

# Dual antiplatelet therapy with thienopyridines and aspirin biology essay

[Science](#), [Biology](#)



## Introduction

Few can dismiss the importance of platelet in hemostasis however when a pathological condition occurs platelets are also the main culprit. Therefore antiplatelet therapy is very significant in conditions that are affected by blood clotting such as coronary artery disease, myocardial infarction, atherosclerosis, and inflammation and even, in many cases, thrombophilia during pregnancy. The dramatic increase of cardiopathies is reaching the dimensions of an epidemic phenomenon making the importance of their prevention even bigger. The numbers regarding the repercussions of the spread of cardiopathies are impressive; almost half of the deaths in EU (42% or 1.9 million, based on official statistics of 2005) are owed to cardiovascular incidents, making them by far the number one cause of death, with neoplasms being second. 50% of the patients that die from CVDs had not presented previously any relative symptoms. CVDs "kill" annually 2.5 times more people than those from all types of cancer. In Europe, the total cost related to CVDs is calculated to be 169 billion Euros per year. Each year 15 million suffer worldwide from cardiac arrests; from them, 5 million die while another 5 million remain disabled. Among the risk factors responsible for death the first place is possessed by hypertension (with a rate of 25%), followed by smoking (19.3%), high cholesterol (11.6%), obesity (8.3%), insufficient physical exercise (5%) and low consumption of fruits-vegetables (3.9%). In the developed countries 7 out of 10 adults, men and women, have increased levels of cholesterol but what is more important is that 1 out of 3 is unaware of the problem. On the other hand almost 80% of CVDs can be remedied via a healthy diet, regular exercise and non-smoking, if diagnosed

early. Bearing all these in mind, EU has already decided to continue funding the research towards prevention of CVDs and study of the genetic risk factors

## **Example of Current Antiplatelet Therapies**

### **Dual Antiplatelet Therapy with thienopyridines and aspirin**

Aspirin irreversibly inhibits cyclooxygenase (COX)-1 by acetylating serine 529, thereby inhibiting the production of thromboxane A<sub>2</sub>, a promoter of platelet aggregation, and prostaglandin I<sub>2</sub> (prostacyclin), a potent inhibitor of platelet aggregation and a powerful vasodilator, in platelets and vascular endothelial cells, respectively. <sup>12</sup> and <sup>13</sup> Of note, in the absence of protein synthesis in platelets, thromboxane A<sub>2</sub> inhibition persists for the lifetime of the platelet compared with vascular endothelial cells, which recover COX-1 activity shortly after exposure to aspirin. Consequently, antithrombotic, rather than prothrombotic, effects dominate in aspirin-treated patients. Accordingly, aspirin has been shown to play a key role in the secondary prevention of atherothrombotic events. <sup>12</sup> and <sup>13</sup> Although aspirin is a cost-effective therapy, a considerable number of patients who take aspirin continue to experience atherothrombotic complications. <sup>14</sup> This has been the reason for the continued search to identify more potent antiplatelet drugs that can be used safely, especially in high-risk patients. The major benefits of clopidogrel over ticlopidine include its better safety profile<sup>24</sup> and its ability to yield antiplatelet effects more rapidly through the administration of a loading dose. <sup>25</sup> The fact that clopidogrel is well tolerated at high doses makes it possible to achieve antiplatelet effects within hours of

administration. This has important clinical implications in patients with ACS and PCI, in whom thrombotic occlusions (eg, reinfarction, stent thrombosis) most commonly occur within the first 24 to 48 hours <http://www.jhoonline.org/content/figures/1756-8722-4-44-1-l.jpg> Figure Different targets for anti-platelet therapy

## **New anti-platelet agents**

Prasugrel is a platelet inhibitor developed by Daiichi Sankyo Co. and industrialised by Ube offered to the US market together with Eli Lilly. Its relevance is with acute coronary syndromes intended for percutaneous coronary intervention (PCI). Its use was approved in order to reduce thrombotic cardiovascular events that include stent thrombosis in patients suffering from acute coronary syndrome under PCI management. Pharmacokinetics Prasugrel is characterized as a prodrug and is metabolized very quickly to a pharmacologically active metabolite and inactive metabolites. The elimination half-life of the active metabolite is about 7 hours (range 2–15 hours). Healthy patients, suffering from stable atherosclerosis, and under PCI management show analogous pharmacokinetics. Ticagrelor is a platelet aggregation inhibitor produced by AstraZeneca. Pharmacokinetics Ticagrelor absorption takes place at the gut, it is bioavailable at 36%, and the peak concentration is reached after 1.5 hours. The key metabolite is AR-C124910XX and is formed via CYP3A4 by dehydroxyethylation at position 5 of the cyclopentane ring.<sup>[7]</sup> The peak is evident after nearly 2.5 hours. Ticagrelor and AR-C124910XX are bound to plasma proteins at a rate of 99.7%, and are active pharmacologically. The

dose is relevant to Blood plasma concentrations in a linear fashion for up to 1260 mg (which is the sevenfold daily dose). The metabolite reaches 30–40% of ticagrelor's plasma concentrations. Both drug and metabolite are mainly excreted via feces and bile. Plasma concentrations of ticagrelor are slightly increased (12–23%) in patients of Asian ethnicity, women, elderly patients, and patients suffering from mild hepatic impairment. They are decreased in patients suffering from severe renal impairment. These variations are believed to be clinically irrelevant however in Japanese people, concentrations are 40% higher than in Caucasians, or 20% after body weight correction. The drug has not been tested in patients with severe hepatic impairment Cangrelor is an inhibitor (P2Y<sub>12</sub>) and its capacity as an antiplatelet drug is under investigation [1] for intravenous application use. It is common to use P2Y<sub>12</sub> inhibitors in clinical practice, quite effectively as inhibitors of adenosine diphosphate-mediated platelet aggregation and activation. [1] Unlike clopidogrel (Plavix), is a prodrug, Cangrelor does not require metabolic conversion (active drug). Terutroban (formerly S18886) is an oral reversible inhibitor of the thromboxane receptor. Its antiplatelet effect is similar to that of aspirin, with an additional antithrombotic effect: a decreased fibrinogen deposition under shear conditions [22]. In animal models, it has also shown to reduce stent thrombosis as effectively as the combination of aspirin and clopidogrel, with a more favorable bleeding profile [23], to prevent atherosclerosis and to induce plaque regression [24]. In a pharmacokinetic-pharmacodynamic study, the maximal inhibitory effect was achieved after 1 h in patients with peripheral artery disease [20]. A single dose of 10 mg improved endothelial function (flow-mediated and

acetylcholine-mediated vasodilatation) in 12 CAD patients [25]. The PERFORM study (Prevention of cerebrovascular and cardiovascular Events of ischemic origin with teRutroban in patients with a history of ischemic stroke or tRansient ischeMic attack) is an ongoing phase III trial for secondary prevention in stroke patients, aiming to collect 18 000 patients ([www.controlledtrials.com/ISRCTN66157730/66157730](http://www.controlledtrials.com/ISRCTN66157730/66157730)) Nitric oxide-releasing aspirins are compounds that can be obtained by adding a nitric oxide-releasing moiety to aspirin. The prototype of this family of molecules is NCX-4016. Its parent molecule (aspirin) is linked to a 'spacer' via an ester linkage, which is in turn connected to a nitric oxide-releasing moiety [26]. The pharmacologic rationale for the development of NCX-4016 is based on the protective role of nitric oxide in the cardiovascular system. Nitric oxide is naturally formed by endothelial cells and is a potent mediator of vasodilatation; it inhibits platelet adhesion and aggregation (both to AA and thrombin) and reduces inflammation, cellular proliferation and apoptosis [27]. NCX-4016 undergoes a substantial first pass effect in the liver and is rapidly metabolized to salicylic acid and NCX-4015. In volunteers, it equally inhibited COX activity as compared with aspirin, caused no gastric damage and significantly reduced the gastrointestinal damage when coadministered with aspirin. In addition, it prevented monocyte activation with tissue factor expression [28]. A phase II trial aiming to evaluate the activity of NCX, as compared with aspirin, on albuminuria, insulin sensitivity and cardiac and renal hemodynamic in patients with type 2 diabetes mellitus has been completed but not yet published ([www.clinicaltrials.gov/NCT00157508](http://www.clinicaltrials.gov/NCT00157508)). In a recent study, nitric oxide-releasing aspirin was shown to induce a significant

and comparable vascular relaxation in saphenous vein segments (in an organ-bath preparation) in both diabetic and nondiabetic patients who underwent coronary artery bypass grafting (CABG) [29]. We are not aware of any ongoing clinical trials with this drug. Indobufen is a reversible potent platelet COX-1 inhibitor. It was shown to be effective as an antithrombotic agent in the prevention of graft occlusion after coronary artery bypass surgery [30] and for the prevention of thromboembolic events in heart disease [31]. In the Studio Italiano Fibrillazione Atriale (SIFA)-I trial, it was compared with warfarin in patients with nonrheumatic atrial fibrillation. There was a slightly higher rate of stroke events, mainly nondisabling (not statistically significant) and less intracranial bleedings [32]. Two studies, including the SIFA-I were included in a Cochrane review on the treatment of atrial fibrillation. The review concluded that anticoagulation is superior to antiplatelet treatment in preventing embolic events; however, it results in more major bleeding events. As many patients with atrial fibrillation are not candidates for warfarin treatment due to the risk of bleeding, we believe that the use of indobufen for this indication is still an open question. Data collection for the SIFA-II trial, which compared indobufen with aspirin for the prevention of thromboembolic events in patients with nonrheumatic atrial fibrillation, has been completed in April 2008 ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and has not been published yet.

## **Limitations**

Dual antiplatelet therapy with thienopyridines and aspirin: limitations Clinical experience with clopidogrel has supported that benefits are achieved with its

adjunctive use in high-risk patients, but has also led to a recognition that clopidogrel has a number of significant limitations. The major limitations of clopidogrel are attributed to its irreversible antiplatelet effects and to the broad variability of platelet inhibition achieved with this agent. 9 The first limitation, which is inherent to the family of thienopyridines, is a significant increase in bleeding risk in patients requiring surgery who have not been withheld clopidogrel treatment for at least 5 to 7 days (ie, the life of the platelet). The development of an antiplatelet agent with a reversible mechanism of action, allowing platelet function to return more rapidly to baseline status, would allow patients to undergo surgery more expeditiously without any increase in bleeding risk. 9 and 11 The second limitation, platelet inhibition variability, may explain why the antiplatelet effects achieved with a loading dose of clopidogrel are not always rapid and why elevated platelet reactivity may persist in some patients despite the adjunctive use of this antiplatelet drug. A further limitation of clopidogrel is its inefficient conversion to the active metabolite, which may, in part, account for the variable and sometimes inadequate antiplatelet effects of clopidogrel as well as its delayed onset of action. 9 The delayed onset of action of clopidogrel is indicated by the minimum of 2 to 4 hours need for achieving its maximal antiplatelet effects, a delay that may have serious consequences for an ACS patient in urgent need of catheterization. Ticagrelor The most common side effects obtainable are shortness of breath (dyspnea, 14%) [6] and a variety of bleeding, ranging from common nosebleed to slight hematoma, gastrointestinal, subcutaneous or dermal bleeding. Allergic skin reactions such as rash and itching have been observed in less than 1% of



patients. Prasugrel Do not use prasugrel in patients with active pathological bleeding, including peptic ulcer or a history of transient ischemic attack or stroke, because there is a higher risk of stroke (thrombotic stroke and intracranial hemorrhage). Cangrelor Poor interim results led to the abandonment of the two CHAMPION clinical trials in mid 2009.[2] The BRIDGE study, for short term use prior to surgery, continues.[3] The CHAMPION PHOENIX trial was a randomized study of over 11, 000 patients published in 2013. It found usefulness of cangrelor in patients getting cardiac stents. Compared with clopidogrel given around the time of stenting, intravenous ADP-receptor blockade with cangrelor significantly reduced the rate of stent thrombosis and myocardial infarction.[4] Reviewers have questioned the methodology of the trial

## **Conclusions**

Given the increase in incidences of and mortality stemming from thrombotic diseases, anti-platelet agents have been significantly researched and developed []. The combined use of anti-platelet drugs with dissimilar mechanisms may be important in anti-thrombotic therapies. Additional research on platelet functions will definitely raise the number of numerous new anti-platelet agents. Pharmacodynamic platelet function investigations and pharmacokinetic trials for personalized and optimized anti-platelet therapy will eventually find their way into clinical use. Nevertheless, more studies are required and on a wider ethnicity scale. Hopefully, new selective platelet inhibitors with high anti-thrombotic efficiencies and low adverse side effects (hemorrhagic effects) can be developed.