

Interventional Cardiology



NEWS



INTERVIEW



Clopidogrel treatment prior to percutaneous coronary intervention questioned by results of recent analysis

Results of a recent meta-analysis add to the debate surrounding clopidogrel treatment prior to percutaneous coronary intervention (PCI). Anne Bellemain-Appaix (La Fontonne Hospital, Antibes, France) and colleagues describe how they found little benefit in patients pretreated with clopidogrel prior to undergoing PCI. It was only in higher-risk ST-elevation myocardial infarction (STEMI) patients, that a small benefit/gain was observed. These STEMI patients had a lower risk of major coronary events, but not a reduction in mortality following clopidogrel pretreatment, according to the article published in the *Journal of the American Medical Association*.

Senior author Gilles Montalescot (Pitie Salpetriere Hospital, Paris, France) explained that when looking at hard clinical outcomes in low-risk patients, especially the elective-PCI patients, pretreatment does not work. Montalescot explained "The primary end point of this meta-analysis was mortality, and nothing comes out for mortality whatever the situation; there is a favorable trend only in STEMI patients, the highest-risk group. There is no signal on major bleeding, so it's almost like we are looking at some kind of placebo effect with pretreatment." Montalescot continued, adding that "It is somewhat disappointing if you believe strongly that pretreatment is useful for your patients and certainly shows that we need more data to support such a recommendation."

Currently there are two ongoing large trials examining pretreatment with new antiplatelet agents, including prasugrel (Effient, Lilly [Hampshire, UK]/Daiichi Sankyo [Tokyo, Japan]) and ticagrelor (Brilinta, AstraZeneca [London, UK]), which will ultimately provide further information

on this issue. ACCOAST in particular, is the largest study ever performed including pretreatment and the use of prasugrel versus placebo prior to PCI in 4000 non-ST-elevation acute coronary syndrome (ACS) patients; results are expected in 2013. In addition, the ATLANTIC trial compares pretreatment with ticagrelor versus placebo before arrival at the hospital in 1800 STEMI patients, and is currently halfway through enrollment.

Commenting on these studies Montalescot said "Let's wait for the results of ACCOAST and ATLANTIC; if these studies with the newer agents that are more potent are negative, I think pretreatment will be in trouble." In the meantime, he believes it is reasonable to continue to pretreat STEMI patients prior to PCI, but not to treat the lower risk non-STEMI or elective-PCI patients. However, Montalescot acknowledges that "It is tough to change practice and here we are talking about a drug that has been around for so long and has been used in this way for so long."

In this study, the authors decided to conduct their review and meta-analysis of data from randomized trials and registries that included patients with coronary artery disease, which could be stable or with ACS, undergoing catheterization for potential revascularization to evaluate the association between clopidogrel pretreatment with mortality and major bleeding after PCI.

The authors found that clopidogrel pretreatment was not significantly associated with a reduction in all-cause mortality compared with no pretreatment (absolute risk: 1.54 vs 1.97%; odds ratio: 0.80; $p = 0.17$), but was associated with a lower risk of major adverse cardiac events (9.83 vs 12.35%; Odds ratio: 0.77; $p < 0.001$) in



the randomized controlled trial cohort. In addition, clopidogrel pretreatment versus no pretreatment was not associated with a significantly increased risk of major bleeding, a fact that was consistent across the observational analyses of randomized controlled trials and observational study analyses.

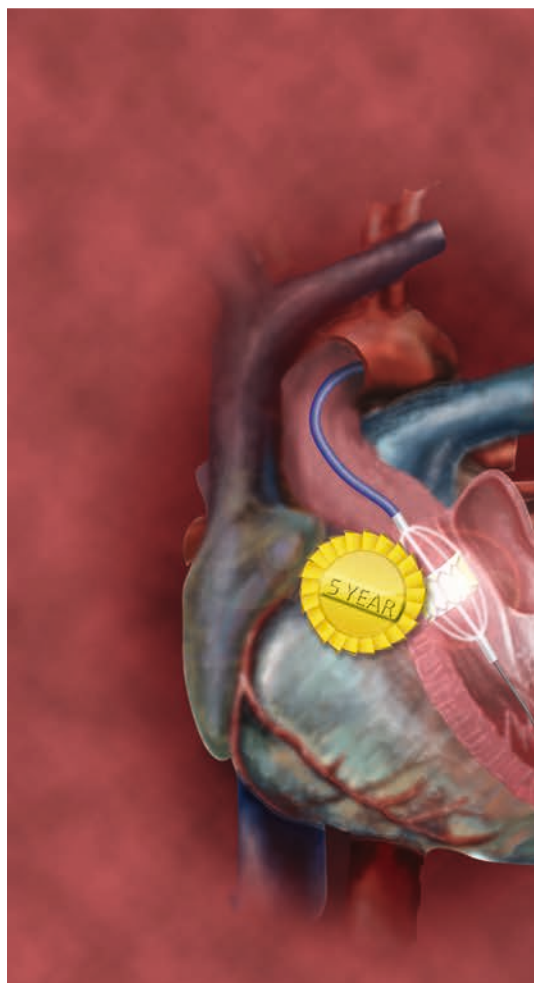
The results appear to question the need for this systematic strategy in low-risk patients as they do not seem reveal anything further on hard outcomes. Commenting further, Montalescot believes that pretreatment is questionable in *ad-hoc* PCI patients. He added “Even at my center, these patients are pretreated with clopidogrel the day before going to the catheterization laboratory for

a simple coronary angiogram; it does not make sense, because you don’t even know if the patient is a candidate for PCI. We run the risk of bleeding and if, or when, they undergo PCI, there is no benefit. We should be careful and not overtreat these patients.”

– Written by Michael Dowdall

Sources: Bellemain-Appaix A, O’Connor SA, Silvain J et al. Association of clopidogrel pretreatment with mortality, CV events and major bleeding among patients undergoing PCI. A systematic review and meta-analysis. JAMA 308, 2507–2517 (2012); New analysis questions clopidogrel pretreatment prior to PCI: www.medscape.com/viewarticle/776374

Study suggests promising long-term results for early transcatheter aortic valve transplantation procedures



A recent study reporting the 5-year outcomes of some of the earliest patients to receive transcatheter aortic valve transplantation (TAVI) has suggested promising data regarding patient mortality and the durability of valves.

The results obtained from St Paul’s Hospital (Vancouver, Canada), and appearing online in the *Journal of the American College of Cardiology*, have provided much needed data on the long-term patient and valve outcomes following TAVI, with the promising hemodynamic results prompting the author to theorize that TAVI devices “may last as long as surgical valves.”

“We did not know if these valves would last 5 years. We now do,” senior author John G Webb explained. “We can now say that patients expected to live longer than 5–10 years have the possibility of long-term benefit from a durable valve. This would represent our current target group for this procedure.”

The study examined the outcomes for a total series involving 111 patients (mean age of 83 years) with severe symptomatic aortic stenosis who were implanted with balloon-expandable Cribier-Edwards or Sapien valve (Edwards Lifesciences, CA,

USA) between January 2005 to March 2007. All patients received lifelong regimens of aspirin and a 3-month dose of clopidogrel. If oral anticoagulation was indicated, patients were treated with warfarin and, if tolerated, a 3-month dose of dual antiplatelet therapy.

In the 88 patients with successful implantation after 30 days, survival rates at 1, 2, 3, 4 and 5 years following TAVI were 83, 74, 53, 42 and 35%, respectively.

“We did not know if these valves would last 5 years.
We now do...”

Adding context, Webb explained: “During this early feasibility study, the procedure was only offered to extremely ill patients who were anticipated to have a poor 5-year survival due to advanced age and other severe comorbidities. The high late mortality was not due to valve deterioration, but due to the types of patients entered into these very early experimental evaluations.”

Although signs of moderate prosthetic valve failure were observed in three patients, the mean 5-year valve hemodynamic results were favorable. The mean aortic valve gradient decreased from 46 to 10 mmHg in patients after receiving TAVI, and was



stable at 11.8 mmHg after 5 years ($p = 0.06$ for post-TAVI trend). The mean aortic valve area increased from 0.62 cm² to 1.67 cm² after TAVI, and was found to be at 1.40 cm² at 5 years ($p < 0.01$ for post-TAVI trend).

No patients were observed to develop severe transvalvular regurgitation or restenosis, and concomitant mitral regurgitation remained improved in the majority of patients at the 5-year follow-up.

After analyzing patients with higher 5-year mortality, the researchers found that

risk of death was significantly increased in patients with chronic obstructive pulmonary disease and moderate paravalvular regurgitation, identifying these patients as an at-risk group and proving more data is required to enable accurate patient selection in TAVI.

– Written by Louise Rishton

Sources: Toggweiler S, Humphries KH, Lee M et al. 5-year outcome after transcatheter aortic

valve implantation. *J. Am. Coll. Cardiol.* S0735–S1097(12), 05533–05537 (2012); Osnabrugge RL, Head SJ, Bogers AJ, Kappetein P. Patient selection for transcatheter aortic valve replacement: what does the future hold? *Expert Rev. Cardiovasc. Ther.* 10(6), 679–681 (2012); 'Favorable' five-year outcomes with early TAVI devices: www.theheart.org/article/1491417.do

Does angiogenic gene therapy represent a safe and effective therapy for coronary artery disease?

Long-term follow-up results appearing in the journal *Human Gene Therapy* have suggested favorable outcomes in coronary artery disease patients treated with angiogenic gene therapy to strengthen blood vessels and reverse coronary ischemia.

The 10-year study followed 31 patients from Weill Cornell Medical College (NY, USA) who were not suitable to be treated with coronary artery bypass surgery.

“After long-term follow-up, the patients who received angiogenic gene therapy appear to have improved outcomes,” reported Ronald G Crystal, professor of Genetic Medicine at Weill Cornell. “The study results give us greater insight into the safety and effectiveness of gene therapy to rebuild blood vessels in patients living with coronary artery disease.”

The therapy AdVEGF121, a direct injection of adenovirus encoding the gene VEGF into the myocardium, aims to rebuild weak and damaged coronary blood vessels to increase blood flow to the heart.

Using medical records, interviews and questionnaires to determine patient outcomes, the group receiving CABG and gene therapy had a 10-year survival rate of 40% compared with the 31% survival rate of patients receiving gene therapy only.

“Overall this group of individuals had an outcome greater than what we believe they would have if they had not received the gene therapy.”

“We only had an idea of what the outcome might be based on promising studies in the lab, so there was concern, but those who received this treatment really had no other treatment options,” reported co-senior author Todd Rosengart, Baylor College of Medicine (TX, USA).

“Overall this group of individuals had an outcome greater than what we believe they would have if they had not received the gene therapy,” Rosengart summarized.

The absence of gene therapy complications in patients, such as rates of malignancy

and retinopathy, was also seen as a significant result in ensuring patient safety in gene therapy. “Given the concerns about gene therapies during the time when this trial originated, this is one of the very few long-term gene therapy studies that is very encouraging from a patient safety basis.”

With future steps by the researchers aiming to include more patients and compare outcomes to a placebo group, more results for the procedure can be expected to follow.

– Written by Louise Rishton

Sources: Rosengart TK, Bishawi MM, Halbreiner MS et al. Long-term follow-up assessment of a Phase 1 trial of angiogenic gene therapy using direct intramyocardial administration of an adenoviral vector expressing the VEGF121 cDNA for the treatment of diffuse coronary artery disease. *Hum. Gene Ther.* doi:10.1089/hum.2012.137 (2012) (Epub ahead of print); *Rebuilding blood vessels through gene therapy*: http://weill.cornell.edu/news/releases/wcmc/wcmc_2012/12_20b_12.shtml

Miracor's PICSO® used for the first time in the UK under CE mark to treat a patient with STEMI

Miracor Medical Systems Pressure-controlled Intermittent Coronary Sinus Occlusion (PICSO®) Impulse System has been used for the first time in the UK under CE mark to treat a patient with STEMI.

In STEMI the application of timely reperfusion of the myocardium using

percutaneous coronary intervention (PCI) remains the most effective treatment for limiting infarct size, reducing left ventricular remodeling and improving clinical outcomes. Even once optimum PCI has been administered, mortality and morbidity following STEMI remains sizeable. It

is evident that PCI alone is not sufficient to rule out the risk of further events.

The PISCO system provides an innovative approach to reduce myocardial injury and to revitalize the ischemic myocardium. The company reports that the early clinical results have demonstrated positive effects



on major adverse cardiac events, restenosis rates and long-term event-free survival. The PICSO system consists of the Miracor PICSO Impulse Console and the disposable, single-use Miracor PICSO Impulse Catheter.

Interventional cardiologist Magdi El-Omar performed the PICSO procedure on his patient at Manchester Royal Infirmary (Manchester, England). El-Omar commented that, in his opinion, “PICSO has the potential to become standard of care in patients presenting with acute STEMI who may benefit from this technology as a complementary procedure following PCI.

By favorably redistributing blood towards ischemic myocardium, PICSO may limit infarct size and thus reduce adverse outcomes, including heart failure, which occurs in up to two in five of these patients, despite a successful percutaneous coronary intervention procedure.”

Commenting after the successful procedure, Jon H Hoem, Miracor CEO added “A successful coronary angioplasty is not adequate in up to 40% of STEMI patients in whom suboptimal myocardial reperfusion still persists, despite achievement of normal epicardial vessel flow. This unsatisfactory outcome is unequivocally linked to adverse outcomes in these patients, including death and heart failure. Results like those obtained by El-Omar are critically important as we establish the clinical necessity for

the PICSO procedure as a requisite complement to PCI in severe heart attack patients. Clinical use of the PICSO technology in normal care will shorten the learning curve for Miracor and our key opinion leaders, thereby improving outcomes and reducing long-term health care costs. In addition to routine use of the PICSO technology, our 40-patient ‘Prepare RAMSES’ is underway and expected to further demonstrate that PICSO considerably amplifies redistribution of blood into the blood-starved myocardium of severe heart attack patients, even after a successful PCI procedure.”

– Written by Michael Dowdall

Source: Miracor Medical Systems news: www.miracormedical.com/p-66762.html

About the News and Views

The News and Views highlights some of the most important events and research in the field of interventional cardiology. If you have newsworthy information, please contact: Michael Dowdall, Managing Commissioning Editor, *Interventional Cardiology*, Future Medicine Ltd, Unitec House, London, N3 1QB, UK; m.dowdall@futuremedicine.com