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## Research Article

# Antiplatelet Therapy in Secondary Prevention in Patients with Ischaemic Peripheral Arterial Disease

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ABSTRACT

**Introduction:** Globally, peripheral arterial disease affects almost 200 million individuals at high risk of developing another type of cardiovascular disease with an annual incidence of cardiovascular events and cardiovascular mortality of 4-5% and a risk of acute limb ischaemia and amputation of 5%. All patients with clinical symptomatology of peripheral arterial disease should be treated with statins and antiplatelet drugs.

**Evidence Acquisition:** The authors provide an overview, from the perspective of a clinical pharmacologist, of the pharmacokinetic properties of the antiplatelet agents available, mechanisms of their action, and differences among individual agents in side effects, efficacy and safety as well as a comparison of clinical trials.

**Evidence Synthesis:** In a significant proportion of patients, therapy with clopidogrel is modified, with genetic polymorphism demonstrably preventing effective therapy in a proportion of patients. In cases where an antiplatelet agent other than aspirin is chosen, clopidogrel therapy is rational only if a genetic mutation resulting in ineffective therapy has been ruled out. Effective therapy can be accomplished using the more modern antiplatelet agents with balanced pharmacokinetic and pharmacodynamic properties.

**Conclusions:** Several questions related to treatment of patients with peripheral arterial disease remain to be answered. Expert views on recommended antiplatelet therapy diverge. It would be unethical to ignore the fact that therapy may be ineffective in a proportion of clopidogrel-treated patients. Guidelines for the treatment and prevention of peripheral arterial disease should offer alternative antiplatelet drugs or recommendations to verify a patient´s genetic predisposition. Further clinical trials are warranted to assess the efficacy of individual antiplatelet agents and doses thereof in patients with peripheral arterial disease.



## Introduction

According to current literary data, peripheral arterial disease (PAD) affects over 200 million individuals across the globe [1-3]. These patients show a higher incidence of other types of cardiovascular disease (CVD) such as coronary heart disease and carotid or renal artery atherosclerosis. In this particular subpopulation, the annual incidence of myocardial infarction, stroke and cardiovascular death is in the range of 4-5% or, in those developing acute limb ischaemia with an imminent risk of amputation, as high as 1-2% [4-6]. In 2017, the European Society of Cardiology (ESC) published its Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, developed in collaboration with the European Society for Vascular Surgery (ESVS) and recommending, in indicated cases, antiplatelet therapy combined with statin-based lipid-lowering therapy [1, 2, 4-7]. While there has been clear consensus on statin therapy, several questions related to PAD patients remain to be answered, with experts largely discordant on the role of antiplatelet therapy as recommended. This fact is acknowledged by authors suggesting that the efficacy of individual types of antiplatelet therapy and antiplatelet doses in PAD patients be assessed in more detail in future clinical trials [6, 8, 9].

Antiplatelet therapy is not recommended in patients with asymptomatic PAD. In clinically symptomatic PAD, the drug of choice is aspirin

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(acetylsalicylic acid) or, possibly, clopidogrel as an alternative [1, 2, 4-6]. The recommendation for dual antiplatelet therapy (i.e., a combination of aspirin and clopidogrel) is to provide it for at least a month after the revascularization procedure [6, 8-13]. While based on the results of the clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) trial- preferential use of clopidogrel instead of aspirin has been subject to ongoing debate, this change in preferences has not been incorporated into the guidelines [9, 13]. Compared with atherosclerotic disease involving other vascular territories, antiplatelet therapy in PAD patients has its specific features and its efficacy is also likely to be slightly different [14].

Aspirin-based antiplatelet therapy reduces the risk of patients with symptomatic PAD of developing a cardiovascular thrombotic event by as much as 23%. The benefit of antiplatelet therapy with aspirin has been documented by the Critical Leg Ischaemia Prevention Study (CLIPS) showing a significant reduction in the incidence of thrombotic events (stroke, myocardial infarction or pulmonary embolism) as well as critical limb ischaemia in patients treated with low-dose aspirin (12 versus 28 events; p = 0.013; HR 0.42; 95% CI 0.21 to 0.83) without a statistically significant increase in bleeding complication rates [8]. The alternative to aspirin in the prevention of thrombotic events, as proposed in the guidelines, is clopidogrel [11-15]. While the latter has been long used in clinical practice, problems related to its efficacy in a proportion of patients have been subject of ongoing debate. The issue has become even more topical at the present time given the availability of more modern antiplatelet agents with pharmacokinetic properties less variable than those of clopidogrel.

Clopidogrel, a second-generation thienopyridine derivative, is an irreversible antagonist of the adenosine diphosphate (ADP) $P2Y_{12}$ receptor on the platelet surface [16, 17]. It is a prodrug activated in two steps. The first step involves the formation of pharmacologically inactive 2-oxo-clopidogrel, an intermediary metabolite of clopidogrel, converting subsequently to the pharmacologically active metabolite (clop-AM) [18]. Clop-AM binds irreversibly to the $P2Y_{12}$ receptor thus preventing its activation. Inhibition of the $P2Y_{12}$ receptor terminates the cascade of processes potentially leading to glycoprotein IIb/IIIa activation as well as release of substances promoting thrombus aggregation and stabilization [16]. Literary reviews show that only 2% of clopidogrel is converted to 2-oxo-clopidogrel to be subsequently converted to the active metabolite [15]. A role in the biotransformation is played by a number of the cytochrome P450 enzymes, specifically and mainly by hepatic $CYP2C_{19}$ and, partly, $CYP1A_2$, CYP $2B_6$, and CYP $3A_4$ in the case of 2-oxo-clopidogrel [15-19]. The conversion conceivably occurs via CYP1A2 in 35.8%, CYP2B6 in 19.4% and CYP2C19 in 44.9%; an effect of CYP3A4, $CYP3A_5$ and CYP2C9 is also assumed [15]. The cytochrome enzymes involved in the formation of the active metabolite clop-AM include CYP2B6 (32.9%), CYP2C9 (6.79%) CYP2C19 (20.6%) and CYP3A4 (39.8%) [16, 17].

## Evidence Synthesis

The therapeutic efficacy of clopidogrel is characterized by considerable inter-individual variability with clopidogrel therapy being ineffective in 4% to 44% of patients for a variety of reasons while excess platelet inhibition is associated with an increased risk of bleeding complications in a proportion of patients [19, 20]. Patients with reduced CYP2C19 activity, referred to as poor metabolizers (2% in the white population; 4% in the black population, and 14% in the Chinese population), may show, also as a result of drug-to-drug interaction, reduced inhibition of platelet reactivity increasing the risk of ischaemic events in a dose-dependent manner [21, 22]. Table 1 discusses this issue. The therapeutic efficacy and prognosis of clopidogrel-treated patients have been shown to be affected by a host of well identified factors [23]. These include differences in the rates of absorption and P glycoprotein activity, CYP2C19 genetic variability, age, body weight as well as diabetes and renal insufficiency among comorbidities, drug-to-drug interactions such as those related to proton pump inhibitors, statins, calcium-channel blockers, oral hypoglycemic agents (sulfonylureas), serotonin reuptake inhibitors and, also, by some food interactions [23-34].

**Table 1:** Metabolism phenotype and therapeutic efficacy.

| Metabolism phenotype | Proportion in the European population | Therapeutic efficacy |
|---|---|---|
| Ultrafast | 1.8% | Increased and/or effective therapy |
| Fast | 26.2% | |
| Normal | 46.5% | Effective therapy |
| Slower | 23.0% | Less effective efficacy |
| Very slow | 2.4% | Ineffective therapy |

The prerequisites for rational pharmacotherapy, i.e., safety and efficacy of routine clopidogrel administration, are not met in almost one in three patients [35]. Moreover, a higher incidence of bleeding complications is anticipated in a proportion of patients. The Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilization, Management, and Avoidance (CHARISMA) trial reported an increase in the incidence of mild bleeding within the first 2 months of initiation of therapy with clopidogrel and aspirin (2.0% vs. 1.3%; p = 0.004) [10, 27]. As the issue of therapeutic efficacy and platelet reactivity affecting a patient´s prognosis is a most intricate one, it is reasonable to consider assessment of therapeutic efficacy. To date, no method has been unanimously recognized to reliably estimate the efficacy of clopidogrel therapy [36-39]. The technique of genetic testing to identify at-risk patients is not commonly available and performed on an everyday basis. Limiting factors include time and costs as well as genetic testing unavailability in routine practice and for patients having experienced acute events [40-42]. The effect of clopidogrel can be assessed using platelet stimulation by adenosine diphosphate (ADP) or, e.g., phosphorylation of the vasodilator-stimulated phosphoprotein as measured by flow cytometry or the enzyme-linked immunosorbent test, light transmission aggregometry (LTA), whole blood impedance platelet aggregometry (e.g., Multiplate), the VerifyNow PRUTest, TEG PlateletMapping or INNOVANCE PFA-200 systems [37, 38].

## Results

The results of individual tests do not correlate with patient´s prognosis and exhibit considerable intra-individual variability [17, 21, 23, 36, 39]. The efficacy of clopidogrel therapy varies during treatment and requires ongoing and repeat follow-up visits [43]. No clear consensus has been reached to date as to which test should be used to assess the efficacy of antiplatelet therapy with clopidogrel [16, 36-39, 44]. Based on data from some small trials that documented the benefit of antiplatelet treatment with clopidogrel monitoring, the 2016 AHA/ACC guideline on the management of patients with lower extremity peripheral arterial disease included assessment of the efficacy of clopidogrel therapy [15, 43, 45].

The results of other larger studies including GRAVITAS, ARCTIC, ANTARTIC, DANTE, and TRIGGER-PCI have not consistently supported the importance of monitoring of a patient´s prognosis; however, it should be noted that their outcomes have not been generally accepted by experts in the field [24, 25, 37, 46, 47].

The question is whether or not prasugrel and ticagrelor, the two relatively new platelet aggregation inhibitors shown to have smaller inter-individual variability in pharmacokinetic parameters compared with clopidogrel, are associated with greater benefit for PAD patients. Results of several clinical trials are currently available [48, 49]. Higher efficacy and a beneficial effect on the prognosis of PAD patients treated with 75 mg clopidogrel versus 325 mg aspirin in secondary prevention were documented in CAPRIE. The incidence of ischaemic cardiovascular events (myocardial infarction, ischaemic stroke and cardiovascular death) in all clopidogrel- versus aspirin-treated patients was 5.32% and 5.83%, respectively ($p = 0.043$; RR 8.7%) with identical bleeding complication rates [9, 50]. Treatment with clopidogrel prevented 10 thrombotic events per 1000 patients treated over a period of 2 years (confidence interval 0-20%). Those benefiting most from therapy were PAD patients and, yet more specifically, patients with a history of myocardial infarction (RRR=23.7%, CI 8.9-36.2, $p = 0.003$).

The superiority of ticagrelor (9.8%) over clopidogrel (11.7%; HR 0.84; 95% CI 0.77-0.92; $p < 0.001$) was demonstrated by PLATO [PLATelet Inhibition and Patient Outcomes], a trial enrolling 18,624 patients. The study also furnished evidence that patients with PAD are at higher risk of bleeding and thrombotic complications than those with atherosclerotic disease involving other parts of the vascular bed. After one year of treatment, the incidence of ischaemic and bleeding complications in the group of PAD patients was 19.3% compared with 10.2% ($p < 0.001$) in patients diagnosed to have other forms of atherosclerotic vessel disease. Bleeding complications alone occurred in 14.8% of patients receiving ticagrelor versus 17.9% in those treated with clopidogrel ($p = 0.43$). The incidence of major fatal or life-threatening bleeding was 5.8 in either group ($p = 0.698$) [51].

The Examining Use of Ticagrelor in Peripheral Artery Disease (EUCLID) study including 13 885 patients did not find any differences in its endpoints (cardiovascular death, myocardial infarction or ischaemic stroke) or the incidence of bleeding complications in PAD patients treated either with ticagrelor or clopidogrel. When interpreting the study results, it should be noted that the patients were homozygous individuals with a loss of function allele ineligible for inclusion. The primary composite endpoint occurred in 10.8% in the ticagrelor-treated group versus 10.6% in the group receiving clopidogrel (HR 1.02; 95% CI 0.92-1.13; $p = 0.65$). A more recent therapeutic strategy referred to as dual antiplatelet therapy is beneficial only in high-risk patients such as those with coronary artery disease or in cytochrome P450 2C19 (CYP2C19) metabolizers [52, 53]. No benefit of combination therapy with aspirin and clopidogrel has been shown in PAD patients in the CHARISMA trial enrolling 15,603 patients. The incidence of cardiovascular death, myocardial infarction and stroke in the group of patients treated with the aspirin/clopidogrel combination was 6% as compared with 8.9% in the group on aspirin in monotherapy (HR 0.85; 95% CI 0.66-1.08; $p = 0.18$) [8, 9, 53].

The benefit of dual antiplatelet therapy (aspirin + ticagrelor) was documented in the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54 (PEGASUS-TIMI 54) trial including a subgroup of PAD patients. Treatment of aspirin 100-200 mg and ticagrelor 60 mg reduced the absolute risk of cardiovascular death, stroke and myocardial infarction by 4.1% while increasing the absolute risk of bleeding by 0.12%. In addition, the investigators reported a statistically significant reduction in the risk of acute limb ischaemia or peripheral revascularization for ischaemia (HR 0.65; 95% CI 0.44-0.95) [54]. Summing up the results of the above studies, one can say that, in terms of therapeutic efficacy, clopidogrel and ticagrelor in secondary prevention in patients with PAD are clearly superior to aspirin whereas that of prasugrel versus with clopidogrel has not been estimated to date. Clinical trials assessing potential superiority of clopidogrel over ticagrelor in terms of efficacy, prognosis and safety provided mixed, not consistent, results. This may be explained by the fact that ticagrelor superiority over clopidogrel was reported in a trial not excluding metabolizers with a defective CYP 2C19 gene present in up to 25.4% of the European population. If excluding the above subpopulation from the trial, the results and side effects are virtually identical.

While routine combination therapy with aspirin and clopidogrel is not associated with any benefit for the patient, dual antiplatelet therapy with aspirin + ticagrelor showed a beneficial effect on prognosis at the expense of a small increase in the risk of bleeding complications. As a result, one cannot clearly conclude which of the combinations, whether aspirin + ticagrelor or aspirin + clopidogrel, is associated with a brighter prognosis irrespective of the metabolism genotype. In line with recommendations of the most recent guidelines and rational therapy, the most recent data suggest that personalized antiplatelet therapy based on genotyping is justified in all clopidogrel-treated patients. The benefit of personalized therapy with ADP inhibitors based on the results of genotyping has been documented by several smaller studies. Given the objective risk of ineffective therapy in a proportion of patients at least until the completion of two large studies (POPular Genetics and TAILOR-PCI) designed to assess the effect of pharmacogenetic testing on prognosis, every patient treated with clopidogrel should have their genotype determined and those with a non-functional genotype switched to another ADP blocker [55-59].

## Conclusion

A personalized approach to patients with peripheral arterial disease is needed and the choice of antiplatelet therapy is always at the physician´s discretion while taking into account the other risk factors.

## Competing Interests

None.

## Author Contributions

The corresponding author confirms that they and the co-authors believe that this form and all accompanying files describe truthful facts. The corresponding author also certifies that they and each co-author have participated to a sufficient degree to take public responsibility for this manuscript, that their contributions and relevant conflicts of interest are accurately and completely reported on this form.

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