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MINIREVIEWS

Current status of high on-treatment platelet reactivity in patients with coronary or peripheral arterial disease: Mechanisms, evaluation and clinical implications

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Abstract

Antiplatelet therapy with aspirin or clopidogrel or both is the standard care for patients with proven coronary or peripheral arterial disease, especially those undergoing endovascular revascularization procedures. However, despite the administration of the antiplatelet regiments, some patients still experience recurrent cardiovascular ischemic events. So far, it is well documented by several studies that *in vitro* response of platelets may be extremely variable. Poor antiplatelet effect of clopidogrel or high on-treatment platelet reactivity (HTPR) is under investigation by numerous recent studies. This review article focuses on methods used for the *ex vivo* evaluation of HTPR, as well as on the possible underlying mechanisms and the clinical consequences of this entity. Alternative therapeutic options and future directions are also addressed.

Key words: Coronary disease; Clopidogrel; Aspirin; High on treatment platelet reactivity; Peripheral arterial disease; Antiplatelet therapy; Ticagrelor; Prasugrel

Core tip: Recent data related high on-treatment platelet reactivity (HTPR) with adverse clinical outcomes, such as stent thrombosis and repeat procedures, following coronary or peripheral endovascular revascularization procedures. Notably, the incidence of patients suffering from peripheral arterial disease demonstrating inadequate response to clopidogrel is around 50%, which is much higher than the approximately 30% reported for patients suffering from coronary artery disease. Novel more potent antiplatelet P2Y12 agents seem to overcome the phenomenon of HTPR decreasing ischemic events with the cost of increased bleeding risk. Until today no major trial demonstrated clinical improvement for patients undergoing platelet function test-guided individualized antiplatelet therapy. Prescription of new antithrombotic agents aims in avoiding major cardiovascular adverse events, as well as sustaining vessel patency following revascularization. Therefore, improving antiplatelet therapy, considering the risk/benefit ratio, is imperative

especially in HTPR patients. Further large-scale studies are awaited to elucidate the role of individualized therapy.

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INTRODUCTION

Thrombus generation resulting from platelet activation and aggregation is the established main process involved in atherosclerotic vascular disease, including coronary artery disease (CAD) and peripheral arterial disease (PAD)[1,2].

Therefore, antiplatelet therapy has been the cornerstone therapy in patients with documented arterial disease, especially in those undergoing coronary or peripheral percutaneous endovascular procedures[3-5]. However, a variable amount of these patients continue to experience recurrent ischemic events[6,7]. This clinical phenomenon has been correlated with various parameters among which poor antiplatelet effect of clopidogrel or aspirin, described by consensus as high on-treatment platelet reactivity (HTPR) initially identified in patients with CAD[8,9]. HTPR in patients with PAD, especially those undergoing percutaneous peripheral angioplasty (PTA) has recently been documented by several studies[10,11].

This review focuses on the clinical significance of HTPR, the possible mechanisms and the common tests used to measure the phenomenon, as well as future perspectives of novel antiplatelet agents and platelet function-guided antiplatelet therapy.

HTPR DEFINITION

Despite the fact that the optimal method to define HTPR has not been clarified in the literature the clinical challenge of inter-individual variability of the inhibitory effect of antiplatelet agents on platelet function, initially named non-responsiveness or resistance, should be definitely considered as failure of the antiplatelet drug to inhibit its target of action[12]. HTPR has been strongly associated with an increased incidence of major adverse cardiovascular events (MACEs) especially for patients on clopidogrel. Clopidogrel is an adenosine diphosphate (ADP)-receptor antagonist that obstructs platelet activation and aggregation by irreversibly binding to both ADP receptors (P2Y1 and P2Y12)[13]. Therefore, the basic principles of assessing HTPR are to quantify the activity of the target receptor after administration of the antiplatelet agent by using a laboratory method and to determine consensus HTPR cut-off values for various assessment methods[14].

MEASURING HTPR

Numerous tests are available for measuring HTPR. Light transmission aggregometry is the most well established laboratory method for the determination of HTPR. It evaluates the response of the platelet to ADP agonist as an increase in light transmittance measuring as maximal platelet aggregation. However, because it is time and labor intensive, today it is seldom used for monitoring response to clopidogrel[15]. Many other platelet function assays are now available but the most common platelet function tests (PFTs) used in everyday clinical practice are the flow cytometric vasodilator-stimulated phosphoprotein phosphorylation (VASP) analysis and the VerifyNow P2Y12 assay[16].

The VASP assay uses flow cytometry to measure inhibition of VASP phosphorylation by ADP *via* the P2Y12 receptor. The ratio of VASP phosphorylation is indicative for the receptors' activity and reported as platelet reactivity index (PRI). Several studies reported high correlation between high PRI values and recurrent stent thrombosis after percutaneous coronary intervention (PCI)[17]. However, the specific method has been gently criticized for its lack of standardization and therefore the inability of establishing a universal PRI cut-off value[18,19].

The most widely used method of routinely monitoring platelet function is the VerifyNow bedside assay. It is a very practical, rapid and well-standardized point-of-care test that measures platelet-induced aggregation to fibrinogen-coated beads in whole blood in response to an ADP induced stimulus[20,21]. Results are expressed as P2Y12 reaction units (PRU) reflecting P2Y12 mediated platelet reactivity. Published studies using this instrument have demonstrated the relationship between HTPR values and long-term cardiovascular events after PCI[14,22].

Several additional PFTs are also available but rarely used in clinical research: PFA-100, Impedance Aggregometry (Multiplate Analyzer) and whole blood thromboelastography[23-25]. Wisman *et al*[26] in a recent meta-analysis of 59 studies using 15 different tests stated that HTPR was associated with a significant 2.8 times higher risk of MACE. Based on all the available evidence and according to the most recent expert consensus paper issued by the Working Group on Thrombosis of the European Society of Cardiology, the recommended assays for monitoring P2Y12 platelet inhibition are the VerifyNow P2Y12 assay, the Multiplate device with the ADP kit and the VASP assay[27].

HTPR CUT-OFF VALUES

In order to overcome the lack of universally defined cut-off values for the various PFTs for HTPR, Bonello *et al*[14] based on numerous studies using receiver operating characteristic (ROC) established consensus values for HTPR for every major platelet function test: (1) > 46% maximal for a 5-μmol/L ADP-induced aggregation; (2) > 50% PRI using the Platelet VASP test; and (3)

Table 1 Common platelet function assays

Test	LTA	VASP	VerifyNow
Function	Increase in light transmittance	Flow cytometric measurement of VASP phosphorylation	Measurement of platelet-induced aggregation to fibrinogen-coated beads
Receptor	P2Y1 and P2Y12	P2Y12	P2Y12
Results	MPA	PRI	PRU
Cut-off value	> 46%	> 50%	230-240

LTA: Light transmission aggregometry; VASP: Vasodilator-stimulated phosphoprotein phosphorylation; MPA: Maximal platelet aggregation; PRI: Platelet reactivity index; PRU: P2Y12 reaction units.

230-240 P2Y12 reaction units PRU by the VerifyNow P2Y12 assay (Table 1).

However, the majority of the data for this consensus were extrapolated from the coronary studies, given the lack of data from PAD patients. The PRECLOP study, a prospective single-center trial was the first study suggesting the optimal HTPR cut-off value exclusively in patients with PAD using the VerifyNow test[28]. ROC analysis performed in this trial revealed an identical to CAD patients' cut-off value (PRU $\geqslant$ 234; area under the curve 0.883; 95%CI: 0.811-0.954; P = 0.0001).

HTPR MECHANISMS

The antiplatelet effect of clopidogrel is based on the inhibition of platelet aggregation by irreversibly binding to the P2Y12-ADP receptor. It is basically an inactive prodrug that undergoes two consecutive oxidations by the hepatic cytochromes P450 (CYP) to create an active metabolite. This accounts for 15% of the drug metabolism[29]. Multiple potential factors for HTPR have been proposed mainly correlated with distorted activity of cytochrome P450 isoenzymes[30,31].

Genetic factors

Several studies initially documented that poor response to clopidogrel may be greatly heritable[32]. Specifically, genetic polymorphisms to the hepatic CYP450 enzymes, especially to CYP2C19 that is involved in both steps of clopidogrel's biotransformation might disturb the metabolism and therefore the effect of the drug[33]. It has been described that carriers of at least one low function CYP2C19 allele experience a reduction of the active metabolite in plasma up to 32.4% in comparison to healthy gene carriers[34]. The most notorious *2 allele follows an autosomal co-dominant inheritance[35]. Therefore, the highest risk profile group links with those who are homozygous for *2 allele[36]. Latest clinical trials have also suggested that alternative alleles (CYP2C19*3 and *4), as well as polymorphisms in alternative CYP450 enzymes (CYP2C9 and CYP2B6), may also induce HTPR[37]. Another genetic factor responsible for low response to clopidogrel is the ABCB1 gene polymorphisms responsible for reduced enteric absorption of the drug[33]. Notably, the Food and Drug Administration issued a boxed warning on clopidogrel stating that the clinical antiplatelet effectiveness is reduced for poor metabolizers, indicating that genetic tests are available to identify poor metabolizers and highlighting their emerging role in clopidogrel treatment decisions. Nonetheless, genotype accounts for approximately 2% to 12% of inter-individual variability of response to clopidogrel and various demographic and clinical factors largely contribute to the phenomenon[27].

Clinical factors

Beside the genetic background, a major issue in the field of HTPR has been the interaction with other concomitant drugs that are also metabolized by the CYPP450 system. Proton-pump inhibitors, especially omeprazole, were the first class of drugs to be investigated for possible interference with clopidogrel metabolism in early studies. Initial data outlined high incidence of HTPR in patients with CAD after PCI[38]. However, a large randomized control trial investigating clopidogrel with or without concomitant use of omeprazole following PCI revealed no significant difference in terms of MACEs between the two groups[39]. Drug-drug interactions between antiplatelet agents and calcium-channel blockers or statins were also originally reported[40,41] but additional studies demonstrated conflicting findings[42,43]. As a result according to updated guidelines there is no contraindication for the concomitant use of the above mentioned drugs with clopidogrel[27].

On the other hand, clinical entities such as chronic kidney disease (CKD) and diabetes mellitus (DM) seems to be associated with HTPR according to recent studies[44,45]. CKD, an established cardiovascular risk factor, has been recognized as an independent factor of HTPR in patients with CAD[46], while several studies also revealed poor response to clopidogrel and high incidence of stent thrombosis in diabetic patients after PCI, especially those requiring insulin therapy[47]. The possible causes include various pharmacokinetic processes such as the increased platelet turnover and the up-regulation of P2Y12 pathway in these patients[48,49]. Finally, body mass index (BMI) may be another contributing factor to attenuated platelet inhibition. Limited studies reported that overweight patients (BMI > 25 kg/m^2) while on clopidogrel demonstrated reduced antiplatelet effect[50]. However, available data are scarce and further data from larger trials are awaited.

HTPR IN CAD

Numerous studies have demonstrated that the insuffi-

cient response to clopidogrel may lead to adverse clinical outcomes, such as stent thrombosis (acute or subacute) and myocardial infarction. Moreover, recent meta-analysis including thousands of patients treated with PCI either for ST-elevation myocardial infarction (STEMI) or non-STEMI using several platelet function tests reported the correlation between high on-clopidogrel platelet reactivity and MACE, while the incidence of CAD patients detected with HTPR is approximately 35%[26,51].

Müller *et al*[52] published one of the first studies associating poor response to clopidogrel among patients experiencing MACEs after stent implantation in 2003. Successively, Gurbel *et al*[53], in a thorough analysis of the CREST study identified HTPR as a risk factor for stent thrombosis. Subsequently, the possible correlation of the phenomenon with stent thrombosis was investigated by numerous studies[54-56]. The ARMYDA-PRO study (Antiplatelet therapy for Reduction of Myocardial Damage during Angioplasty-Platelet Reactivity Predicts Outcome) was the first study investigating HTPR by using the user-friendly point-of-care assay VerifyNow and overcoming technical limitations of previous traditional platelet function methods[57]. The authors supported the concept of bedside monitoring platelet inhibition in clinical practice by proving a strong correlation between HTPR and MACEs at 30-d follow-up after PCI. These findings were amplified by latter similar studies with longer follow-up periods. Price *et al*[58] documented HTPR as a risk factor for cardiac death and stent thrombosis after drug eluting stent (DES) implantation at 6 mo follow-up. The authors also noted the perspective of modifying the antiplatelet regimen.

Of note, all the previously mentioned studies reported the correlation between high on-clopidogrel platelet reactivity and MACE, while until today there are no data indicating an analogous correlation between response to aspirin and stent thrombosis or adverse clinical events[27]. Notably, in 2014 the French VERIFRENCHY, multi-center, prospective trial published data regarding the prognostic value of testing antiplatelet response to clopidogrel and aspirin with the VerifyNow assay, in an intermediate-risk population (1.001 patients) undergoing elective stent implantation due to stable coronary disease or non-ST-segment elevation acute coronary syndrome. Overall 36.0% and 8.6% of the patients demonstrated HTPR to clopidogrel or aspirin, respectively. According to one year results, although ischemic events were numerically more in patients with high on-clopidogrel platelet reactivity (composite endpoint 3.9% of *vs* 2.3% and definite or probable stent thrombosis: 1.1% *vs* 0.3%) results did not reach statistical significance, while there was no difference in rates of major bleeding. In patients receiving aspirin there was also no significant difference in ischemic endpoints[59]. These results indicate that either HTPR may not affect clinical outcomes or that it is difficult to statistically prove the role of HTPR in populations at low to intermediate risk of stent thrombosis, due to the low number of ischemic events.

HTPR in PAD

Contrary to CAD, there is a lack of high quality evidence demonstrating the possible correlation between HTPR and adverse clinical events in patients with PAD undergoing peripheral endovascular procedures. The MIRROR single-blinded, single-center, randomized controlled trial was the first to report the existence of low response to clopidogrel in patients undergoing PTA[11]. The authors alongside with the clinical superiority of dual antiplatelet therapy following femoropopliteal angioplasty or stenting, also reported a 30% HTPR rate, similar to that identified in coronary studies. Subsequently, Pastromas *et al*[60] in a retrospective audit of 113 patients treated with clopidogrel after angioplasty or stenting, noticed an even higher HTPR incidence rate (approximately 54%). The authors speculated that this difference was mainly driven by high comorbidity rates and advanced arterial disease characteristic in critical limb ischemia (CLI) cohorts. The specific study also originally associated HTPR with significantly higher re-intervention rates. In American College of Cardiology (ACC) 2012, Kliger *et al*[61] presented the results from a study investigating responsiveness in patients undergoing PCI or PTA, which also detected a higher HTPR incidence in PAD patients.

Following these initial results, Spiliopoulos *et al*[28] further investigated the phenomenon in the PRECLOP study (NCT01744613) and established the optimal cut-off value for HTPR in PAD patients using the VerifyNow assay (PRU $\geqslant$ 234). In total 100 patients were screened with the VerifyNow assay and were stratified according to PRU values in four quartiles. The study's primary endpoint was the 1-year composite of cardiovascular death, major amputation and re-intervention events. Results revealed patients with HTPR demonstrated a less than 40% event-free survival at 1-year, while an approximately 90% event-free survival at 1 year was noted in patients with an adequate response to clopidogrel. Moreover, high on-clopidogrel platelet reactivity was identified as an independent predictor of increased events (mainly repeat revascularization procedures; HR = 16.9; 95%CI: 5-55; $P = 0.0001$). The incidence of HTPR was 51%, considerably higher than that reported in CAD trials, and was again correlated to CLI, DM and chronic kidney disease[28].

High on-aspirin platelet reactivity has been also investigated by several authors and its incidence has be reported to range between 4%-40%, a variability attributed to the multiplicity of methods used and the small sample studied. Moreover, Karnabatidis *et al*[62] and Spiliopoulos *et al*[63] reported that nearly 12% of PAD patients on dual antiplatelet therapy, demonstrated HTPR for both clopidogrel and aspirin. However, the clinical implication of low response to aspirin remains controversial and more data are needed.

NOVEL ANTIPLATELET AGENTS

Recently, novel and stronger antiplatelet agents, such as prasugrel and ticagrelor, have been introduced in

everyday clinical practice in patients suffering from acute coronary syndrome (ACS) undergoing PCI[64,65].

Prasugrel, a third generation thienopyridine agent is also a prodrug that requires metabolism before its active metabolite will bind to ADP receptor and inhibits platelet aggregation. The PRINCIPLE-TIMI 44 trial proved that prasugrel promotes platelet inhibition more rapidly and effectively in comparison with clopidogrel, showing that the degree of inhibition of platelet aggregation achieved with prasugrel within 30 min after treatment is comparable to the peak effect of clopidogrel 6 h after administration[66].

The first trial dedicated to the clinical outcomes of prasugrel was the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38[67]. Over 13000 patients with ACS receiving prasugrel or clopidogrel scheduled for endovascular treatment were enrolled in this large multi center trial. The results demonstrated a significant reduction in the rate of periprocedural myocardial infarction and stent thrombosis. However, high incidence of major bleeding in some patients of the subgroup receiving prasugrel was noted. The authors concluded that prasugrel reduces the rate of recurrent ischemic events compared with clopidogrel, but with a significantly higher bleeding risk. Based on these results, the 2011 updated ACC/American Heart Association guidelines do not recommend the use of prasugrel in patients > 75 years old, or weight < 60 kg (with a recommended decreased dose of 5 mg), history of stroke or pathologic active bleed[68]. Moreover, Bonello *et al*[69] investigating the clinical effect of prasugrel in CAD patients after PCI identified a persistent high rate of HTPR (approximately 25%) correlated with high incidence of MACEs at 30 d follow-up.

Ticagrelor, in contrast to clopidogrel, binds reversibly to the P2Y12 receptor and therefore prevents binding of ADP. Another major advantage of this novel P2Y12 antagonist is that it does not require metabolic activation, in order to exert its effect.

The DISPERSE-2 trial examined the effect of ticagrelor *vs* clopidogrel in non-STEMI patients with ACS and documented higher rate of platelet inhibition in the subgroup of the patients' cohort receiving ticagrelor[70]. Following these results, the PLATO (Platelet Inhibition and Patient Outcomes) multi-center, randomized, controlled trial compared the clinical outcomes of loading doses of ticagrelor *vs* clopidogrel in patients with ACS admitted to the hospital for prevention of cardiovascular death[71]. The results demonstrated significantly less incidence of the primary endpoint (time of occurrence of CV death, MI or stroke) in ticagrelor group than in clopidogrel group. Furthermore, the rates of major bleeding were not significantly different between the two groups. Nevertheless, after carefully analyzing bleeding events ticagrelor was associated with an increase in combined major and minor PLATO bleeding rates by 11% ($P = 0.008$)[72].

PFT-GUIDED INDIVIDUALIZED ANTIPLATELET THERAPY

Given the possibility to measure the response to clopidogrel and to use alternative antiplatelet agents in selected patients, investigators began to investigate PFT-guided antiplatelet protocols. The GRAVITAS study, a multicenter randomized double blind control trial, investigated the effect of high-dose *vs* standard-dose clopidogrel using the VerifyNow assay to identify HTPR in 2.214 patients undergoing PCI. Patients with HTPR were given high-dose platelet (600 mg loading dose and 150 mg daily doses) *vs* the standard-dose (300 mg loading dose and 75 mg daily doses). The study showed that although double-dose clopidogrel significantly reduced - but not completely abolished-HTPR, it failed to reduce MACEs at 6 mo follow-up. Specifically, HTPR was reduced by only 22% at one month[73]. This observation was further demonstrated by Alexopoulos *et al*[74] reporting that although double clopidogrel dose further inhibits platelet reactivity compared to standard dose, 35.8% of the patients under double dose remained non-responders, while for HTPR patients switching to prasugrel the percentage of non-responders was reduced to 7.0% ($P < 0.0001$).

However, two recent multi-center randomized controlled trials failed to demonstrate a clinical benefit PFT-guided antiplatelet therapy in CAD patients. The testing platelet reactivity in patients undergoing elective stent placement on clopidogrel to guide alternative therapy with prasugrel (TRIGGER-PCI) compared HTPR patients (PRU > 208) with stable CAD receiving prasugrel or clopidogrel following PCI using DES the study was prematurely terminated as the primary endpoint of death or MI at 6 mo occurred only in one patient of the clopidogrel group. The authors concluded that although prasugrel significantly reduced HTPR (mean PRU values from 245 to 80 at 3 mo) the small incidence of adverse events in elective DES procedures would not allow to prove the effectiveness of PFT-guided antiplatelet therapy[75].

The ARTIC trial compared conventional (1227 patients) *vs* PTF-guided (1213 patients) antiplatelet therapy after PCI for the composite endpoint of cardiovascular death, MI, stent thrombosis stroke and revascularization at one year follow-up. In total 37% of the patients suffered a non-ST-segment elevation acute coronary syndrome (NSTE-ACS), while the remaining had severe stable CAD. In the conventional therapy group 6% of the patients received prasugrel and only 12% in the PFT-guided group, while in the rest of non-responders double clopidogrel dose was used to treat HTPR. There was no significant difference in the primary outcome or bleeding events between the two study groups at one year follow-up[76] (Table 2). Nevertheless, the fact that the vast majority of the patients were offered double clopidogrel dose to overcome HTPR, a strategy previously reported as less effective compared

Table 2 Highlighted multicenter randomized control trials investigating platelet function tests-guided antiplatelet therapy

Study	Gravitas	Arctic	Trigger-PCI
Study population (*n*)	2214	2440	423
PFT assay	VerifyNow	VerifyNow	VerifyNow
High-dose clopidogrel	100%	80%	-
High-dose Aspirin	-	45%	-
Prasugrel	-	12%	100%
Results (primary endpoint)	2.3% *vs* 2.3%	31.1% *vs* 34.6%	0.0% *vs* 0.5%

PFT: Platelet function tests; PCI: Percutaneous coronary intervention.

to switching to novel antiplatelet agents (prasugrel or ticagrelor) in overcoming HTPR, as well as the small percentage of patients with ACS enrolled, probably negatively influenced outcomes in the PFT-guided group.

Finally, Aradi *et al*[77], conducted a meta-analysis to investigate the safety and efficacy of tailored antiplatelet therapy based on platelet reactivity testing in patients after PCI. The authors included 10 randomized controlled trials (5 multi-center, 2 double-center and 3 single-center) with a total of 4213 patients and concluded that PFT-guided intensified antiplatelet therapy was associated with decreased cardiovascular mortality and stent thrombosis. Nevertheless, the authors emphasized that the net benefit of personalized antiplatelet therapy depends on the risk of stent thrombosis and should be applied in patients at high risk. This extremely significant observation may also explain the early termination of the TRIGGER-PCI trial, where no stent thrombosis occurred in more than 400 HTPR patients, the results of the French VERIFRENCHY trial investigating patients of intermediate risk presenting with stable CAD and NSTE-ACS, as well as the negative results of the ARTIC trial where less than half of the patients suffered from ACS[78]. Of note, the ARTIC study was not included in this meta-analysis.

In the PAD arena, data about the clinical efficacy of novel antiplatelet agents and PFT-guided antiplatelet therapy modification are scarce. Torngren *et al*[78] in a study including PAD patients receiving ticagrelor because of previous ACS reported enhanced peripheral endothelial function compared to clopidogrel or prasugrel, while in a recently published post hoc analysis of the PLATO trial involving 1.144 patients with peripheral arterial disease, ticagrelor reduced the rate of cardiovascular death and MI to 16.7% compared to 21.5% in the clopidogrel group (P = 0.045)[79]. Spiliopoulos *et al*[80], recently published a study observing the clinical effect ticagrelor in 37 consecutive HTPR patients suffering from CLI undergoing angioplasty or stenting of complex lesions (long occlusions, advanced infrapopliteal disease). According to this initial experience switching therapy from clopidogrel to ticagrelor managed to overcome HTPR in all patients with documented increased platelet aggregation (PRU $\geqslant$ 234). Specifically, mean PRU during clopidogrel therapy (308.4 ± 41.8) was significantly reduced when switched to ticagrelor (67.0 ± 52.8; P < 0.0001). This was accompanied with very satisfactory clinical outcomes for the specific CLI cohort where major amputation can usually reach 25% at one year. Kaplan-Meier analysis estimated that the one-year primary composite endpoint of event-free survival was 92.0%, while revascularization-free survival rate was 67.3% at one year follow-up.

Currently, a global, multi-center, double blind, randomized, controlled, trial involving 900 sites in 25 countries (EUCLID trial; sponsored by AstraZeneca), enrolled approximately 13500 symptomatic PAD patients in order to investigate the safety and efficacy of ticagrelor *vs* clopidogrel. Primary outcome measures will be cardiovascular death, MI and ischemic stroke and results are expected within 2016. The authors speculate that individualized therapy using PTF as to identify CAD or PAD patients on increased ischemic or bleeding risk, will gradually earn its way in everyday clinical practice as long as future well-designed large-scale trials demonstrate its utility. Novel antiplatelet agents should be prescribed with consciousness as they have been related with increased bleeding events.

CONCLUSION

Following the CAPRIE trial in which clopidogrel achieved a further 24% relative risk reduction and 0.51% per year absolute risk reduction (P = 0.043) in major cardiovascular events compared to aspirin in symptomatic PAD patients, its use in every day clinical practice has been remarkably increased over the years[81]. It is generally a safe and effective drug commonly combined with aspirin, in selected patients undergoing coronary or peripheral revascularization procedures, to prevent cardiovascular ischemic events. However, a notable percentage of vascular patients present poor response to traditional antiplatelet therapy. High on-clopidogrel platelet reactivity, a clinical entity has recently emerged in the ambit of coronary and peripheral arterial disease seems to negatively affect clinical outcomes and certainly merits further investigation. The same phenomenon of low response to aspirin has been also described, however until today its clinical significance remains unproven. As modern clinical practice can support the routine use of platelet monitoring, given the fact that today platelet function tests are user-friendly, accurate and affordable in the immediate future personalized antiplatelet therapy could become a safe and efficient option in patients with low response to clopidogrel. Nonetheless, the potential risk of bleeding should always be under concern, especially in patients at high hemorrhagic risk. Consideration of the individual's genetic profile could also be an appropriate tool regarding tailored antiplatelet therapy. However, it is a fact that until today the benefit of PFT-guided personalized therapy in clinical outcomes remains to be determined and more data from meticulously designed trials are necessary.

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