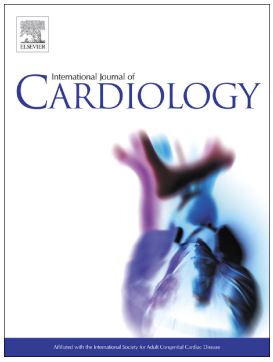
Safety of FFR-guided revascularisation deferral in Anatomically prognostiC diseasE (FACE: CARDIOGROUP V STUDY): A prospective multicentre study



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Safety of FFR-guided revascularisation deferral in Anatomically prognostiC diseasE (FACE: CARDIOGROUP V STUDY): a prospective multicenter study.

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ABSTRACT

Background: FFR-guided coronary intervention is recommended for patients with intermediate stenoses. However, concerns exist with this approach in anatomically prognostic disease.

Methods: In this prospective, multicentre study, we consecutively enrolled patients found to have FFR negative lesions in anatomically significant sites: left main; proximal LAD; last remaining patent vessel; and multiple vessels with concomitant impaired left ventricular systolic function (EF< 40%). As per recommendation, revascularisation was deferred, and patients included into a registry.

The primary endpoint was MACE (death, myocardial infarction and unplanned target lesion revascularization). Secondary endpoints were the above individual components. Subgroup analyses were performed for clinical presentation (stable vs. ACS), localization of lesion (ostial vs. non ostial) and renal function.

Results: The registry included 292 patients with 297 deferred stenoses. After 1-year, the primary endpoint occurred in 5% of patients, mainly driven by TLR (2.7%). Cardiovascular death occurred in 0.8% and AMI in 0.8%. During a follow-up of 22.2±11 months, MACE occurred in 11.6%. Cardiovascular death occurred in 1.8% and AMI in 2.1%. After multivariate analysis, impaired renal function (OR 1.99; CI 95% 1.74-5.41; p=0.046) and ostial disease (OR 2.88; CI 95% 1.04-7.38; p=0.041) were found to be predictors of MACE. Impaired renal function also predicted TLR (OR 2.43; CI 95% 1.17-5.02; p=0.017).

Conclusion: FFR-guided revascularisation deferral is safe in the majority of anatomically prognostic disease. However, further evaluation is required in the risk stratification of those patients with ostial disease and renal disease. Registered on ClinicalTrials, NCT02590926.

INTRODUCTION

Percutaneous coronary intervention (PCI) is a frequently adopted revascularization strategy for patients with coronary artery disease (CAD) [1,2]. Its acceptance with high-risk cases is also increasing, with improved available tools [3-5]. However, recent focus has been drawn to revascularisation deferral in non-ischaemic lesions, owing to the introduction of Fractional Flow Reserve.

The technique involves the use of a pressure wire, and its implementation has resulted in significant changes to clinical practice, namely reduction in unnecessary PCI, as demonstrated in DEFER [6] and FAME [7]. And interestingly, reduction in MACE rates as demonstrated in FAME 2 [8].

Unsurprisingly therefore, both the ESC [9] and ACC-AHA [10] guidelines reflect this evidence, by recommending FFR-guided PCI in stable patients. This includes those with anatomically prognostic disease: left main and proximal LAD disease, severe multivessel disease with heart failure, and those with a single remaining vessel. However, on closer interrogation, evidence specifically for the use of FFR in these challenging cases is limited. In both DEFER and FAME, patients with LM disease were in fact excluded [6,7]. And the mean ejection fraction was above normal. FAME 2 did have broader enrolment criteria, but still only 56 pateints had an EF < 50%. And despite 276 pateints having at least one significant lesion in the proximal or mid left anterior descending artery, no subgroup analyses were conducted for these patients [8]. Thus, despite the many papers quoted in the ESC guidelines on revascularisation [8,11-19], doubts still remain over the prognostic value of FFR guided deferral in anatomically significant disease.

Due to the relevant impact of these coronary lesions [20,21], which may also potentially be treated with surgery [22], it appears mandatory to evaluate data on outcomes of those deferred for revascularisation as per FFR in this setting.

The aim of the FACE study (Safety of FFR-guided Revascularisation Deferral in Anatomically Prognostic Disease) therefore, is to investigate the outcomes of patients with intermediate stenoses (i.e. between 50% and 90% - as defined by ESC) in anatomically prognostic sites [9], deferred for revascularisation.

METHODS

Study design and population. This is a multicentre, prospective, observational study, including patients with intermediate stenoses on coronary angiography, with a negative FFR (>0.80).

Inclusion and exclusion criteria. In each centre, (see web appendix) all patients between 18 and 90 years of age undergoing coronary angiography from September 2014 to May 2016, were consecutively enrolled if showing at least one of the following features:

- An angiographic stenosis of more than 50% and less than 90% in the left main stem (with an FFR > 0.8);
- Any stenosis of more than 50% and less than 90% of the proximal anterior descending artery (with an FFR > 0.8);
- Two or three vessel disease with a stenosis of more than 50% and less than 90%, and a left ventricular ejection fraction less than 40% (with an FFR > 0.8);
- Single remaining patent coronary artery with stenosis >50% and less than 90% (with an FFR > 0.8).

Exclusion criteria were: severe aortic stenosis, acute ST-segment elevation MI at presentation, or in the previous 5 days, cardiogenic shock, on going pregnancy, the presence of abundant collaterals which can affect FFR measurements and the presence of severe left ventricular hypertrophy.

Procedural details and FFR measurement. During standard coronary angiography, a coronary pressure wire was advanced and equalised with the pressure sensor at the tip of

the guiding catheter. Hereafter, the pressure wire was advanced into the coronary artery, sufficiently distal to the lesion under investigation. Maximal coronary hyperaemia was induced with the central venous infusion of adenosine (140-180 μg/kg per minute), or through intracoronary injections (40-80 μg), according to centre's and operator's preference. Once hyperaemia was achieved, FFR was calculated as the ratio of the mean distal coronary pressure obtained with the guidewire, divided by the mean aortic pressure obtained with the guiding catheter. If the FFR was less than or equal to 0.80, PCI of the respective stenosis was performed with either a bare metal stent, drug-eluting stent, or bioreabsorbable scaffold, as per physician choice. If the FFR was > 0.8, revascularisation was deferred, and the patient enrolled into the trial. All patients received optimal medical therapy for secondary prevention of coronary artery disease, including aspirin, beta-blockers, statins, and a P2Y12 inhibitor if necessary.

Clinical and procedural data collection. All clinical (baseline risk factors and clinical presentation) and interventional features (access, angiographic features and vessel type) were recorded on a pre-specified online website (http://www.cardiogroup.org/FACE/index.php?cat=home). Random checks were done to assess inserted data.

Outcomes. The primary end-point of the study was the occurrence of MACE (a composite of death, myocardial infarction [AMI], and unplanned target lesion revascularization) during the follow-up. The secondary end-points were the individual components of MACE, the occurrence of cardiac death (death for which a clear non cardiac cause could not be demonstrated) and target lesion revascularization (TLR), defined as revascularisation of lesions initially deferred during index procedure with FFR > 0.8. Events were assessed at each site and verified by source documentation (cardiac enzymes, electrocardiogram changes, PCI reports, and cause of death). A committee to verify checked all adverse events at follow up. Subgroup analyses were performed for the type of clinical

presentation (stable vs. ACS), localization of lesions (ostial vs. non ostial excluding left main) and for each individual inclusion criteria.

Clinical follow-up. After study enrolment, visits were performed at 6, 12 and 18 months. Phone calls accounted for follow up in those patients unable to attend for a clinical visit.

Statistical analysis. All statistical analyses were performed using SPSS version 21 (SPSS Inc. Chicago, IL, USA). Continuous variables are expressed as the mean ± standard deviation, and categorical variables are expressed as numbers and percentages. Continuous variables were compared using the Student t test and the ANOVA test. Categorical or dichotomous variables were compared with the chi-square test. Multivariate models were constructed using Cox proportional hazards analysis to investigate predictors of MACE and of TLR using all variables clinically relevant [23].

The FAME 2 trial showed a MACE rate of approximately 18% after 2 years [24]. Therefore in accordance with the work of Peduzzi et al [25], at least 280 patients were needed to test in a multivariate model of 4 variables (ostial disease, chronic kidney disease, ACS at presentation and diabetes).

Ethics statement. The study was approved by the local ethics committees, and registered on ClinicalTrials.gov, number NCT02590926. Each enrolled patient signed to provide informed consent.

RESULTS

Patients and angiographic characteristics

The FACE registry enrolled 292 patients, with a total of 297 coronary stenoses assessed and deferred for invasive revascularisation (owing to an FFR > 0.80).

The clinical characteristics of this patient group have been summarised in table 1. The majority were male (74%), and had an average age of 68 ± 10 years. Cardiovascular risk factors were unsurprisingly prevalent, and 29% (84 patients) had moderately impaired renal function (eGFR < 60 mL/min). Mean ejection fraction was 53% ± 10%, but 40 patients had an EF ≤40%. Of these, 4 had a stenosis in the left main, 26 in the proximal LAD, 9 in two vessels, and 1 in their last remaining vessel.

Stable CAD (70%) was the most frequent indication for coronary angiography, whilst ACS accounted for the remaining 30%.

The majority of patients included in the FACE trial had a proximal LAD stenosis (78%, 228 see figure 1 in the Web Appendix). One patient who was enrolled as a deferred left main case had bifurcation disease (Medina 1,1,1). FFR was obtained for both braches, and followed up accordingly. Another deferred left main case was enrolled and analysed as part of a last remaining vessel. (Full angiographic characteristics are reported in table 3 in the web appendix).

All patients received adenosine as the hyperaemic agent. Administration was as per operator preference, with 80% (234 patients) receiving intravenous adenosine, and the others intracoronary (table 3 in the web appendix).

Clinical outcome

Mean follow-up was 22.2±11 months. A total of 283 (96.2%) patients completed the study, as 9 were lost to follow-up. Thirthy-three patients received PCI and a single stent implantation for a single critical stenosis on a vessel different to the one that was investigated with FFR, whilst 6 patients received two different angioplasty with stenting during the same PCI procedure. Event-free survival at follow-up was 88.5% (figure 1). The one-year incidence of MACE was 5%, of AMI was 0.8%, while incidences of deferred vessel need for revascularization was 2.7%.

During the study period, the primary end-point (MACE) occurred in 11.6% of patients (n= 33). Death occurred in 11 patients (3.8%), but only 5 were from cardiovascular causes (1.8%), one of them due to AMI. Six patients suffered AMI (2.1%). And 17 patients (6%) needed revascularization of the previously deferred stenosis under investigation owing to symptoms, despite medical therapy. In 8 patients the stenosis was judged to have progressed on angiography alone, or with IVUS/OCT. 2 patients had suffered an NSTE-ACS and one an NSTEMI. For the remaining 6 patients, a positive stress test was the indication for repeat angiography and revascularisation. Of these patients, 11 underwent PCI and 6 were treated with bypass surgery (table 2).

Subgroup analysis.

No statistically significant differences were noted in the event rates between stable patients and those presenting with an ACS (MACE: 10.8% vs 12.4%, p=0.71). Significant differences in MACE (17.5% vs 9%, p=0.04) and AMI (5% vs 0.9%, p=0.029) were noted however for those with reduced eGFR. Similarly, rates of MACE (26.5% vs 8.2%, p=0.001) and AMI (8.2% vs 0.8%, p=0,001), but also CV death (6.4% vs 0.9%, p=0.009) and target lesion revascularization (14.3% vs 4.1%, p=0.002) were higher in patients with ostial coronary disease (i.e. ostial stenoses excluding LM involvement vs disease elsewhere). No differences in outcomes were noted between patients in whom FFR was derived through adenosine intra venous injection and intra coronary injection.

Outcomes according to the type of challenging lesion is displayed in table 2 of the Web appendix. The event rates were higher in patients with LM involvement, with MACE at 1 and 2 years being 6.4% and 30.3% respectively, driven mainly by AMI and TLR (table 6 in the web appendix).

Independent determinants of outcomes

At multivariate analysis, chronic kidney disease (CKD, i.e. eGFR<60 mL/min) (OR 1.99; CI 95% 1.74-5.41; p=0.046) and ostial stenosis (OR 2.88; CI 95% 1.04-7.38; p=0.041) were predictors of MACE (figure 2, Table 4 and 5 in the web appendix). The impact on MACE is also well visualised on Kaplan-Meier analysis (figure 1).

However, only impaired renal function was found to be a significant predictor of target lesion revascularisation (OR 2.43; CI 95% 1.17-5.02; p=0.017).

DISCUSSION

In our study we examined the incidence and predictors of adverse events following FFR-guided revascularisation deferral, in anatomically prognostic disease. To our knowledge, this is the first registry specifically designed to investigate this subset of patients as a whole.

Our findings conclude:

- Deferral of revascularisation with an FFR > 0.8 in anatomically prognostic disease is on the whole safe, but with a few caveats.
- Caution must be taken with left main stem disease, ostial disease and CKD, as FFR alone in these circumstances may not be sufficient for risk stratification.

Based on the event rates noted in our study, it would appear FFR guided revascularisation deferral in this patient population is safe. The 1-year incidence of MACE, AMI and need for revascularisation were 5%, 0.8% and 2.7% respectively. At a mean of 2.2 years, the incidence was 11.6%, 2.1%, and 5.9%. In fact, these event rates are similar to those obtained in the FFR validation trials: Namely the registry cohort of FAME 2 (3% MACE, 1.8% AMI, 3.6% vessel revascularisation) [8]; and the CVIT-DEFER Registry (3.2% MACE and 3.15% vessel revascularisation) at 1 year. [26].

However, firm conclusions based on the results of our study alone, could be flawed, owing to unequal representation of all the anatomically prognostic subgroups. 78% of our cohort had a proximal LAD lesion, whilst only 4% had multi-vessel disease with EF < 40%. This reflects the challenges of recruitment in this study, and would of course be a limitation, affecting power. However, much can be learnt through analysis of the individual subgroups, and cautious comparisons thereof.

In the case of proximal LAD disease, the rates of MACE, MI and vessel revascularisation were 8.3%, 0.05% and 5.8% respectively, at two years. These interestingly are lower than the overall event rates, and may suggest safety of an FFR guided approach in this subgroup. This certainly would be supported by Muller et al, whose trial included 564 deferred proximal LAD lesions, without adverse MACE over a 5-year follow-up [27].

But this suggests a higher signal in the other subgroup of patients, which was found in the deferred left main cohort. The rate of MACE at 1 and 2 years was 6.4% and 30.3% respectively. These findings are significant, and especially important considering that many trials from which the guidelines were devised excluded these patients. However the small sample size is a limitation, which unsurprisingly is also a problem with the already published trials in this area [28].

A meta-analysis aiming to improve power has however drawn these studies together [29]. It compromises 525 patients, with 308 deferred lesions. During a mean follow-up of 26.5±4 months, the primary end-point (a composite of death, myocardial infarction and any revascularization) occurred in 19.4%, and all cause death in 4.5% (in the deferred arm). Interestingly however, despite the high event rates, no statistically significant difference was noted between the treated group, where 94% received CABG. There was also no statistical difference in the rate of non-fatal myocardial infarction (OR: 1.23, 95% CI 0.34-

4.48; p=0.76). But a significant increase was noted in the need for revascularisation (OR: 3.24, 95% CI: 1.51-6.93; p=0.002).

In our study, need for revascularisation was a driver, but we also noted a higher incidence of death: 9.1%. This is hard to ignore, but our left main cohort were more pre-morbid in comparison to the randomised trial by Hamilos et al, with a greater number of previous myocardial infarctions and PCI. But also had a higher coronary artery disease burden, with less isolated unprotected left main disease, and a high proportion of concomitant right coronary artery disease, which previously was associated with a poorer outcome [29,30]. This may well explain in part the disparity of results. However, it seems cautious risk stratification ought to be devoted to left main cases, and FFR alone may not suffice.

Other noteworthy findings from our study include 2 other patient characteristics associated with a worse outcome: the impaired kidney function and the presence of ostial lesions. As regards the first, perhaps its association with microvascular disease [31] plays an important role. But our study found a statistically significant higher event rate in this patient cohort. This result may be related to quicker disease progression in such patients. But interestingly, the FREAK registry [32] noted higher FFR values in patients with low eGFR, leading to the suggestion of a higher rate of false negative FFR. The presence of impaired kidney function might lead more frequently to higher FFR values, and may explain the significantly higher event rates seen in our study.

The other important patient characteristic associated with a worse outcome in our study includes ostial lesions. We postulate whether this may be owing to the large amount of myocardium subtended, and the resultant greater risk of ischaemia. But the challenging procedure itself in these cases may in part play a role [33]. During FFR measurement, the guiding catheter in the coronary ostium can result in iatrogenic stenosis, which of course will vary according to the size of the catheter and artery. In the absence of ostial disease,

the presence of the guide catheter does not induce a pressure gradient. However, when flow increases over the ostial segment during hyperemia, the presence of the guide catheter may induce a pressure drop. This can therefore result in an artificial decrease in proximal pressure (Pa), and an increase in post-stenotic distal pressure (Pd). As such, the value of FFR can be overestimated, and thus in this setting, it is not reliable. Despite proven for LM and RCA ostial stenoses [34], some authors suggest how it could also be possible for ostial LAD lesions [33], and this fact could explain some of the events in the LAD group. This is obviously a hypothesis, and should be directly verified with an ad hoc study, but we suggest in the interim, disengaging the guide catheter from the coronary ostium when evaluating left main stem and ostial lesions to note any changes in FFR, so as not to miss a functionally significant stenosis. For similar reasons reaching complete and adequate hyperaemia is mandatory when evaluating such challenging lesions, and if doubts still persist, IVUS study should be performed.

Based on our data, the ESC guidelines on FFR guided revascularisation of anatomically prognostic disease is on the whole safe. We do not doubt that by in large their prognostic impact comes from ischaemia induction. And proving limited ischaemia will confer prognostic advantage. These lesions subtend a large area of myocardium, and it was important to assess this cohort, as a large proportion of patients in the FAME and FAME 2 trials had lesions distal in the coronary tree, and likely to carry limited prognostic impact.

LIMITATIONS

This is a prospective registry specifically designed to address a particular population among the broad field of coronary artery disease. Enrolment was intended to include a specific subset of lesions. However many patients were enrolled from the cath lab after

treatment of their culprit, owing to presence of bystander disease. It was this bystander disease that was investigated in the study, provided inclusion criteria were met. Thus not all patients enrolled were in a similar stable state, and coronary artery disease burden. Further, to that effect, equal recruitment of the prognostic lesions was not achieved, leading to varying subgroup sizes.

Another limitation is the lack of information and therefore consistency with regard to target lesion revascularisation. This was left up to the physician, and it was not fully known in what context, and with what investigations (including repeat FFR, or additional functional test) this decision was made.

Lack of control group is a limit but this is due to the retrospective nature of the study focused on the outcome of deferred patients with negative FFR, therefore patients with negative FFR who eventually received stenting for other reasons were not enrolled. Likewise, patients with positive FFR were promptly treated due to the high anatomical risk.

Lastly, it is important to note that ESC recommendations for the use of FFR-guided deferral apply only to asymptomatic patients. Our patients in fact were largely symptomatic, with over 86% admitted for ACS or angina (see table 1 in the web appendix). Thus, our data would support guidelines. But if patients are symptomatic with concomitant left main stem disease, ostial stenosis and impaired renal function, FFR should be used with caution, and not the sole risk stratification marker.

CONCLUSION

Guidelines advocate the use of FFR in asymptomatic patients with intermediate coronary disease in anatomically prognostic sites. This is for the purpose of risk stratification, and to guide revascularisation. Our data by in large would support this, but very close attention and further risk stratification should be obtained for those patients with

left main disease, ostial stenoses, and impaired renal function. In these cases, a statistically significant higher event rate was noted, despite a negative FFR.

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FIGURES

Figure 1: Kaplan-Meier curves of event-free survival at follow-up, with significant differences between patients with or without impaired kidney function and between patients with or without ostial stenosis. No difference is shown according to clinical presentation.

Figure 2: predictors of MACE and TLR at multivariate analysis.

TABLES

Table 1. Characteristics of the patient with a challenging stenosis with FFR >0.80 and in whom stenting was deferred because of that. Data are presented as mean ± standard deviation or as total number with percentage referred to total population of 292 patients into brackets.

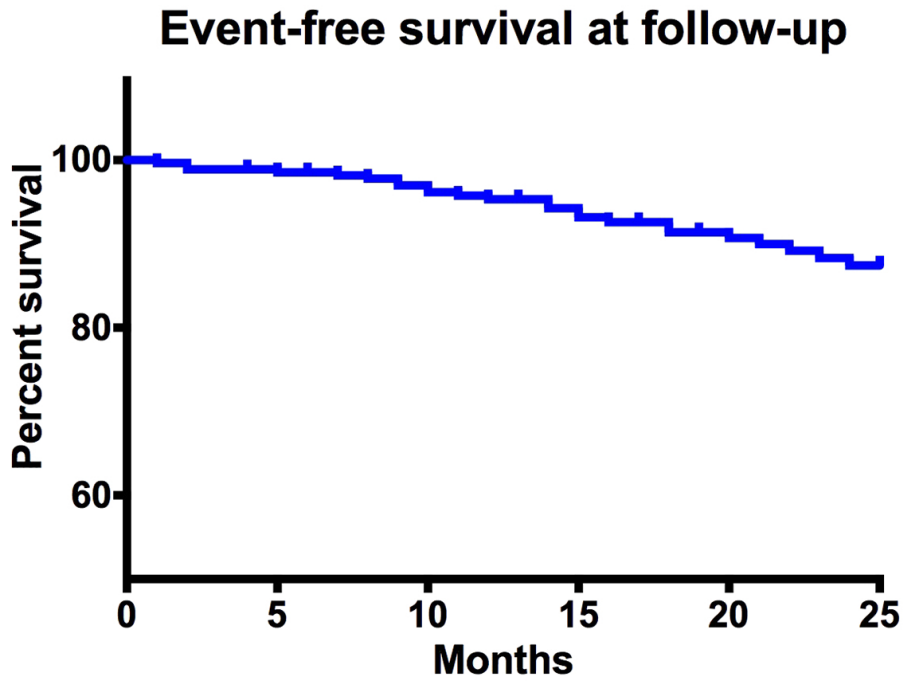
	n. of patients = 292
Age (years)	68±10
female sex	75 (25.7%)
hypertension	212 (73%)
dyslipidemia	198 (68%)
NIDDM	88 (27%)
IDDM	9 (3%)
active smoker	103 (35%)
previous smoker	7 (2.5%)
Heigth (cm)	168±9
Weigth (kg)	79±13
eGFR	79±24 ml/min
eGFR < 60 mL/min	84 (29%)
EF %	53±10
Previous AMI	98 (33%)
ACS in the last 12 month	28 (9.6%)
Previous PCI	138 (47%)
Previous CABG	4 (1.4%)

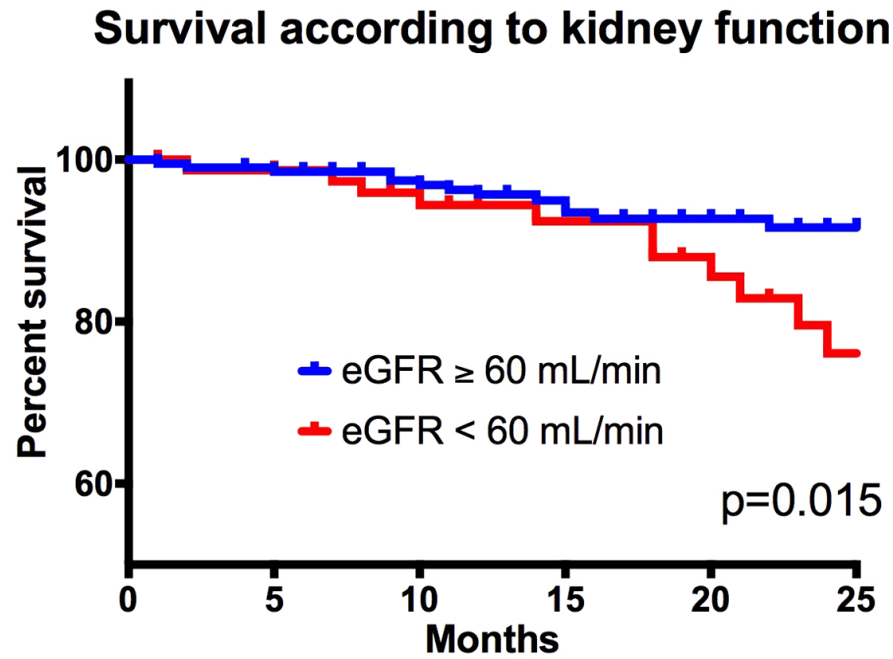
Table 2. Event rates at 1 year after enrolment and total follow-up (mean follow up 22.2±15 months, range 12-69 months). Numbers are number of events with percentage into brackets. MACE: major adverse cardiovascular events. CV: cardiovascular. AMI: acute myocardial infarction. TLR: target lesion revascularization. PCI: percutaneous coronary intervention. CABG: coronary artery bypass grafts.

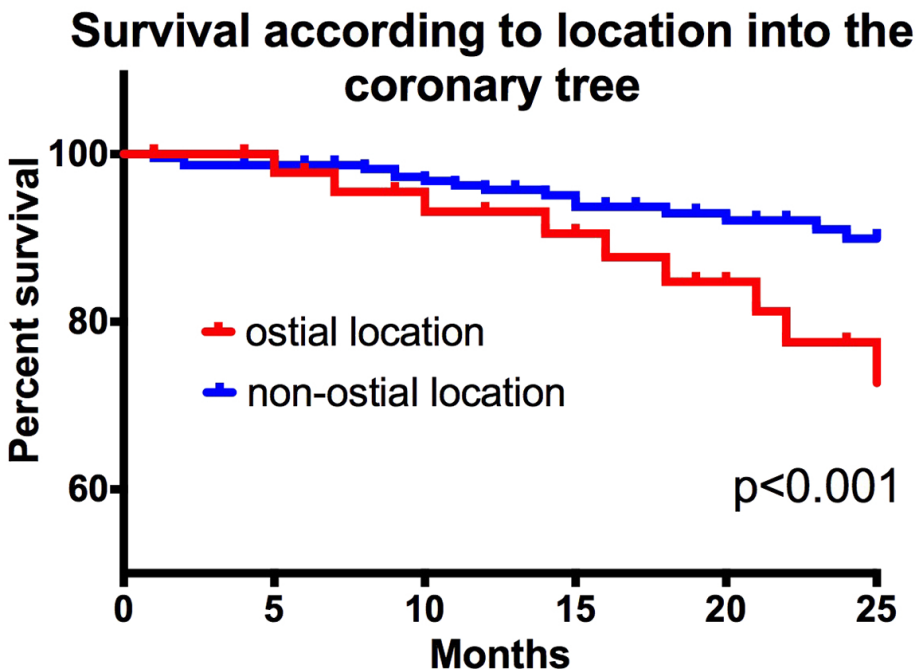
	After 1 year		Total occurrence of events	
MACE	13	(5%)	33	(11.6%)
Death	4	(1.5%)	11	(3.8%)
CV Death	2	(0.8%)	5	(1.8%)
AMI	2	(0.8%)	6	(2.1%)
TLR	7	(2.7%)	17	(5.9%)
PCI	4	(1.6%)	11	(3.8%)
CABG	3	(1.1%)	6	(2.1%)

Highlights

- The registry of stenosis carrying high prognostic impact included 292 patients with 297 deferred stenosis.
- FFR-guided revascularisation deferral is safe in the majority of anatomically prognostic disease: after 1-year, the primary endpoint occurred in 5% of patients, mainly driven by TLR (2.7%).
- However, further evaluation is required in the risk stratification of those patients with ostial disease and renal disease.


Event-free survival at follow-up
Percent survival
100
80
60
0
5
10
15
20
25
Months


Survival according to kidney function
Percent survival
100
80
60
eGFR ≥ 60 mL/min
eGFR < 60 mL/min
p=0.015
0
5
10
15
20
25
Months


Survival according to location into the coronary tree
Percent survival
100
80
60
ostial location
non-ostial location
p<0.001
0
5
10
15
20
25
Months

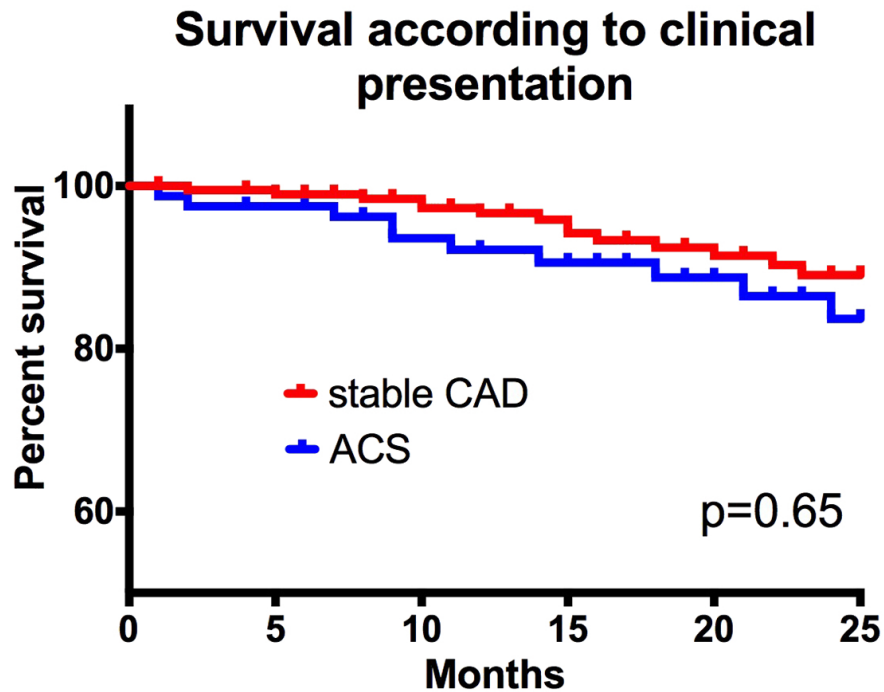
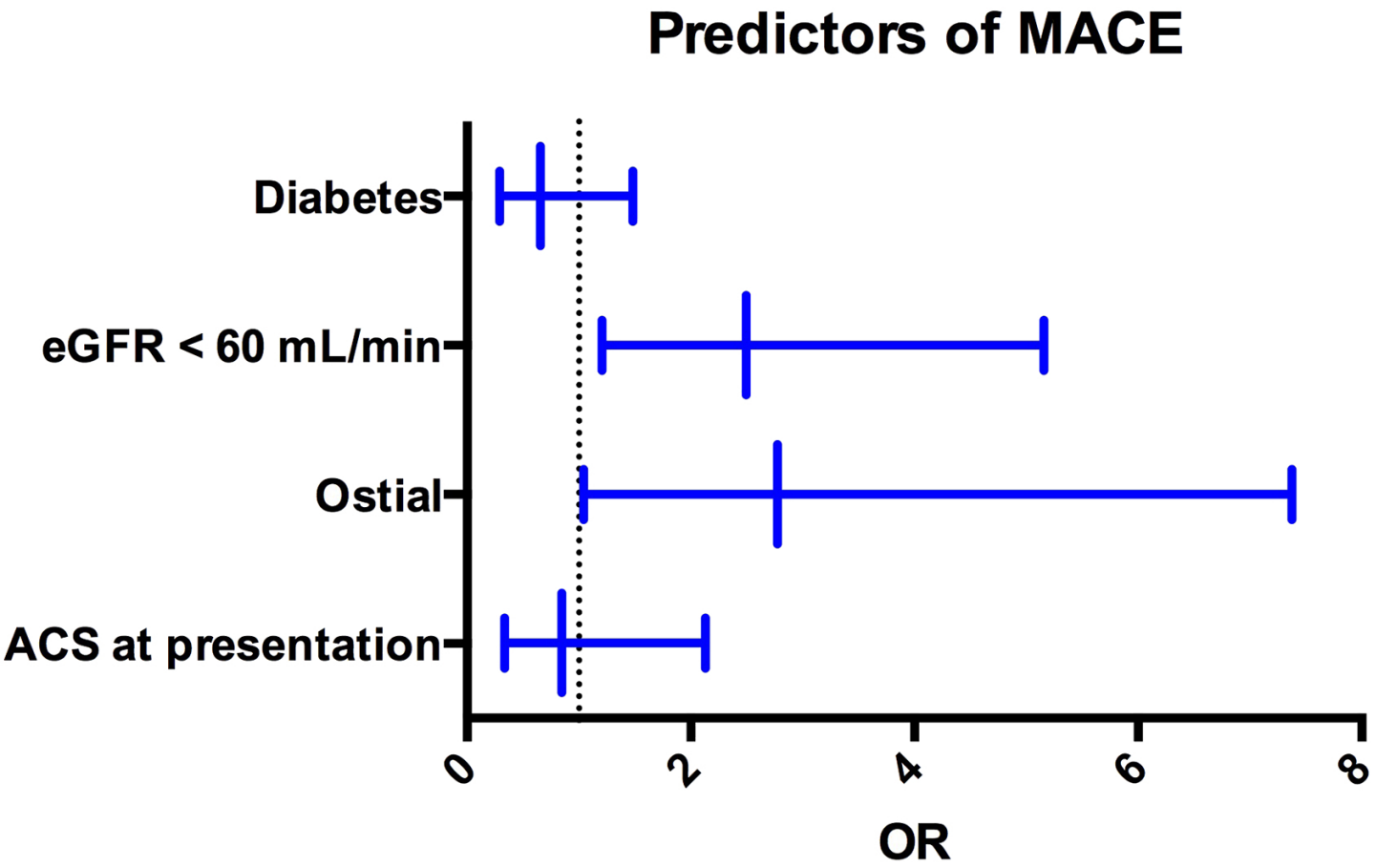

Survival according to clinical presentation
Percent survival
100
80
60
stable CAD
ACS
p=0.65
0
5
10
15
20
25
Months

Figure 1


Predictors of MACE
Diabetes
eGFR < 60 mL/min
Ostial
ACS at presentation
0
2
4
6
8
OR

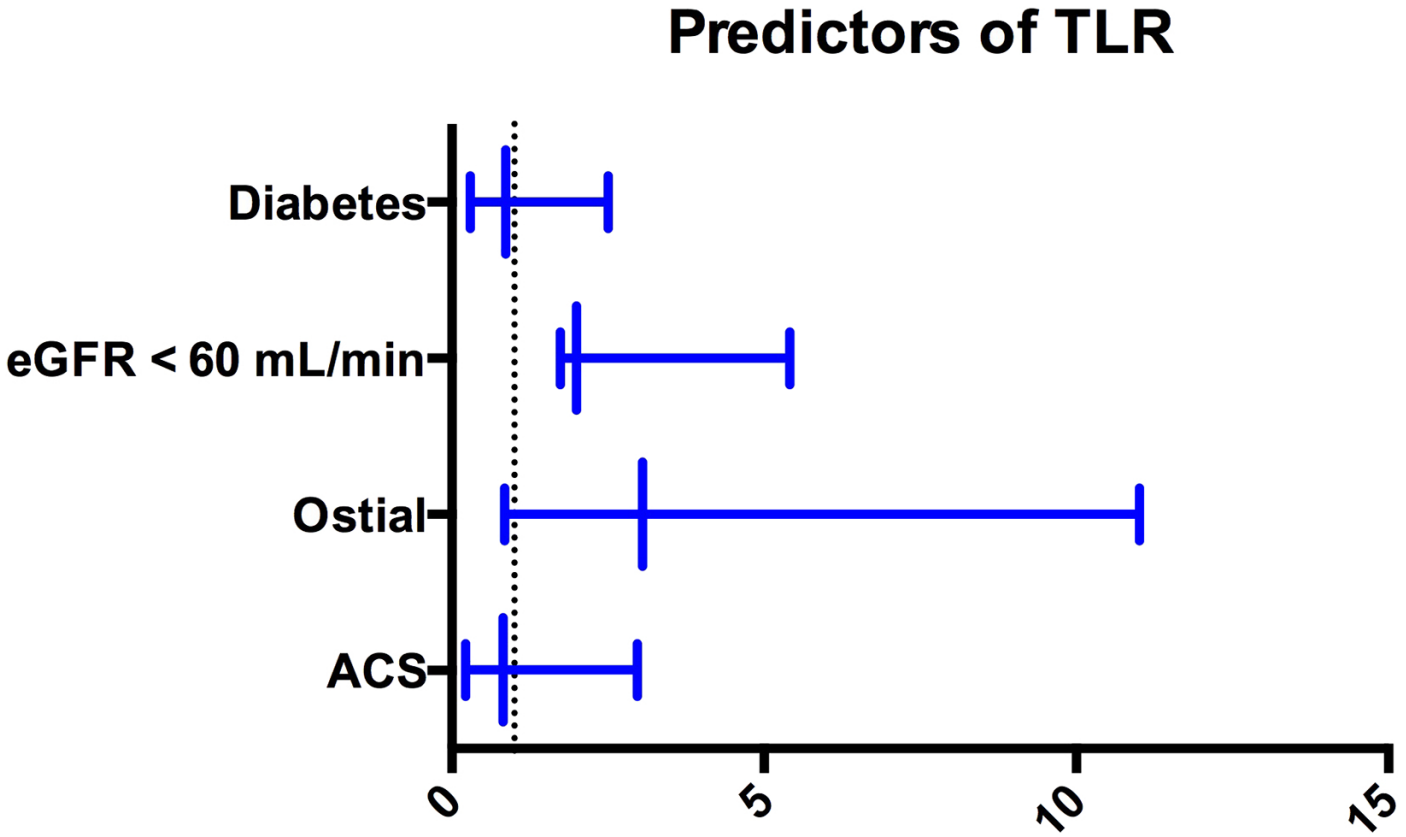

Predictors of TLR
Diabetes
eGFR < 60 mL/min
Ostial
ACS
0
5
10
15

Figure 2