“Preventive” angioplasty in acute ST-segment elevation myocardial infarction: beyond the culprit artery. The PRAMI trial

Practice guidelines recommend that percutaneous coronary intervention (PCI) as a reperfusion strategy in the context of acute ST-segment elevation myocardial infarction (STEMI) should be limited to the “culprit artery”. A PCI to the coronary arteries which are not responsible for the myocardial infarction has always been considered as a potential source of complications, with risks exceeding the possible benefits. The PRAMI trial poses a challenge to this perception.

The trial, conducted in five centers in the UK between 2008 and 2013, enrolled consecutive patients with acute STEMI who after the culprit artery had been successfully treated with PCI, had ≥50% stenosis in other coronary artery territories which were deemed to receive PCI treatment. Patients with cardiogenic shock, ≥50% stenosis in the left main stem or the ostia of both the left anterior descending and circumflex arteries, or if the only noninfarct stenosis was a chronic total occlusion, were excluded from the study. After the completion of PCI in the infarct artery, the patients were randomly assigned to undergo no further PCI procedures or to undergo immediate PCI in noninfarct arteries with stenoses (the so-called preventive PCI). The study design was rigid: patients randomly assigned to preventive PCI should have had angina with an objective assessment of ischemia and lack of response to medical therapy to justify a PCI in another artery in the following days after AMI. The primary outcome was a composite of death from cardiac causes, nonfatal AMI, or refractory angina, and each component was also assessed individually.

In January 2013, recruitment was stopped after including 465 patients (234 in the preventive PCI group and 231 in the standard treatment group) based on a highly significant between-group difference in the incidence of the primary outcome favoring multivessel PCI. After a mean follow-up of 23 months, the primary outcome occurred in 9% of the patients in the preventive-PCI group versus 23% in the standard treatment group (HR 0.35. 95% CI 0.21-0.58; p < 0.001). The difference between both groups became evident within 6 months. The risk reduction was similar for each of the components of the primary outcome analyzed separately and for the incidence of repeat revascularization. There were no differences in the incidence of complications. The results were not affected by age, sex, diabetes, infarct location and the number of coronary arteries with stenosis.

Previous studies with smaller number of patients and, therefore, with less power, had anticipated the result of this trial which goes against practice guideline recommendations. Percutaneous coronary intervention of all the arteries with significant stenosis could offer better outcome compared to PCI only of the infarct artery (which limits the procedure in other arteries only to extreme cases of refractory angina). However, these findings do not address the question of performing delayed PCI of the other non-culprit arteries in the days following the AMI either during the same hospitalization or even scheduling the procedure after hospital discharge. Further research is needed to evaluate this intermediate strategy, which could offer the advantage of complete revascularization without the risks of several procedures in the same day of the AMI. “It is also unclear whether a strategy based on early PCI of only the non culprit lesions with decreased fractional flow reserve would not be the best choice. Therefore, a definite conduct can not yet be recommended.

Macitentan, an endothelin-receptor antagonist, improves the outcome of pulmonary artery hypertension The SERAPHIN trial

Current therapy for group 1 pulmonary artery hypertension (PAH) (idiopathic or hereditary PAH, PAH secondary to connective tissue diseases, drug use, HIV or congenital heart disease) includes phosphodiesterase type 5 inhibitors, endothelin-receptor antagonists and prostanoids. All these drugs have demonstrated to improve exercise capacity as measured by the 6 minute walk distance. This end point is becoming more questioned as its relation with the outcome is not entirely clear. In fact, the results of meta-analyses evaluating the ability of pharmacological treatment to improve the outcome are still controversial. The SERAPHIN trial represents a progress in this sense by demonstrating that macitentan, an endothelin-receptor antagonist, can exert a positive influence on the event rate.

The study included 742 patients with group 1 PAH in functional class (FC) II-III who had a 6-minute walk distance ≥50 m. Concomitant treatment with oral phosphodiesterase type 5 inhibitors, oral or inhaled prostanoids, calcium-channel blockers, or l-arginine was allowed. Patients receiving endothelin-receptor antagonists or intravenous or subcutaneous prostanoids were excluded. Patients were randomly assigned to receive oral placebo (n = 250) once daily; oral macitentan at a once-daily dose of 3 mg (n = 250),
or 10 mg (n = 242). The primary end point (which is different from previous publications) was death from any cause or worsening of PAH (defined by worsening of FC or signs of right heart failure that did not respond to oral diuretic therapy) a decrease in the 6-minute walk distance of at least 15% from baseline, and the need for additional treatment for PAH. Mean age was 45.6 years and 76.5% were women. Idiopathic PAH was present in 55% of patients and was secondary to connective tissue diseases in 30%. Functional class II was present in 52.4% of patients and 45.6% were in FC III. Median follow-up was 115 weeks and the incidence of the primary end point was 46.4% with placebo, 38% with macitentan 3 mg (HR vs. placebo 0.70, 97.5% CI 0.52-0.96) and 31.4% with macitentan 10 mg (HR vs. placebo 0.55, 97.5% CI 0.32-0.76). The difference was due to worsening of PAH and the need of hospitalization, while death from any cause as a first event was similar (6.8%, 8.4% and 6.6%, respectively). There was a trend toward reduction in the rate of death with the 10-mg dose of macitentan. At 6 months, the prognostic improvement was accompanied by a significant increase in the 6-minute walk distance (from -9.4 m with placebo, to +12.5 m with 10 mg), by improvement in the FC (13% with placebo, vs. 20% and 22% with 3 mg and 10 mg, respectively) and in the hemodynamic parameters. The adverse event rate did not differ between placebo and drug and ranged from 10.7% to 13.6%. The most common adverse events with macitentan were anemia, headache and nasopharyngitis.

This study surpasses previous trials of PAH focused on improving paraclinical end points, by demonstrating that a specific treatment is also capable of improving the clinical outcome. These findings do not mean that macitentan is better than other therapies for PAH as this study did not address the efficacy of macitentan compared with other drugs.

Influenza vaccination and risk of cardiovascular events: a meta-analysis


Several epidemiological studies have shown the presence of an inverse association between influenza vaccination (IV) and the incidence of cardiovascular events. At the same time, small clinical trials have explored the same hypothesis. The meta-analysis here presented will strengthen this theory.

A systematic review was done of randomized clinical trials with a sample size of at least 50 adults and follow-up between 28 days and 1 year, comparing IV with placebo or control or a strategy of more intense vaccination (a higher dose, higher antigenicity or a higher concentration) vs. standard vaccination. The primary end point was the incidence of cardiovascular events (cardiovascular death, hospitalization for myocardial infarction, unstable angina or heart failure, stroke or urgent coronary revascularization).

The main analysis included 6 randomized clinical trials (four efficacy studies, two safety studies) comparing intramuscular or intranasal vaccine vs. placebo or control. Overall, 6735 patients were followed-up for a mean duration of 7.9 months; 36% of them had a history of cardiovascular events. The incidence of the primary end point was of 2.9% with the vaccine versus 4.6% with placebo or control (RR 0.64, 95% CI 0.49-0.84; p = 0.001). In a subgroup analysis of three trials of patients with stable coronary artery disease or acute coronary syndromes, an interaction phenomenon was observed: the vaccine reduced the incidence of events in patients with a history of recent acute coronary syndrome (10.25% vs. 23.1%; RR 0.45, 95% CI 0.32-0.63) but not in patients with stable coronary artery disease (6.9% vs. 7.4%; RR 0.94, 95% CI 0.65-1.61).

Six additional trials comprising 16857 patients randomized to standard vs. more intense vaccination strategies did not reveal significant differences in the incidence of cardiovascular events.

The pathophysiological correlation between influenza and cardiovascular events still remains unclear but may be related to rupture of a vulnerable atherosclerotic plaque, myocarditis, arrhythmia, or heart failure. The meta-analysis presented does not clarify all the doubts, but it undoubtedly contributes to consolidate the indication of vaccination (a measure that is taken once a year) in patients with history of cardiovascular disease.

Saxagliptin and cardiovascular events in type 2 diabetes: lack of beneficial effect. The SAVOR TIMI 53 trial


The majority of patients with diabetes die of cardiovascular disease. Up to the present, it is still uncertain whether any particular glucose-lowering agent is capable of producing a consistent reduction of cardiovascular risk and in different subgroups of patients. Dipeptidyl peptidase 4 (DPP-4) inhibitors improve glycemic control and previous studies suggest that they can reduce the risk of cardiovascular events.

The SAVOR TIMI 53 trial was a multicenter, randomized, double-blind and placebo-controlled study that evaluated the safety and efficacy of saxagliptin, a DPP-4 inhibitor, with respect to cardiovascular outcomes in patients with type 2 diabetes mellitus. The study included patients with a glycated hemoglobin level of 6.5% to 12.0% with one of the following crite-
ria: a) they had to be at least 40 years old and have a history of established cardiovascular disease (history of coronary artery disease, cerebrovascular disease or peripheral vascular disease); or, b) patients with cardiovascular risk factors with at least one of the following additional risk factors: dyslipidemia, hypertension, or active smoking, had to be at least 55 years of age (men) or 60 years of age (women). Patients were excluded if they were undergoing dialysis, had undergone a renal transplantation, or had a serum creatinine level > 6 mg/dL. Patients were randomly assigned to receive saxagliptin at a dose of 5 mg daily (or 2.5 mg daily in patients with a glomerular filtration rate ≥ 50 ml per minute) or placebo. Randomization was stratified according to renal function and to categorization in groups a) or b). The primary efficacy and safety end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal ischemic stroke. A secondary efficacy end point included the primary composite end point plus hospitalization for heart failure, coronary revascularization, or unstable angina.

A total of 16492 patients underwent randomization (mean age 65 years, 33% were women) with a median diabetes mellitus duration of 10 years and mean glycated hemoglobin of 8%. The median follow-up period was 2.1 years. At 2 years, mean glycated hemoglobin level was 7.5% in the saxagliptin group and 7.8% in the placebo group (p < 0.001). However, there were no significant differences in the incidence of the primary end point (3.7% per year in both groups) and secondary end point (6.6% per year with saxagliptin and 6.5% with placebo). More patients in the saxagliptin group were hospitalized for heart failure: 3.5% vs. 2.8% at 2 years. The incidence of major hypoglycemic events (2.1% vs. 1.7%) and minor hypoglycemic events (14.2% vs. 12.5%) was also greater in this group.

These results may be due to several reasons. Probably, a median follow-up period of 2 years may not have been long enough for a disease with median duration of 10 years. The use of other glucose-lowering agents in the placebo group or a large proportion of patients receiving statins, antiplatelet therapy, and blood-pressure–lowering agents may have mitigated the difference. Probably the macrovascular risk is not reduced by glycemic control. The greater incidence of heart failure should be confirmed by further studies. It does not seem that the use of DPP-4 inhibitors will be abandoned by these results; however, if these findings are confirmed by other studies, the investigation of the therapeutic link between glucose level reduction and major cardiovascular events should continue.

Colchicine is clearly indicated for the treatment of recurrent pericarditis. The therapeutic effect seems to be related to its ability to disrupt microtubules and to concentrate especially in granulocytes. The ICAP study was a multicenter, randomized, double-blind, placebo-controlled trial designed to evaluate the efficacy and safety of colchicine to treat a first attack of acute pericarditis and to prevent recurrences.

The study included patients with a first episode of acute pericarditis (idiopathic, viral, after cardiac injury, or associated with connective-tissue disease). Patients with neoplastic, tuberculous or bacterial pericarditis, creatinine levels > 2.5 mg/dL or high troponin levels were excluded from the study. The primary end point was the incidence of recurrent pericarditis (recurrence after 6 weeks of the initial pericarditis) or incessant pericarditis (persistent pericarditis or its recurrence less than 6 weeks after the index event). Patients were randomly assigned to receive colchicine at a dose of 0.5 to 1.0 mg daily or placebo for 3 months. The lower dose was given to patients weighing 70 kg or less and to those who had side effects at the higher dose of 1 mg. All the patients also received conventional treatment for acute pericarditis: either 800 mg of aspirin or 600 mg of ibuprofen given orally every 8 hours for 7 to 10 days, followed by tapering during a period of 3 to 4 weeks. Prednisone was administered to patients with contraindications to aspirin and ibuprofen or a history of side effects.

A total of 240 patients were included, 77% with idiopathic pericarditis. More than 90% of cases received treatment with aspirin or ibuprofen. During a minimum of 18 month follow-up, the primary end point occurred in 16.7% of patients receiving colchicine and in 37.5% with placebo (RRR 0.56, 95% CI 0.30–0.72; p < 0.001), which means treating only 4 patients to prevent one event. The recurrence rate was 9.2% in the colchicine group and 20.8% in the placebo group (p = 0.02). Colchicine also reduced the frequency of symptom persistence (19.2% vs. 40.0%, P=0.001) and the rate of hospitalization (5.0% vs. 14.2%, P=0.02). The incidence of adverse events and specifically of gastrointestinal disturbances (9.2% vs. 8.3%) was similar in both groups.

This study opens a new pathway in the treatment of acute pericarditis by adding colchicine to standard therapy. Although the results cannot be extrapolated to the forms excluded per protocol, most pericarditis forms treated in our daily practice correspond to those considered in this trial. Probably, the use of lower doses than those recommended for the treatment of recurrent pericarditis could be responsible for the good tolerance to the medication. The robustness of these findings is supported by the agreement of all the items considered.

Anticoagulation in patients with mechanical heart valves: failure of thrombin inhibitors
Mechanical heart valves in the aortic or mitral position require lifelong anticoagulant therapy. The use of vitamin K antagonists provides excellent protection against thromboembolic complications but requires lifelong coagulation monitoring and interacts with food, alcohol, and drugs. Dabigatran is an oral direct thrombin inhibitor that was shown to be as effective as warfarin in the treatment of patients with atrial fibrillation in the RE-LY study in a dosing regimen of 110 mg bid and superior to warfarin in a dosing regimen of 150 mg bid.

The RE-ALIGN trial was a phase 2, prospective, open-label trial with blinded end-point adjudication, designed to compare dabigatran versus usual anticoagulation therapy in patients with mechanical heart valves. Two types of patients were included: A) those undergoing implantation of a mechanical valve in the aortic or mitral position or both, and B) those having undergone implantation of a mechanical mitral valve (with or without mechanical aortic-valve replacement) more than 3 months before randomization.

In the dabigatran group, the objective was a plasma level of ≥ 50 ng/ml; thus, the dosing regimen was 150 mg twice daily in patients with a creatinine clearance < 70 ml/min, 220 mg twice daily in those with a creatinine clearance of 70 to 109 ml/min, and 300 mg twice daily in those with a clearance ≥ 110 ml/min. If the plasma level of dabigatran was less than 50 ng/ml, or the creatinine clearance fell below 30 ml/min or if there was a decrease of 50% or more from the baseline creatinine clearance, dabigatran was discontinued and usual anticoagulation therapy was administered. In the warfarin group, the target INR was 2 to 3 in patients who had a mechanical aortic valve with no additional thromboembolic risk factors and 2.5 to 3.5 in patients who had a mechanical aortic valve with additional risk factors or a mechanical mitral valve.

The primary end point was dabigatran plasma level, with the hypothesis that this dosing regimen would result in less than 10% of patients having a dabigatran level < 50 ng/ml. The study duration was 12 weeks. Thereafter, trial participants could choose to stop the study drug and switch to warfarin or they could choose to enroll in an extension trial for a planned interval of 7 years.

After 252 patients had been included (168 with dabigatran, 84 with warfarin), the data and safety monitoring board decided to stop the study. Seventy-nine percent of patients belonged to group A. Valve location was aortic in 68% of cases, mitral in 28%, and both in 4%. Seventy-one percent of patients were deemed to be at intermediate or high risk for thromboembolic complications. On the basis of a linear interpolation method, patients in the dabigatran group had the targeted plasma level for 84% of the time in group A and 96% of the time in group B. In the warfarin group, the time in the therapeutic range was 49% in group A and 51% in group B.

In the dabigatran group, stroke occurred in 5% of patients, AMI in 2% and asymptomatic valve thrombosis in 3%. There were no cases in the warfarin group. The composite of stroke, AMI, systemic embolism, or death was 8% with dabigatran versus 2% with warfarin (p = 0.11). The incidence of bleeding of any type was also greater with dabigatran: 27% vs. 12%; p = 0.01.

The results of the RE-ALIGN trial indicate that direct thrombin inhibitors are not appropriate in patients with mechanical heart valves. Probably, a dabigatran level higher than the one evaluated here could have prevented more thromboembolic events but with increased risk of bleeding. Warfarin is likely to be more effective than thrombin inhibitors because of its action on diverse mechanisms (it inhibits the activation of coagulation induced by tissue factor and by contact with the surface of the valve and sewing ring and also inhibits the synthesis of thrombin and Xa factor).

### Is thrombus aspiration during ST-segment elevation myocardial infarction useful? Apparently contradictory results of a randomized study and a meta-analysis


the discretion of the treating physicians. The primary end point was mortality at 30 days; the secondary end points included reinfarction at 30 days, stent thrombosis, target-vessel revascularization, target-lesion revascularization, and the composite of mortality or reinfarction at 30 days. A total of 60% of the patients considered were enrolled in the study. Median time from the onset of symptoms to PCI was higher than 180 minutes. At 30 days there were no significant differences in mortality with TA or without TA: 2.8% vs. 3%, but there was a trend toward a lower rate of reinfarction in the TA group: 0.5% vs. 0.9%, HR 0.61, 95% CI 0.34-1.07; p = 0.09. There were no significant differences in the other end points.

At the same time the results of the TASTE trial were published, a meta-analysis of 25 studies comparing thrombectomy and PCI vs. conventional PCI in STEMI (18 with TA and 17 with mechanical thrombectomy) was published. A total of 5334 patients were analyzed. In the studies using TA, after a mean follow-up of 5.9 months, all-cause mortality decreased significantly: 2.7% vs. 3.9% for PCI alone (RR 0.71, 95% CI 0.51-0.99; p = 0.049). This difference was only evident after 6 months of follow-up. There was also a trend toward a lower incidence of reinfarction or target-vessel revascularization. Yet, mechanical thrombectomy did not show any advantage compared to conventional PCI.

Are the results of both publications contradictory? It does not seem so. Previous meta-analyses have already demonstrated the absence of reduction in 1-month mortality with TA, so this meta-analysis and the TASTE trial are consistent in this topic. The mechanism whereby manual TA could reduce mortality at 6 and 12 months is not totally clear; yet one reason could be the strong trend toward a reduction in reinfarction at 1 month in the TASTE trial and at 6 months or more in the meta-analysis. Is this information about long-term mortality definite? No, because in a sensitivity analysis, when the TAPAS study was excluded from the meta-analysis, the mortality was the same with TA or without TA. The longer follow-up period in the TASTE trial should confirm or refute this assumption.

Fixed-dose drug combinations in primary and secondary prevention. The UMPIRE trial

Fixed-dose combinations (FDCs) of drugs in chronic diseases improve adherence and reduce treatment re-