Clinical evaluation of clopidogrel across the whole spectrum of indications: primary and secondary prevention of coronary artery disease

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Clopidogrel has been evaluated across the spectrum of secondary and primary prevention. Initially, the CAPRIE trial randomized patients with recent myocardial infarction, ischemic stroke or symptomatic peripheral arterial disease to either clopidogrel or aspirin and followed them for up to three years. That study found clopidogrel to be superior to aspirin, with subsequent post hoc analyses finding the greatest benefit in higher risk subgroups. Favorable data from multiple clinical trials of aspirin plus clopidogrel in percutaneous coronary intervention and acute coronary syndromes led to the CHARISMA study. This trial randomized patients to clopidogrel plus aspirin versus placebo plus aspirin for a median of 28 months. Patients with stable coronary artery disease, cerebrovascular disease, or peripheral arterial disease (meant to represent secondary prevention) or with multiple risk factors (meant to represent primary prevention) were enrolled. The trial did not find a significant reduction in cardiovascular death, myocardial infarction, or stroke with dual antiplatelet therapy in the overall population, though the subgroup of patients with documented cardiovascular disease did appear to have some benefit. Further analysis of the CHARISMA data set and future trials should further refine which patients are most likely to benefit from intensification of antithrombotic therapy beyond aspirin alone.

KEYWORDS
Aspirin; Clopidogrel; Myocardial infarction; Peripheral arterial disease; Stroke

Introduction

The humanitarian and economical impact of cardiovascular ischaemic events has lead to extensive investigation in the field of atherothrombosis. Antiplatelet therapy has been a very successful pharmacological strategy and is still being evaluated in a wide range of indications (different vascular territories, different population subgroups, primary and secondary prevention, acute treatment, etc.). The constant demand for better clinical efficacy beyond aspirin monotherapy lead to the production of different molecules such as the second generation thienopyridine clopidogrel. After a decade of scientific evidence provided by randomized clinical trials, clopidogrel has emerged as a major agent in the medical armamentarium for the prevention and treatment of ischaemic events.

Clopidogrel in the prevention of coronary events: antiplatelet monotherapy

The Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)¹ was the first randomized, blinded, international trial to evaluate the efficacy and safety of clopidogrel in the prevention of arterial ischaemic events (ischaemic stroke, myocardial infarction, or vascular death). The population was composed of individuals with a recent history of ischaemic stroke (≥1 week and ≤6 months) or myocardial infarction (≤35 days) or symptomatic peripheral arterial disease. The mean age

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was 62.5 ± 11.1 years with 72% males, 95% Caucasians, 20% with diabetes, 52% with hypertension, 41% with hypercholesterolaemia, 30% current smokers, 49% former smokers, 17% with previous myocardial infarction, 22% with stable angina, and 9% with a history of unstable angina. A total of 19 185 patients were randomized (1:1) to receive clopidogrel 75 mg daily or medium dose aspirin (325 mg daily). The mean follow-up time was 1.91 years (1–3 years). Patients treated with clopidogrel had an annual 5.32% risk of ischaemic stroke, myocardial infarction, or vascular death compared with 5.83% with aspirin, reflecting a significant (P = 0.043) relative risk reduction of 8.7% in favour of clopidogrel. Regarding myocardial infarction (non-fatal and fatal), patients treated with clopidogrel had an annual risk of 1.56% compared with 1.90% with aspirin with a relative risk reduction of 17.9% in favour of clopidogrel. Clopidogrel was an independent factor for protection from myocardial infarction and was superior to aspirin despite the number of risk factors.2

There were no major differences regarding safety, namely intracranial haemorrhage (clopidogrel 0.33% vs. aspirin 0.47%) and gastrointestinal haemorrhage (clopidogrel 0.52% vs. aspirin 0.72%).

A post hoc analysis of the CAPRIE trial3 revealed a statistically significant decrease in rehospitalizations for ischaemic or bleeding causes in the clopidogrel arm (relative risk reduction of 9.1%, P = 0.018). The results were consistent when ischaemic (any cause, angina, transient ischaemic attack, limb ischemia) or bleeding (any cause, intracranial, gastrointestinal) indications for hospitalization were analysed separately. Rehospitalization rates provide useful information to establish risk and economical burden related to therapeutic strategies. Other post hoc analyses of CAPRIE demonstrated a greater degree of benefit with clopidogrel vs. aspirin in higher risk subgroups such as those with prior ischaemic events,4 coronary artery bypass surgery,5 or diabetes.6

### Clopidogrel in the prevention of coronary events: dual antiplatelet therapy

Trials such as The Clopidogrel Aspirin Stent Intervention Cooperative Study (CLASSICS),7 Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE)8,9 and Clopidogrel for the Reduction of Events During Observation (CRED0910 introduced the concept of aspirin and clopidogrel as dual antiplatelet therapy in the secondary prevention of cardiovascular events. Dual platelet inhibition demonstrated a reduction of cardiovascular events from 28 days7 to up to 1 year8,9 in patients undergoing elective7,10 or urgent8,9 percutaneous coronary intervention or post-myocardial infarction with11 or without8,9 ST-elevation. Whether even longer term protection with dual platelet therapy was beneficial in a broader population of stable patients was an issue that had to be addressed by clinical trials. The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial12,13 was designed to address this issue in primary and secondary prevention in high-risk patients. CHARISMA was a randomized, double blinded, event-driven, international trial that included 15 603 high cardiovascular risk patients ≥45 years old who were randomized to one of two arms (clopidogrel 75 mg/day plus aspirin 75–162 mg/day vs. placebo 1 tablet/day plus aspirin 75–162 mg/day). For inclusion, the patients had to have at least one of the following criteria: (i) documented coronary disease (previous myocardial infarction, previous multivessel percutaneous intervention, previous multivessel bypass surgery, or stable angina with documented multivessel disease); (ii) documented cerebrovascular disease (ischaemic stroke or transient ischaemic attack in the last 5 years); (iii) documented symptomatic peripheral arterial disease (intermittent claudication with ankle-brachial index ≤0.85 or previous related interventions); (iv) high cardiovascular risk profile without documented prior events. The high risk profile was defined as having (i) two major risk factors or (ii) one major and two minor risk factors or (iii) three minor risk factors. The major risk factors were treated diabetes, diabetic nephropathy, ankle-brachial index ≤0.85, asymptomatic carotid stenosis ≥70%, and the presence of at least one carotid plaque. The minor risk factors were systolic blood pressure ≥150 mmHg, despite therapy, primary hypercholesterolaemia, smoking, male ≥65 years, or female ≥70 years. The exclusion criteria were requirement for clopidogrel (e.g. recent stenting or acute coronary syndrome without ST-segment elevation), chronic therapy with high-dose aspirin (>162 mg/day) or non-steroidal anti-inflammatory drugs (except COX-2 inhibitors), other oral anti-thrombotic medications (e.g. warfarin), or planned revascularization procedure. The primary efficacy endpoint was the first occurrence of (i) myocardial infarction (fatal or non-fatal), (ii) stroke (any cause, fatal, or non-fatal), and (iii) cardiovascular death (including haemorrhagic death). The secondary efficacy endpoint was the first occurrence of (i) any of the primary endpoint events and (ii) hospitalization for unstable angina or transient ischaemic attack or revascularization. The primary safety endpoint was severe bleeding according to the GUSTO criteria, including fatal bleeding or intracranial haemorrhage. The population had a median age of 64 years and consisted of 70% males, 80% Caucasians, 20% current smokers, 49% former smokers, with documented cardiovascular disease in 78% and multiple risk factors in 21%. The median follow-up was 28 months. The primary efficacy endpoint rate (Figure 1A) was 7.3% in the placebo group vs. 6.8% in the clopidogrel group (relative risk reduction of 7.1% in dual antiplatelet therapy) which was not significantly different (P = 0.22). The secondary efficacy endpoint (Figure 1B), which included hospitalization for ischaemic events, was significantly higher in the placebo group (17.9 vs. 16.7%), with a relative risk reduction of 7.7% in favour of dual antiplatelet therapy (P = 0.04). Comparing single efficacy endpoints, significant differences were found in non-fatal stroke (placebo 2.4% vs. clopidogrel 1.9%, P = 0.03) and hospitalization (placebo 12.3% vs. clopidogrel 11.1%, P = 0.02) rates.
In terms of the overall population primary safety endpoints, the results were not significantly different between treatments, despite a trend to more frequent GUSTO severe bleeding in the clopidogrel plus aspirin arm (clopidogrel 1.7% vs. placebo 1.3%, \( P = 0.09 \)). Fatal bleeding and primary intracranial bleeding, analysed separately, were not different between groups. GUSTO moderate bleeding, the secondary safety endpoint, was significantly higher in the clopidogrel arm (2.1 vs. 1.3%, \( P < 0.001 \)).

Analysing separately the primary (~20%) from the secondary prevention subgroups (~80%), it was found that the primary efficacy endpoint was significantly lower with dual antiplatelet therapy in patients enrolled with documented previous cardiovascular disease (regardless of the arterial territory). The multiple risk factor subgroup showed no benefit. The overall outcome appeared to be influenced by these divergent findings in this pre-specified analysis (Figure 2). The divergence of results between the primary and secondary prevention subgroups was also noted in GUSTO severe bleeding, with rates higher with dual therapy in the multiple risk factor subgroup but not in the documented cardiovascular disease subgroup. Other safety endpoints showed rates similar to the overall population. In summary, in the CHARISMA trial, dual antiplatelet therapy was not beneficial in the subgroup of patients with multiple risk factors without documented arterial disease. This subgroup also had increased severe bleeding. In secondary prevention patients, (documented coronary, cerebral, or peripheral arterial disease) long-term dual antiplatelet therapy provided a 12.5% relative and 1% absolute risk reduction in the composite of myocardial infarction/stroke/cardiovascular death (6.9 vs. 7.9%, \( P = 0.046 \)) with no significant increase in GUSTO severe bleeding (1.6 vs. 1.4%, \( P = 0.39 \)).

![Figure 1](https://example.com/charismafig1.png)

**Figure 1** Cumulative incidence of the primary and secondary endpoints in the CHARISMA trial. (A) Composite of myocardial infarction, stroke, or death from cardiovascular causes. (B) Secondary endpoint including hospitalization for ischemia. Reprinted with permission from *New England Journal of Medicine*.6
Conclusions

Clopidogrel has been proved to be beneficial in several clinical settings. However, as with other antiplatelet and antithrombotic strategies, the overall benefit depends on a delicate balance between baseline ischaemic and bleeding risk and potential antithrombotic benefit. Patients should be stratified according to data provided by clinical trials in order to select the appropriate antiplatelet therapy. The Women’s Health Study and the CHARISMA trial provide clear examples that not all populations benefit from the same strategy, especially at the lower end of the risk spectrum.

Clopidogrel as antiplatelet monotherapy is beneficial in the secondary prevention of cardiovascular events in patients with documented atherothrombotic disease, with incremental benefit in high-risk patients. Clopidogrel combined with aspirin provides a safer way to offer dual antiplatelet therapy when compared with ticlopidine plus aspirin. It is widely used in secondary prevention after percutaneous interventions and acute coronary syndromes. The CHARISMA trial suggested a
modest benefit of clopidogrel plus aspirin with long-term use (median 28 months) over monotherapy with aspirin for secondary prevention in patients with documented arterial disease. It prevented approximately nine events (cardiovascular death, myocardial infarction, or stroke) per 1000 patients treated, potentially balanced by two severe GUSTO bleeds; it reinforced the place of clopidogrel as an antiplatelet agent in secondary prevention. Regarding primary prevention, even in high-risk patients, the combination was not beneficial and is therefore not recommended. Further analysis of the CHARISMA data set and future trials will further refine just which patients most greatly benefit from intensification of antithrombotic therapy beyond aspirin.

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References