Archives of Cardiovascular Disease (2010) 103, 497—501

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SCIENTIFIC EDITORIAL

Dual antiplatelet therapy in the secondary prevention of atherothrombosis: Need for new therapeutic approaches

Association d'antiagrégants plaquettaires dans la prévention secondaire de l'athérothrombose : de nouvelles approches thérapeutiques sont nécessaires

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Received 30 April 2010; received in revised form 25 June 2010; accepted 28 June 2010
Available online 3 November 2010

KEYWORDS
Dual antiplatelet therapy;
Atherothrombosis

MOTS CLÉS
Association d'antiagrégants plaquettaires ;
Maladie thrombotique

More than 22 million Americans are estimated to take aspirin daily; 3—5% of patients covered by health insurance in France received a prescription for antiplatelet drugs in 2006, representing an estimated 200,000 to 300,000 new patients each year. Aspirin, which inhibits the formation of platelet thromboxane, is a major treatment to reduce ischaemic complications in patients with atherothrombotic disease. Clopidogrel, a thienopyridine derivative, selectively inhibits the platelet adenosine phosphate receptor and is a potent inhibitor of platelet aggregation. Dipyridamole reduces platelet aggregation by raising the antiplatelet level of cyclic adenosine monophosphate and cyclic guanosine monophosphate, but has non-bleeding side effects. Cilostazol, a phosphodiesterase 3 inhibitor, is an alternative to aspirin for the prevention of stent restenosis, which works through a different mechanism.

When clopidogrel is used with aspirin, the antiplatelet effect is synergistic [1]. The clinical benefit of this combination comes mainly from its use in the management of patients with unstable angina and non-ST or ST-elevation myocardial infarction [2,3] as well as patients undergoing a percutaneous coronary intervention (PCI) [4]. Clopidogrel added to aspirin is considered a standard regimen in acute coronary syndromes (ACS) [5,6]. Accordingly, most patients who receive long-term dual antiplatelet therapy have undergone either stent PCI or had an ACS. However, some patients still experience cardiovascular events in

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1875-2136/$ — see front matter
doi:10.1016/j.acvd.2010.06.007

spite of treatment with aspirin and/or clopidogrel. This may be caused by low responsiveness, which has been reported to range from 1—45% for the two drugs [7]. In particular, clopidogrel is a prodrug that needs to be metabolized to the active thiol metabolite by the cytochrome P450 system. This activation is a source of significant inter-individual variability in clopidogrel responsiveness.

When considering the long-term or chronic condition of atherothrombosis, it is unclear whether dual antiplatelet therapy provides superior efficacy over single antiplatelet therapy. Moreover, the risk/benefit balance could be unacceptable because of the increased haemorrhagic risk of dual antiplatelet therapy. The aim of this review is to clarify chronic atherothrombosis situations in which dual antiplatelet therapy can bring additional benefit compared with monotherapy. We will not discuss here the benefit of dual antiplatelet therapy in ACS or in atrial fibrillation or haemodialysis graft patency, as described recently elsewhere [8,9].

Four recent randomized controlled trials—namely the MATCH, CHARISMA, PROFESS and ESPRIT studies—compared dual antiplatelet therapy with monotherapy in patient populations at high risk of atherothrombotic events [10—13]. Selected populations were similar, except that patients in the CHARISMA trial had multiple risk factors. Moreover, in the ESPRIT and PROFESS studies, diabetes and prior stroke were less prevalent. In these trials, efficacy was assessed using a composite endpoint consisting of myocardial infarction, stroke or death from cardiovascular causes, except in the MATCH trial where efficacy was assessed using these three same events plus rehospitalization for an acute ischaemic event. In the PROFESS and ESPRIT studies, the composite outcome was a secondary endpoint. In all studies, major bleeding was considered as a safety outcome and was defined as any intracranial bleeding, any fatal bleeding or any bleeding requiring hospital admission. The results of these trials are summarized in Table 1 and Fig. 1.

The MATCH study compared clopidogrel and aspirin with clopidogrel alone [10]. The combination did not reduce the incidence of the composite endpoint significantly, but increased the risk of major bleeding in 7599 high-risk patients with recent ischaemic stroke or transient ischaemic attack and at least one additional vascular risk factor, followed over a mean of 18 months from randomization.

The CHARISMA study compared clopidogrel and aspirin with aspirin alone [11]. There was no significant benefit associated with the combination therapy in reducing the incidence of the composite endpoint in 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors followed for a median of 28 months. However, there was a suggestion of benefit in patients with symptomatic atherothrombosis (including those with documented myocardial infarction). The rate of major bleeding was increased but the difference was not statistically significant.

The PROFESS study compared, over 2.5 years on average, aspirin plus dipyridamole with clopidogrel alone in 20,332 patients who had had a stroke [13]. Aspirin plus dipyridamole did not yield benefit compared with monotherapy, with more major haemorrhagic events among patients receiving the combination therapy.

The ESPRIT study compared aspirin plus dipyridamole with aspirin alone among 2739 patients with a prior transient ischaemic attack or minor stroke of presumed arterial origin followed over 3.5 years on average [12]. Aspirin plus dipyridamole was more effective than aspirin alone in preventing the composite outcome, with a reduction of the risk of major bleeding.

The comparison of aspirin plus dipyridamole with aspirin alone has been addressed in previous trials, with similar populations. In the ESPS2 [14], there was a marginally significant benefit associated with the dual therapy in reducing the composite outcome of stroke or death (risk reduction [RR] 0.87, 95% confidence interval [CI], 0.75—1.00), while the risk of moderate to severe or fatal bleeding was non-significantly increased (RR 1.13, 95% CI, 0.79—1.63) in 3299 patients with recent transient ischaemic accident or completed ischaemic stroke followed for 24 months. Two other trials before ESPS2 compared aspirin plus dipyridamole with aspirin alone [15,16] in patients with recent stroke, who were followed up for 36 and 25 months, respectively. They showed no effect of dual antiplatelet therapy on the composite outcomes (stroke or death: RR 0.94, 95% CI, 0.57—1.56 [15]; stroke, retinal infarction or death from any cause: RR 1.00, 95% CI, 0.76—1.31 [16]). Data concerning major bleeding were not reported for these two trials.

The diversity of comparisons and populations precludes the performance of a formal meta-analysis of these studies in the secondary prevention of cardiovascular events. ESPRIT was the only trial to demonstrate the superiority of a dual antiplatelet therapy (aspirin and dipyridamole) over aspirin alone for both efficacy and safety outcomes. This was confirmed by two meta-analyses assessing the efficacy and safety of the association of aspirin and dipyridamole versus aspirin alone in ischaemic stroke: both showed a significant benefit of this association in reducing the incidence of cardiovascular events [12]. On the other hand, there was no evidence of superiority of aspirin combined with dipyridamole over clopidogrel in the PROFESS trial. In the CHARISMA trial, a subgroup analysis suggested that in secondary prevention patients (i.e. with documented history of established vascular disease), the combination reduced the incidence of the composite endpoint (hazard ratio [HR] 0.88, 95% CI 0.77—1.00). The rate of major bleeding was not significantly increased (HR 1.14, 95% CI 0.85—1.52). In the CASPAR trial, which compared clopidogrel and aspirin with aspirin alone in 851 patients with peripheral arterial disease and successful venous or prosthetic grafts, dual antiplatelet had no effect on the incidence of a composite endpoint including cardiovascular death, myocardial infarction or stroke (RR 1.07, 95% CI 0.65—1.77) with a tendency for an increased risk of major bleeding (RR 1.80, 95% CI 0.64—5.10) [17]. A meta-analysis confirmed a 50% excess risk of haemorrhagic complications with dual antiplatelet therapy, which should be considered when choosing the optimal strategy [18]. This increase in risk does not seem clinically important with the association aspirin—dipyridamole, as confirmed recently in haemodialysis grafts (RR 0.86, 95% CI 0.55—1.35) [9], but undoubtedly the dual association aspirin—clopidogrel carries an increased risk of major bleeding.

In conclusion, recent large-scale trials have brought limited evidence of benefit associated with dual antiplatelet therapy in the long-term secondary prevention of myocardial infarction, stroke or death from cardiovascular causes. A benefit is observed for the combination of aspirin and dypiri-