FUnctional Testing Underlying REvascularization
The FUTURE trial

Gilles Rioufol, Nathan Mewton, Muriel Rabilloud, Bernadette Vaz, François Roubille, Thibault Perret, Pascal Motreff, Michel Ovize, Gérard Finet, on behalf of the FUTURE trial investigators, France

NCT01881555

Inserm
Institut national
de la santé et de la recherche médicale
INSERM U1060

CarMeN Lyon

Background (I)

- At least one-third of significant (>50% diameter reduction) anatomic coronary stenosis display a 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 signficantly 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]

Wether 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*

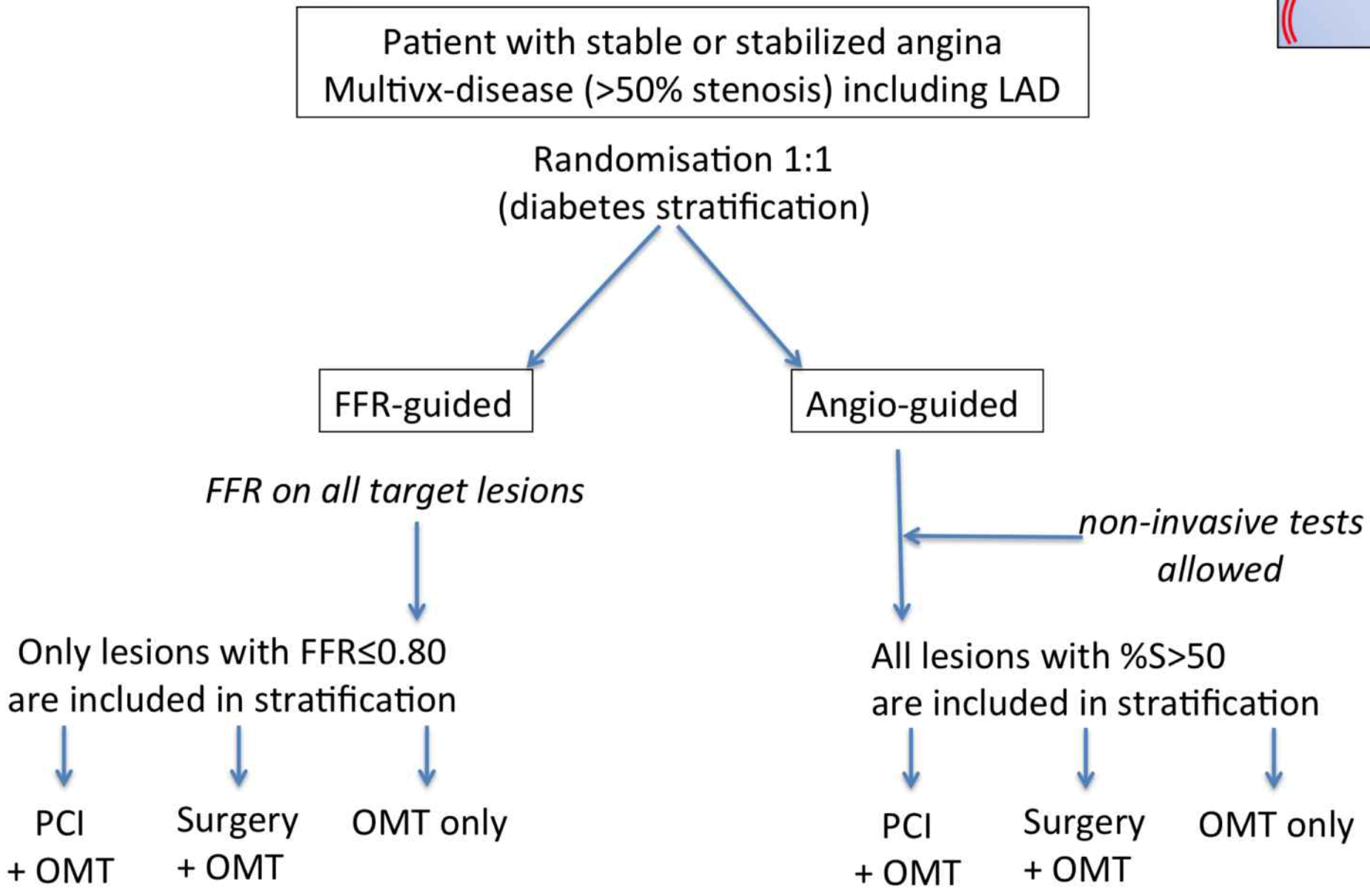
FUTURE Study Hypothesis

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 <u>one year</u>

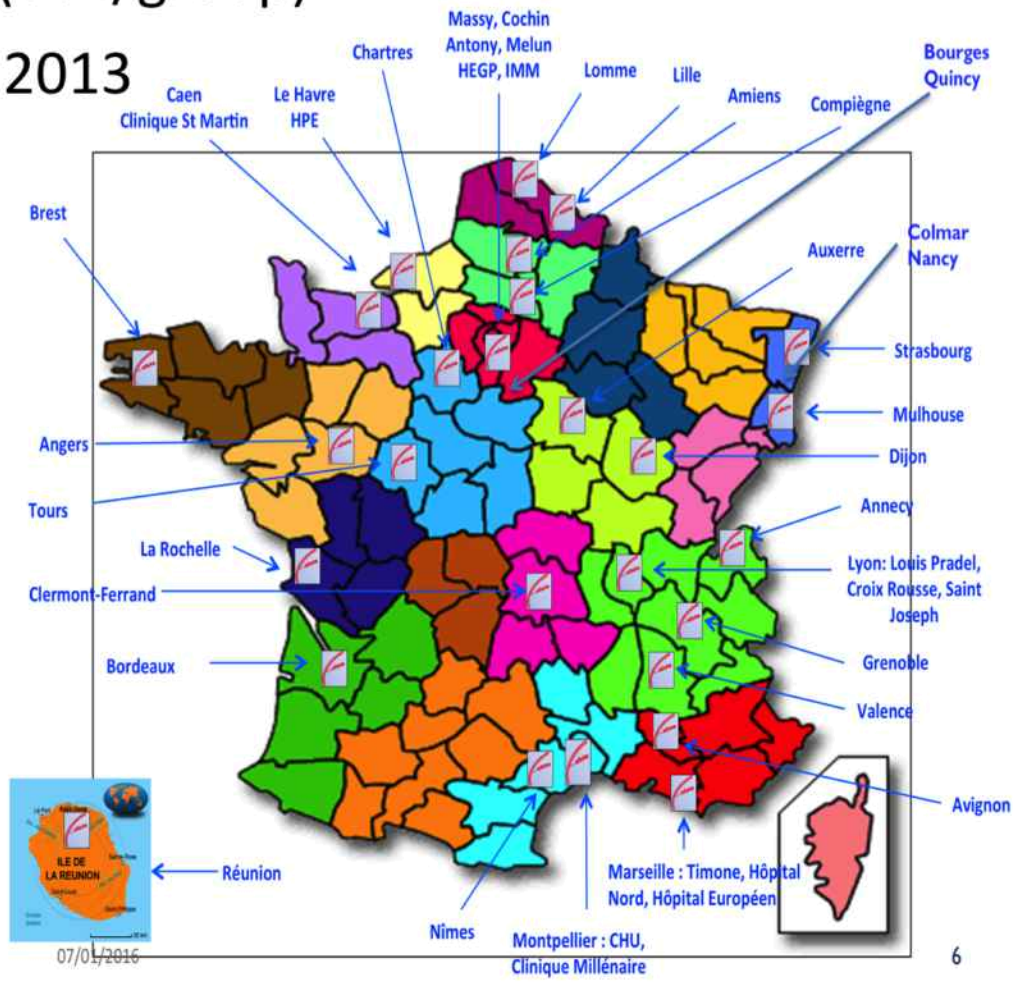
- *All cause mortality*
- *Myocardial Infarction*
- *Repeat revascularization*
- *Stroke*

Study design (I)

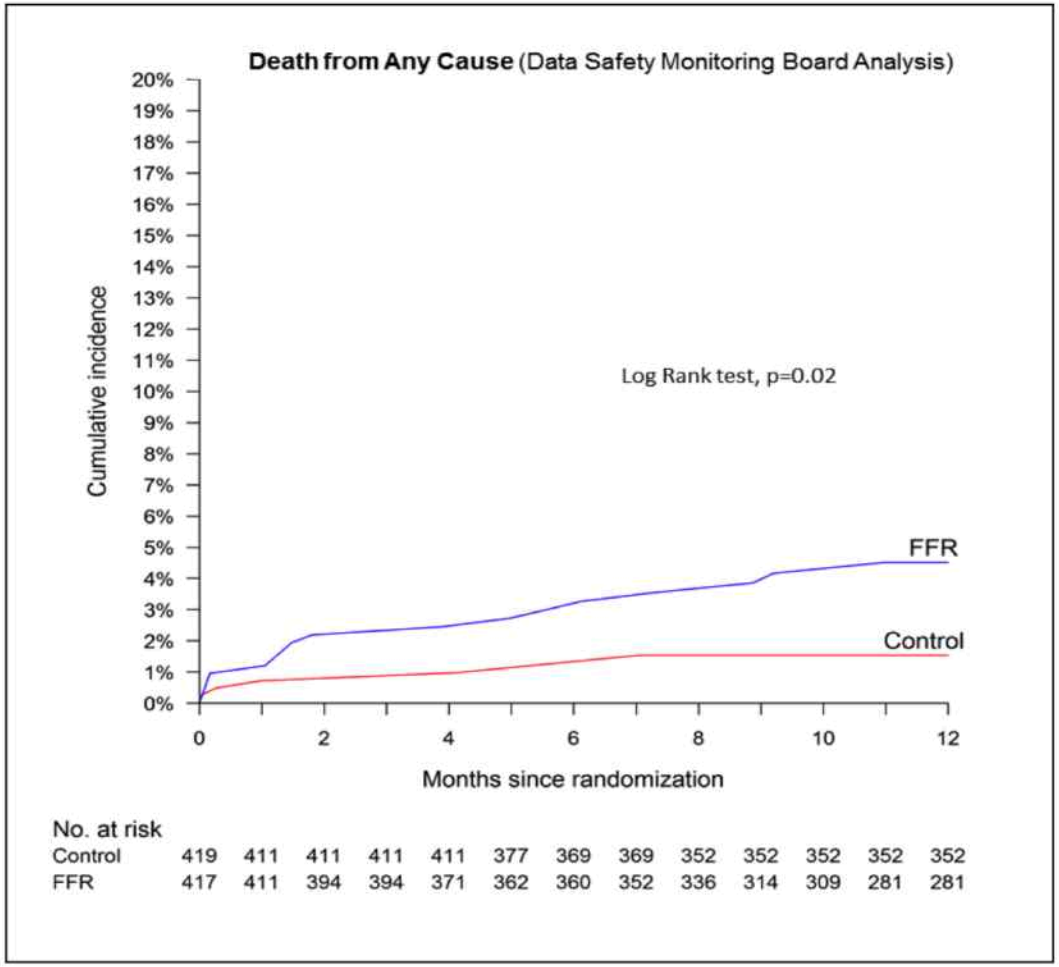


Study design (II)

- 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 recruitement 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
Including STEMI (%)	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
% positive test (%)	157/196 (80)	141/176 (80)	0.40
LVEF %	56±11 (343)	55±12 (336)	0.56

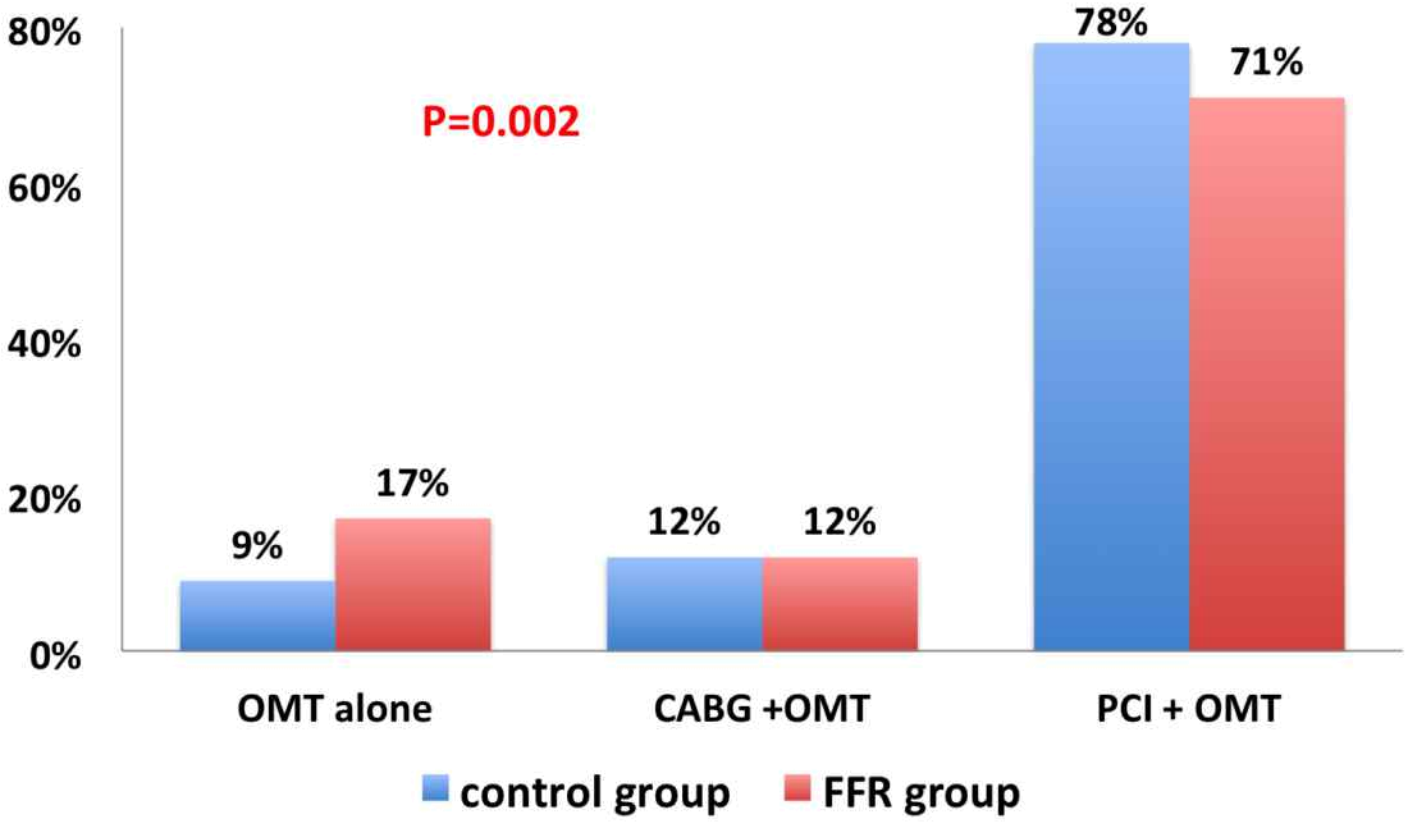
Angiographic findings

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

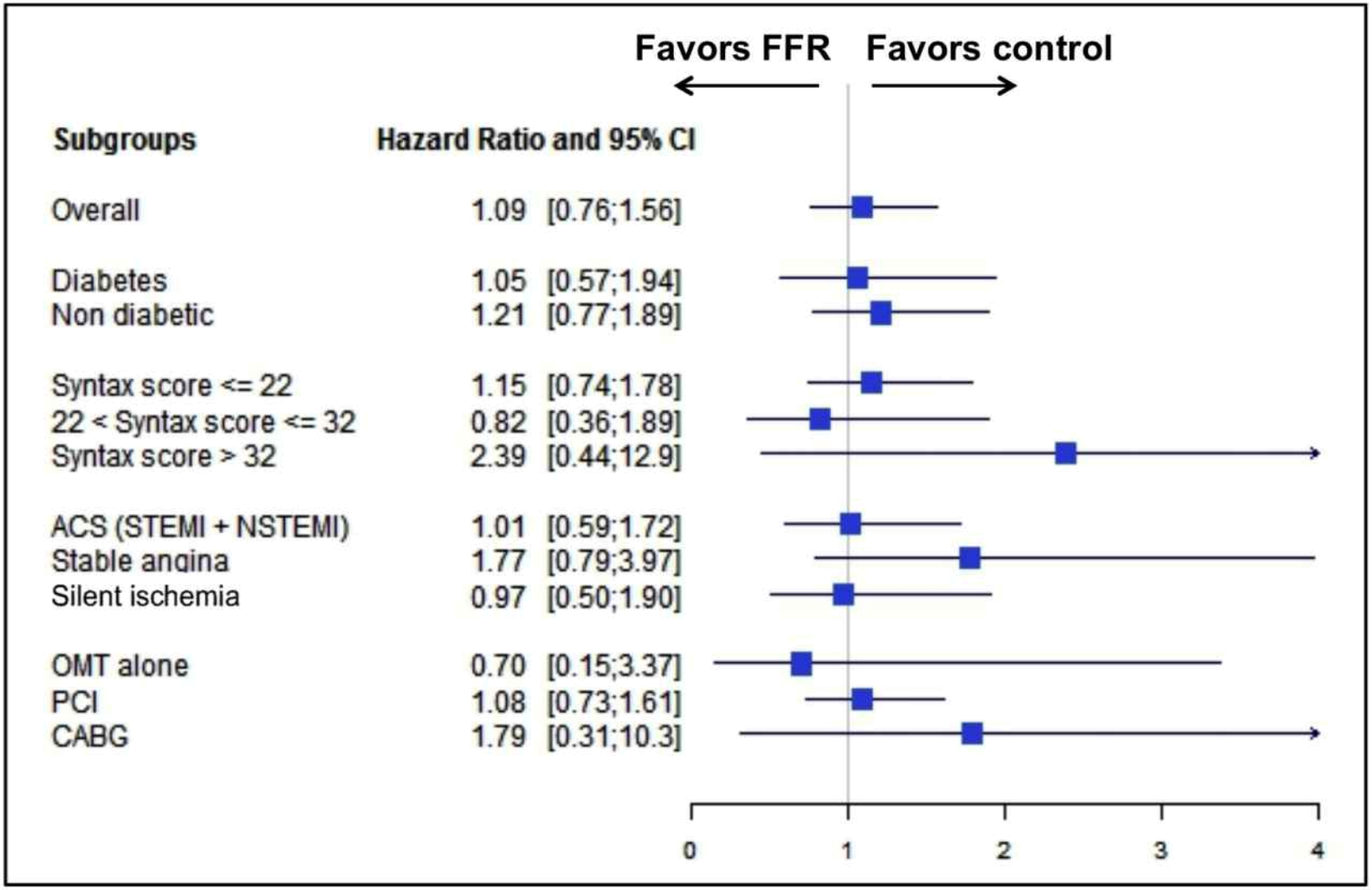


Clinical Events at One Year*

Variable	Control group (n=398)*	FFR Group (n=399)*	HR (95%CI)	P vlue
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 persitent 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 ?