



# The Full Revasc (Ffr-gUIdance for complete non-culprit REVAScularization) Registry-based randomized clinical trial

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## Abstract

**Background** Complete revascularization in ST elevation myocardial infarction (STEMI) patients with multivessel disease has resulted in reduction in composite clinical endpoints in medium sized trials. Only one trial showed an effect on hard clinical endpoints, but the revascularization procedure was guided by angiographic evaluation of stenosis severity. Consequently, it is not clear how Fractional Flow Reserve (FFR)-guided percutaneous coronary intervention (PCI) affects hard clinical endpoints in STEMI.

**Methods and Results** The Ffr-gUIdance for complete non-culprit REVAScularization (FULL REVASC) – is a pragmatic, multicenter, international, registry-based randomized clinical trial designed to evaluate whether a strategy of FFR-guided complete revascularization of non-culprit lesions, reduces the combined primary endpoint of total mortality, non-fatal MI and unplanned revascularization. 1,545 patients were randomized to receive FFR-guided PCI during the index hospitalization or initial conservative management of non-culprit lesions. We found that in angiographically severe non-culprit lesions of 90-99% severity, 1 in 5 of these lesions were re-classified as non-flow limiting by FFR. Considering lesions of intermediate severity (70%-89%), half were re-classified as non-flow limiting by FFR. The study is event driven for an estimated follow-up of at least 2.75 years to detect a 9.9%/year > 7.425%/year difference (HR = 0.74 at 80% power ( $\alpha = .05$ )) for the combined primary endpoint.

**Conclusion** This large randomized clinical trial is designed and powered to evaluate the effect of complete revascularization with FFR-guided PCI during index hospitalization on total mortality, non-fatal MI and unplanned revascularization following primary PCI in STEMI patients with multivessel disease. Enrollment completed in September 2019 and follow-up is ongoing. (Am Heart J 2021;241:92–100.)

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Almost half of all patients presenting with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention have a significant stenosis in one or more major non-culprit coronary arteries, in addition to the culprit lesion<sup>1</sup>. It has been a clinical dilemma if and when non-culprit artery stenoses should be revascularized. Complete revascularization in STEMI patients with multivessel disease has resulted in reduction in composite clinical endpoints including repeat revascularization or refractory angina in previous tri-

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als. Since these studies were relatively small, PRAMI had 465 patients<sup>2</sup> and CvLPRIT 296 patients<sup>3</sup>, and were not in accordance with observational studies and guidelines, it was difficult to draw conclusions regarding revascularization strategy.

The use of fractional flow reserve (FFR) to determine ischemia-inducing lesions is superior to angiography-guided PCI in both stable angina and in non-ST-elevation myocardial infarction (NSTEMI)<sup>4,6</sup>, but the role in guiding revascularization of non-culprit lesions in STEMI is insufficiently studied. Compare-Acute (885 patients) showed a benefit of complete FFR-guided revascularization. However, the primary endpoint was driven by repeat revascularization with no significant differences in death or MI<sup>7</sup>. PRIMULTI was a similar smaller study (650 patients) where the primary endpoint was reduced by FFR-guided PCI, but this was entirely driven by repeat revascularization<sup>8</sup>. None of the above studies were designed to investigate effects on the hard endpoints of death and MI.

Only one recently published trial (COMPLETE, 4,041 patients) was powered for effect on hard clinical endpoints, but the revascularization procedure was guided by angiographic evaluation of stenosis severity. It showed that complete revascularization significantly reduced the co-primary endpoint of cardiovascular (CV) mortality and MI, as well as the co-primary endpoint of CV mortality, MI and ischemia-driven revascularization<sup>9</sup>. These results were clear in subgroups with high grade non-culprit lesions with >80% stenosis grade. However, the effect of a true FFR-guided complete revascularization that includes both high grade and intermediate stenoses remains to be investigated.

Also in NSTEMI, the strategy of multivessel PCI for suitable significant stenoses—rather than PCI limited to the culprit lesion—has not been evaluated in an appropriate, randomized fashion according to European Society of Cardiology (ESC) guidelines on myocardial revascularization<sup>10</sup>.

Therefore, the aim of the present study was to investigate whether in patients undergoing primary PCI for STEMI, rescue PCI or planned PCI for risk evaluation following successful thrombolysis or very high risk NSTEMI, FFR-guided PCI of non-culprit lesions during the index hospitalization will improve cardiovascular outcomes compared to an initially conservative approach of non-culprit lesions.

## Methods and design of the FULL REVASC study

This is a prospective international multicenter registry-based randomized controlled trial (R-RCT) with endpoint evaluation including adjudication for some of the primary and secondary endpoints.

The FULL REVASC study was originally planned to include 4,052 patients. However, because of the results of the COMPLETE trial<sup>9</sup>, the Sponsor Karolinska University Hospital and the steering committee decided to stop inclusion of more patients into the FULL REVASC study. This decision was made following discussions with the Data and Safety Monitoring Board (DSMB), not because of preliminary outcome data (blinded to the Investigators) in the FULL REVASC study, but because of the clear published data in the COMPLETE trial. It was considered unethical to randomize patients with non-culprit lesions of >80% angiographic stenosis to receive incomplete revascularization. To modify the protocol to include only patients with intermediate lesions 50-80% was considered unfeasible.

### Objective and primary endpoint

The primary objective is to test the hypothesis that following primary PCI, a strategy of complete revascularization with FFR-guided PCI during the index hospitalization, reduces long term clinical outcomes as compared to initial conservative management of non-culprit lesions. The original primary outcome was defined as a composite of all-cause mortality and myocardial infarction. Following recommendations from the DSMB and discussions in the steering committee, the primary composite endpoint was changed to the composite of all-cause mortality, myocardial infarction, and unplanned revascularization. For the primary endpoint, all events will be collected in the study until 2-3 years after enrollment of the last patient. The study is event driven and the exact follow-up period will be decided when a sufficient number of events have been adjudicated to allow for the best estimate of the event rate.

### Secondary endpoints

Key secondary endpoints are the combined endpoint of all-cause mortality and MI at a minimum follow-up of 2-3 years and unplanned revascularization (PCI/CABG) at a minimum follow-up of 2-3 years. Exploratory secondary endpoints include the composite endpoint of all-cause mortality, MI, and unplanned revascularization (PCI/CABG) in pre-specified subgroups. The composite and its individual components will be evaluated at 30 days, 1 year, and at a minimum follow-up of 2-3 years. In addition, angina pectoris according to the Seattle Angina Questionnaire-7 (SAQ-7) will be evaluated at these time points in all patients. Quality of life will be evaluated according to the questionnaire EQ-5D at two months and/or one year for patients <80 years enrolled in Sweden. Furthermore, a health economic evaluation of direct and indirect costs will be evaluated.

### Safety evaluations and adverse events

Contrast volume, x-ray duration, neurological complications during index PCI and during randomized FFR

**Table 1.** Inclusion and Exclusion Criteria

<i>Inclusion Criteria</i>	
1.	Symptoms indicating acute myocardial ischemia with a duration >30 min and occurring ≤ 24 h prior to randomization or presentation.
2.	One of the following: <ol style="list-style-type: none"> <li>STEMI: ST elevation above the J-point of ≥0.1 mV in ≥ two contiguous leads or LBBB</li> <li>Rescue PCI</li> <li>Risk evaluation following successful thrombolysis</li> <li>Very high risk NSTEMI: dynamic STT changes or ongoing chest pain or acute heart failure or hemodynamic instability independent of ECG changes or life-threatening ventricular arrhythmias.</li> </ol>
3.	PCI performed of infarct-related artery.
4.	One or more non-culprit lesions at least 2.5 mm on angiogram (visually assessed as 50-99%) amenable for PCI.
5.	Age >18 years.
6.	Ability to provide informed consent.
<i>Exclusion Criteria</i>	
1.	Previous CABG.
2.	Left main disease of >50% stenosis requiring intervention.
3.	Cardiogenic shock necessitating therapy in addition to revascularization (LV support device or vasopressors)

guided PCI of non-culprit lesions and new renal insufficiency during index hospitalization lesions have been collected. Data on major bleeding, stroke, and rehospitalization due to heart failure are collected at 30 days, 1 year, and before data base lock.

### Criteria for participation

The study protocol instructed that all patients should undergo primary PCI according to local clinical practice. Patients enrolled in the FULL REVASC study needed to have multivessel coronary artery disease defined as ≥1 lesion in a non-culprit artery with a diameter of at least 2.5 mm and a visually graded stenosis of 50-99%. Patients with a chronic total occlusion (CTO) non-culprit artery could be randomized into this study only if there was at least one stenosis of 50-99% in another non-culprit artery. If unclear which lesion was culprit it was at the discretion of the PCI-operator to perform PCI of >1 lesions – but then there had to be at least one more (non-culprit) lesion present that matched the inclusion criteria for the patient to be randomized. Full list of inclusion and exclusion criteria are shown in [Table 1](#).

### Informed consent and randomization

When the index PCI was performed and the patient fulfilled all the other inclusion criteria and did not meet an exclusion criterion, oral informed consent (Sweden, Latvia, Serbia, and Australia only) or written informed consent for participation in the study was obtained. Randomization (1:1) was performed by means of an on-line randomization module using permuted block randomization stratified by site within the SWEDEHEART (Swedish Web system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry in Swe-

den and through a separate web page in other participating countries.

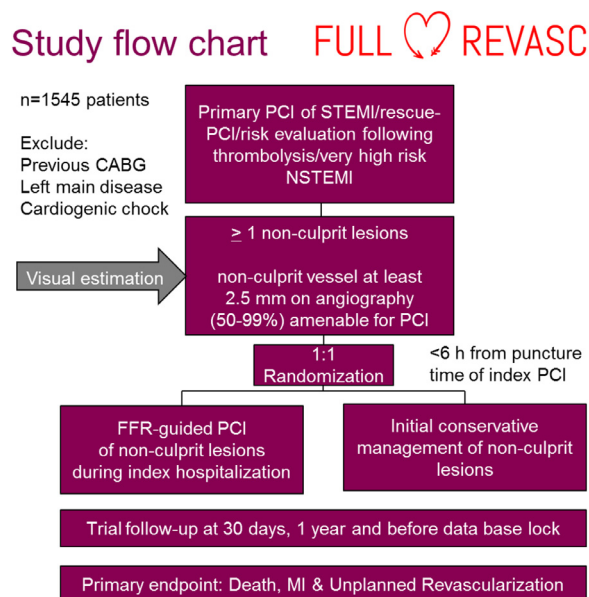
It was strongly recommended that randomization was performed directly following primary PCI of the ACS culprit lesion. However, it was possible to randomize the patient within 6 h from puncture time of the index procedure ([Figure 1](#)). The patients were assigned in a 1:1 ratio to one of the following treatment arms following acute PCI of the culprit lesion(s):

- Full revascularization arm: FFR-guided PCI of non-culprit lesions at any time during *index* hospitalization or
- Conservative arm: Initial conservative management of non-culprit lesions

### Full revascularization arm

Following index PCI of the infarct related artery FFR-guided PCI of non-infarct related lesion(s) could be done either during the index procedure or later during the index hospitalization at the discretion of the operator. For visually estimated stenosis grade 90-99%, FFR was recommended, but not mandated. An FFR value of ≤0.80 was considered significant for ischemia with a recommendation that non-culprit PCI was performed. It was up to the operator to decide whether to use intravenous (standard dose of 140 mcg/kg/min) or intracoronary (IC) adenosine during FFR, with a recommended IC dose of 100 mcg in the right coronary artery and 200 mcg in the left coronary artery<sup>11</sup>. An FFR of >0.80 was to be considered non-significant for ischemia with a recommendation that medical management was pursued as per guidelines. IC nitroglycerine (200-300 mcg) was recommended prior to FFR, as was drift check after FFR as a quality measure. The procedural steps for FFR recommended to all operators are shown in the Supplement.

**Figure 1**



Schematic illustration of the study procedure. Following primary PCI 1,545 patients were randomized to either FFR-guided PCI during index hospitalization ( $n=765$ ) or initial conservative management of non-culprit lesions ( $n=778$ ). The study is event driven with an expected median follow-up of 2.75 years for the primary endpoint. CABG, coronary artery bypass graft surgery; FFR, fractional flow reserve; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

**Pressure wires:** Only Fractional Flow Reserve pressure wires from Abbott or Boston Scientific were to be used for the study mandated FFR measurement in the full revascularization arm.

### Conservative treatment arm

During the index hospitalization, only the infarct-related artery was to be treated with PCI in the conservative treatment arm. Guideline recommended medical therapy for secondary prevention was mandated and medical therapy for angina pectoris was at the investigators discretion. Clinical follow-up of symptoms was recommended, but it was also acceptable to make a plan at hospital discharge for a later outpatient non-invasive stress-test. It was not acceptable to plan for an elective PCI in this treatment arm without signs of ischemia or symptoms.

### Angina pectoris after the study mandated treatment

After the study mandated treatment strategy, patients with stable angina pectoris that could not be medically managed, were recommended to undergo an imaging-

based non-invasive stress test before deciding on a new elective coronary angiography according to current guidelines. If patients in both groups were found to have signs of significant ischemia on a stress-test or still had significant angina and were sent for elective coronary angiography, then FFR was allowed according to current ESC guidelines for stable coronary artery disease<sup>12</sup> at the discretion of the patient's responsible physician. However, it was recommended that a non-invasive stress test was performed as first option if a patient presented with angina.

### Ethical considerations

The Ethics Committees in all participating countries approved the protocol, informed consent form, and subject information sheet. The study is conducted in full conformity with the principles of the current revision of the Declaration of Helsinki (last amended 2013) and in full conformity with relevant regulations.

### Study organization

This is an academically initiated study led by researchers at Karolinska Institutet, Stockholm, and Uppsala University, Sweden. The National Coordinators and Principal Investigators are presented in the Supplementary Table. The Uppsala Clinical Research Center (UCR), Sweden, is the clinical and data coordinating center. Data generated in the study will belong to the Sponsor Karolinska University Hospital.

### Data collection

All data is collected in an electronic data capture system (EDC). In Sweden, study specific questions are shown in the SWEDEHEART registry. Answers to these questions and a selection of registry data are automatically transferred to the EDC.

### Study follow-up

Telephone and medical record review will be performed by a research nurse after 30 days, 1 year, and prior to data base lock primarily to see if the patient has experienced anything of the following: MI, revascularization (PCI/CABG), major bleeding, stroke or rehospitalization due to heart failure. Furthermore, the Seattle Angina Questionnaire-7 (SAQ-7) will be used to evaluate effects on angina pectoris.

### Long term registry follow-up

In Sweden, data on hospitalization for myocardial infarction, PCI, CABG, and secondary prevention from the SWEDEHEART registry or corresponding registries in other countries will be collected on all patients when possible. For deceased patients, data on cause of death will be collected from the Swedish Death Cause Registry or from the medical records. In addition, data from

Swedish patients who were eligible, but not randomized into the study will be analyzed based on the SWEDEHEART registry. Baseline data from index hospitalization, angiography/PCI procedure data, and outcome data from registries will be analyzed on these screened patients.

### Clinical Safety Assessments by the DSMB

The Data and Safety Monitoring Board (DSMB) had the possibility to recommend the sponsor to stop enrollment due to safety or futility. Even though the trial was stopped early, the results will be presented in a similar fashion as originally planned.

### Adjudication of Events

All new MIs/suspected MIs and unplanned revascularizations (PCI/CABG) or attempted revascularizations will be adjudicated by the Clinical Events Adjudication (CEA) Committee at UCR. See CEA Charter as supplement.

Definition of unplanned revascularization (adapted from the FAME2 study definition):

Revascularization was considered to be unplanned when a patient was admitted to hospital (or during index hospitalization) with persistent or increasing symptoms (with or without changes in the ST segment or T wave or elevated biomarker levels) and a revascularization procedure was performed during the same hospitalization. All unplanned revascularizations including attempted unplanned revascularizations will be adjudicated by the independent CEA Committee, to determine the type of trigger (STEMI, NSTEMI, unstable angina, stable angina, other, and unknown). The severity of angina (according to the criteria of the Canadian Cardiovascular Society [CCS]) that led to the procedure will be entered via the SWEDEHEART registry or directly in the eCRF.

### Statistical analysis

Analyses will primarily be performed on the intention-to-treat (ITT) set, defined as all intentionally randomized patients, by randomized treatment. There will also be per protocol analysis taking into account those who cross over to another group. All endpoints will be analyzed using Cox proportional hazards regression with randomized treatment, country, and gender as factors, and age as a continuous covariate, and treatment contrasts presented as hazard ratios with 95% confidence interval and associated p-values. Patients that withdraw from follow-up will be considered censored on the day of withdrawal. For endpoints that do not include all-cause death, patients that die without reaching an endpoint will be considered censored on the day of death. The primary analysis will be based on time-to-first-event of all follow-up time of each patient at time of data base lock. Formal type I error control will be ensured for the primary and the key secondary endpoint by a sequential procedure where significance for the key secondary endpoint is accepted only if the primary end point is significant, at a

two-sided  $\alpha=0.05$ . A detailed statistical analysis plan will be completed before end of study and unblinding of the steering committee to treatment differences.

### Determination of sample size

The sample size calculation was updated based on preliminary unadjudicated outcome data from December 2019 in order to approximate the number of total events so far (blinded to the Investigators regarding treatment arms). After inclusion in the study was halted based on the COMPLETE study data<sup>9</sup> in September 2019, the number of randomized patients was 1,545. In order to increase the power with the 1,545 patients the power calculation was changed from the original difference in proportion approach to be based on the pre-defined time-to-event analysis and to incorporate all follow-up time among the included patients. However, the primary analysis is still time-to-first-event, not counting recurrent events for each patient. The combined primary endpoint of death and MI was also changed to include also unplanned revascularization.

Using Schoenfeld's formula for event-based power, 80% power for  $HR = 0.74$ , at a two-sided  $\alpha = 0.05$ , requires 346 observed events.  $HR = 0.74$  is chosen to approximate the risk ratio of 0.75 at one year of the original power calculation, assuming a control group rate of 9.9%/year.

Follow-up time to obtain the targeted number of events was calculated by approximating the enrollment of the 1,545 patients as uniform enrollment of 25% during the first 1.5 years and 75% during 1.5 years, and assuming rates of 8.7% events during the first year and 5.7% events during subsequent years, in both trial arms combined. Using the method of Lachin and Foulkes<sup>13</sup>, an expected follow-up was estimated to 2.75 years after last-patient-in, meaning that the 346 events could be collected by continuing follow-up for less than three years from September 2019. A blinded re-estimation of the follow-up time will be performed when most patients have completed their 1-year visit, and cleaning and adjudication of outcome data is under way.

## Results

Thirty-two hospitals in seven countries participated in including the following no of patients in the study; Sweden 796, Denmark 332, Serbia 318, Finland 64, Latvia 14, Australia 13, and New Zealand 6. Patients were included from August 8, 2016 to September 11, 2019. See Supplementary Table for details. Baseline characteristics of included patients are shown in Table 2. Patients are aged 65 +/- 11 years and 76% were male. Prescription of medication on discharge followed current clinical practice guidelines. There was no difference in peak creatinine during the index hospitalization between the groups. Procedural characteristics are shown in Table 3.

**Table 2.** Baseline characteristics of included patients

	FFR (n = 765)	Conservative (n = 778)	Total (n = 1543)
Age, years (SD)	65.0 (10.3)	65.7 (10.6)	65.3 (10.5)
Female sex (%)	163 (21.3%)	202 (26.0%)	365 (23.7%)
BMI	27.62 (4.40)	27.59 (4.26)	27.60 (4.33)
Diabetes (%)	122/764 (16.0%)	127/777 (16.3%)	249/1541 (16.2%)
Previous MI (%)	73/761 (9.6%)	53/776 (6.8%)	126/1537 (8.2%)
Smoker (%)	266/744 (35.8%)	251/748 (33.6%)	517/1492 (34.7%)
Ex-smoker (%)	215/744 (28.9%)	208/748 (27.8%)	423/1492 (28.4%)
Hypertension (%)	385/764 (50.4%)	405/776 (52.2%)	790/1540 (51.3%)
Dyslipidemia treatment (%)	178/761 (23.4%)	171/772 (22.2%)	349/1533 (22.8%)
Previous PCI (%)	72/765 (9.4%)	63/778 (8.1%)	135/1543 (8.7%)
Symptom onset to index PCI ≤6 h	539/754 (71.5%)	569/763 (74.6%)	1108/1517 (73.0%)
6-12 h	121/754 (16.0%)	110/763 (14.4%)	231/1517 (15.2%)
> 12 h	94/754 (12.5%)	84/763 (11.0%)	178/1517 (11.7%)
Killip class I/II/III (%)	34/748 (4.5%)	37/765 (4.8%)	71/1513 (4.7%)
ECG to index PCI in STEMI patients, median(Q1-Q3)	1.13 (0.78-1.73)	1.12 (0.75-1.64)	1.13 (0.78-1.67)
Peak creatinine	91.1 (29.4)	90.1 (34.0)	90.6 (31.8)
Medications at discharge			
Aspirin (%)	743/762 (97.5%)	758/777 (97.6%)	1501/1539 (97.5%)
P2Y12 inhibitor			
Any	747/759 (98.4%)	764/777 (98.3%)	1511/1536 (98.4%)
Ticagrelor	675/759 (88.9%)	677/777 (87.1%)	1352/1536 (88.0%)
Clopidogrel	72/759 (9.5%)	87/777 (11.2%)	159/1536 (10.4%)
Beta blocker	621/762 (81.5%)	628/777 (80.8%)	1249/1539 (81.2%)
ACE-inhibitor or ARB	608/762 (79.8%)	610/777 (78.5%)	1218/1539 (79.1%)
Statin	743/761 (97.6%)	752/776 (96.9%)	1495/1537 (97.3%)

Patients with data; BMI N=1523, ECG to index PCI in STEMI patients N=1346, Peak Creatinine during index hospitalization N=1534.

ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; ECG, electrocardiogram; FFR, fractional flow reserve; MI, myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

**Table 3.** Procedural characteristics

Indication	FFR (n = 765)	Conservative (n = 778)	Total (n = 1543)
STEMI	675 (88.2%)	690 (88.7%)	1365 (88.5%)
STEMI/Rescue PCI	14 (1.8%)	18 (2.3%)	32 (2.1%)
Risk evaluation following successful thrombolysis	7 (0.9%)	7 (0.9%)	14 (0.9%)
Very high risk NSTEMI	69 (9.0%)	63 (8.1%)	132 (8.6%)
Radial access	713 (93.2%)	727 (93.4%)	1440 (93.3%)
Location of culprit lesion			
Left main coronary artery	6 (0.8%)	1 (0.1%)	7 (0.5%)
Left anterior descending artery	260 (34.0%)	264 (33.9%)	524 (34.0%)
Circumflex artery	155 (20.3%)	166 (21.3%)	321 (20.8%)
Right coronary artery	351 (45.9%)	356 (45.8%)	707 (45.8%)
Number of residual coronary arteries with 50-99% stenosis*			
1	564 (73.7%)	549 (70.6%)	1113 (72.1%)
≥2	201 (26.3%)	229 (29.4%)	430 (27.9%)
Location of non-culprit lesions (50-99%)			
Left main coronary artery	2 (0.3%)	2 (0.3%)	4 (0.3%)
Left anterior descending artery	394 (51.5%)	436 (56.0%)	830 (53.8%)
Proximal LAD	161 (21.0%)	157 (20.2%)	318 (20.6%)
Circumflex artery	338 (44.2%)	336 (43.2%)	674 (43.7%)
Right coronary artery	231 (30.2%)	233 (29.9%)	464 (30.1%)
Most severe lesion in a non-culprit coronary artery excluding CTO			
50-69%	267 (34.9%)	325 (41.8%)	592 (38.4%)
70-89%	364 (47.6%)	328 (42.2%)	692 (44.8%)
90-99%	133 (17.4%)	124 (15.9%)	257 (16.7%)
CTO (+other non-culprit stenosis)	42 (5.5%)	35 (4.5%)	77 (5.0%)

\* The one vessel category includes also patients with non-culprit stenosis in culprit main artery area only (i.e first diagonal was culprit, mid-LAD was non-culprit; n=31), and two incorrectly included patients with no recorded non-culprit lesion. CTO, chronic total occlusion; FFR, fractional flow reserve; LAD, left anterior descending artery; NSTEMI, non-ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-elevation myocardial infarction.

**Table 4.** Study-mandated fractional flow reserve (FFR)

FFR during index procedure	159 (20.8%)
FFR performed or attempted*	742/765 (97.0%)
Lowest FFR per patient <sup>†</sup>	0.76 (0.14)
50-69% per vessel	0.83 (0.09)
70-89% per vessel	0.79 (0.11)
90-99% per vessel	0.71 (0.12)
Any FFR ≤ 0.8 <sup>‡</sup>	446/742 (60.1%)
FFR ≤ 0.8 of FFR-measured arteries <sup>§</sup>	
Left main coronary artery	1/2 (50.0%)
Left anterior descending artery	268/410 (65.4%)
Circumflex artery	144/327 (44.0%)
Right coronary artery	98/227 (43.2%)

\* FFR performed or not possible to pass with FFR wire or visually assessed as 90%-99%

<sup>†</sup> Non-culprit arteries with stenosis visually assessed as 90%-99% counted as FFR=0.5

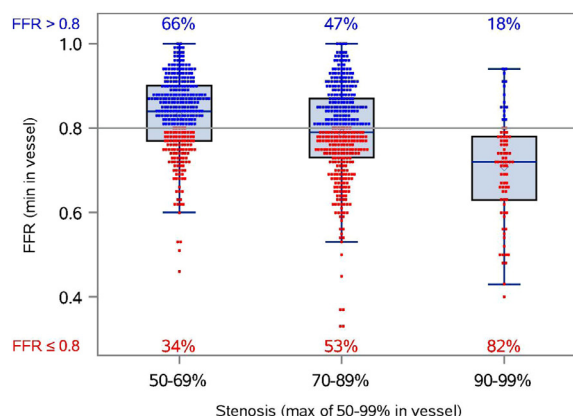
<sup>‡</sup> Includes patients with non-culprit vessel stenosis visually assessed as 90%-99% (n = 32) and lesions that was not possible to pass with FFR wire (n = 5)

<sup>§</sup> Non-culprit arteries with stenosis visually assessed as 90%-99% stenosis included in both numerator and denominator

The majority of patients presented with STEMI, but almost 9% of the patients were very high risk NSTEMI patients. Furthermore, approximately 54% of patients had a non-culprit lesion located in the LAD.

FFR data are shown in Table 4. In 21% of patients FFR measurements were performed during the index PCI procedure, while the remaining were performed later during the index hospitalization as a staged procedure. In the full revascularization arm, the study allocated strategy was followed for 97% of the patients. In the conservative arm, the study allocated strategy was followed for 99.6% of the patients – FFR was performed in only 3 patients in this arm. The mean FFR value for the most severe lesion per patient was 0.76. Furthermore, 60% of patients that followed the randomized strategy had at least one non-culprit lesion at the significance threshold level; FFR ≤ 0.80 or a lesion visually assessed as 90-99% stenosis grade or a lesion that was not possible to pass with FFR wire and therefore considered significant. In addition, a majority of non-culprit lesions (65%) had a FFR value ≤ 0.80 in the LAD, which was significantly more than in the LCX ( $P < 0.001$ ) or the RCA ( $P < 0.001$ ).

In intermediate lesions (50-69% stenosis grade) evaluated by FFR only a minority (34%) were physiologically significant (FFR ≤ 0.8), as shown in Figure 2. Also, in relatively tight lesions (70-89% stenosis grade on visual estimation), a large proportion (47%) were not physiologically significant (FFR > 0.80). Furthermore, we found that in angiographically severe non-culprit lesions of 90-99% severity by visual estimation, 1 in 5 of these lesions were re-classified as non-flow limiting by FFR.

**Figure 2**

Fractional flow reserve (FFR) versus visual estimation of stenosis severity. Study-mandated minimum FFR value per maximum stenosis grade according to visual estimation in non-culprit vessels. All blue dots are FFR values > 0.80. All red dots are FFR values ≤ 0.80. Number of measured vessels in each category of stenosis severity: 50-69%; n = 331, 70-89%; n = 370 and 90-99%; n = 82 vessels. It is evident that visual estimation of stenosis grade is a poor predictor of FFR in intermediate non-culprit lesions.

## Discussion

The FULL REVASC study is designed to determine whether FFR-guided complete revascularization following PCI of culprit lesions in STEMI and very high risk NSTEMI patients with multivessel disease can reduce the combined primary endpoint of all-cause mortality, MI, and unplanned revascularization. The optimal evaluation method and strategy for non-culprit lesions in multivessel disease STEMI and very high risk NSTEMI patients is still not clear.

Fractional flow reserve-guided PCI has been shown to be a reliable method for detecting flow-limiting lesions and improve prognosis<sup>4,6</sup> in patients with stable angina. Therefore, incorporating FFR measurements of non-culprit lesions in multivessel STEMI patients seems to be a logical step. The DANAMI-3-PRIMULTI trial tested this strategy with staged FFR-guided PCI of non-culprit lesions during the index hospital admission<sup>8</sup>. The COMPARE-ACUTE trial showed that it was feasible and safe to perform FFR-guided multivessel PCI in STEMI patients also in the acute phase<sup>7</sup>. However, due to lack of power, neither of these trials could detect any significant difference of death and/or MI. The recent FUTURE study was stopped early by the DSMB due to an unexpected increase in all-cause mortality in the FFR arm, although the combined primary outcome was neutral<sup>14</sup>. Furthermore, the results of the CULPRIT-SHOCK showed that the combined endpoint of all-cause mortality and MI

was significantly higher among patients randomized to receive immediate multivessel PCI as compared to treating the culprit lesion only, however, in patients with AMI and cardiogenic shock<sup>15</sup>. The studies above all imply that there is a need for a larger randomized study to determine whether FFR-guided PCI of non-culprit lesions is of clinical benefit.

The FULL REVASC trial has some unique features; it has the largest sample size of the FFR-guided multivessel PCI strategy trials at this point. The trial was designed as an R-RCT embedded in a clinical continuous clinical registry for patients enrolled in Sweden and through a separate web page in other countries. This increased the all-comer perspective and has the potential of complete follow-up of events and high inclusion rate at a lower cost than traditional RCTs. The trial has a pragmatic approach so that FFR-guided PCI can be performed at any time during index hospitalization to follow the clinical work-flow. Also, FULL REVASC is truly FFR-guided whereas in COMPLETE <1% of patients had FFR-guided PCI. So, especially for intermediate non-culprit lesions with 50-80% stenosis grade, the FULL REVASC results may influence our understanding of the optimal strategy in these patients. Lastly, also very high risk NSTEMI patients where primary PCI is performed, are included in FULL REVASC. The findings of COMPLETE and FULL REVASC will therefore complement each other.

The trial successfully enrolled the types of patients it aimed for. The mean FFR value was 0.76 and more than half of included patients had a non-culprit LAD lesion. This suggests that the 1,545 patients included is a very large cohort with relatively high risk. Furthermore, we confirm the results from previous studies that visual estimation of stenosis grade is a poor predictor of FFR significance. In fact, among patients with angiographically highly significant non-culprit lesion of 90-99%, 1 in 5 of these lesions were re-classified as non-significant by FFR. Among those with intermediate lesion severity (70-89%), half of the lesions were non-significant by FFR. Interestingly, 60% of lesions among patients randomized to undergo FFR-guided complete revascularization had a significant FFR ( $\leq 0.80$ ) that qualified for revascularization. Thus, 40% of the lesions were potentially spared from potentially hazardous revascularization procedures. Therefore, the trial has a potential to evaluate if FFR-guided complete non-culprit revascularization following primary PCI in patients with multivessel disease can reduce the combined primary endpoint of all-cause mortality, MI, and unplanned revascularization.

## Author contributions

Felix Böhm: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Supervision; Validation; Visu-

alization; Roles/Writing - original draft; Writing - review & editing.

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Ollie Östlund: Formal analysis; Methodology; Writing - review & editing.

Thomas Engström: Conceptualization; Investigation; Methodology; Writing - review & editing.

Eigil Fossum, Colin Berry, Christoph Liebetrau, and Claes Held: Methodology; Writing - review & editing.

Goran Stankovic and Oskar Angerås: Investigation; Methodology; Writing - review & editing.

Andrejs Ērglis, Madhav Menon, Carl Schultz, and Mika Laine: Investigation; Writing - review & editing.

Andreas Rück: Data curation; Investigation; Methodology; Project administration; Supervision; Writing - review & editing.

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## Perspectives

The FULL REVASC study is an Investigator-initiated prospective, multicenter registry-based (R-RCT) based in Europe and Australia/New Zealand in which 1,545 patients are included. Enrollment was halted prematurely in September 2019 based on the results of the COMPLETE study. We demonstrate that visual estimation of stenosis severity is a poor predictor of FFR for non-culprit lesions in STEMI. This trial will assess if FFR-guided complete revascularization of non-culprit lesions in patients with multivessel disease following primary PCI results in reduction in all-cause mortality, MI, and unplanned revascularization compared to the culprit lesion-only strategy. The study is event-driven and we anticipate that the primary endpoint results will be ready in 2022.

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## Supplementary materials

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