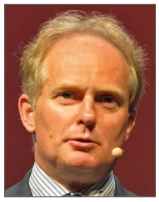
EuroIntervention 2020;16:225-232 published online April 2020

Fractional flow reserve-guided multivessel angioplasty in myocardial infarction: three-year follow-up with cost benefit analysis of the Compare-Acute trial



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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00012

KEYWORDS

- clinical trials
- fractional flow reserve
- multiple vessel disease
- STEMI

Abstract

Aims: The Compare-Acute trial showed superiority of fractional flow reserve (FFR)-guided acute complete revascularisation compared to culprit-only treatment in patients with ST-segment elevation myocardial infarction (STEMI) and multivessel disease (MVD) at one year. The aim of this study was to investigate the outcome at three years, together with cost analysis of this strategy.

Methods and results: After primary percutaneous coronary intervention (PCI), 885 patients with STEMI and MVD were randomised (1:2 ratio) to FFR-guided complete revascularisation (295 patients) or infarct-related artery (IRA)-only treatment (590 patients). After 36 months, the primary endpoint (composite of death, myocardial infarction, revascularisation, stroke) occurred significantly less frequently in the FFR-guided complete revascularisation group: 46/295 patients (15.6%) versus 178/590 patients (30.2%) (HR 0.46, 95% CI: 0.33-0.64; p<0.001). This benefit was driven mainly by the reduction of revascularisations in the follow-up (12.5% vs 25.2%; HR 0.45, 95% CI: 0.31-0.64; p<0.001). Cost analysis shows benefit of the FFR-guided complete revascularisation strategy, which can reduce the cost per patient by up to 21% at one year (8,150€ vs 10,319€) and by 22% at three years (8,653€ vs 11,100€).

Conclusions: In patients with STEMI and MVD, FFR-guided complete revascularisation is more beneficial in terms of outcome and healthcare costs compared to IRA-only revascularisation at 36 months.

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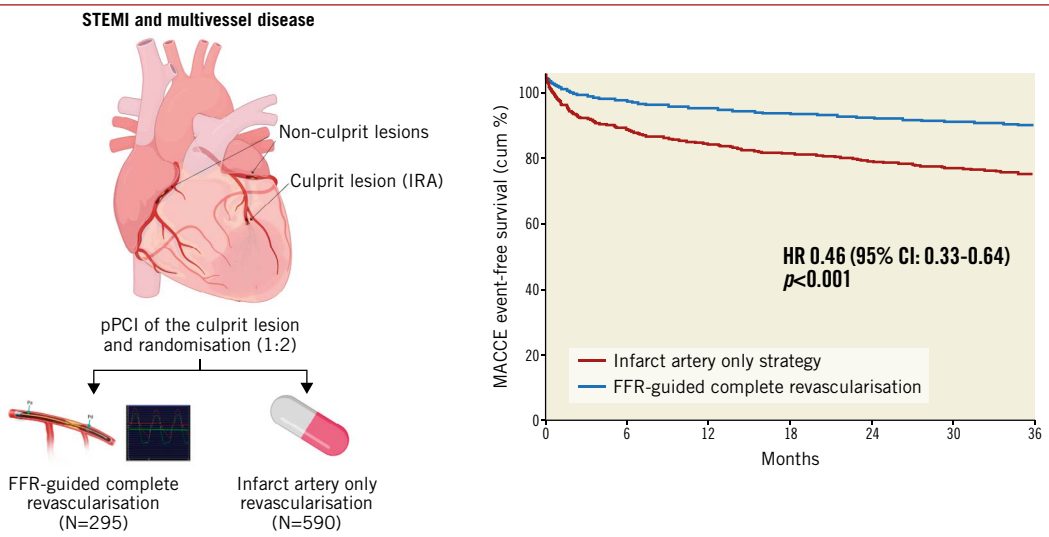
SUBMITTED ON 23/12/2019 - REVISION RECEIVED ON 27/02/2020 - ACCEPTED ON 03/04/2020

DOI: 10.4244/EIJ-D-20-00012



Visual summary. *Three-year follow-up of FFR-guided complete revascularisation versus IRA-only strategy in patients with STEMI and multivessel disease.*

Abbreviations

DRGs	diagnosis-related group systems
FFR	fractional flow reserve
IRA	infarct-related artery
MVD	multivessel disease
PCI	percutaneous coronary intervention
QCA	quantitative coronary angiography
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis In Myocardial Infarction

Introduction

Primary percutaneous coronary intervention (PCI) of the infarct-related artery (IRA) is the mainstay of treatment of patients with ST-segment elevation myocardial infarction (STEMI), provided it is performed in a timely manner and by an experienced team[1]. Around half of the patients presenting with STEMI exhibit multivessel coronary artery disease (MVD). This subpopulation is known to have worse short- and long-term prognosis[2]. The correct therapeutic strategy for non-culprit lesions has been extensively debated.

Five recent randomised trials have shown that an angiography-guided strategy (PRAMI[3], CvLPRIT[4], COMPLETE[5]) and a fractional flow reserve (FFR)-guided strategy (DANAMI-3-PRIMULTI[6] and Compare-Acute[7]) of complete revascularisation are beneficial compared to IRA-only revascularisation. The recently published COMPLETE trial[5], having randomised more than 4,000 STEMI patients with multivessel disease, showed that angiography-guided complete revascularisation provides a significant reduction in the composite outcome of cardiovascular death and myocardial infarction (MI) at a median follow-up of three years.

Pressure-derived FFR provides information about the functional severity of coronary stenosis and is currently the standard of care in guiding revascularisation in the presence of intermediate stenosis, both in patients with single-vessel and in those with multivessel disease. FFR ≤0.80 defines haemodynamically significant coronary stenosis that warrants revascularisation[8].

The role of FFR in the acute setting is less established. The DANAMI-3-PRIMULTI study randomised 627 patients with STEMI and MVD to PCI of the IRA only versus FFR-guided complete revascularisation in a staged strategy. At a median follow-up of 27 months, the primary endpoint (a composite of all-cause mortality, non-fatal reinfarction, and ischaemia-driven revascularisation) occurred more frequently in the group that underwent PCI of the IRA only[6].

Compare-Acute (ClinicalTrials.gov identifier: NCT01399736) was an investigator-initiated, prospective, multicentre, randomised trial that involved 24 sites, in which 885 patients with STEMI were randomised 1:2 to FFR-guided complete revascularisation or IRA-only revascularisation, with the aim of demonstrating that FFR-guided complete revascularisation in the acute setting of STEMI treatment was superior to IRA-only revascularisation[9].

After one year of follow-up, patients randomised to complete revascularisation showed a lower incidence of the primary endpoint, a composite of all-cause mortality, non-fatal MI, any revascularisation and cerebrovascular events (MACCE), compared to the IRA-only revascularisation arm. This difference was driven mainly by an increased number of revascularisations in the IRA-only revascularisation arm during the 12 months of follow-up[7].

The long-term outcome and the cost benefit of this strategy are unknown. We hereby present the results of the three-year outcome of the Compare-Acute trial and its cost analysis.

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Methods

STUDY DESIGN AND POPULATION

The design of the Compare-Acute study has been described previously[9]: 885 patients from 24 centres in Europe and Asia, with

STEMI and MVD, were enrolled and randomised in a 1:2 ratio (295 patients vs 590 patients) to FFR-guided complete revascularisation or to IRA-only revascularisation.

A full list of inclusion and exclusion criteria has been published previously[7].

The study was approved by the ethics committee of each participating site and informed consent was obtained before the procedure according to the International Conference on Harmonisation Good Clinical Practice guidelines.

FFR MEASUREMENT, TREATMENT AND FOLLOW-UP

After successful primary PCI of the IRA, eligible patients underwent randomisation (1:2 ratio). FFR measurement was performed in both groups, but the result was blinded to the patient and treating physician in the case of patients randomised to IRA-only revascularisation. FFR measurement, treatment and follow-up strategy have been described previously[7]. **Figure 1** shows the randomisation and follow-up of patients.

STUDY ENDPOINTS

The primary endpoint was defined as the composite of all-cause mortality, non-fatal MI, any revascularisation and cerebrovascular events (MACCE) at one year.

Secondary endpoints included the primary endpoint at 36 months, each component of the primary endpoint, the composite of all-cause mortality and MI; the composite of cardiac death, MI, any revascularisation, stroke, and major bleeding (NACE); the composite of hospitalisation for heart failure, unstable angina, chest pain, NSTEMI and STEMI; stent thrombosis; treatment costs. A revascularisation was defined as "urgent" by the following definition: any revascularisation for recurrent ischaemia that in the investigator's opinion cannot be delayed for more than 24 hours and/or is defined by the investigator as a non-elective procedure.

Moreover, three subgroup analyses were pre-specified: a comparison of patients in both groups with treated lesions with FFR ≤0.80 versus patients with untreated lesions with FFR ≤0.80; a comparison of acute versus staged treatment for lesions with FFR ≤0.80; a comparison of patients with treated versus untreated lesions with FFR >0.80.

COST ANALYSIS

Cost analysis was performed with a healthcare payer perspective, meaning that unit costs (each patient's costs) will be the reimbursement prices according to the healthcare system. Diagnosis-related group systems (DRGs) is a form of reimbursement used in many healthcare systems, in which any procedure has a fixed reimbursement cost that covers all expenses. The reimbursement is different in each country participating in the Compare-Acute trial; thus, the cost analysis was performed using DRGs from different countries – the Netherlands, Germany, Sweden and Poland.

Procedure costs (including events in the follow-up) were collected in the respective countries of interest as the reimbursement furnished by the healthcare system, and account for the year 2018 **(Table 1)**. Average costs per strategy arm were calculated

Table 1. Reimbursement amounts.

2018 reimbursement amounts	the Netherlands	Germany	Sweden	Poland
Index PCI procedure	7,449	3,182	5,485	2,175
Myocardial infarction	2,830	2,660	1,932	747
Stroke	7,895	3,403	4,486	747
CABG	6,099	4,334	5,485	1,696
Cardiac-related (re) hospitalisation	1,910	2,282	4,598	220
Reimbursement amount (in euros) for each country of interest for the year 2018.				

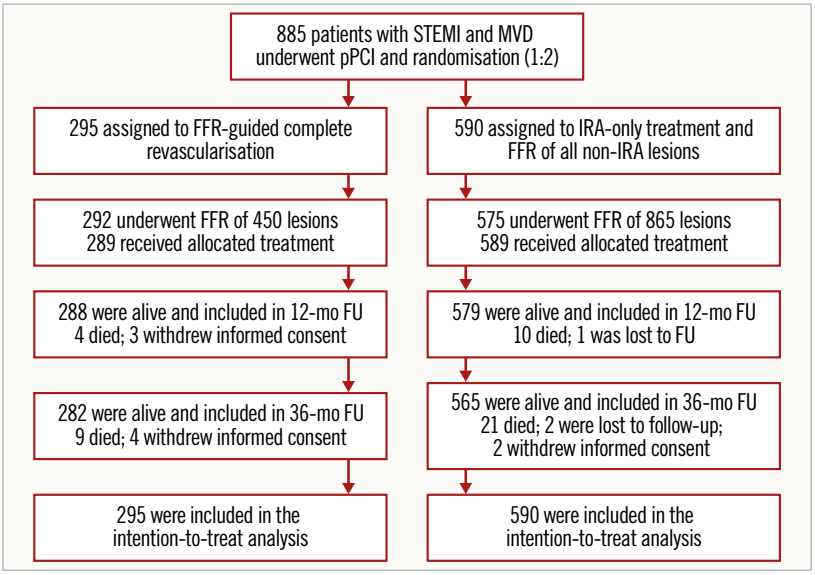

Figure 1. *Randomisation, treatment and follow-up. FU: follow-up; MVD: multivessel disease; STEMI: ST-elevation myocardial infarction*

by multiplying the respective procedure or event cost with the number of procedures or events, divided by the total number of patients (average cost = {Σ costs of index procedures + Σ (costs per event*number of events)}/number of patients).

STATISTICAL ANALYSIS

Statistical analysis and sample sizing have been described previously elsewhere[9]. All analyses were performed on an intention-to-treat basis. A *post hoc*, per-protocol analysis including all patients according to the received treatment was also performed. Continuous data are presented as means with standard deviations for normally distributed variables and as medians with minimum and maximum values for variables that were not normally distributed. Differences between both groups for continuous data were assessed with the use of an unpaired t-test when data were normally distributed and with the Mann-Whitney U test when not. Categorical data were analysed with the use of the chi-square test (or Fisher's exact test if a cell contained a number <5). A two-sided p-value of ≤0.05 was considered to indicate significance. Kaplan-Meier time-to-event plots were constructed for clinical events, and treatment groups were compared with the use of the log-rank test. Cox proportional hazards models were fitted to estimate hazard ratios with 95% confidence intervals (CIs) for treatment comparisons. Statistical analysis was performed with the use of SPSS software, Version 25.0 (IBM Corp., Armonk, NY, USA).

Results

BASELINE DATA

Baseline characteristics, angiographic and procedural data are shown in **Table 2** and **Table 3**.

In the complete revascularisation group, 158 of 292 patients (54.1%) had positive FFR (FFR ≤0.80) and thus underwent complete revascularisation. Five additional patients had PCI of non-IRA lesions that were not based on FFR values. Most PCIs of the non-IRAs were performed during the index procedure (136/163, 83.4%); the remainder of patients (27/163, 16.6%) underwent complete revascularisation during the same hospital stay (mean waiting time, 2.1 days).

Two hundred and seventy-five of 575 patients in the IRA-only group (47.8%) had positive FFR lesions at baseline. In this arm, 59 patients underwent staged revascularisation within 45 days (not considered as an event, as per protocol) and, among these, 44 patients had one or more non-IRAs with positive FFR. Median hospital stay was not different in the two groups (4 days vs 4 days; p=0.36).

ENDPOINTS

After three years, eight patients (1.1%), four in each group, were lost to follow-up or withdrew consent **(Figure 1)**.

After 36 months, the primary endpoint MACCE occurred in 15.6% of patients (46/295) in the complete revascularisation group versus 30.2% (178/590) in the IRA-only group (hazard ratio [HR] 0.46, 95% CI: 0.33-0.64; p<0.001) **(Figure 2)**.

Table 2. Patient baseline characteristics.

	Complete revascularisation N (%); (n=295)	IRA-only treatment N (%); (n=590)	*p*-value
Age, years	62±10	61±10	0.22
Male sex, n (%)	233 (79.0)	450 (76.3)	0.37
Medical history			
Diabetes, n (%)	43 (14.6)	94 (15.9)	0.60
Hypertension, n (%)	136 (46.1)	282 (47.8)	0.63
Current smoker, n/total n (%)	120/294 (40.8)	287/589 (48.7)	0.03
Hypercholesterolaemia, n (%)	95 (32.2)	176 (29.8)	0.47
Family history of premature coronary artery disease, n/total n (%)	103/294 (35.0)	223/590 (37.8)	0.42
Previous stroke, n (%)	10 (3.4)	26 (4.4)	0.47
Previous myocardial infarction, n (%)	22 (7.5)	48 (8.1)	0.73
Previous PCI, n (%)	25 (8.5)	44 (7.5)	0.60
Renal impairment, n (%) [§]	3 (1.0)	7 (1.2)	0.82
Peripheral vessel disease, n (%)	10 (3.4)	23 (3.9)	0.71
Location of infarct, n (%) [¶]			
Posterior	53 (18.0)	96 (16.3)	0.53
Anterior	105 (35.6)	206 (34.9)	0.84
Inferior	149 (50.5)	307 (52.0)	0.67
Lateral	41 (13.9)	86 (14.6)	0.79
Impossible to determine	3 (1.0)	4 (0.7)	0.59
Time from symptom onset to primary PCI, n (%)			
<6 hrs	225 (76.3)	462 (78.3)	0.58
6–12 hrs	47 (15.9)	84 (14.2)	
>12 hrs	23 (7.8)	44 (7.5)	
Arteries with stenosis, n (%)			
2	204 (69.2)	396 (67.1)	0.54
3	91 (30.8)	194 (32.9)	
Killip class ≥2, n (%)	15 (5.1)	30 (5.1)	1.00
Maximum creatine kinase level (IU/litre)			
Median	1,040	1,125	0.62
Range	102-8,182	112-11,052	

Values presented as mean±SD or as number and percentage of total (in brackets). [§] Patients described as having renal impairment had a creatinine level of more than 1.5 mg per decilitre (133 µmol per litre) or were receiving dialysis. [¶] The location of the infarct was determined with the use of electrocardiography. The p-value applies to all three sets of comparisons in accordance with the Mantel-Haenszel test of trend (or linear-by-linear association).

The incidence of all-cause mortality (9 patients vs 21 patients; 3.1% vs 3.6%; HR 0.86, 95% CI: 0.39-1.8; p=0.71), MI (20 patients vs 53 patients, 6.8% vs 9.0%; HR 0.74, 95% CI: 0.44-1.24; p=0.28) and cerebrovascular events (1 patient vs 7 patients; 0.3% vs 1.2%; HR 0.29, 95% CI: 0.03-2.3; p=0.24) remained numerically lower in the FFR-guided complete revascularisation group, but did not reach statistical significance. However, the incidence of revascularisation (PCI or coronary artery bypass grafting [CABG]) was significantly lower in the FFR-guided complete revascularisation group compared to the IRA-only revascularisation group (37 patients vs 149 patients; 12.5% vs 25.2%; HR 0.45, 95% CI: 0.31-0.64; p<0.001).

Table 3. Procedural data.

	Complete revascularisation N (%); (n=295)	IRA-only treatment N (%); (n=590)	*p*-value
Mean time for index procedure, min	65±31	59±28	0.001
Mean volume of contrast material used during index PCI, ml	224±104	202±75	0.007
FFR procedure successful, n (%)	292 (99.0)	575 (97.5)	0.13
Patients with lesions, n/total n (%)			
FFR ≤0.80	158/292 (54.1)	275/575 (47.8)	0.08
FFR >0.80	134/292 (45.9)	300/575 (52.2)	
Mean FFR value	0.78±0.12	0.79±0.12	0.42
Patients with treated (FFR-guided) non–infarct-related coronary artery lesions, n/total n (%)	163/295 (55.3)†	NA	
During index PCI procedure	136/163 (83.4)		
Delayed during index hospitalisation‡	27/163 (16.6)		
Treatment method, n/total n (%)			
Drug-eluting stent only	161/163 (98.8)	NA	
Bare metal stent only	1/163 (0.6)		
Balloon dilation only	1/163 (0.6)		
Mean no. of stents used per patient	1.6±0.9	NA	
Dimensions of stents, mm			
Mean length	34.3±21.0	NA	
Mean diameter	2.9±0.4	NA	
Length of hospital stay, days			
Median	4	4	0.36
Range	1-35	1-71	
Patients receiving pre-discharge non-invasive stress tests, n/total n (%)	21/294 (7.1)	71/590 (12.0)	0.03

Plus-minus values are means±SD, and NA denotes not applicable. † In four patients, non-infarct-related coronary artery lesions were also treated because no measurement was obtained for FFR, and in one patient these lesions were treated even though the FFR was higher than 0.80. The decision to treat was based on the angiographic results. ‡ There was a mean delay of 2.1±1.0 days after the primary PCI procedure.

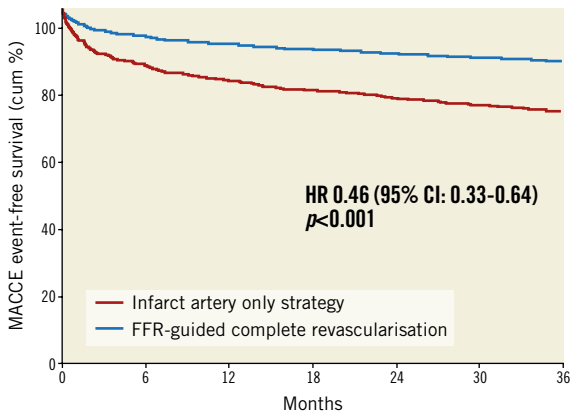

Figure 2. *Kaplan-Meier event curves of the combined primary outcome at 36 months. MACCE is a composite of all-cause mortality, non-fatal myocardial infarction, any revascularisation, and cerebrovascular events.*

The majority of these revascularisations had an urgent indication and occurred more frequently in the IRA-only revascularisation group (22 patients vs 85 patients; 7.5% vs 14.4%; HR 0.46, 95% CI: 0.29-0.73; p<0.001).

The composite of all-cause death and MI was slightly less frequent in the complete revascularisation group: 28 patients vs 73 patients in the IRA-only group, without reaching statistical significance (9.5% vs 12.4%; HR 0.75, 95% CI: 0.49-1.17; p=0.20).

The secondary endpoint of NACE (composite of cardiac death, MI, any revascularisation, stroke and major bleeding) occurred in 15.3% of patients (45/295) in the complete revascularisation group versus 36.4% of patients (215/590) in the IRA-only group (HR 0.35, 95% CI: 0.26-0.49; p<0.001).

Finally, hospitalisations for heart failure, unstable angina, atypical chest pain, typical angina, NSTEMI and STEMI were lower in the FFR-guided complete revascularisation group, despite not reaching statistical significance (30 patients vs 87 patients; 10.2% vs 14.7%; HR 0.67, 95% CI: 0.44-1.02; p=0.06). Outcome data are summarised in **Table 4**.

The results of the three pre-specified subgroup analyses, the *post hoc* per-protocol analysis, and the *post hoc* one-year landmark analysis are shown in **Supplementary Appendix 1, Supplementary Appendix 2** and **Supplementary Figure 1**.

COST ANALYSIS

According to the Dutch system, and using the data derived from the one-year follow-up study, the average cost per patient was 8,150€ in the FFR-guided complete revascularisation group, and 10,319€ in the IRA-only revascularisation group, accounting for a reduction of 21% of the per-patient cost. An FFR-guided complete revascularisation strategy is cost-saving also after three years of follow-up: the average cost per patient was 8,653€ in the complete revascularisation group and 11,100€ in the IRA-only revascularisation group (22% cost reduction).

The same three-year data were confirmed using DRG analysis according to the German system (complete revascularisation 4,887€ vs IRA-only 5,200€; 6.0% cost reduction) and the Swedish system (complete revascularisation 6,205€ vs IRA-only 8,133€; 24% cost reduction). An FFR-guided complete revascularisation strategy was not cost beneficial according to the Polish system (complete revascularisation 3,704€ vs IRA-only 3,685€; 0.5% cost increase). All data are shown in **Figure 3**.

Discussion

The 36-month follow-up of the Compare-Acute trial demonstrates the benefit of an FFR-guided complete revascularisation strategy in patients with STEMI and multivessel disease in reducing a composite endpoint of all-cause mortality, non-fatal MI, any revascularisation and cerebrovascular events. This benefit was driven mainly by an increased incidence of any revascularisation in patients treated with an IRA-only strategy. Moreover, the FFR-guided complete revascularisation strategy in the acute setting of STEMI is also cost-saving from a payer perspective.

Table 4. Outcome data at 36 months.

Endpoint	Complete revascularisation N (%); (n=295)	IRA-only treatment N (%); (n=590)	Hazard ratio (95% CI)	*p*-value
Primary endpoint at 36 months				
MACCE	46 (15.6)	178 (30.2)	0.46 (0.33-0.64)	<0.001
All-cause death	9 (3.1)	21 (3.6)	0.86 (0.39-1.80)	0.71
Cardiac cause	5 (1.7)	8 (1.4)	1.25 (0.41-3.83)	0.70
Myocardial infarction	20 (6.8)	53 (9.0)	0.74 (0.44-1.24)	0.28
Spontaneous event	17 (5.8)	40 (6.8)	0.84 (0.48-1.49)	0.56
Periprocedural event	3 (1.0)	13 (2.2)	0.46 (0.13-1.61)	0.19
Revascularisation	37 (12.5)	149 (25.3)	0.45 (0.31-0.64)	<0.001
PCI	34 (11.5)	144 (24.4)	0.42 (0.29-0.62)	<0.001
Coronary artery bypass graft	3 (1.0)	5 (0.8)	1.05 (0.25-4.41))	0.94
Elective	15 (5.1)	64 (10.8)	0.43 (0.25-0.76)	0.002
Urgent	22 (7.5)	85 (14.4)	0.46 (0.29-0.73)	<0.001
Cerebrovascular event	1 (0.3)	7 (1.2)	0.29 (0.03-2.30)	0.24
Secondary endpoints at 36 months				
NACE (any first event)	45 (15.3)	215 (36.4)	0.35 (0.26-0.49)	<0.001
All-cause death or MI	28 (9.5)	73 (12.4)	0.75 (0.49-1.17)	0.20
Any bleeding	12 (4.1)	32 (5.4)	0.75 (0.39-1.46)	0.39
Hospitalisation for HF, UA and/or MI	28 (9.5)	75 (12.7)	0.72 (0.47-1.12)	0.14
Hospitalisation for HF, UA, chest pain, NSTEMI and STEMI	30 (10.2)	87 (14.7)	0.67 (0.44-1.02)	0.06
Stent thrombosis	4 (1.4)	12 (2.0)	0.46 (0.21-2.06)	0.47

MACCE is the composite of all-cause mortality, non-fatal myocardial infarction, any revascularisation, and cerebrovascular events. HF: heart failure; MI: myocardial infarction; NACE: net adverse clinical events (the composite of cardiac death, myocardial infarction, any revascularisation, stroke, and major bleeding); UA: unstable angina

Although almost half of the patients presenting with STEMI have multivessel disease, the decision as to whether to perform complete revascularisation is still debated. To date, five randomised trials including Compare-Acute have addressed this question. All of them have provided positive results in favour of complete revascularisation. Despite extensive questioning about the reliability of FFR measurement in the acute setting, we believe that adding functional evaluation of non-culprit coronary lesions will provide additional information about those stenoses that will actually benefit from revascularisation and also reduce the number of unnecessary PCIs. In the DANAMI-3-PRIMULTI study, 69% of intermediate lesions proved functionally significant (FFR ≤0.80), whereas around 50% of lesions in the Compare-Acute population were FFR positive[6].

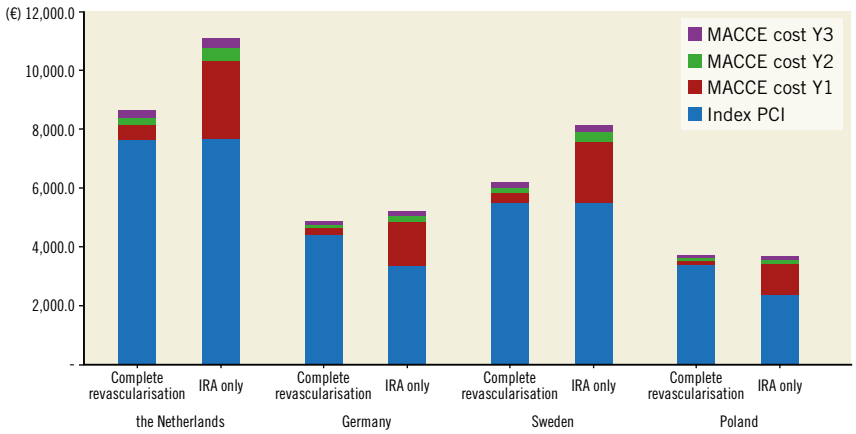

Figure 3. *Governmental average cost per patient at 36 months. The Figure shows the cumulative per-patient average cost in four different countries using a diagnosis-related group (DRG) system of reimbursement.*

Our study provides additional evidence on the importance of physiological evaluation of non-IRA lesions in the setting of MI, not only for the idea that FFR-positive lesions warrant revascularisation, but also for the safety of deferring revascularisation of FFR-negative lesions even in the acute setting **(Supplementary Figure 2, Supplementary Figure 3)**. Importantly, in our subgroup analysis comparing patients with FFR-positive lesions who underwent PCI and patients with FFR-positive lesions who received only medical treatment, we found that the number not only of revascularisations, but also of MIs was increased at follow-up in the group of patients treated medically (**Supplementary Appendix 1**, Subgroup analysis 1), confirming what is known from FFR data in stable angina patients (DEFER trial and FAME 2) and adding extra evidence for FFR in the subset of acute coronary syndrome patients[10,11]. Despite the increased incidence of MACCE in the IRA-only group being driven mainly by an increased number of revascularisations, we found that most revascularisations in the follow-up were clinically urgent and more frequent in the IRA-only group.

The recently published COMPLETE trial[5] randomised patients with STEMI and multivessel disease to angiography-guided complete revascularisation or IRA-only treatment. Its results strengthen the evidence of the Compare-Acute trial, showing that complete revascularisation reduces not only the number of revascularisations in the follow-up but also the composite outcome of death and MI.

Another common question is whether revascularisation of non-culprit lesions should be performed during the primary PCI or in a staged procedure. Although our trial was not designed for this analysis, our data (**Supplementary Appendix 1**, Subgroup analysis 2) suggest that there is no substantial difference in choosing either of those strategies. In line with our findings, a recent sub-analysis of the COMPLETE trial demonstrated that the benefit of complete revascularisation emerges mainly at longer follow-up and is maintained irrespective of the timing of complete revascularisation[12].

Finally, not only does complete revascularisation give benefit in terms of outcome, but it can also reduce healthcare-related costs: by reducing the total number of procedures and adverse events, this approach can save up to 22% of the per-patient cost.

Limitations

Some limitations of the trial must be considered. Since it was designed as open-label, there might have been some bias by the referring physicians of patients in the IRA-only group towards revascularisation. However, most of the staged and non-staged revascularisations in this group were performed in FFR-positive lesions. Furthermore, although clinical hard endpoints, such as death and MI were numerically lower in the FFR-guided complete revascularisation group, this trial was not sufficiently powered to detect statistical significance for these low-frequency events. Other than the COMPLETE trial[5], a meta-analysis on individual patient-level data of FAME 2, DANAMI-3-PRIMULTI and Compare-Acute shows that FFR guidance for complete revascularisation can result in a combined cardiac death and MI benefit compared to an optimal medical strategy[13].

Finally, we performed cost analysis on bundle payment (DRGs) from a payer perspective, but no detailed cost-effectiveness analysis, because we obtained no information on quality of life and actual healthcare consumption costs.

Conclusions

The three-year follow-up of the Compare-Acute trial demonstrates the benefit of an FFR-guided complete revascularisation strategy in reducing the incidence of a composite outcome of death, myocardial infarction, cerebrovascular events and revascularisation in patients with STEMI and multivessel disease. The benefit of this strategy is driven mainly by the reduction in revascularisations (the majority of which are urgent) during follow-up and can result in reduction of healthcare costs.

Impact on daily practice

The results of the three-year follow-up of the Compare-Acute trial, in line with recent findings, demonstrate the benefit of a complete revascularisation strategy in patients with STEMI and multivessel disease in terms of outcome. Moreover, this strategy appears more cost-effective.

Acknowledgements

We acknowledge the help of Mrs Ria van Vliet for assistance with the conduct of the trial, and Mrs Hanneke Fischer, M.Sc, for assistance with the cost analysis.

Funding

This work was supported by Maasstad Cardiovascular Research BV, which received research grants from Abbott Vascular and St. Jude Medical.

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Conflict of interest statement

P.C. Smits reports grants from Abbott Vascular and St. Jude Medical during the conduct of the study. F-J. Neumann reports grants from Abbott Vascular, Medtronic, GlaxoSmithKline and St. Jude Medical during the conduct of the study, personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, Daiichi Sankyo, Ferrer, The Medicines Company and Novartis, and grants and personal fees from Pfizer, Boston Scientific, Biotronik, Edwards Lifesciences and Bayer Healthcare, outside the submitted work. O. Angerås reports personal fees from Abbott Medical and Boston Scientific, outside the submitted work. G.W. Frederix received a fee from Abbott Vascular to perform the cost analysis. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Appendix 1. Three pre-specified subgroup analyses.

Supplementary Appendix 2. Post hoc, per-protocol analysis.

Supplementary Figure 1. One-year landmark analysis for MACCE-free survival.

Supplementary Figure 2. Subgroups according to randomisation, FFR result and treatment.

Supplementary Figure 3. MACCE-free survival for each subgroup.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-00012

Supplementary data

Supplementary Appendix 1. Three pre-specified subgroup analyses

Subgroup analysis 1: FFR+/PCI+ vs FFR+/PCI-

When comparing patients having FFR-positive lesions that underwent revascularisation during the index procedure or in staged procedures within 45 days (groups A+C, n=202 patients) with patients having FFR-positive lesions that did not undergo revascularisation (group D, n=231 patients), we found that the incidence of MACCE at 36 months was significantly higher in the FFR+/PCI- group (35/199 patients vs 90/229 patients; 17.6% vs 31.6%; $p<0.01$).

The incidence of death (5 patients vs 5 patients; 2.5% vs 2.2%; p=0.82) and stroke (1 patient vs 1 patient; 0.5% vs 0.5%; p=1.00) in the FFR+/PCI+ subgroup did not differ from the FFR+/PCI- subgroup, but the incidence of myocardial infarction in the FFR+/PCI+ subgroup was significantly lower compared to the FFR+/PCI- subgroup (13 patients vs 30 patients; 6.7% vs 13.3%; p=0.03), as was the incidence of any revascularisation (25 patients vs 85 patients; 12.8% vs 37.6%; $p<0.01$).

Subgroup analysis 2: acute vs staged

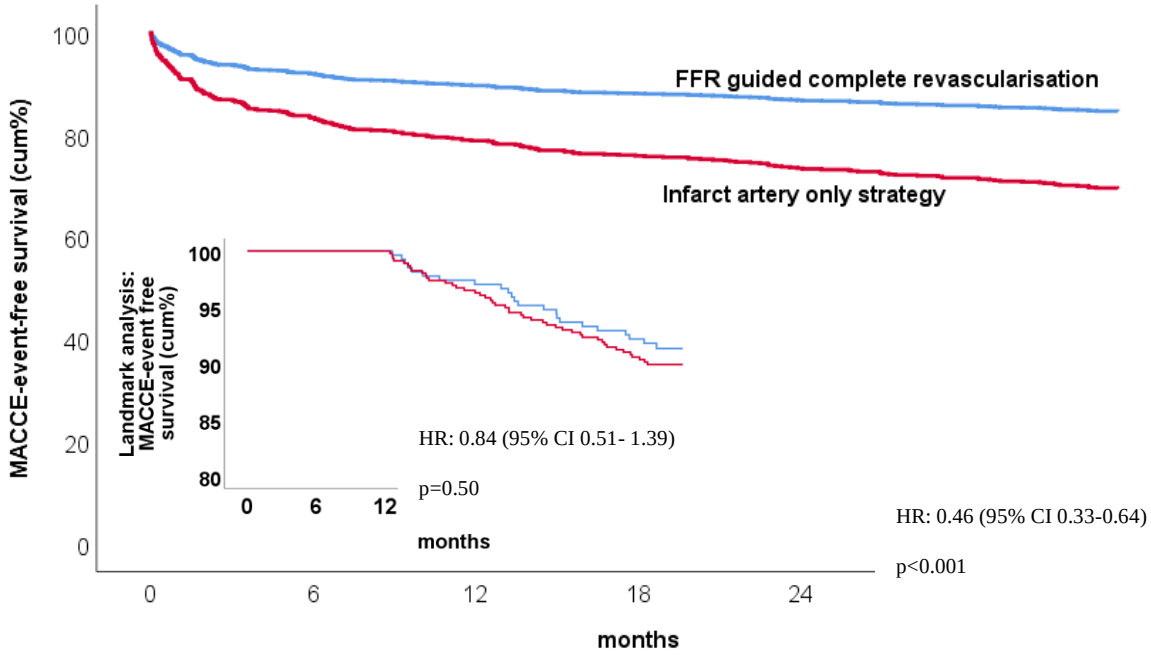
In the second pre-specified subgroup analysis, we compared acute versus staged treatment for lesions with FFR ≤0.80 (group A vs group C): there was no statistically significant difference in MACCE between the two strategies (25/155 patients with acute treatment vs 10/44 patients with staged treatment; 16.1% vs 22.7%; p=0.31) at 36 months.

Subgroup analysis 3: PCI vs medical therapy in FFR- lesions

The third pre-specified subgroup analysis compared patients receiving staged PCI treatment of FFR-negative lesions in the non-IRA (decision made by referring physician who was blinded to FFR results) and patients receiving medical therapy for FFR-negative lesions in the non-IRA (group E vs groups B+F). Although the numbers were small, an increased incidence of MACCE in the group of patients who received PCI treatment of FFR-negative lesions in the non-IRA was observed: 6/13 patients vs 91/418 patients (46.1% vs 21.8%; p=0.04).

Supplementary Appendix 2. Post hoc, per-protocol analysis

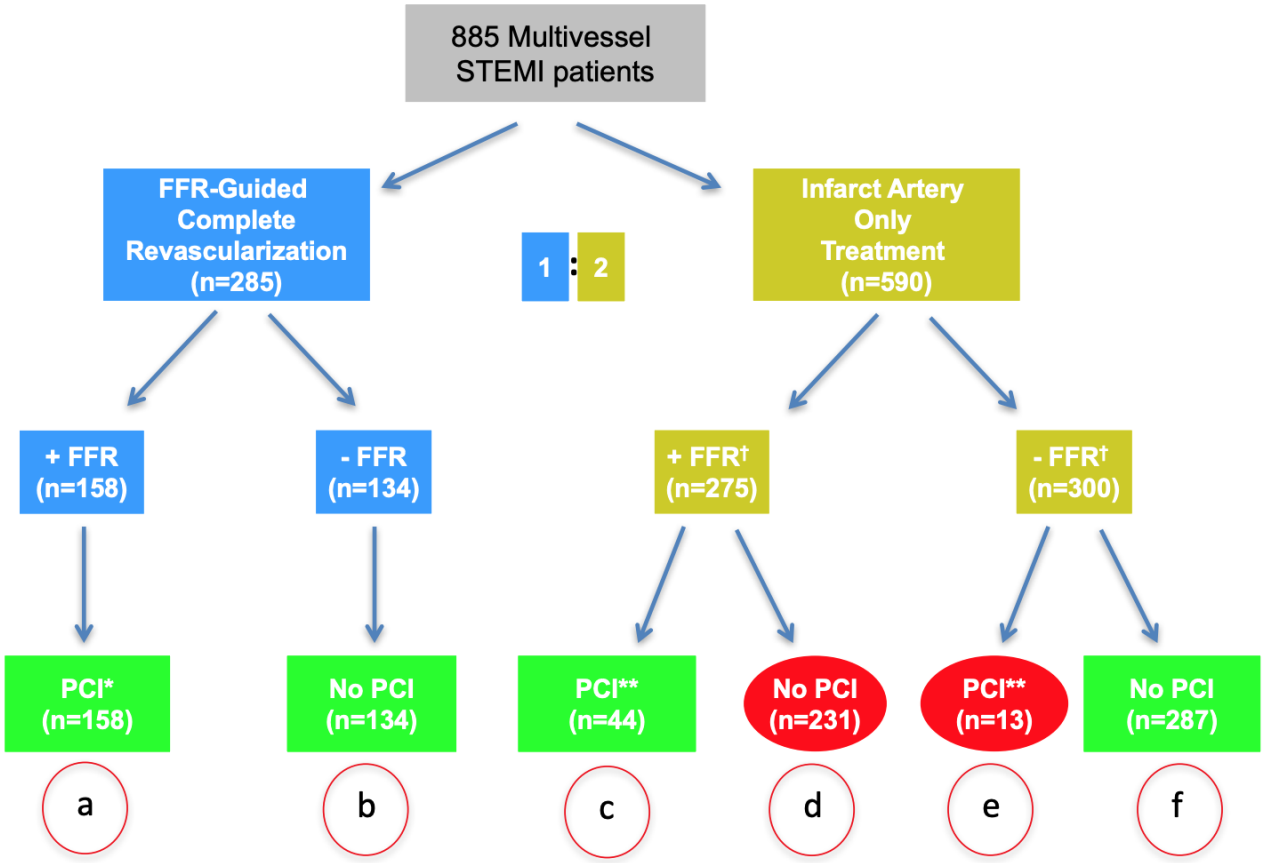
In the post hoc, per-protocol analysis, 328 patients underwent FFR-guided complete revascularisation and 550 patients underwent IRA-only treatment. After 36 months, the primary endpoint MACCE occurred in 16.8% of patients (55/328) in the complete revascularisation group versus 30.5% (168/550) in the IRA-only group ($p<0.01$).



Supplementary Figure 1. One-year landmark analysis for MACCE-free survival.

Above are the Kaplan-Meier curves of the primary outcome, and of the landmark analysis after one year.

The primary outcome occurred after 12 months in 23/272 patients (8.4%) in the complete revascularisation group versus 57/469 patients (12.1%) in the IRA-only group (HR 0.84, 95% CI: 0.51-1.39; p=0.50).

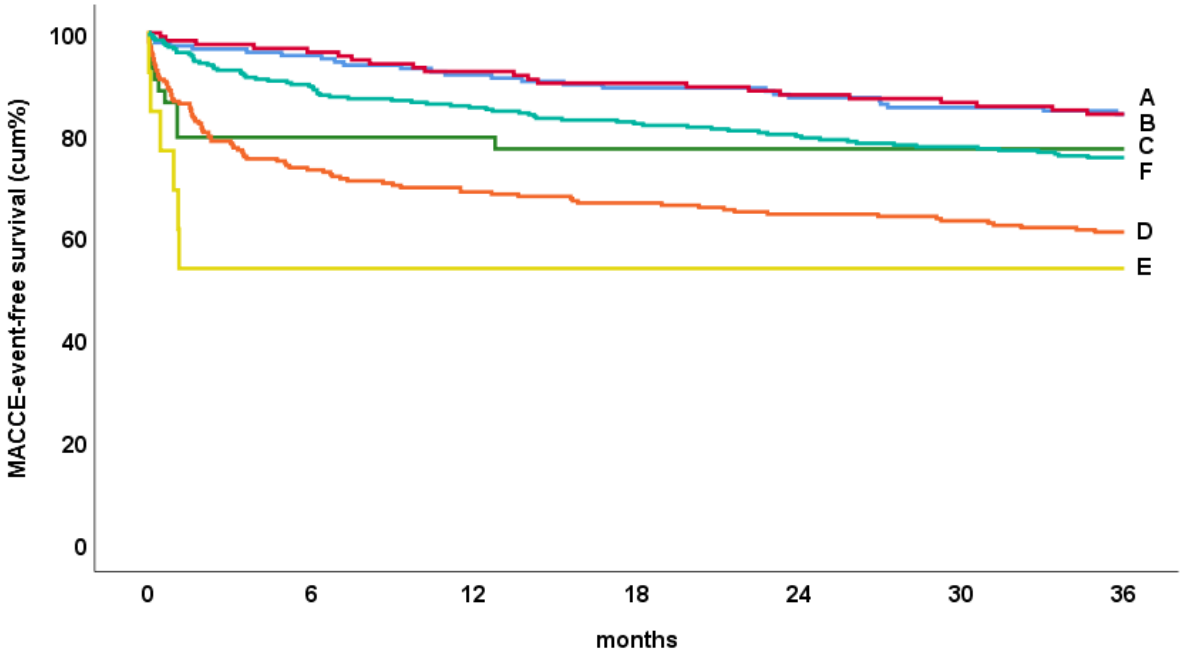


Supplementary Figure 2. Subgroups according to randomisation, FFR result and treatment.

PCI*: FFR-guided PCI of non-infarct-related arteries performed during primary PCI procedure (83%) or within 72 hours after primary PCI procedure (17%).

PCI**: staged PCI performed of non-infarct-related arteries within 45 days after primary PCI procedure.

FFR†: FFR procedure with blinded result for treating physicians.



Supplementary Figure 3. MACCE-free survival for each subgroup.

A and B are the subgroups within the FFR-guided complete revascularisation arm (A: FFR+, PCI+; B: FFR-, PCI-), C to F are the subgroups within the infarct artery-only treatment arm (C=FFR+, staged PCI; D=FFR+, PCI–; E=FFR-, staged PCI+; F=FFR-, PCI-). The MACCE rates per subgroup at 36 months were: group A 25/158, 15.8%, group B 21/132, 15.9%, group C 10/44, 22.7%, group D 92/231, 39.8%, group E 6/13, 46.1%, group F 71/287, 24.7%.