President's Page

Clopidogrel and Cardiovascular Diseases: Recommendations for Its Correct Use

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The question of the use of antiplatelet medications is front page news nowadays, for various reasons. Apart from the purely scientific dimensions, other aspects have received much attention, for example the matter of economics, given that these drugs (and especially their main representative, clopidogrel) have the second highest turnover—after statins (atorvastatin)—in worldwide drug sales. In view of the economic crisis that is affecting Greece along with the rest of the world, the use of clopidogrel needs to be rationalised. The aim of this article is to provide a brief but comprehensive review of all the evidence relating to this category of drugs and to set out recommendations for their use in patients with cardiovascular diseases.

New antiplatelet drugs have made their appearance in recent years. These include the thiopyridines (clopidogrel, prasugrel), cangrelor, phosphodiesterase inhibitors—represented, apart from dipyridamole, by cilostazol—triflusal, as well as glycoprotein IIb/IIIa inhibitors.

Fifteen randomised clinical trials, including more than 200,000 patients, have been published in the international literature in an attempt to evaluate the efficacy and safety of clopidogrel, either as monotherapy, or in the form of new regimens for co-administration with aspirin. It is noteworthy that, after the completion of large, randomised clinical trials, the use of aspirin, mainly for the secondary prevention of cardiovascular diseases due to atherothrombosis, remains the cornerstone of treatment.

The main representative of the newer antiplatelet drugs, because of its wide use, is clopidogrel. The indications for the administration of clopidogrel in combination with aspirin include:

- Percutaneous angioplasty with stenting
- Acute coronary syndromes, without stenting and
- Atrial fibrillation in cases where oral anticoagulants cannot be given.

These indications arose from an analysis of the main endpoints of large clinical trials.[1-3]

Percutaneous coronary intervention (PCI) is ultimately performed in 60-70% of patients with acute coronary syndromes who undergo diagnostic coronary angiography. Without clopidogrel, the fortunes of angioplasty with stenting would be uncertain. Specifically, in acute coronary syndromes treated with angioplasty, apart from aspirin (325 mg) a loading dose of clopidogrel (600 mg) is recommended, followed by 150 mg clopidogrel per day for 7 days. In patients with myocardial infarction, thrombolysed or not, who undergo primary angioplasty, the optimum loading dose of clopidogrel (300 or 600 mg) is not yet known. In patients with acute coronary syndromes who are to undergo high-risk angioplasty for in-stent thrombosis (e.g. diabetics) prasugrel administration is an alternative therapy. The recent guidelines on myocardial infarction have no clear position on the use of clopidogrel or prasugrel.[4]

The duration of clopidogrel or prasugrel administration depends on the type of stent implanted. In the case of bare metal stents, the duration should be at least one month (up to a year) and for drug-eluting stents at least one year. The most recent guidelines on myocardial infarction recommend that clopidogrel should be given for one year in both cases, with discontinuation of treatment if there is haemorrhage.[4]

The continuation of clopidogrel administration beyond the first year in the case of drug-eluting stents

is a hot topic of discussion in invasive cardiology. The guidelines may recommend one year, but the practice of most physicians is to give the drug for longer, even for life. In all studies, the risk of haemorrhage is counterbalanced by the benefit. Premature discontinuation of clopidogrel is the strongest risk factor for stent thrombosis, a devastating complication of percutaneous coronary intervention which remains unsolved as it is poorly predicted and prevented. However, the dilemma for clinicians is not simply whether it is safe to discontinue thienopyridine treatment before 12 months after drug-eluting stent revascularisation, but instead whether continuing long-term dual antiplatelet therapy is both effective and safe.

In cases with acute coronary syndromes where angioplasty is not performed, clopidogrel should be given for at least one month and should be continued for one year in patients with a low risk of haemorrhage.

The combination of aspirin and clopidogrel compared to aspirin in patients with atrial fibrillation in whom anticoagulants are contraindicated reduces the incidence of stroke at the cost of an increased risk of haemorrhage.[3] Of course, oral anticoagulants remain the most efficacious therapy in high risk patients with atrial fibrillation, provided that the international normalised ratio is within the therapeutic target range of 2-3. However, the acceptance of anticoagulation in the "real world," is less than satisfactory

Clopidogrel as monotherapy is recommended in cases where there is a contraindication for aspirin, such as true allergy or intolerance. Other indications for which clopidogrel is recommended as monotherapy include peripheral arterial disease in patients with or without diabetes, in diabetics (mainly type 1), patients with a history of coronary artery bypass surgery, and in patients with a history of an ischaemic cardiac or cerebrovascular event in the past.[5-7] In the latter category the combination of aspirin and clopidogrel has also been shown to be beneficial.[8]

The above indications arise from analyses of subgroups in two large clinical trials, CAPRIE and CHARISMA.[9,10] In these trials clopidogrel was compared with aspirin, and aspirin with aspirin-clopidogrel combined therapy, respectively, in patients with known cardiovascular disease (recent myocardial infarction, or stroke, and symptomatic peripheral arterial disease). In the CAPRIE trial the superiority of clopidogrel over aspirin was borderline. In the CHARISMA trial the combination of aspirin and clopidogrel was not superior to aspirin alone. Indeed, in those with a high risk, such as patients with risk factors (primary prevention) the combination therapy appeared to be harmful. Clinical studies that administered dual antiplatelet medication to patients with known cardiovascular disease showed that the risk of haemorrhage is around 2% per year.

In patients with ischaemic stroke, the usual treatment is aspirin, or triflusal[10] and the combination of aspirin and dipyridamole. Clopidogrel as monotherapy is an alternative solution, since the combination of aspirin with either clopidogrel or dipyridamole was not shown to be superior in two large studies of secondary prevention.[11,12]

For patients with carotid artery disease there are no data from large trials to support the use of clopidogrel, except in the case of endarterectomy or angioplasty with stenting. In these cases, however, although the duration of dual antiplatelet treatment should be one month, in practice it is continued for longer periods.

An analysis of a subgroup in the CAPRIE trial[9] showed that patients with peripheral arterial disease benefited more from clopidogrel, whereas similar patients in the CHARISMA trial did not benefit from the aspirin-clopidogrel combination.[14] In patients with peripheral arterial disease, with or without diabetes, clopidogrel administration is also encouraged by the ineffectiveness of aspirin, which has been shown in

Table 1. Indications for clopidogrel.

Monotherapy	In combination with aspirin
When aspirin is contraindicated	Angioplasty with stenting (for 1 year)
Diabetes mellitus (type 1) Peripheral arterial disease, with or without diabetes*	Acute coronary syndromes without stenting (for 1 month to 1 year)
History of coronary artery bypass surgery*	Atrial fibrillation (if oral anticoagulants are contraindicated or the target range of INR 2-3 cannot be achieved)
Patients with known cardiovascular disease (history of ischaemic cardiac or cerebrovascular event in the past)*	Patients with known cardiovascular disease (history of ischaemic cardiac or cerebrovascular event in the past)*

*These indications arise from the analysis of subpopulations in the CAPRIE and CHARISMA trials.

studies of such patients.[15,16] Interpretation of the results requires special care, since analysis of a subgroup is likely to lack the statistical power to answer the specific question being investigated. In these cases, a statistically significant result may be simply due to chance.

Dual antiplatelet therapy is not without risk. Like all antithrombotic agents, both aspirin and clopidogrel increase the risk of bleeding compared with placebo. When compared with aspirin, clopidogrel may be associated with lower risk of gastrointestinal bleeding.[9] However, when clopidogrel was combined with aspirin and administered for up to 2 years, randomised trials demonstrated an absolute increase (ranging from 0.4% to 1%) in major bleeding compared with aspirin.[1,3,10]

The different and complex endpoints, the different definitions of haemorrhage, the different dosages, time and duration of administration of antiplatelet drugs, as well as adjunctive treatment (glycoprotein IIb/IIIa inhibitors, anticoagulants, statins, proton pump inhibitors) and different types of stent, make comparisons between studies difficult.

In cases such as ischaemic stroke, where clopidogrel administration is equally as effective as other drug interventions, the decision about its use should take account of the financial cost. Current evidence raises more questions and leaves several outstanding issues unaddressed in clinical practice. Factors that should also be taken into consideration include the temporary interruption of clopidogrel before non-cardiac procedures, the question of resistance and interactions with other drugs (statins, proton pump inhibitors, non-steroid anti-inflammatory drugs) and the need for co-administration of an oral anticoagulant, as in cases where angioplasty is performed in patients with atrial fibrillation or a mechanical heart valve. Finally, will measurable differences exist between clopidogrel and newer, direct P2Y12 inhibitors (e.g. prasugrel, ticagrelor) with prolonged therapy after PCI in real-world settings? These outstanding issues have important implications for both clinical research and routine clinical decision making.

Conclusions

It is significant that there are large trials to support the indications for monotherapy or combined therapy with clopidogrel and aspirin, or a comparison with other antiplatelet medications. Replication of the results in more than one study leads to more reliable conclusions.

Despite that, the results from analyses of subgroups, on which the indications for clopidogrel monotherapy are based, should be interpreted with caution. They need to be confirmed by randomised clinical trials designed to have sufficient statistical power for the purpose. In addition, the design of cost-effectiveness studies could assist in decision making, taking into account the socio-economic aspect, with regard to the administration of appropriate antiplatelet medication. Finally, it is essential to have studies of the safety of clopidogrel, which will co-evaluate the heterogeneous factors so as to provide clear conclusions about the risk in relation to the benefit from the use of this drug.

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