rivaroxaban	Pharmacokinetic modelling data showed that exposure of rivaroxaban was similar in Japanese patients with NVAF who received a 15 mg OD dose than in Caucasian that received 20 mg QD [35, 62].
	The efficacy and safety of rivaroxaban (15 mg OD) for S/SE prevention among NVAF Japanese patients were comparable to 20 mg QD in Europe and the USA [48, 52].
	Asian patients with ACS treated with aspirin (100 mg OD) or rivaroxaban (2.5 mg BID) on top of clopidogrel or ticagrelor, had the highest risk of significant bleeding and numerically the lowest risk of ischemic events as compared with Westerners [68].
Edoxaban	In East Asians, edoxaban (60/30 mg QD) provided similar efficacy to warfarin while reducing major bleeding risk [69]. These findings appear to be due to the lower trough edoxaban concentration and anti-FXa activity in Asians [63].

References for this table will appear in Supplementary material online, *Table S3*.
AA, African Americans; ACT, activated clotting time; ACS, acute coronary syndrome; AF, atrial fibrillation; BID, twice daily; CYP2C9, cytochrome P450 family 2 subfamily C member 9; CYP4F2, cytochrome P450 family 4 subfamily member 2; DOACs, direct oral anticoagulants; ICH, intracerebral haemorrhage; INR, international normalized ratio; NVAF, non-valvular atrial fibrillation; PCI, percutaneous coronary intervention; QD, once daily; S/SE, stroke or systemic embolism; UFH, unfractionated heparin; VKAs, vitamin K antagonists; VKORC1, vitamin K epoxide reductase complex 1; VTE, venous thromboembolism.

a difference in prevalence between ethnicities. Asian patients were more likely to have coronary spasms than Caucasians: for example, 24.3% in Japanese vs. 7.5% in Caucasians.[9] Similar high prevalence has been observed in South Korea.[10] Although these figures are frequently cited to represent the epidemiology of the condition, it has also been suggested that current estimates of the global prevalence of vasospastic angina are greatly affected by differential rates of formal testing by distinct countries.

Clinical implication

It is important to consider what this information means for clinical and pharmacotherapy decision-making. In fact, there is very little data to support our approach based on ethnicity, perhaps with exceptions regarding the reduced prescription of clopidogrel and ticagrelor in favour of other antiplatelets in North-Asian populations[11] and the widely known association between the reduced effectiveness of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in Black populations.[12] Otherwise, we may adjust the relative weight we place on targeting specific cardiovascular risk factors depending on the ethnic group—for example, identifying and aggressively treating high body mass index (BMI) and hypertension in Black and South Asian populations,[13] insulin resistance and diabetic control in South Asian populations, and metabolic syndrome and insulin resistance in Hispanic communities.[14]

Because of the higher prevalence of coronary spasm in the Japanese than in the Western populations, it is also possible that calcium channel blockers have more potential in the Japanese population for secondary prevention. In two prospective randomized controlled studies in Japanese patients, calcium channel blockers had a protective effect similar to that of β-blockers for cardiovascular events.[15]

Secondary prevention of CAD: does 'the lower the better' apply to Asians?

PCSK9 inhibitors in addition to statins to achieve the LDL-C target

Lowering LDL-cholesterol (LDL-C) levels by statins in CAD is associated with a reduced risk of major cardiovascular events. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors have been developed as LDL-C-lowering therapies to be used in combination with statins, and their clinical application is gaining significant traction. PCSK9 inhibitors reduced serum LDL-C levels by ≥60%. The pivotal Fourier[16] and Odyssey Outcomes[17] randomized, double-blind, placebo-controlled trials examined the effects of two monoclonal antibodies, evolocumab and alirocumab, against PCSK9 for the suppression of cardiovascular events. Both trials demonstrated that PCSK9 inhibitors in combination with statins can, in addition to lowering LDL-C levels, prevent recurrent cardiovascular events. Based on this fact, the concept of 'the lower, the better' was established for LDL-C in the secondary prevention of CAD, and recommendations were made to lower target LDL-C levels in patients with acute coronary syndrome (ACS). For example, the European Society of Cardiology guidelines on dyslipidaemia state that the LDL-C control target is <55 mg/dL.[18] Aggressive lipid-lowering therapy may be beneficial, particularly in high-risk groups. However, most patients in the Fourier and Odyssey outcomes trials were non-Asian (~85% and 80%, respectively).

Asians' characteristics in LDL-C lowering for secondary prevention

In general, Asians have a higher prevalence of diabetes mellitus than the Western population but a lower BMI and prevalence of dyslipidaemia, and the effect of statins on coronary plaque regression is attenuated in obese patients. Less obese Asians respond better to statins than Westerners do, who have a higher proportion of obese patients. In terms of the dose-response (LDL-C reduction) relationship of statins, the dose of statins required to achieve the same degree of LDL-C reduction is ~30% less among Asians than among Westerners. Thus, statin dosages in Asia are lower than those in Europe and the USA, probably because genetic polymorphisms in *SLCO1B1* and *ABCG2* that determine plasma statin levels and statin-induced rhabdomyolysis are more common in Asians.[3] Additionally, even at the same cholesterol level, the incidence of myocardial infarction is much lower in Asians than in Europeans and Americans. There remains a controversy about the significance of aggressively lowering LDL-C to, for example, <50 mg/dL, using PCSK9 inhibitors in Asians who originally have low LDL-C and experience fewer cardiovascular events.

The target value for LDL-C management in the Japanese Circulation Society's Guidelines for ACS (revised in 2018) is <70 mg/dL.[15] Recently, a sub-analysis of the Fourier trial in patients with ACS reported the safety and efficacy of evolocumab in Asians ($n = 2723$) compared

Table 4 Racial/ethnic differences in the pharmacodynamics/pharmacokinetics of antiplatelet drugs

Drugs	Racial/ethnic differences in response to drug therapy
Antiplatelets	East Asians may have a different risk-benefit profile for antithrombotic therapy (antiplatelet and anticoagulation therapy), namely a lower risk of thrombosis and an increased risk of bleeding [1–3].
	Compared with non-Asian patients, Asian patients had a significantly higher risk of haemorrhagic events when given antiplatelet monotherapy for secondary prevention after non-cardioembolic stroke/transient ischaemic attack [4].
Aspirin	With low-dose aspirin for primary prevention, the risk of ICH is higher in Asians than in non-Asians treated with aspirin [5].
	Gastrointestinal bleeding increased in East Asians as compared with Westerners [6–8]. Bleeding risk can be reduced by 30–40% decreasing the dose to 75 or 150 mg OD [9].
	COX-2 and *ITGA2* genetic polymorphisms increase the risk of aspirin resistance, especially in Chinese populations [10].
Clopidogrel	Clopidogrel is a porodrug that is converted into its active metabolite via CYP2C19 (and CYP3A4, 2C9, and 2B6).
	The prevalence of clopidogrel resistance is higher in East Asians (40–81%) compared with Westerners (20–35%) [11–14]. In Asians, clopidogrel may not achieve adequate platelet inhibition [13–16].
	Despite less activation of clopidogrel, the recommended dose in Japan is the same as in the USA or Europe (60/10 mg OD) [11,17]. In Japan, however, the dose is reduced to 50 mg QD from 3 months to 1 year, most commonly in patients with stable IHD undergoing PCI [11]; this dose is also approved for prevention of recurrent cerebral infarction in aged and/or underweight patients [18].
	Despite a higher level of platelet reactivity during clopidogrel treatment, East Asians show a similar or lower risk of ischemic events after PCI and a higher bleeding risk compared with White patients (East Asian paradox) [11, 16, 19].
	East Asians were more likely to bleed than Westerners with the same platelet reactivity [11, 16, 20, 21].
	The incomplete response to clopidogrel is primarily related to the presence of *carriers of CYP2C19* LoF allele (*CYP2C*19*2/*3) associated with poor metabolism of the drug, increased platelet aggregation, and poorer cardiovascular outcome [15, 22–24].
	The higher clopidogrel resistance in East Asians compared with Caucasians is partly due to different frequencies of *CYP2C19* LoF allele (mostly *2 or *3) carriers between Asians (up to 60%) as compared with Caucasians (15–25%) [11, 14, 15, 17].
	Homozygosity for the *CYP2C19**2 LoF allele was described in 2% of Whites, 4% of Blacks, and 14% of East Asians, and heterozygosity in 18% of Mexican Americans, 30% of Whites, 40% of Blacks, and up to 50–65% of East Asians [11, 15, 25].
	Among Asians, only 2 LoF CYP2C19 mutant allele carriers had a reduced effect of clopidogrel, and the reduced effect was significant only after the 30th day of treatment. Among Westerners, both 1 and 2 reduced-function CYP2C19 allele carriers had the reduced effect, and it mainly occurred within the first 30 days [25].
	In patients with IHD treated with clopidogrel undergoing PCI, carriers of *CYP2C19* LoF alleles (*2, *3, *4, or *5) have lower levels of the active metabolite, higher platelet reactivity, and higher rates of MACE and stent thrombosis than non-carriers during follow up [16, 22–24].
	In *CYP2C19**2 or *3 heterozygous carriers, recommended alternative strategies are to use higher doses of clopidogrel (LD/MD: 600–1200/150 up to 300 mg QD) or to use ticagrelor or prasugrel [11, 16, 17, 30–34]. CYP2C19*2 homozygous carriers cannot achieve the desired antiplatelet effect even with 300 mg/day of clopidogrel.
	Blacks have a higher prevalence of the *CYP2C19*2* LoF allele and higher on-treatment platelet reactivity to clopidogrel compared with Whites [11, 35].
	Carriers of the *CYP2C19*17* GoF allele (<5% in East Asians, up to 30% in European and African populations) had a higher level of the active metabolite, higher clopidogrel-induced platelet inhibition, and a higher risk of bleeding [36–39].
	Carriers of the *ABCB1* 3435 TT genotype have reduced platelet inhibition and are at increased risk of recurrent of cardiovascular death, MI, or stroke during clopidogrel treatment [24].
	Among patients with stable CVD, a maintenance dose of clopidogrel of 225 mg/day in *CYP2C*19*2 heterozygotes achieved levels of platelet reactivity similar to those seen with the 75-mg dose in noncarriers; in contrast, for *CYP2C*19*2 homozygotes, doses as high as 300 mg/day did not result in comparable degrees of platelet inhibition [40].
Prasugrel and ticagrelor	Their bioactivation, plasma levels and platelet inhibition are less (prasugrel) or not dependent (ticagrelor) on CYP2C9 activation; they seem less susceptible to genetic variations than clopidogrel [15, 22, 40–46].
	The degree of platelet inhibition with prasugrel and ticagrelor is higher in East Asians than in Whites [16, 47], but because they markedly increase the risk of bleeding, they present less favourable net clinical benefit in East Asians compared with Caucasians with ACS [16, 46–49].
	They should replace clopidogrel in *CYP2C19* poor and intermediate metabolizers [16, 50].

Table 4 ***Continued***

Drugs	Racial/ethnic differences in response to drug therapy
Prasugrel	The levels of its active metabolite are 30–48% higher in East Asians than in Caucasians [11, 16, 51].
	Lower LD/MD of prasugrel (20/3.75 mg; i.e. one third of the dose approved in European American or Korea guidelines 60/10 mg) present similar efficacy as clopidogrel and were approved for Japanese patients with stable or ACS undergoing PCI [17, 52–55].
Ticagrelor	Higher exposure to ticagrelor and its major active metabolite (30–48%) and increased platelet inhibition in East Asians as compared with Westerners, which correlates with the level of platelet inhibition [11, 16, 21, 56].
	East Asians can reach a similar degree of platelet inhibition at a lower dose than that used in Westerners [57, 58].
	Southeast Asian patients also appeared to experience higher rates of ischaemic events and bleeding than East Asian patients [59].
	Ticagrelor dose is lower in Japanese (60 mg BID) than in the ACC/AHA, ESC, and Korean Society of Cardiology guidelines (90 mg BID) [55].
P2Y12 receptor inhibitors	There are significant differences in the use of these drugs clopidogrel/reduced dose of prasugrel/ticagrelor in patients undergoing PCI between Japan (37.7%/53.6%/0.1%) and the USA (57.0%/9.6%/31.8%) [60].
DAPT therapy	Optimal DAPT duration may be shorter in East Asians [3, 16, 61]. After PCI, short-term vs. long-term DAPT strategy significantly increased ischemic events only in non-East Asians, while bleeding events were decreased by short-term DAPT in both ethnicities.
	The ischaemia/bleeding trade-off may be different between East Asians and non-East Asians. In East Asians, prolonged DAPT may have no effect in reducing the ischaemic risk while significantly increasing the bleeding risk [3].

References for this table will appear in Supplementary material online, *Table S4*.
AA, African–Americans; ACS, acute coronary syndrome; ADP, Adenosine diphosphate; aPPT, activated partial thromboplastin time; BID, twice a day; COX-2, cyclooxygenase-2; CYP2C19, cytochrome P450 family 2 subfamily C member 19; DAPT, dual antiplatelet therapy; GP, glycoprotein; GoF, gain-of-function; ICH, intracerebral haemorrhage; ITGA2, integrin subunit alpha 2; LD/MD, loading/maintenance doses; LoF, loss-of-function; MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention; QD, once daily.

with individuals of other racial origins ($n = 24\,841$).[19] With regard to the patients' background, myocardial infarction was significantly less prevalent in Asians than in individuals of other races, whereas diabetes mellitus and stroke were more common in Asians. Compared with individuals of other races, BMI and LDL-C levels were significantly lower among Asians, and the use of potent statins was less common in Asians (33.3% Asians vs. 73.3% other races; $P < 0.001$). The rate of LDL-C reduction with evolocumab was greater among Asians (66%) than among those of other races (58%; $P < 0.001$), although there was no difference in the incidence of serious adverse reactions. In terms of cardiovascular events, the reduction was similar between Asians [hazard ratio (HR) 0.79; 95% confidence interval (95% CI) 0.61–1.03] and those belonging to other races (HR 0.86; 95% CI 0.79–0.93; *P* interaction = 0.55). This sub-analysis suggests that lowering the LDL-C level to <50 mg/dL is safe in Asians and may help reduce cardiovascular events to levels similar to those in individuals belonging to other racial groups. However, a regional sub-analysis of Odyssey Outcomes comparing alirocumab vs. placebo showed a significant benefit in Europe and the USA but a neutral trend (no benefit) in the Asian population.[17] Although potent lipid-lowering therapy with PSCK9 inhibitors may be helpful in Asians because of their inherently low risk of developing cardiovascular events, it may be better to target patients with higher cardiovascular event risk.

To treat dyslipidaemia as a secondary prevention for CAD, administering the maximum dose of statins is the first priority. From both medical and economic perspectives, it is necessary to further clarify which patients truly require more aggressive lipid-lowering therapy with PCSK9 inhibitors while accounting for racial differences.

Ethnic differences in antiplatelet therapy after percutaneous coronary intervention

'East Asian paradox'

There were significant differences between East Asian and Caucasian patients in the incidence of thrombotic and bleeding events after percutaneous coronary intervention (PCI) and in the pharmacokinetic and pharmacodynamic profiles of antiplatelet drugs (*Tables 1* and *4*).

Dual antiplatelet therapy (DAPT) with aspirin plus a $P2Y_{12}$ inhibitor is the standard treatment after PCI. During DAPT, patients with high on-treatment platelet reactivity to adenosine diphosphatase are at an increased risk of thrombotic events.[20] Therefore, we need to consider an appropriate 'therapeutic window' for the use of antiplatelet drugs. The prevalence of patients with high on-treatment platelet reactivity is higher in East Asia than in the USA or Europe. This might be explained by the higher prevalence of *CYP2C19* LoF alleles in East Asians, the major determinant of platelet inhibitory activity in clopidogrel.[20] Nevertheless, East Asians have a lower incidence of cardiovascular events and a higher incidence of bleeding events than Caucasians. This phenomenon, called the 'East Asian paradox,' might be explained by several factors related to the differences in variants of some haemostatic genes.[20] The G1691A variant of the factor V gene and the 20210A variant of the prothrombin gene are associated with an increased risk of ischemic events, and the prevalence of these haemostatic gene polymorphisms is higher in Caucasians than in Asians. In addition, Asian patients have lower thrombogenic, proinflammatory, and endothelial dysfunction markers, healthier diet habits, and a lower prevalence of obesity than non-Asian patients (*Table 1*).

Which $P2Y_{12}$ inhibitor should be used after PCI in Asians and non-Asians?

New $P2Y_{12}$ inhibitors, such as prasugrel and ticagrelor, which are faster acting and more potent than clopidogrel, have been demonstrated to be superior to clopidogrel in patients with acute coronary ACS. Therefore, in the latest European and American guidelines, DAPT with aspirin and prasugrel or ticagrelor is recommended after PCI in patients with ACS, while DAPT with aspirin and clopidogrel is recommended after PCI for patients with chronic coronary syndrome;[21] however, a reduced-dose ticagrelor strategy has not been evaluated in East Asian patients.[22]

In the PRASFIT-ACS trial in Japan, a reduced dose of prasugrel (3.75 mg) with aspirin compared with clopidogrel with aspirin was associated with a lower risk of cardiovascular events and a similar risk of bleeding events (*Table 4*, prasugrel). In the A-MATCH trial comparing the de-escalation strategy (prasugrel 5 mg or platelet function test-guided) and standard-dose strategy (prasugrel 10 mg) in East Asians, the prevalence of patients within the therapeutic window was significantly higher in the de-escalation group than in the standard-dose group, and bleeding events were lower in the de-escalation group than in the standard-dose group.[23] These data support the inappropriate use of the standard dose of prasugrel in East Asian patients. Based on these trials, in Japan, only a reduced dose of prasugrel (20 mg loading followed by 3.75 mg maintenance) was approved for patients with ACS. Prasugrel is more commonly used among $P2Y_{12}$ inhibitors in Japan (54%) than in the USA (9.6%).[24]

In both the PHILO[25] and TICAKOREA[26] trials in East Asia, ticagrelor (90 mg bid) with aspirin compared with clopidogrel (75 mg OD) with aspirin was associated with higher rates of both bleeding and cardiovascular events. Thus, among $P2Y_{12}$ inhibitors, ticagrelor is much less frequently used in Japan (0.1%) than in the USA (32%).[24]

Genotype-guided strategy for P2Y12 inhibitors

In contrast to the effectiveness of clopidogrel, that of prasugrel or ticagrelor is independent of *CYP2C19* polymorphisms.[20] Therefore, a *CYP2C19* genotype-guided strategy for $P2Y_{12}$ inhibitor use has been proposed and evaluated in several randomized clinical trials (RCTs). In patients with CYP2C19 LoF allele carriers enrolled in the TAILOR-PCI trial, the genotype-guided strategy (85% of this group received ticagrelor) compared with conventional therapy (99% clopidogrel) numerically reduced major cardiovascular events, but did not reach statistical significance (HR 0.66; 95% CI 0.43–1.02; $P = 0.06$).[27] A whole population of this trial included 23% of East Asian patients. The effect of genotype-guided therapy relative to conventional therapy was consistent regardless of race. In the POPular Genetics trial, the genotype-guided strategy (carriers of CYP2C19 LoF alleles received ticagrelor or prasugrel and non-carriers received clopidogrel) compared with the standard strategy (ticagrelor or prasugrel) in all-comes patients with STEMI was associated with similar rates of cardiovascular events and lower rates of bleeding events.[28] A very small proportion of Asian patients was included in this trial (2.9%). The efficacy of the genotype-guided strategy for the all-comes population could depend on the prevalence of CYP2C19 LoF alleles. The genotype-guided strategy might be attractive in East Asian patients due to the high prevalence of CYP2C19 LoF alleles, whereas the absolute benefit of potent P2Y12 inhibitors in reducing ischemic events might be small in East Asian patients due to the low ischemic risk in this population. Further studies will be needed to evaluate the efficacy and safety of the genotype-guided strategy for P2Y12 inhibitors in all races and ethnics, including Asian, American, and European patients.

Short DAPT period in Asians and non-Asians

Recently, concerns have been raised regarding the increase in bleeding events associated with prolonged DAPT, especially in East Asian patients due to their high bleeding risk.[22] In a meta-analysis of six RCTs, $P2Y_{12}$ inhibitor monotherapy reduced major bleeding without increasing cardiovascular events compared with DAPT, and this result was observed regardless of the patient's region (Asia/North America/Europe).[29] However, the majority of patients enrolled in these clinical trials used ticagrelor monotherapy, whereas clopidogrel monotherapy was evaluated only in a limited number of East Asian patients. In the STOPDAPT-2 trial, which enrolled patients with both ACS and chronic coronary syndrome undergoing PCI, clopidogrel monotherapy after 1 month of DAPT was associated with a significantly lower rate of bleeding compared with 12 months of DAPT with aspirin and clopidogrel (HR 0.64; 95% CI 0.42–0.98). However, cardiovascular events were similar between 1 month (1.96%) and 12 months (2.51%) of DAPT groups. In contrast, the STOPDAPT-2 ACS trial, which included only ACS but not chronic CAD patients, demonstrated that clopidogrel monotherapy after 1 month of DAPT was associated with a slight increase in cardiovascular events compared with 12 months of DAPT (HR 1.50; 95% CI 0.99–2.26), despite a significant reduction in major bleeding (HR 0.41; 95% CI 0.20–0.83).[30] A meta-analysis suggested that the optimal DAPT duration may be different between East Asians and other ethnic groups.[31] Therefore, the ideal antiplatelet regimen may be distinct between East Asians and other ethnic groups, between ticagrelor and clopidogrel, and between ACS and chronic CAD. Further studies are warranted to explore the best antithrombotic regimen after PCI in Asian, American, and European patients.

Ethnic differences in anticoagulant therapy

Anti-coagulation therapy in AF

Atrial fibrillation (AF) is an important cause of stroke and systemic embolism, and anticoagulant therapy is the only therapeutic intervention that improves the survival of patients with AF. There are important racial and ethnic differences in the risk of ICH associated with warfarin therapy in American patients with non-valvular AF (NVAF). Under warfarin administration, targeting an international normalized ratio (INR) of 2.0–3.0, compared with Whites, Blacks, and Hispanics develop ICH 2.2 times more often, whereas Asians develop it 6.5 times more often. A Japanese study found no differences in secondary prevention of stroke between the low-intensity warfarin (INR 1.9; 1.5–2.1) and conventional-intensity groups (INR 2.5; 2.2–3.5), although the rate of major haemorrhagic complications was higher in elderly people assigned to the conventional-intensity group. Based on these data, many Asian countries have adopted a lower INR target range (e.g. 1.6–2.5 instead of 2.0–3.0).

In patients with NVAF, the risk of ischemic events among patients treated with direct oral anticoagulants (DOACs) is generally equivalent to or slightly lower than that among those in the warfarin group (HR 0.66–1.13).[32] However, the risk of major bleeding, particularly ICH, in the DOAC group was clearly lower than that in the warfarin group (HR 0.30–0.73). Therefore, for patients with NVAF, DOACs are preferred over warfarin in all ethnic groups. However, under same-dose use of DOACs, the risk of ICH in Asian patients with AF remains higher than that in non-Asians.[21,32,33] For instance, the frequency of ICH was 0.45%/year in Asians and 0.29%/year in non-Asians receiving dabigatran at 150 mg twice daily and 0.67%/year in Asians and 0.30%/year in non-Asians receiving apixaban at 5 mg twice daily. Under 110 mg bid dabigatran, the frequency of ICH was maintained at 0.23%/year in both non-Asian and Asian populations. In a South

Table 5 Racial/ethnic differences in drug prescription and adverse drug reactions

Differences in drug therapy
There is no rationale for restricting the use of cardiovascular drugs based on ethnic differences [1].
AA, American non-White Hispanics, and other ethnic minorities are less likely to receive optimal preventive cardiovascular care (antihypertensive, lipid-lowering, and glucose-lowering drugs) or achieve adequate control of CV risk factors, including hypercholesterolaemia or T2DM than Whites [1–7].
Non-Hispanic blacks and Mexican Americans had 40% higher odds of uncontrolled BP compared with non-Hispanic Whites after adjustment for sociodemographic and clinical characteristics [8]. When achieve adequate BP control, AA presents similar reductions in the incidence of CVD as does Whites [8, 9].
African Americans with acute MI are less likely to receive evidenced-based treatments [1].
Blacks and Hispanics less likely to take aspirin than Whites [10].
It has been suggested that there should be different approaches to treatment for Caucasian and Asian patients who have undergone PCI [11, 12].
Clinicians treating Asian patients should keep in mind the interethnic variabilities in drug efficacy and safety when prescribing antithrombotic drugs [13–15].
The use, monitoring, and effectiveness of warfarin therapy are suboptimal, especially in Blacks and Hispanics [16].
Medication non-concordance remains a huge challenge in health care and is a major cause of suboptimal prophylaxis and treatment of CVD [17].
Blacks, Hispanics, or Asians are less likely to fill a warfarin prescription than Whites [18]. Thus, 7%, 10%, and 12% of excess strokes among these ethnic groups could be prevented if the warfarin prescription is equalized to that in Whites.
In Japan, approximately one third of new drugs approved have lower standard dosages than those approved in the USA and Europe [19]. This should be taken into consideration when prescribing to patients with Asian ancestry.
Differences in adverse drug reactions
The risk of cough and angioedema with ACEIs was 3–4-fold higher in Blacks and Asians than in White Americans [20].
Chinese patients are more susceptible to myopathy with high-dose statins [21].
Asian ancestry is a predisposing factor for statin-induced myalgias [22].
The *SLCO1B1* c.521T > C variant has been linked to statin-induced myopathy [23–25], especially in individuals receiving simvastatin.
*SLCO1B1*15* alone and *SLCO1B1*15* and *SLCO1B1*17* haplotypes impair statin clearance, increase their exposures and are a risk factor for severe myopathy with high doses of simvastatin [26].
Asian patients have a higher risk of bleeding during management of IHD [27–31].
The relative risk of ICH with thrombolytics is higher in Blacks compared with non-Black patients [32].

References for this table will appear in Supplementary material online, *Table S5*.
AA, African American; ACEI, angiotensin-converting enzyme inhibitor; BP, blood pressure; CV, cardiovascular; CVD, cardiovascular disease; ICH, intracranial haemorrhage; IHD, ischemic heart disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; SLCO1B1, soluble organic anion—transporting polypeptide 1B.

Korean cohort study, 75% of the patients received a low dose of dabigatran (100 mg twice daily).[33] Nevertheless, compared with warfarin, thromboembolic events were fewer (HR 0.76; 95% CI 0.75–0.81) and the risk of major bleeding was kept low (HR 0.81; 95% CI 0.69–0.95). In addition, two East Asian cohort studies reported that underdosing of DOACs was associated with a comparable risk of thromboembolism and bleeding with their regime-dose use.[34,35] In contrast, underdosed DOACs have been associated with a 2.5-times increased risk of thromboembolism compared with regime-dosed DOACs.[35] Despite such contradictory results, overdosing increases the risk of major bleeding. ICH is more common in Asians than in non-Asians among patients with AF being administered DOACs. Pharmacokinetic modelling showed that exposure to rivaroxaban was similar in Japanese patients with NVAF who received 15 mg once daily and Caucasians who received 20 mg once daily. This Japanese-specific rivaroxaban dose was not inferior to warfarin but reduced the rates of ICH compared with warfarin;[32] therefore, it may be preferable for Asians.

Anti-coagulation therapy in COVID-19

Severe acute respiratory syndrome Coronavirus 2, which causes coronavirus disease (COVID-19), binds to the angiotensin converting enzyme 2 receptor, which is widely expressed in vascular endothelial cells and damages these cells.[36] COVID-19 predisposes patients to venous and arterial thrombotic complications due to excessive inflammation, platelet activation, endothelial dysfunction, and stasis.[37] Multiple studies have strongly suggested that anticoagulant therapy improves the prognosis of patients with COVID-19, and thromboprophylaxis is currently recommended for patients requiring hospitalization in Europe and America.[38] The risk of venous thromboembolism in Asians is lower than that in Caucasians and much lower than that in African Americans.[36] The incidence of thrombotic events in hospitalized patients with COVID-19 has been reported to be 16% in New York[39] but only 1.9% in Japan.[40] Coagulative and fibrinolytic activities are markedly increased in COVID-19 patients, and this increase provides a big impact on their prognosis.[36–40] Therefore, the International Society on Thrombosis and Haemostasis issued an interim guidance recommending the measurement of D-dimer, fibrinogen, prothrombin time, and platelet count in all COVID-19 patients.[38] For the treatment of COVID-19-associated hypercoagulability, the interim guidance proposes the use of anticoagulation therapy for a wide range of patients, recommending prophylactic administration of low-molecular-weight heparin for hospitalized COVID-19 patients. Prophylactic anticoagulation therapy is performed in >80% of patients in Europe and the USA and in only 30% of patients in Asia,[41] probably because of the high bleeding susceptibility. Therefore, ethnic differences need to be considered when determining thromboprophylaxis strategies for patients with COVID-19, and further evidence is needed to make appropriate decisions for Asian, European, and American patients.

Table 6 Differences in allelic variations in genes encoding DMEs (*CYP2C9*, *CYP2C19*, and *VKORC1*) and transporters (ABCG2 and VKORC1) among major ethnic groups

	CYP2C9*2 (c.430C > T, LoF)	CYP2C9*3 (c.1075A > C)	CYP2C19*2 (c.681G > A, LoF)	CYP2C19*3 (c.636G > A, LoF)	CYP2C19*4/*5 (LoF)	CYP2C19*17 (c.-806C > T, GoF)
American Caucasians	8–16%	4–10%	12% (8–20%)	<1%	0–0.2%/0%	15–18%
African–Americans	1–4.5%	0.5–4.5%	12–22%	<1%	0	14–22%
European Caucasians	10–18%	3–10%	9–15%	<0.5%	0–0.2%/0	12–25%
Africans	1.2%	0–3%	15% (4.5–22%)	0.2%	0–0.4/0	10–18%
East Asians	0–0.1%	1–4%	29–50%	7–13%	<0.1%/0%	<5%
South Asians	0–1%	1.5–4%	28–50%	0.4–6%	<0.1%/0%	<5%
Oceanian	0–3%	1–4%	12–70%	2–30%	0%/ND	3–6%
Middle Easterns	5–27%	2–19%	6–24%	1.5%	ND/ND	15–25%
White Hispanics	0–07%	0.05%	12%	0.1%	0–0.3/0%	14–19%
	ABCG2	**SLCO1B1*1A**	**SLCO1B1*1B**	**SLCO1B1*5**	**SLCO1B1*15**	**VKORC1 (1173C > T)**
Caucasians	12%	56%	26%	2%	16%	42%
African–Americans	5%	22%	76%	0%	1%	16%
East Asians	11–15%	25%	63%	0%	12%	89%
South Asians		52%	39%	0%	9%	14–90%
Subsaharian Africans		21%	77%	0%	2%	

References for this table will appear in Supplementary material online, *Table S6*.
ND, not determined;
ABCG2, ATP Binding Cassette Subfamily G Member 2; CYP, cyrochrome P450 isoform; SLCO1B1, solute carrier organic anion transporter family member 1B1; VKORC1, Vitamin K Epoxide Reductase Complex Subunit 1.

Gaps in knowledge on ethnic/racial differences

We describe important racial/ethnic differences between and within ethnic groups (e.g. East vs. South Asians) in the prevalence, risk factors, haemostatic factors, anti-inflammatory and endothelial markers, recurrence, and outcomes of CVD (*Table 1*). There are also important differences in the selection, doses, and response (efficacy and ADRs) in patients treated with antithrombotics (warfarin, heparin, and P2Y12 receptor antagonists) or lipid-lowering drugs (*Tables 2–5*). Differences in drug response are mainly related to racial/ethnic differences in the frequency of polymorphisms in genes encoding DMEs and drug transporters[3,20] (*Table 6*). These polymorphisms markedly influence the pharmacokinetics, dose requirements, and safety of warfarin (*CYP2C9* and *VKORC1*), clopidogrel (*CYP2C19*), and statins (*SLCO1B1* and *ABCG2*). A better understanding of the genetic differences between and among populations is important to identify patients who may experience an ADR or a lack of drug response, thus optimizing therapy and improving outcomes. They may also explain why the approved doses of some antithrombotics and statins are lower in Asia than in the USA and Europe. Based on the different risk profiles for ischemic and bleeding events among Caucasians, Blacks, and East Asians, ethnicity-tailored antithrombotic strategies for East Asians have been proposed.[21,42] These differences should be considered by clinicians treating Asian patients and when designing and interpreting the results of RCTs to optimally treat diverse populations.

A main limitation in understanding ethnic/racial differences is related to the fact that minorities with a disproportionate burden of cardiovascular risk factors, poor outcomes, and low drug concordance have been systematically under-represented in RCTs, and this trend continues today. In pivotal efficacy RCTs supporting the approval of new cardiometabolic drugs from 2008 to 2017, 81% of the recruited patients were Whites, while Blacks, Asians, and Hispanos/Latinos represented only 5%, 12%, and 11% of the population, respectively. Neither are Africans (17% of the world population) proportionately represented in American and European trials nor are African Americans or Hispanics represented in European trials, and the study results with respect to Asians (60% of the world population) are confounded by important differences between East and South Asians and rarely translated into major clinical practice guidelines. Furthermore, many RCTs do not describe baseline demographic data or analyse the efficacy and safety of cardiovascular drugs stratified by race/ethnicity.[42] In parallel, important differences in the phenotypic expression of DMEs among races/ethnicities have been primarily analysed in Caucasians and individuals belonging to some other ethnicities but have been poorly analysed among people of developing or semi-peripheral countries (Africa and the Arab world).[2] Underrepresentation of some ethnicities in pivotal RCTs has important implications, as it prevents extrapolation of the efficacy and safety of cardiovascular drugs observed in Westerners to those of individuals of other underrepresented ethnic subgroups. Therefore, the 'one-size-fits-all' pharmacotherapy strategy based on dose regimens tested mainly in Caucasians may not be optimal for individuals of other ethnic groups, including Asians and Africans.

The US Food and Drug Administration published guidance documents that encourage the adequate enrolment of representative populations and analysis of drug efficacy and safety based on race/ethnicity to increase acceptability in global applications.[43] Additionally, regulatory agencies can request additional post-marketing studies to confirm safety and efficacy in specific ethnic groups and to incorporate possible differences in drug labels.[42]

Future development of pharmacogenomics

Carriers of *CYP2C19* LoF alleles undergoing PCI are more frequent in Asian populations than in Africans or Caucasians (*Table 6*). They present significantly lower levels of the active metabolite, higher platelet reactivity, and a greater risk of major adverse cardiovascular events and stent thrombosis when clopidogrel is prescribed.[44] However, some evidence suggests that in these patients, genotype-guided selection of an oral P2Y12 inhibitor reduces the risk of cardiovascular events without increasing the risk of major bleeding.[44,45] This has not been confirmed in a recent meta-analysis[46] or in a pragmatic study recruiting *CYP2C19* LoF carriers with ACS and stable CAD undergoing PCI.[47] Thus, based on available evidence, *CYP2C19* genotyping is not routinely recommended in patients with stable CAD for the initiation of clopidogrel prescription.[4,48,49] Genotyping, however, might be considered in high-risk patients, such as those who had a cardiovascular event while on clopidogrel or at high risk of thrombosis or bleeding, in patients scheduled for PCI who are P2Y12 receptor inhibitor naïve to decide whether they should be treated with higher doses of clopidogrel or an alternative P2Y12 inhibitor (prasugrel, ticagrelor), and in patients on clopidogrel to predict the cardiovascular risk (bleeding and ischemic events) after elective PCI in stable CAD or after PCI for ACS.[4,48,49]

When genotyping is not available, clinicians may have to rely on the patient's ethnicity (frequently regarded as a proxy of the patient's probable genotype) to guide individualized prescribing.[2] The greater the understanding of the differences in the genetic variants of DMEs and transporters that determine the differences in the exposure, efficacy, and safety of cardiovascular drugs between races/ethnicities, the greater the probability that personalized medicine will become a reality.

Conclusion

Finally, although risk factors and CVD burden are more prevalent in some ethnic groups, many of the same groups simultaneously experience greater barriers to care and are less likely to receive and follow clinical practice guideline-recommended drugs for the prophylaxis and treatment of CVD. Therefore, it remains challenging to obtain full evidence of the benefits of cardiovascular drugs in these populations. Awareness of racial/ethnic disparities represents a key challenge for healthcare systems that attempt to provide effective healthcare and to reduce existing inequalities in the use of and adherence to guideline-recommended cardiovascular drugs to improve CVD clinical outcomes.[49] A strategy to reduce these inequalities is to take a holistic approach encompassing not only pharmacogenomic diversity but also differences in lifestyle, healthcare provision, socio-economic-cultural determinants, and/or CV risk profiles.[50]

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

Not applicable, as this is a review paper.

References

1. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS *et al.* American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics-2022 update: a report from the American Heart Association. *Circulation* 2022;**145**:e153–e639.
2. Shah RR. Inter-ethnic differences in drug response: implications for drug development and complying with drug regulation. *Clin Res Reg Affairs* 2015;**32**:88–98.
3. Naito R, Miyauchi K, Daida H. Racial differences in the cholesterol-lowering effect of statin. *J Atheroscler Thromb* 2017;**24**:19–25.
4. Magavern EF, Kaski JC, Turner RM, Drexel H, Janmohamed A, Scourfield A *et al.* The role of pharmacogenomics in contemporary cardiovascular therapy: a position statement from the European Society of Cardiology Working Group on Cardiovascular Pharmacotherapy. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:85–99.
5. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet North Am Ed* 2020;**396**:1204–1222.
6. Khan MA, Hashim MJ, Mustafa H, Baniyas MY, Al Suwaidi SKBM, AlKatheeri R *et al.* Global epidemiology of ischemic heart disease: results from the Global Burden of Disease Study. *Cereus* 2020;**12**:e9349.
7. Woodward M. Cardiovascular disease and the female disadvantage. *Int J Environ Res Public Health* 2019;**16**:1165.
8. Li S, Fonarow GC, Mukamal KJ, Liang L, Schulte PJ, Smith EE *et al.* Sex and race/ethnicity—related disparities in care and outcomes after hospitalization for coronary artery disease among older adults. *Circ Cardiovasc Qual Outcomes* 2016;**9**:S36–S44.
9. Kunadian V, Chieffo A, Camici PG, Berry C, Escaned J, Maas AHEM *et al.* An EAPCI expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology Working Group on Coronary Pathophysiology & Microcirculation endorsed by Coronary Vasomotor Disorders International Study Group. *Eur Heart J* 2020;**41**:3504–3520.
10. Shin DI, Baek SH, Her SH, Han SH, Ahn Y, Park KH *et al.* The 24-month prognosis of patients with positive or intermediate results in the intracoronary ergonovine provocation test. *JACC: Cardiovasc Interv* 2015;**8**:914–923.
11. Jafrin S, Naznin NE, Reza MS, Aziz MA, Islam MS. Risk of stroke in CYP2C19 LoF polymorphism carrier coronary artery disease patients undergoing clopidogrel therapy: an ethnicity-based updated meta-analysis. *Eur J Internal Med* 2021;**90**:49–65.
12. Helmer A, Slater N, Smithgall S. A review of ACE inhibitors and ARBs in black patients with hypertension. *Ann Pharmacother* 2018;**52**:1143–1151.
13. Hossain FB, Adhikary G, Chowdhury AB, Shawon MSR. Association between body mass index (BMI) and hypertension in south Asian population: evidence from nationally-representative surveys. *Clin Hypertens* 2019;**25**:28.
14. Graham G. Disparities in cardiovascular disease risk in the United States. *Curr Cardiol Rev* 2015;**11**:238–245.
15. Kimura K, Kimura T, Ishihara M, Nakagawa Y, Nakao K, Miyauchi K *et al.* Japanese Circulation Society Joint Working Group. JCS 2018 Guideline on diagnosis and treatment of acute coronary syndrome. *Circ J* 2019;**83**:1085–1196.
16. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA *et al.* FOURIER Steering Committee and Investigators. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med* 2017;**376**:1713–1722.
17. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R *et al.* ODYSSEY OUTCOMES Committees and Investigators. Alirocumab and cardiovascular outcomes after acute coronary syndrome. *N Engl J Med* 2018;**379**:2097–2107.
18. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L *et al.* ESC Scientific Document Group. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. *Eur Heart J* 2020;**41**:111–188.
19. Keech AC, Oyama K, Sever PS, Tang M, Murphy SA, Hirayama A *et al.* FOURIER Study Group. Efficacy and safety of long-term evolocumab use among Asian subjects—a subgroup analysis of the further cardiovascular outcomes research with PCSK9 inhibition in subjects with elevated risk (FOURIER) Trial. *Circ J* 2021; **85**: 2063–2070.
20. Levine GN, Jeong YH, Goto S, Anderson JL, Huo Y, Mega JL *et al.* Expert consensus document: World Heart Federation expert consensus statement on antiplatelet therapy in East Asian patients with ACS or undergoing PCI. *Nat Rev Cardiol* 2014;**11**:597–606.
21. Valgimigli M, Bueno H, Byrne RA, Jean-Philippe Collet JP, Costa F *et al.* 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in

collaboration with EACTS: the task force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2018;**39**:213–260.
22. Kim HK, Tantry US, Smith SC, Jeong MH, Park SJ, Kim MH *et al.* The East Asian paradox: an updated position statement on the challenges to the current antithrombotic strategy in patients with cardiovascular disease. *Thromb Haemost* 2021;**121**:422–432.
23. Jeong YH, Oh JH, Yoon HJ, Park Y, Suh J, Lee SW *et al.* Pharmacodynamic profile and prevalence of bleeding episode in East Asian patients with acute coronary syndromes treated with prasugrel standard-dose versus de-escalation strategy: a randomized A-MATCH Trial. *Thromb Haemost* 2021;**121**:1376–1386.
24. Inohara T, Kohsaka S, Spertus JA, Masoudi FA, Rumsfeld JS, Kennedy KF *et al.* Comparative trends in percutaneous coronary intervention in Japan and the United States, 2013 to 2017. *J Am Coll Cardiol* 2020;**76**:1328–1340.
25. Goto S, Huang CH, Park SJ, Emanuelsson H, Kimura T. Ticagrelor vs. clopidogrel in Japanese, Korean and Taiwanese patients with acute coronary syndrome—randomized, double-blind, phase III PHILO study. *Circ J* 2015;**79**:2452–2460.
26. Park DW, Kwon O, Jang JS, Yun SC, Park H, Kang DY *et al.*TICAKOREA Investigators. Clinically significant bleeding with ticagrelor versus clopidogrel in Korean patients with acute coronary syndromes intended for invasive management: a randomized clinical trial. *Circulation* 2019;**140**:1865–1877.
27. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V *et al.* Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI Randomized Clinical Trial. *JAMA* 2020;**324**:761–771.
28. Claassens DMF, Vos GJA, Bergmeijer TO, Hermanides RS, van 't Hof AWJ, van der Harst P *et al.* A genotype-guided strategy for oral $P2Y_{12}$ inhibitors in primary PCI. *N Engl J Med* 2019;**381**:1621–1631.
29. Valgimigli M, Gragnano F, Branca M, Franzone A, Baber U, Jang Y *et al.* P2Y12 inhibitor monotherapy or dual antiplatelet therapy after coronary revascularisation: individual patient level meta-analysis of randomised controlled trials. *BMJ* 2021; **373**: n1332.
30. Watanabe H, Domei T, Morimoto T, Natsuaki M, Shiomi H, Toyota T *et al.* Effect of 1-month dual antiplatelet therapy followed by clopidogrel vs 12-month dual antiplatelet therapy on cardiovascular and bleeding events in patients receiving PCI the STOPDAPT-2 randomized clinical trial. *JAMA* 2019;**321**:2414–2427.
31. Ki YJ, Kang J, Park J, Han JK, Yang HM, Park KW *et al.* Efficacy and safety of long-term and short-term dual antiplatelet therapy: a meta-analysis of comparison between Asians and non-Asians. *J Clin Med* 2020;**9**:652.
32. Bang OY, Hong KS, Heo JH. Asian patients with stroke plus atrial fibrillation and the dose of non-vitamin K oral anticoagulants. *J Stroke* 2016;**18**:169–178.
33. Cho MS, Yun JE, Park JJ, Kim YJ, Lee J, Kim H *et al.* Outcomes after use of standard and low-dose non-vitamin K oral anticoagulants in Asian patients with atrial fibrillation. *Stroke*; doi:10.1161/STROKEAHA.118.023093. Published online ahead of print 3 December 2018.
34. Yu HT, Yang PS, Jang E, Kim TH, Uhm JS, Kim JY *et al.* Label adherence of direct oral anticoagulants dosing and clinical outcomes in patients with atrial fibrillation. *J Am Heart Assoc* 2020;**9**:e01417.
35. Lee KN, Choi JI, Boo KY, Kim DY, Kim YG, Oh SK *et al.* Effectiveness and safety of off-label dosing of non-vitamin K antagonist anticoagulant for atrial fibrillation in Asian patients. *Sci Rep* 2020;**10**:1801.
36. Komiyama M, Hasegawa K. Anticoagulant therapy for patients with coronavirus disease 2019: urgent need for enhanced awareness. *Eur Cardiol Rev* 2020;**15**:e58.
37. Bikdeli B, Madhavan MV, Jimenez D, Chuich T, Dreyfus I, Driggin E *et al.* Global COVID-19 Thrombosis Collaborative Group,Endorsed by the ISTH, NATF, ESVM, and the IUA, supported by the ESC Working Group on Pulmonary Circulation and Right Ventricular Function. COVID-19 and thrombotic or thromboembolic disease: implications for prevention, antithrombotic therapy, and follow-up: JACC state-of-the-art review. *J Am Coll Cardiol* 2020;**75**:2950–2973.
38. Spyropoulos AC, Levy JH, Ageno W, Connors JM, Hunt BJ, Iba T *et al.* Subcommittee on Perioperative,Critical Care Thrombosis, Haemostasis of the Scientific, Standardization Committee of the International Society on Thrombosis and Haemostasis. Clinical guidance on the diagnosis, prevention, and treatment of venous thromboembolism in hospitalized patients with COVID-19. *J Thromb Haemost* 2020;**18**:1859–1865.
39. Bilaloglu S, Aphinyanaphongs Y, Jones S, Iturrate E, Hochman J, Berger JS. Thrombosis in hospitalized patients with COVID-19 in a New York city health system. *JAMA* 2020;**324**:799–801.
40. Horiuchi H, Morishita E, Urano T, Yokoyama K, Questionnaire-survey Joint Team on the COVID-19-related thrombosis. COVID-19-related thrombosis in Japan: final report of a questionnaire-based survey in 2020. *J Atheroscler Thromb* 2021;**28**:406–416.
41. Moonla C, Sosothikul D, Chiasakul T, Rojnuckarin P, Uaprasert N. Anticoagulation and in-hospital mortality from coronavirus disease 2019: a systematic review and meta-analysis. *Clin Appl Thromb Hemost* 2021;**27**:107602962110089.
42. Gibson CM, Yuet WC. Racial and ethnic differences in response to anticoagulation: a review of the literature. *J Pharm Pract* 2021;**34**:685–693.
43. Guidande Document. E17 general principles for planning and design of multi-regional clinical trials. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/e17-general-principles-planning-and-design-multi-regional-clinical-trials. (18 July 2018).
44. Cavallari LH, Lee CR, Beitelshees AL, Cooper-DeHoff RM, Duarte JD, Voora D *et al.* Multisite investigation of outcomes with implementation of CYP2C19 genotype-guided antiplatelet therapy after percutaneous coronary intervention. *JACC: Cardiovasc Interv* 2018;**11**:181–191.
45. Notarangelo FM, Maglietta G, Bevilacqua P, Cereda M, Merlini PA, Villani GQ *et al.* Pharmacogenomic approach to selecting antiplatelet therapy in patients with acute coronary syndromes: the PHARMCLO Trial. *J Am Coll Cardiol* 2018;**71**:1869–1877.
46. Kheiri B, Osman M, Abdalla A, Haykal T, Pandrangi PV, Chahine A *et al.* CYP2C19 pharmacogenetics versus standard of care dosing for selecting antiplatelet therapy in patients with coronary artery disease: a meta-analysis of randomized clinical trials. *Catheter Cardiovasc Interv* 2019;**93**:1246–1252.
47. Pereira NL, Farkouh ME, So D, Lennon R, Geller N, Mathew V *et al.* Effect of genotype-guided oral P2Y12 inhibitor selection vs conventional clopidogrel therapy on ischemic outcomes after percutaneous coronary intervention: the TAILOR-PCI Randomized Clinical Trial. *JAMA* 2020;**324**:761–771.
48. Sibbing D, Aradi D, Alexopoulos D, Ten Berg J, Bhatt DL, Bonello L *et al.* Updated expert consensus statement on platelet function and genetic testing for guiding $P2Y_{12}$ receptor inhibitor treatment in percutaneous coronary intervention. *JACC: Cardiovasc Interv* 2019;**12**:1521–1537.
49. National Institutes of Health Minority Health and Health Disparities Strategic Plan 2021–2025. https://www.nimhd.nih.gov/docs/nimhd-strategic-plan-2021-2025.pdf. (14 January 2022).
50. Ski CF, Thompson DR, Fitzsimons D, King-Shier K. Why is ethnicity important in cardiovascular care? *Eur J Cardiovasc Nurs* 2018;**17**:294–296.