

TOP Journal Club

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Long-term safety of cilostazol in patients with peripheral artery disease: The CASTLE study (Cilostazol: A Study in Long-term Effects).

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BACKGROUND: Cilostazol, a phosphodiesterase III inhibitor, is indicated to treat the symptoms of intermittent claudication and increase walking distance in patients with peripheral arterial disease (PAD). At the time of approval, the United States Food and Drug Administration required an additional long-term safety study to evaluate the effect cilostazol on mortality. **METHODS:** A total of 1899 subjects with a clinical diagnosis of PAD and symptoms of claudication were screened for participation in a randomized, double-blinded, placebo-controlled safety study of cilostazol. The intent-to-treat (ITT) population, which was the primary analysis (n = 1435), was defined as all randomized patients who received at least one dose of study medication and included patients who were followed up >30 days after discontinuation of study drug. A total of 717 patients received cilostazol and 718 received placebo. Cilostazol was administered at a primary dose of 100 mg twice daily. The dose could be reduced to 50 mg twice daily if patients experienced an adverse event that might have been drug related. **RESULTS:** Long-term adherence to study medication was poor, with >60% of participants discontinuing therapy by 36 months. The mortality analysis therefore focused on deaths during the period on-treatment, defined as the period during which the study drug was taken plus a 30-day follow-up period after dosing. Total patient-years of exposure were 1046 on-treatment for cilostazol and 1090 for placebo. On-treatment, there were 18 deaths on cilostazol and 19 deaths on placebo for a hazard ratio of 0.99 (95% confidence interval [CI], 0.52-1.88). Cardiovascular deaths on-treatment occurred in 14 patients on cilostazol and 14 on placebo. In the full ITT population at 36 months, there were 101 deaths, 49 on cilostazol and 52 on placebo, with hazard ratio of 0.94 (95% CI, 0.64-1.39). Thus, most deaths occurred >30 days after study drug discontinuation. Serious bleeding events affected 18 patients taking cilostazol in the on-treatment population and 22 taking placebo. The rates of bleeding events were similar in patients who used aspirin, aspirin plus clopidogrel, or anticoagulants at anytime during the course of the study **CONCLUSIONS:** This long-term study demonstrated no safety signal for cilostazol on all-cause or cardiovascular mortality. The study, however, was underpowered to detect a small adverse impact of cilostazol on mortality (hazard ratio upper bound of the 95% CI was 1.88 in the on-treatment population). Serious bleeding events appeared not to be increased by cilostazol.

Randomized Comparison of Cilostazol vs Clopidogrel After Drug-Eluting Stenting in Diabetic Patients Cilostazol for Diabetic Patients in Drug-Eluting Stent (CIDES) Trial

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Background Previous studies have shown that cilostazol may not only prevent stent thrombosis, but may also have positive effect in the prevention of restenosis. However, the effect of cilostazol on restenosis after successful deployment of drug-eluting stent (DES) in patients with diabetes mellitus has not been evaluated. **Methods and Results** A total of 280 patients at 8 clinical sites were randomized. The patients (61.7±9.9 years old, 163 males) who underwent successful stenting were randomized to aspirin and cilostazol (group I, n=141, 61.2±9.6 years old) vs aspirin and clopidogrel (group II, n=139, 62.0±10.0 years old) after 1 month of aspirin, cilostazol, and clopidogrel combination treatment. There were no significant differences in baseline characteristics of the groups. The type of DES implanted did not differ between the groups. There were no differences in angiographic and procedural characteristics of the groups. Major adverse cardiac events, including acute and subacute stent thrombosis within 1 month, did not occur in either group. Cases of angiographic late stent thrombosis were 1 (0.9%) in group I and 1 (0.8%) in group II. Follow-up coronary angiography was performed in 237 patients (84.6%). Mean follow-up duration was 7.1 months. The rate of angiographic restenosis (stent plus 5-mm borders) was 9 (8.0%) in group I and 20 (16.1%) in group II, p=0.041). The minimal luminal diameter at follow-up period in group I was 2.55±0.63 mm compared with

2.41±0.83 mm in group II (p=NS). **Conclusions** Combination therapy with aspirin and cilostazol for the prevention of stent restenosis is comparable or superior to that of aspirin and clopidogrel in diabetic patients who undergo DES implantation.

Therapy with nebulized beta2 agonists (procaterol) in asthmatic children: pulmonary function and plasma levels after inhalation.

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BACKGROUND: Relationship between post administrative changes in plasma drug levels and bronchodilation remains unknown. In this study, we measured plasma levels of procaterol, a beta2-agonist, when being inhaled through nebulizers in children with bronchial asthma to examine relationship between improvement of pulmonary function and the plasma levels. **METHOD:** Six asthmatic children with the mean age of 9.8 years, inhaled 0.3 ml of 0.01% procaterol solution through a nebulizer. We examined changes in pulmonary function and plasma procaterol levels before and after inhalation. **RESULTS:** Procaterol was detected in the plasma 2 minutes after inhalation when it already rose to the maximum level, and kept the steady until showing a decline in 30 minutes. The measured highest value was 87.8±45.1 pg/ml. FEV 1.0 remarkably increased 2 minutes after inhalation and was maintained until 60 minutes after inhalation. Other lung function parameters also improved. There was no significant change in the heart rate, but serum potassium concentrations significantly dropped in all patients 60 minutes after inhalation. **CONCLUSION:** Plasma procaterol levels promptly rose to the peak at 2 minutes after inhalation and decreased 30 minutes later. Improvement of pulmonary function started promptly at minutes after inhalation and it became a peak 60 minutes later.

A review of therapeutic strategies for risk reduction of recurrent stroke

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Although cardiovascular disease (CVD) is a major source of morbidity and mortality in the United States, a relatively small percentage of deaths related to CVD result from ischemic stroke. However, the impairment and costs associated with stroke are large-and largely preventable. Large-scale trials have demonstrated benefit with antihypertensive therapy for secondary prevention, showing significantly reduced rates of stroke and cardiovascular events. Statins have shown efficacy in primary stroke prevention, and one trial showed reduced incidence of stroke and cardiovascular events in patients with recent stroke or transient ischemic attack (TIA). The merits of antiplatelet therapy in primary and secondary stroke prevention have been demonstrated across numerous trials and meta-analyses. Trials assessing aspirin plus clopidogrel or aspirin plus extended-release dipyridamole for preventing secondary stroke have produced somewhat contradictory findings. This review discusses the relationship between CVD and risk of secondary stroke or TIA and summarizes secondary prevention strategies, focusing on antiplatelet agents, to provide guidance for the practicing cardiologist. Certain combination therapies appear to be more effective for secondary prevention of stroke or TIA than therapy with single antiplatelet agents. The choice of agents may be important, based on results of several trials. The ongoing, large-scale, comparative Prevention Regimen for Effectively Avoiding Second Strokes (PREVENT-2) trial should provide cardiologists with more definitive recommendations.

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