



FUunctional **T**esting **U**nderlying **RE**vascularization The **FUTURE** trial

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Background (I)

- At least one-third of significant ($>50\%$ diameter reduction) anatomic coronary stenosis display a $\text{FFR} > 0.80$ ¹
- In registries, FFR modifies PCI revascularization strategy :
 - in nearly 4 /10 patients ²
 - in nearly 50% of patients even with prior non-invasive testing ²
- One third of multivessel disease patients significantly decrease their SYNTAX score when only ≤ 0.80 FFR arteries are taken into account ³

¹ Tonino et al. NEJM 2009;360:213

² Van Belle et al. Circulation 2014;129:173

³ Nam et al. JACC 2011;58:1211

Background (II)



- FFR is recommended to identify haemodynamically relevant coronary lesions when evidence of ischaemia is not available (2014 ESC/EACTS guidelines: level IA)¹
- FFR is recommended for guiding PCI in multivessel disease patients (IIaB)¹
- FFR has equal value to anatomy (>50% stenosis LM, >70% stenosis non LM CAD) without firmer statement for strategy (2014 ACC/AHA guidelines)²

Whether FFR helps to decide among different treatment strategies (PCI or CABG or medical treatment only) remains unknown

¹ Windecker et al. *EHJ* 2014;35:2541

² Fihn et al. *Circulation* 2014;130:1749



FUTURE Study Hypothesis

In multivessel disease patients, does FFR help to guide treatment strategy (PCI or CABG or medical treatment only) and thereby improve clinical prognosis compared to traditional management ?

FUTURE Primary Composite Endpoint, at one year

- *All cause mortality*
- *Myocardial Infarction*
- *Repeat revascularization*
- *Stroke*



Study design (I)

Patient with stable or stabilized angina
Multivessel-disease (>50% stenosis) including LAD

Randomisation 1:1
(diabetes stratification)

FFR-guided

Angio-guided

FFR on all target lesions

*non-invasive tests
allowed*

Only lesions with $FFR \leq 0.80$
are included in stratification

All lesions with $\%S > 50$
are included in stratification

PCI
+ OMT

Surgery
+ OMT

OMT only

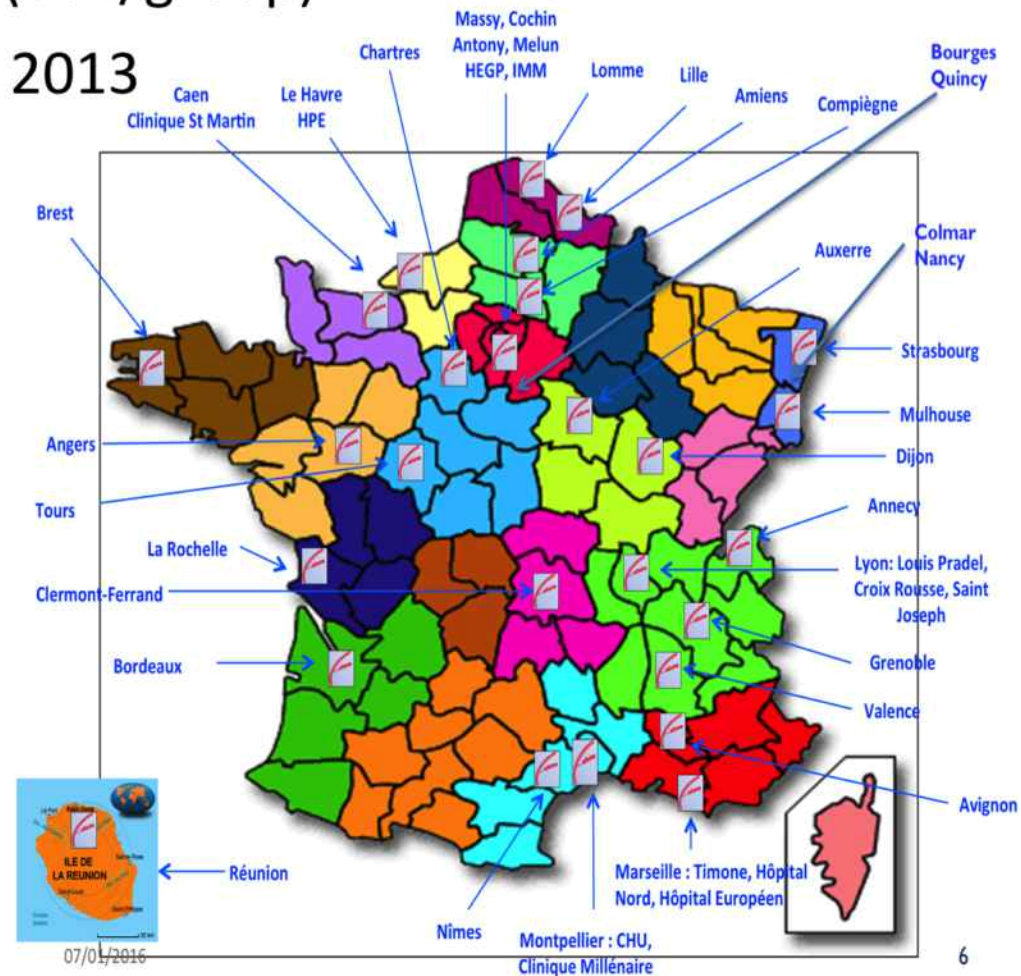
PCI
+ OMT

Surgery
+ OMT

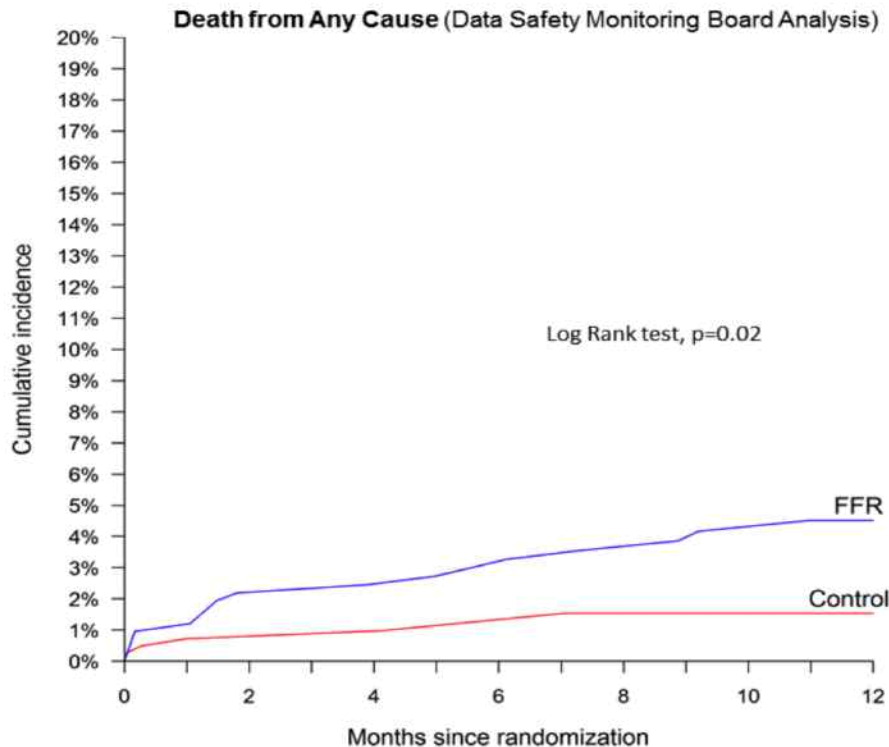
OMT only

Study design (II)

- Multicenter, randomized, open-label, controlled study in 31 centers in France.
- Superiority design for 30% RRR MACE at 1 year in the FFR group
- 1721 patients to be recruited (864/group)
- First randomisation, May 27th 2013



DSMB: unexpected excess mortality in FFR group compared to control during safety analysis



Over $n = 836$ first patients

All-cause deaths at 12 months($n=24$):

- control : 7 (2%)

- FFR : 17 (4%)

P=0.02

Cardiovascular death :

72% of all deaths

Sponsor and Steering Committee decided to follow DSMB recommendation and stopped recruitment at $n=936$ patients

Results and follow-up are presented at end of monitoring visits, June 20th 2016

Demographics



Variable	Control group (n=469)	FFR group (n=465)	P-value
Age (yr)	66±11	65±10	0.16
Male (%)	386/469 (82)	399/465 (86)	0.14
BMI	27±5	28±5	0.07
Current smoking (%)	118/469 (26)	110/465 (24)	0.78
HTA (%)	285/469 (61)	269/465 (58)	0.34
Dyslipidemia (%)	288/469 (61)	278/465 (60)	0.58
Diabetes (%)	148/469 (32)	146/465 (31)	0.96
Renal failure (%)	182/469 (39)	191/465 (41)	0.48
History of MI (%)	100/469 (21)	93/465 (20)	0.64
History of PCI (%)	127/469 (27)	117/465 (25)	0.52
History of stroke (%)	27/469 (6)	13/465 (3)	0.03

Clinical presentation



Variable	Control group (n=469)	FFR group (n=465)	P-value
ACS (%)	213/467 (46)	217/464 (47)	0.76
<i>Including STEMI (%)</i>	88/467 (19)	91/464 (20)	0.77
Stable angina (%)	105/467 (23)	88/464 (19)	0.19
Silent Ischemia (%)	149/467 (32)	159/464 (34)	0.44
CCS ≥ 2 (%) ¶	200/469 (43)	178/465 (39)	0.19
Previous NI Test (%)	196/465 (42)	176/461 (38)	0.24
<i>% positive test (%)</i>	157/196 (80)	141/176 (80)	0.40
LVEF %	56 $\pm$ 11 (343)	55 $\pm$ 12 (336)	0.56

Angiographic findings



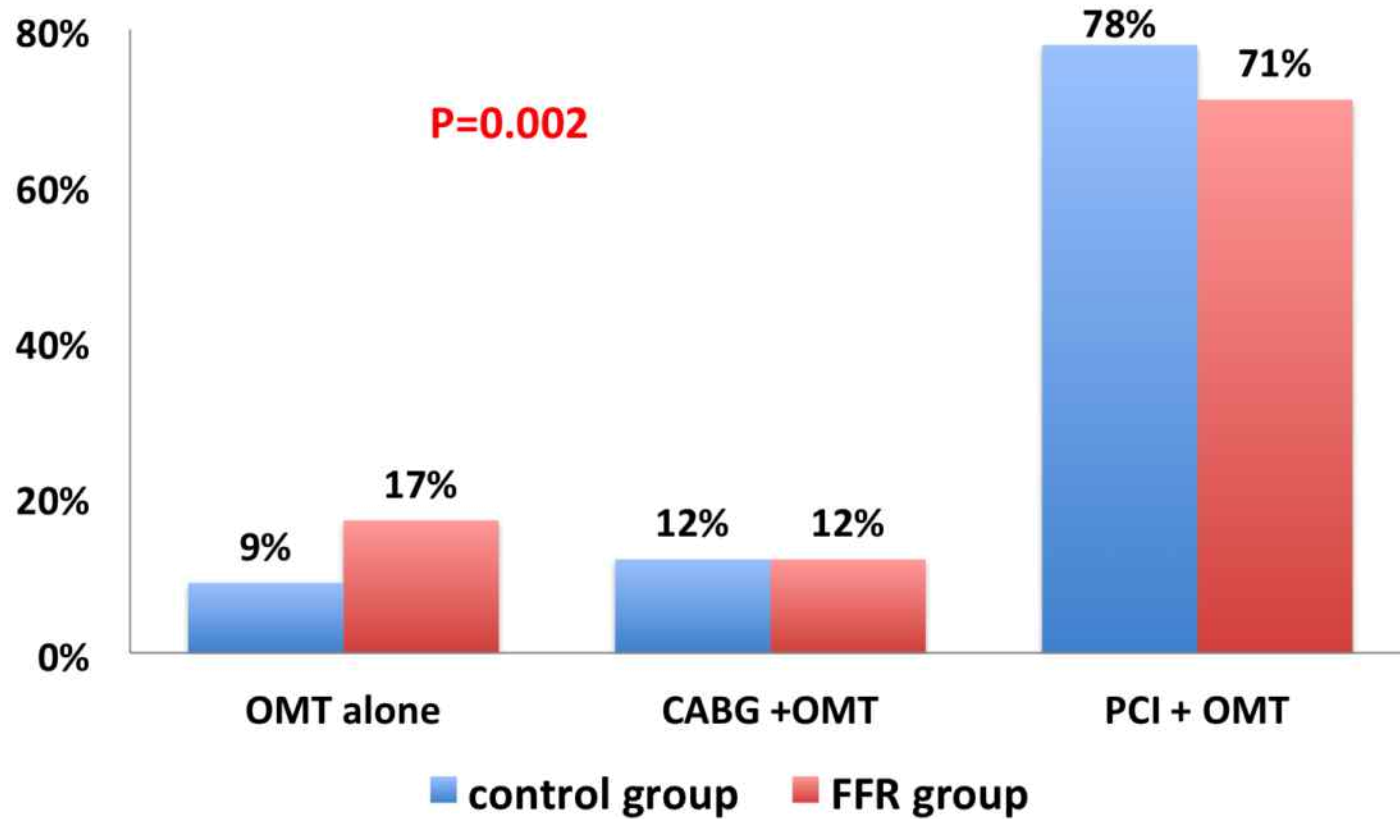
Variable	Control group (n=469)	FFR group (n=465)	P-value
2-vessel disease (%)	225/469 (48)	201/465 (43)	0.34
3-vessel disease (%)	229/469 (49)	251/465 (54)	
LAD involved (%)	453/469 (97)	448/465 (96)	0.84
Left main (%)	51/469 (11)	59/465 (13)	0.39
SYNTAX score	18±8 (442)	19±8 (446)	0.15
Nb FFR measures	NA	1141	
FFR-related complications (%)	NA	4 (0.8)	
Nb FFR / patient	NA	2.4±0.9	
Mean FFR	NA	0.77±0.13	
FFR>0.80 Lesions (%)	NA	474/1103 (43)	

Therapeutic management: Optimal Medical Treatment



Variable	Control group	FFR group	P-value
Aspirin (%)	440/469 (94)	446/465 (96)	0.15
Other antiplatelet (%)	409/469 (87)	389/465 (84)	0.12
Beta-blocker (%)	383/469 (82)	388/465 (83)	0.47
Statin (%)	419/469 (89)	425/465 (91)	0.29
ACE inhibitor-ARBs (%)	353/469 (75)	349/465 (75)	0.94
Insulin (%)	39/469 (8)	59/465 (13)	0.03
Oral Antidiabetic (%)	110/469 (23)	87/465 (19)	0.07

Therapeutic management



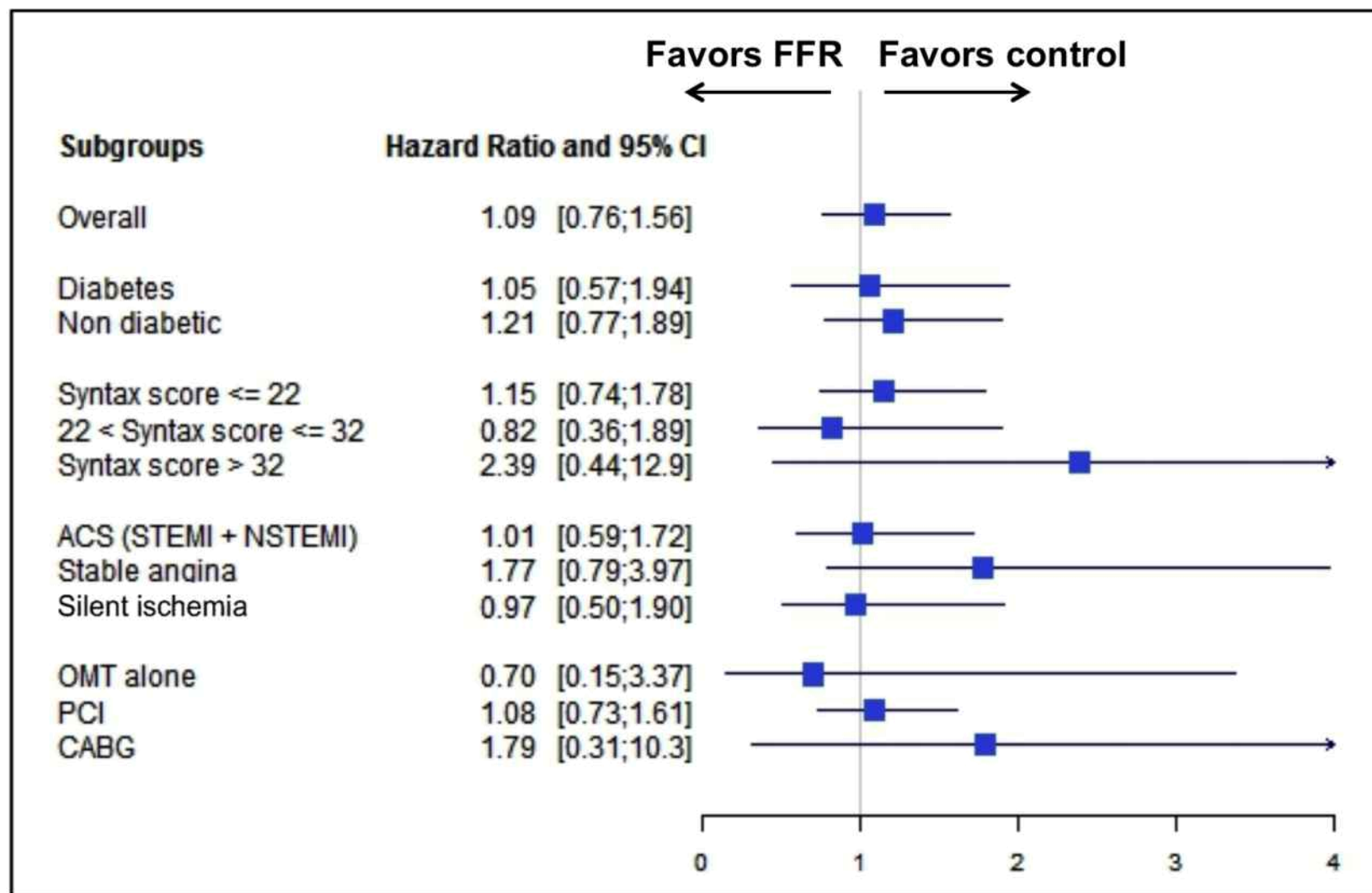


Clinical Events at One Year*

Variable	Control group (n=398)*	FFR Group (n=399)*	HR (95%CI)	P value
Death from any cause (%)	8 (1.8)	17 (3.9)	1.98 (0.85–4.60)	0.07
Cardiovascular death (%)	6 (1.3)	12 (2.7)	1.88 (0.70-5.01)	0.16
MACE(%)	58 (13.2)	65 (15.1)	1.09 (0.76-1.56)	0.63
Myocardial infarction (%)	24 (5.3)	29 (6.5)	1.23 (0.71-2.11)	0.46
Stroke (%)	4 (0.9)	2 (0.4)	0.48 (0.09-2.62)	0.40
Repeat revascularization (%)	33 (7.6)	32 (7.6)	0.97 (0.60-1.58)	0.91
EQ-5D – visual analogue scale	71±18	70±17		0.51

*only for patients having reached the one-year endpoint

Pre-specified subgroups analysis



Summary



Our hypothesis was that FFR might help improve clinical outcome through an optimal distribution of patients toward PCI, CABG or medical treatment only

- The FUTURE trial was prematurely halted due to an excess of the 12-month all-cause mortality ($p=0.02$) in the group of patients with FFR assessment (DSMB evaluation on $n=836$ pts)
- As of today, the follow-up of $n=797$ pts (out of 941 recruited) indicates a persistent but non significant ($p=0.07$) difference in the 12-month all-cause mortality
- The FUTURE trial does not demonstrate any improvement in the composite endpoint after more than 50% of the anticipated recruitment suggesting futility to pursue the trial.

Conclusion – Open Questions



✓ Major Limitations:

- Lack of statistical power to conclude on the primary endpoint
- Absence of significant difference in all-cause mortality ($p=0.07$)

✓ What should we do ?

- **Ignore the warning** (*« the DSMB unnecessarily terminated this trial based on a spurious mortality signal and very little can be learned from this trial »*)?
- **Be cautious:** examine whether some conditions (e.g. Syntax score) are key for a more thorough FFR-based decision of therapeutic strategy in this high-risk population ?