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FAME II trial demonstrates the importance of targeting treatment to the right patients

A ground breaking international trial, presented yesterday at EuroPCR, has demonstrated for the very first time the true value of percutaneous coronary intervention (PCI) in patients with stable coronary artery disease. The study highlights the critical importance of targeting these interventions to patients with ischemia and may revolutionise the patient selection procedure for PCI.

The FAME II study is the first of its kind and has shown that targeting fractional flow reserve (FFR) guided PCI and optimal medical treatment (OMT) to patients with ischemia (having at least one stenosis with FFR ≤ 0.80) can reduce the need for revascularisation by a factor of between 6 - 11 compared with OMT alone. This study also provides clear evidence that patients without ischemia do not need to undergo PCI and can be successfully managed using OMT alone.

This randomised, prospective study was conducted among a cohort of over 1,200 patients across 28 centres in Europe and the US. Patients with ischemia were randomised to receive either FFR-guided PCI and OMT or OMT alone. PCI was conducted using the very latest second generation drug eluting stent systems (DES). Patients without ischemia received treatment with OMT alone. The primary end point recorded was a composite of all cause death, myocardial infarction (MI) and unplanned hospitalisation leading to urgent revascularisation. Patients were only considered as urgent revascularisation cases if they entered the hospital through the emergency ward and their revascularisation procedure was performed during the same hospitalisation episode, or if they presented at the clinic with increased angina symptoms requiring urgent revascularisation.

Bernard DeBruyne believes that these results will have a major impact on clinical practice and outcomes for these patients, “This study has the potential to change the way that we target treatment in the future. Many patients in whom we consider placing stents have no ischemia, this study has shown us that these patients can do very well with medical treatment alone. Targeting PCI to the right patients and the right lesions using second generation DES systems can have a major impact on the success rate for these interventions.”

The study was halted prematurely due to an overwhelming difference in primary end point outcomes between the treatment arms with a major advantage for PCI and OMT. The safety management board (SMB) considered that it was not ethically or scientifically justified to submit patients to a risk that had been identified. Patient enrolment began in May 2010 and the study was halted in January 2012, with 90% of recruitment taking place in 2011.

COMPARE II trial

First generation drug eluting stents (DES) have been shown to be superior in preventing re-stenosis compared to bare metal stents (BMS), though at an increased risk of late stent thrombosis due to delayed re-endothelialisation and healing, specifically when used in a real life /off-label setting.

In an attempt to overcome these unwanted late effects of DES, new generation DES with other limus analogues and more biocompatible durable polymers or biodegradable polymers have been developed. One of the new generation DES is the biolimus eluting Nobori stent, with an abluminal biodegradable polymer, which dissolves in approximately 9 months, leaving behind a ‘bare metal’ stent.

Recent meta-analyses and editorial opinion supports the cobalt chromium everolimus eluting stent (CoCr-EES; Xience/Promus) as the standard against which future stent designs should be compared

and therefore the COMPARE II trial was conceived to compare the abluminal biodegradable polymer biolimus eluting Nobori stent with the current golden standard, the CoCr EES, in a real life situation.

This is one of the largest, prospective randomised trials in an all-comer setting. The trial is physician initiated and sponsored by the Research Foundation of the Cardiology Department of the Maasstad Hospital, Rotterdam, The Netherlands, which received an unrestricted grant from Terumo, the manufacturer of the Nobori stent. Terumo had no role in data collection, data interpretation or data reporting. All events were adjudicated by an independent clinical research organisation and core lab (Cardialysis, Rotterdam, The Netherlands).

Pieter Smits presented the data for the primary endpoint at one year during the late breaking trial sessions at EuroPCR 2012, though follow-up is due to continue for five years.

At one year the biolimus eluting Nobori stent is non-inferior compared to the current Everolimus eluting Xience/Promus stent. Primary endpoints (composite of cardiac death, MI and clinically indicated TVR) and secondary endpoints (composite of cardiac death, MI and clinically indicated TLR) were not significantly different between both stent groups with similar cardiac death (0.8%) and low ST rates (≤ 1.0%) observed in this real life patient population.

Pieter Smits summarises: "It's good that we have a new device available which shows very good results in efficacy and safety. We need longer term data above one year to give a better idea as to whether the biodegradable polymer will solve very late thrombosis or not ... stent thrombosis as a whole is an important issue for the patient."

COMFORTABLE AMI trial

New efficacy and safety data released yesterday supports the use of the BioMatrix drug eluting stent (DES) in ST-segment elevation acute myocardial infarction (STEMI) patients. The COMFORTABLE AMI trial is the very first trial to compare the use of this newer generation biostent eluting biolimus from a biodegradable polymer (BioMatrix) with bare metal stent (BMS) devices and shows that both safety and efficacy are improved in STEMI patients receiving this device. The study results are reported only shortly after the publication of two meta-analyses raising concern regarding the long-term safety of early generation DES in STEMI patients.

This randomised, multi-centre trial was conducted among 1,161 STEMI patients across 11 sites in Europe and Israel. A total of 575 patients received the BioMatrix stent and 582 patients received a BMS comparator. At one year, an overall relative risk reduction of 51% for the primary end point was reported in favour of the BioMatrix stent. The primary end point was a composite of cardiac death, target vessel re-infarction and ischemia driven target lesion revascularisation. This was driven by a substantial reduction in both safety and efficacy end points, notably a relative risk reduction of 80% for target vessel re-infarction and 72% for target lesion revascularisation.

Lorenz Räber from Bern University Hospital, Switzerland presented these data at the EuroPCR late breaking trial session on Tuesday 15th May 2012 in Paris. He is encouraged by the safety and efficacy improvements reported in this trial, “the data provide robust evidence that biolimus-eluting stents with biodegradable polymer are superior to BMS of otherwise identical design, with a number needed to treat of 24 in order to prevent one major adverse cardiac event.” He further comments that “differences in favour of the biolimus-eluting stent were not limited to efficacy but also driven by a reduction in target vessel reinfarction, which has not been observed in previous randomised trials comparing DES and BMS among STEMI patients.”

The study was supported by the Swiss National Scientific Foundation and an unrestricted grant from Biosensors Europe.

Largest ever clinical trial involving a drug-eluting stent is announced

Plans for a new trial were announced yesterday at EuroPCR by Patrick W. Serruys. The GLOBAL LEADERS trial will compare two different anti-platelet strategies in patients who have received a drug eluting stent (DES) with an abluminally coated biodegradable polymer.

GLOBAL LEADERS is an investigator-driven trial supported by Biosensors and AstraZeneca and aims to enrol around 16,000 patients from an "all-comers" population to compare the effectiveness of two different pharmaco-intervention strategies. All patients will receive BioMatrix Flex, and then be randomised to either a study treatment strategy of one month's aspirin (ASA) plus the novel anti-platelet therapy ticagrelor, followed by 23 month's ticagrelor monotherapy; or a reference treatment strategy of 12 month's dual anti-platelet therapy (ASA plus ticagrelor for ACS patients; ASA plus clopidogrel for elective patients), followed by 12 month's ASA monotherapy. Recruitment is due to commence by the end of this year in what will be the largest ever randomised clinical trial involving a DES. Patients will be followed up for two years. This latest plan for the trial represents an evolution in the concept, protocol, management and support of GLOBAL LEADERS as announced at EuroPCR last year, which it supersedes and replaces.

GLOBAL LEADERS is being independently designed, implemented and analysed by the study investigators, led by Patrick W. Serruys (Erasmus Medical Center, Rotterdam, Netherlands), Stephan Windecker(University Hospital, Bern, Switzerland) and Marco Valgimigli (University of Ferrara, Italy).

Notes for editors:
The BioMatrix stent system is coated with an anti-restenotic drug called Biolimus A9 in combination with a biodegradable poly-lactic acid (PLA) polymer. The PLA polymer breaks down to form carbon dioxide and water over a 6-9 month period as the anti-restenotic drug is released.

LEADERS FREE trial

A groundbreaking new trial design was unveiled on Tuesday May 15 at EuroPCR, focusing on a complex subset of patients who are usually excluded from clinical trials. The LEADERS FREE trial will examine safety and efficacy outcomes in patients receiving treatment with a new generation of drug coated stent (the Biofreedom stent) compared with an early generation bare metal stent (BMS) device in patients that cannot be treated for more than one month with dual anti-platelet treatment. It is hoped that this study will address the current unmet need for improved care among this patient group.

This randomised, double blind, international multicentre study will take place in 70 centres across Europe, Asia and America. Approximately 2,500 people will be enrolled on the study that will focus on a patient population with a high risk of bleeding, many of whom will display a complex set of co-morbidities. Until now, these patients have been excluded from drug eluting stent (DES) clinical trials because they are considered too old, are receiving medication that may contraindicate dual anti-platelet treatment, have cancer or have a high risk of bleeding.

Marie-Claude Morice is enthusiastic about the design of this trial, "We are very excited about the LEADERS FREE trial because these patients do not usually benefit from the new generation of DES devices that improve outcomes. These people are usually treated with BMS but, due to their fragile condition, they may be better suited to the new generation devices that we are examining in this study".

The new generation DES device examined in this study is a drug coated stent called Biofreedom systemis. It is coated with an anti-restenotic drug called Biolimus A9 that is directly released from the surface of the stent, without any polymer. This allows normal healing of the artery, identical to that of a BMS, but with the advantage associated with a drug coated stent of providing a dramatic reduction in restenosis. The study design has been submitted for ethical and regulatory approval. This research will be supported by an unrestricted grant from Biosensors International and conducted by CERC, Massy, France under the guidance of the three principal investigators: Philip Urban, Alexander Abizaid and Ian Meredith.

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