Fractional Flow Reserve-Guided Percutaneous Coronary Intervention plus Optimal Medical Treatment versus Optimal Medical Treatment Alone in Patients with Stable Coronary Artery Disease

Published: 22-06-2010
Last updated: 01-05-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coronary artery disorders
Study type	Interventional

Summary

ID

NL-OMON38089

Source
ToetsingOnline

Brief title
FAME II

Condition

- Coronary artery disorders

Synonym
coronary artery disease, coronary artery narrowings

Research involving

Human

Sponsors and support

Primary sponsor: St. Jude Medical
Source(s) of monetary or material Support: St. Jude Medical

Intervention

Keyword: Fractional flow reserve, Optimal medical treatment, Randomized trial, Stable coronary artery disease

Outcome measures

Primary outcome

The primary end-point of the FAME II study is the 24-month major adverse

cardiac event rate (MACE) defined as:

• All cause death

• Documented myocardial infarction

• Unplanned hospitalization leading to urgent revascularization

as adjudicated by the Critical Event Committee (CEC).

Secondary outcome

The secondary end-points of the FAME II study include the following:

• Overall MACE and each individual components of MACE and their combination at

each point in time (after 1, 6, 12 month and 1, 3, and 5 years of follow-up).

• Non-urgent revascularization procedures

• Cost and cost-effectiveness at each point in time.

• Functional class at each point in time (including freedom from angina)

• Number of anti-anginal medication at each point in time.

• Rate of non-urgent (repeat) revascularization at each point in time.

• Rate of any cerebrovascular event at each point in time.

as adjudicated by the Critical Event Committee (CEC).

Study description

Background summary

In patients with unstable angina and acute myocardial infarction, randomized trials have demonstrated substantial benefits of percutaneous coronary angioplasty (PCI), including prevention of myocardial infarction and reduced mortality rate.In patients with stable coronary artery disease, PCI has been shown to improve anginal symptoms and quality of life. However, in these patients, PCI has not significantly affected clinical outcomes such as death and non-fatal myocardial infarction.
The COURAGE trial, a randomized trial comparing PCI plus optimal medical treatment with optimal medical treatment alone, demonstrated no difference in the primary end-point of death and myocardial infraction. This study has introduced a sense of uncertainty as regard to the optimal management of patients with stable angina and has had a significant impact on the referral pattern to PCI in the United States and - albeit to a lesser degree - in Europe. The study has been heavily criticized for a number of reasons of which the most important is the very small number of patients finally included in the study as compared to the number of patients screened. In addition, in the COURAGE trial most patients had a non-invasive stress test performed prior to entering the catheterization laboratory while a recent review showed that, in the *real world* only 45% of patients ever had a stress test prior to PCI. This has raised concerns about the applicability of the results to all comers as the potential exist of a selection bias toward low risk patients.

An exploratory analysis of clinical outcomes in patients who underwent serial myocardial perfusion imaging in the COURAGE-trial revealed that, regardless of treatment assignment, (1) the risk of death or MI was proportional to the magnitude of residual ischemia, and (2) that a 5% reduction in ischemia (by whatever treatment) was associated with a significant reduction in this risk. Like many others these data support the idea that revascularization is effective in lesions which are responsible for myocardial ischemia but that lesions that are not associated with ischemia should not be revascularized

mechanically.

The assessment of the hemodynamic significance of coronary atherosclerosis is classically performed non-invasively by exercise ECG, stress echocardiography, and myocardial perfusion imaging. Yet, these tests are not always available at the time of the catheterization.In addition, it is generally acknowledged that non-invasive stress testing is very reliable in patients with one vessel disease and normal left ventricular function but that their usefulness in guiding the need for revascularization is limited in patients with multiple lesions as well as in many other clinical and anatomical subsets.

Pressure-derived fractional flow reserve has been developed and validated as a surrogate for non-invasive testing.This information is more accurate in moderate stenoses, its spatial resolution is unsurpassed and the information is immediately available in the catheterization laboratory thus allowing the operator to decide about the appropriateness of revascularization *on the spot*. Robust clinical outcome data demonstrate the reliability of FFR and can be summarized by saying that when FFR of a given stenosis is larger than 0.80, no revascularization is mandated, while when FFR is lower than this threshold, revascularization should at least be considered.The FAME study conducted in patients with multivessel disease showed that a strategy of stenting only ischemic stenoses but leaving alone non-ischemic stenoses (as assessed by fractional flow reserve [FFR] measurements) was associated with significantly less deaths and/or myocardial infarctions than a strategy of stenting all angiographically visible stenoses. This data reinforce the concept of *functionally (rather than anatomically) complete revascularization*.

In the COURAGE trial as well as in the recent BARI-2D trial it is very likely that lesions have been stented which might actually have been left alone. This hypothesis could - by itself - explain the absence of difference between the PCI plus OMT arm and the OMT alone arm. Nevertheless, the conclusions of these studies have been generalized to all patients with stable CAD and have led to the general believe that in these patients medical treatment without invasive approach is the preferred treatment.

Study objective

The hypothesis of the FAME II trial is that FFR-guided PCI (with DES) plus optimal medical treatment is superior to optimal medical treatment alone. The overall purpose of the FAME II study is to compare the clinical outcomes, safety and cost-effectiveness of PCI plus optimal medical treatment (OMT) versus OMT alone in patients with stable coronary artery disease and in whom both PCI and medical treatment can be considered on the basis of the presently existing scientific evidence.

Study design

The FAME II study is a prospective, multicenter, multinational, multi-continental, randomized clinical trial with an *all comers* design.

All consecutive patients with stable clinical condition and angiographically defined one-, two, or three-vessel coronary artery disease and amenable for PCI should be screened and considered for participation in the trial. However, patients will be randomized only if at least one of the indicated stenoses is hemodynamically significant as defined by an FFR value of less than 0.80. It is expected that in 20% of patients no stenoses will be hemodynamically significant. These patients will be treated according to local practice (optimal medical treatment is advised) and will be followed-up in a registry.

Sixteen hundred patients with at least one hemodynamically significant lesion will be randomized into PCI plus optimal medical treatment or optimal medical treatment alone. Each center will be expected to enroll a minimum of 50 patients. The number of participating centers is projected to be approximately 40, with approximately 20-25 sites in Europe and 15-20 sites in the US.

At the time of the informed consent procedure, patients may refuse to be randomized because of their personal preference for one treatment modality or the other. According to the literature, this group is expected to represent 2-10 % of the patients eligible for randomization.18-20 These patients will not be included in the trial, and data will not be collected.

For prospectively collected data in the randomized trial as well as in the follow-up subset of the registries, an independent Clinical Events Committee (CEC) will adjudicate all clinical endpoints (12-month MACE and at 2 and 5 years). An independent Data Monitoring Committee (DMC) will assess the results with respect to patient safety at frequent pre-specified intervals.
Per amendment the patients from Group B randomised to "no follow-up" will be asked for follow-up after 1, 2 and 5 years

Intervention

Whatever the allocated intervention, all the indicated lesions will be assessed using FFR. When the patient is randomized to optimal medical therapy (OMT) alone, all lesions will be measured but none will be stented (regardless of the FFR value). When the patient is randomized to the PCI+OMT arm, all lesions will be measured and stented if, and only if the FFR is < 0.80.

Study burden and risks

No additional risk applicable because both treatment strategies are accepted therapies for this kind of patients.
The burden for the patient consists of outpatient clinic visits.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Stable coronary artery disease
At least one coronary stenosis of at least 50% diameter stenosis
Eligible for PCI
Signed written informed consent

Exclusion criteria

Preferred treatment is CABG
Left main disease requiring revascularization
STEMI or NSTEMI < 1 week
Prior CABG

LVEF<30%
Extremely tortueus or clacified vessels
Requiring concomitant cardiac surgery
Pregnancy or intention to become pregnant during the trial
Life expectancy less than 2 years
Participation in another trial

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-07-2010
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO Date:	22-06-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-10-2010

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL32430.060.10