



# Clopidogrel

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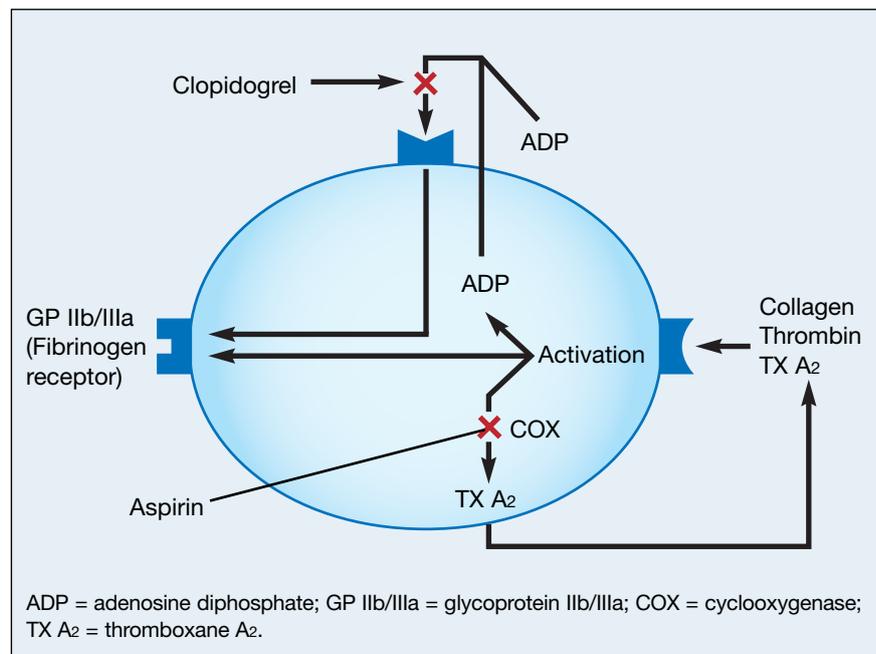
## Introduction

The CAPRIE trial in 1996 marked the arrival of clopidogrel as a new antiplatelet drug. Clopidogrel is principally used in the secondary prevention of atherothrombotic coronary disease, often in combination with aspirin. There is evidence for its use in acute coronary syndromes with or without percutaneous coronary intervention. It is also used as an alternative for patients with allergic responses or intolerance to aspirin. Patients with type 2 diabetes have increased platelet activity and adhesiveness. This, along with concerns about aspirin resistance, has contributed to further attention focused on clopidogrel in primary and secondary prevention in patients with diabetes.

## Pharmacology

Figure 1 outlines the pharmacological action of clopidogrel. Clopidogrel is similar to the antiplatelet agent ticlopidine in chemical structure and function but has fewer side effects. It inhibits both the binding of adenosine diphosphate (ADP) to its platelet receptor and the subsequent ADP-mediated activation of the glycoprotein IIb/IIIa complex. This makes clopidogrel a more potent platelet inhibitor than aspirin, which has its pharmacological effect by inhibiting the conversion of arachidonic acid to thromboxane in platelets. Clopidogrel is activated to a thiol derivative by oxidation, regulated primarily by the cytochrome P450 system, and subsequent hydrolysis. The peak effect of clopidogrel in inhibition of platelet aggregation occurs at three to five days with the standard dose of 75mg/day, but this can be shortened to four to six hours with a loading dose of 300mg. The active thiol derivative binds irre-

**Figure 1.** Diagram of the pharmacological action of clopidogrel compared with aspirin



versibly to platelet receptors meaning the effects last for the lifetime of the platelet (seven to 10 days).

## Trials of safety and efficacy

The CAPRIE study recruited 19 185 patients with atherosclerosis (recent myocardial infarction <35 days, recent ischaemic stroke seven days to six months, or established peripheral artery disease).<sup>1</sup> This blinded trial randomised patients to receive clopidogrel (75mg once daily) or aspirin (325mg once daily). There was a reduction in the risk of a composite outcome cluster of ischaemic stroke, myocardial infarction, or vascular death (relative risk reduction of clopidogrel *vs* aspirin of 8.7%, CI 0.2–16.4,  $p=0.045$ ). However, the subgroup analysis suggested the benefit was more significant ( $p=0.003$ ) in patients enrolled because of periph-

eral artery disease, and analysis of total mortality as a secondary endpoint did not show any significant difference between the drugs.

The CURE study recruited 12 562 patients with non-ST-segment elevation myocardial infarction presenting within 24 hours.<sup>2</sup> Patients were randomised to placebo or clopidogrel, both in combination with aspirin for up to one year. The primary outcome – a composite endpoint of death from cardiovascular causes, non-fatal myocardial infarction, or stroke – occurred in 9.3% of the clopidogrel group and 11.4% of the placebo group (relative risk for clopidogrel compared with placebo 0.80, CI 0.72–0.90,  $p<0.001$ ). However, there were significantly more patients with major bleeding in the clopidogrel group (3.7% *vs* 2.7%, relative risk 1.38,  $p=0.001$ ). A strategy of clopid-

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grel pre-treatment before percutaneous intervention followed by long-term therapy has been demonstrated as beneficial, with a reduction in major cardiovascular events compared with placebo in patients with acute coronary syndromes.

The CLARITY-TIMI 28 study recruited 3491 patients with ST-segment elevation myocardial infarction and who received aspirin and a standard fibrinolytic regimen.<sup>3</sup> The addition of clopidogrel reduced the rate of an occluded infarct-related artery (from 18.4% *vs* 11.7%) and reduced the rate of recurrent myocardial infarction (3.6 *vs* 2.5%), both components of the primary endpoint.

There is no good evidence for clopidogrel use in primary prevention. The CHARISMA study recruited a group with multiple risk factors for cardiovascular events (n=3284).<sup>4</sup> The rate of the primary endpoint (composite of myocardial infarction, stroke or death from cardiovascular causes) was not significantly different for those treated with clopidogrel in addition to aspirin (relative risk for clopidogrel *vs* placebo 1.2, CI 0.90–1.59, p=0.20). Moreover, an increased risk of bleeding on long-term treatment with aspirin in combination with clopidogrel has been shown in high-risk patients with recent ischaemic stroke or transient ischaemic attack.

### Specific evidence for use in diabetes

Retrospective analysis of results from the diabetic subgroup in the CAPRIE study showed that, in 1914 patients with diabetes randomised to clopidogrel, 15.6% had the composite vascular primary endpoint *vs* 17.7% of 1952 diabetic subjects randomised to aspirin therapy (p=0.042). Subgroup analysis from the CURE study showed the significant reduction in primary endpoint (a composite of cardiovas-

cular death, non-fatal myocardial infarction, or stroke) was consistent in patients with diabetes or those with no diabetes. In the CLARITY-TIMI 28 study, there were 289 patients in the clopidogrel group and 286 patients in the placebo group with diabetes (approximately 16.5% of the overall study). No subgroup analysis for these patients is reported. In the CHARISMA study, there were a large number of patients with diabetes in the subgroup with multiple risk factors for cardiovascular disease (82% [n=1360] of patients in the clopidogrel + aspirin arm *vs* 79.7% [n=1295] in the aspirin + placebo arm). Subgroup analysis did not show any benefit of clopidogrel over aspirin.

### Discussion

Clopidogrel is a potent antiplatelet drug with an established role in secondary prevention of cardiovascular disease. Aspirin resistance, a phenomenon reported in patients with type 2 diabetes, has been postulated to increase the risk of major adverse cardiac events in patients with stable coronary artery disease, but subgroup analysis has not shown any additional benefit in using clopidogrel in patients with diabetes. Clopidogrel should be used as the agent of choice for secondary prevention for patients who are intolerant of aspirin. In patients with clinical evidence of aspirin resistance (recurrent vascular events on aspirin) or in those with laboratory evidence of aspirin resistance (platelet aggregation tests), the addition of clopidogrel should be considered after vascular thrombotic risk and bleeding risk have been assessed on an individual basis. Clopidogrel has proven benefit for the treatment of acute coronary syndromes with or without ST-elevation, including patients with diabetes. The only outstanding debate surrounds the optimal length of treatment (three to

### Key points

- Clopidogrel is an antiplatelet drug with a different mode of action from aspirin
- The main indications for clopidogrel are in combination with aspirin following myocardial infarction or coronary artery stenting
- Clopidogrel can be used for secondary prevention in patients who are intolerant of aspirin. There is no evidence for use in primary prevention of cardiovascular events

12 months). However, there is no evidence to support the use of clopidogrel in addition to aspirin in primary prevention of cardiovascular events even in patients with multiple risk factors for cardiovascular disease including diabetes.

### Conflict of interest statement

Dr George and Dr McKay have no conflicts of interest to declare. Dr Fisher has received lecture fees from Bristol-Myers Squibb and Sanofi-Synthelabo.

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