Functional Assessment of Intermediate coronary stenosis to guide revascularization in patients candidates to valvular Replacement: the FAIR study.

Legend.
1- Abstract, page 3
2- Introduction, pages 4,5
3- Methods, pages 6-8
4- References, page 9
ABSTRACT.

Introduction. Safety and efficacy of a surgical approach to coronary revascularization for patient undergoing cardiac surgery based on functional assessment of severity of coronary lesions remain to be assessed.

Methods. All consecutive patients undergoing coronary angiography as evaluation before an intervention for cardiac surgery will be enrolled. For patients presenting with a stenosis of more than 50% at visual estimation of one of the main epicardial vessels, Fractional Flow Reserve (FFR) along with iFR (when available) will be evaluated. Cardiac surgeons will evaluate number of grafts according to FFR/iFR.

Primary end point will be the rate periprocedural myocardial infarction during hospitalization, defined according to the ESC guidelines as an increase of troponin or more than 10 the URL. Major cardiovascular cardiac events (a composite end point of death, myocardial infarction and revascularization) at six months follow up and after at least one year. The secondary ones, along with single components of MACE. Number of grafts planned before and after FFR/iFR and those performed will also be evaluated.

150 patients should give enough accuracy to evaluate at multivariate analysis impact of a negative FFR/iFR on perioperative myocardial infarction
INTRODUCTION.

Coronary artery disease for patients undergoing cardiac surgery.

The standard treatment option for patients with an indication for cardiac surgery and coronary artery disease (CAD) consists in concomitant coronary artery bypass grafting (CABG, 1). This combined procedure, for example, carries a mortality rate nearly double that of isolated AVR (4.4 vs. 9%). Combined AVR/CABG is also less favorable in patients with poor or limited conduit vessels, patients presenting with ACS, and patients requiring valve reoperation. In the majority of the studies, CAD was defined as at least one major epicardial artery (left main trunk, left-anterior descending coronary artery, left circumflex coronary artery, and right coronary artery) with at least 50% stenosis or a history of PCI.

Release of cardiac troponin represents one of the unavoidable consequences of an intervention of cardiac surgery, and more specifically, high rates of myocardial injury have been frequently reported (up to 40%), with a clear relationship with adverse prognosis in hospital and at follow up. (2,3). They may occur even in the absence of graft/coronary occlusion and may relate also to insufficient myocardial protection during cardiopulmonary bypass or with off-pump techniques, air embolism, and regional and global ischemia during the procedure. All features, however, have been directly linked to length of the procedure, which depends, among the others, also by number of performed grafts (3).

An alternative strategy for high-risk surgical patients candidate to aortic valve replacement is currently the Transcatheter Aortic Valve implantation (TAVI). However in this group of subjects the prognostic role of CAD on survival as well as the decision on treat or not an intermediate lesion by means of PTCA remains still an unmet issue
**Fractional flow reserve.**

Recently, fractional flow reserve (FFR) has been shown to be a valuable tool for physiology-guided lesion assessment, and routine FFR in addition to coronary angiography has improved the outcome of percutaneous coronary intervention. In addition, FFR performed during diagnostic coronary angiography is associated to reclassification of the revascularization decision and with a lower number of graft anastomoses and a lower rate of on-pump surgery. (4,5) Only few and not prospective data exist about a FFR guided revascularization in patients with indications to cardiac surgery: the largest study of the group of Barbato (5) recently demonstrated retrospectively long term follow up safety of a FFR based approach for patients undergoing cardiac surgery. Among the others, the major limitations are represented by the retrospective design and the absence of data about periprocedural events, like myocardial injury.

**Above iFR.**

Despite all these advantages (demonstrated especially for patients undergoing percutaneous coronary revascularization) the real world adoption of fractional flow reserve (FFR) remains globally low (6-8%), partly because time consuming, cost and with potential inconvenience associated with vasodilator administration. The instantaneous wave-Free Ratio (iFR) is a pressure-only index of stenosis severity calculated without vasodilator drugs. A hybrid iFR-FFR decision-making strategy has been demonstrated to increase adoption of physiology-guided PCI, halving the need for vasodilator administration and maintaining high classification agreement with an FFR-only strategy (6)
METHODS.

The present protocol is written according to the Strobe Statement (7).

Study design

Prospective multicenter observational study.

Inclusion criteria

All consecutive patients undergoing coronary angiography as a part of the pre-operative evaluation (for both open survey or TAVI) with an intermediate lesion (more than 50%) of at least one major coronary epicardial artery will be enrolled.

Exclusion criteria

1. Infective endocarditis;
2. Life expectancy less than 1 year;
3. Severe Epatic, Renal or Lung disease
4. Recent cerebrovascular accident (<6 months);
5. Obstructive hypertrophic cardiomyopathy;
6. Inability to express informed consent;

Planned procedures

After informed consent was obtained, all procedures will be performed at the operator’s discretion. Pre intervention coronary angiography will be performed according to standard clinical practice, via either a femoral or radial approach.

In each center, decision about grafting will be left to operators’ discretion:

- FFR based approach: All the angiographic intermediate lesions will be grafted with an FFR < 0.80 and deferred with an FFR>0.80, after discussions with at least two cardiac surgeons.
- iFR/FFR Hybrid approach the stenosis will be grafted with iFR ≤ 0.85 and deferred with iFR>0.94. In case of iFR between 0.86 and 0.93, FFR will be performed (as described previously).

The decision to use unfractionated heparin, acetylsalicylic acid, clopidogrel, intra-aortic balloon pumps, inotropic drugs, abciximab, beta-blockers, angiotensin-converting enzyme inhibitors, and diuretics as well the decision to use FFR or iFR/FFR Hybrid approach will be left to the discretion of interventional and coronary care unit cardiologists, as directed by international guidelines. Left ventricular function will be evaluated by echocardiography in all patients during the first 24 hours after admission and at discharge, while trans-esophageal echocardiography could be used during all procedural time to guide and assess intervention. Given the uncertainty of FFR in patients with severe hypertrophied left ventricles, a sensitivity analysis will be performed for those presenting with severe aortic stenosis. (8).

Baseline data collection

The following features will be recorded.

- Clinical: age, gender, cardiovascular risk factors, renal clearance, echocardiography data. Moreover all these data will be summarized onto STS score and logistic EuroScore, two largely validated scores to predict pre-operative surgical risk in cardio surgery.

- Procedural: access site, number and kind of diseased vessels. If available, also the right atrial pressure will be recorded together with FFR/iFR.

- Syntax score will be computed before and after the use of FFR or iFR/FFR evaluation.

FFR/iFR data collection

It will be assessed:
- If decision of interventional cardiologists about severity of coronary lesions was undertaken according to FFR or iFR/FFR hybrid strategy
- Number of grafts planned by surgeons before and after iFR/FFR hybrid strategy and those eventually performed or in case of TAVI, number of vessels to stent planned by interventional cardiologist before and after iFR/FFR hybrid strategy and those eventually performed.

Data Management

A dedicated electronic Case Report Form (eCRF) will be designed and managed by one of the investigators (E.C.) and hosted in the collaborative CardioGroup.org platform. All data will be stored securely and confidentiality.

Primary end point.

Primary end point will be the rate periprocedural myocardial infarction during hospitalization, defined according to the ESC guidelines as an increase of troponin or more than 10 the URL. (9). Major cardiovascular cardiac events (a composite end point of death, myocardial infarction and revascularization) at six months follow up and after at least one year. Secondary end point will be single components of MACE. The only pre-specified subgroup analysis will be patients submitted to TAVI.

Statistical assumptions

Continuous variables are expressed as mean ± standard deviation and were compared with ANOVA. Categorical variables are presented as counts and percentages and were compared with the chi-squared test. A P-value < 0.05 will be considered significant. All statistical analyses will be performed using SPSS 20.0. In the study of Domanski et al (2) up to 40% of the patients reported a myocardial infarction with a negative prognostic impact at 30 days and
at six months follow up after coronary artery bypass graft, as in that of van Geene et al (9) after combined surgery (valvular and CAbG). with consequent absence of surgery revascularization will be tested at multivariate analysis among age, ejection fraction, renal clearance less than 60 ml/min/m2, and Body Mass Index to assess the independent effect on periprocedural myocardial infarction. According to the work of Peduzzi (10) et al recruiting 150 patients in the open surgery group should give enough accuracy for perioperative myocardial infarction.

Regarding TAVI patients, given an incidence of 17% of periprocedural myocardial infarction and 8% of all cause death (mutually exclusive) (9), recruiting 200 patients will give enough accuracy, after adjusting for length of procedure, beta blockers use, age and diabetes mellitus

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