Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: De Bruyne B, Pijls NHJ, Kalesan B, et al. Fractional flow reserve–guided PCI versus medical therapy in stable coronary disease. N Engl J Med 2012;367:991-1001. DOI: 10.1056/NEJMoa1205361

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Table of content of the supplementary appendix

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Data Safety Monitoring Board – S. Windecker (Chairman), B.J. Gersh, S.J. Pocock.

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II. Supplementary Methods

A. Patients inclusion and exclusion criteria

Eligible subjects include patients with stable clinical condition and one-, two- or three vessel disease at coronary angiography and amenable for PCI. Inclusion is based on the combination of the clinical data, the non-invasive testing, when available, and the angiographic data.

Inclusion criteria:

1. Stable angina pectoris (Canadian Cardiovascular Society Class [CCS] 1, 2, 3); or angina pectoris CCS class 4 subsequently stabilized medically (minimum 7 days); or atypical or no chest pain but documented ischemia on noninvasive testing;
2. At least one stenosis of at least 50% diameter reduction in at least one major native epicardial coronary artery with a diameter of at least 2.5 mm and supplying viable myocardium
3. Eligible for PCI
4. Signed written informed consent obtained

Note:

a) Patients with restenosis in native coronary arteries can be included

b) Patients with previous stents and restenosis may be included.

c) Total occlusion can be included if this vessel supplies viable myocardium, and if recanalization is deemed likely and useful by the operator and if it is not the only lesion with a significant FFR. In total chronic occlusions it is not mandated to measure FFR. The FFR value will be set at an arbitrary value of 0.5.

d) Patients who sustained a STEMI or a NSTEMI more than one week ago can be included in the trial (see exclusion criteria)

Exclusion Criteria

1. Patients in whom the preferred treatment is CABG
2. Patients with left main coronary artery disease requiring revascularization
3. Patients with a recent (less than 1 week) STEMI or Non-STEMI
4. Prior CABG
5. Contra-indication to dual antiplatelet therapy
6. LVEF < 30%
7. Severe LV hypertrophy (defined as a septal wall thickness at echocardiography of more than 13 mm)
8. Planned need for concomitant valvular or aortic surgery
9. Extremely tortuous or calcified coronary arteries precluding FFR measurements
10. A life expectancy of less than 2 years
11. Age under 21

12. Pregnancy or intention to become pregnant during the course of the trial
13. Refusal or inability to sign an informed consent. Mental condition (psychiatric or organ cerebral disease) rendering the subject unable to understand the nature, scope, and possible consequences of the trial or mental retardation or language barrier such that the patient is unable to give informed consent
14. Potential for non-compliance towards the requirements in the trial protocol (especially the medical treatment) or follow-up visits
15. Participation or planned participation in another cardiovascular clinical trial before two year follow-up is completed

B. Primary end-points: definitions and DSMB stopping rules

The primary end-point of the FAME II trial was defined as a composite of the 24-month:

- All cause death
- Documented myocardial infarction
- Unplanned hospitalization leading to urgent revascularization

as adjudicated by the Clinical Event Committee.

Death

All patient deaths will be documented on the CRF. The Sponsor or designee must be notified of a patient's death within 24 hours after the clinical site has knowledge of the event. The principal investigator's narrative summary of the circumstances of death is required. Autopsy results, when available, should be reported to the CRO.

In the primary comparison of the two treatment strategies, all deaths will be examined. Death due to specific causes will be investigated and adjudicated by the CEC. All deaths are considered cardiac unless an unequivocal non-cardiac cause can be established.

Cardiac Death:

Any death due to immediate cardiac causes (e.g. MI, low-output failure, fatal arrhythmia). Unwitnessed death and death of unknown cause will be classified as cardiac death.

Vascular Cause death:

Death due to cerebrovascular disease, pulmonary embolism, ruptured aortic aneurysm, dissecting aneurysm, or other vascular cause.

Non-Cardiovascular death:

Any death not covered by the above definitions, including death due to infection, sepsis, pulmonary causes, accident, suicide or trauma.

Myocardial Infarction

A myocardial infarction (MI) will be considered an event whether it occurred within the first 24 hours after randomization or more than 24 hours after randomization. A definite diagnosis of myocardial infarction is made based on the following:

a. *Within 24 hours after randomization or any PCI*:

I. CK-MB above 10 x 99th percentile upper reference limit (URL) determined on a single measurement, OR

II. CPK-MB above 5 x 99th percentile URL determined on a single measurement PLUS at least one of the following:

- new pathological Q waves in at least 2 contiguous leads or new persistent non-rate related LBBB,
- angiographically documented native coronary artery occlusion,
- imaging evidence of new loss of viable myocardium

b. More than 24 hours after randomization:

I. Detection of rise and/or fall of cardiac biomarkers, CK-MB or troponin with at least one value above the 99th percentile of the URL together with evidence of myocardial ischemia with at least one of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block (LBBB)]

OR

II. Development of pathological Q waves (≥ 0.03 seconds in duration and ≥ 1 mm in depth) in ≥ 2 contiguous precordial leads or ≥ 2 adjacent limb leads) of the ECG

OR

III. Imaging evidence of loss of viable myocardium or new regional wall motion abnormality

For each MI adjudicated by the CEC, the type of MI will also be described as:

- ST-Elevation MI (STEMI)
  - Also categorize as:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- Non-ST-Elevation MI (NSTEMI)
  - Also categorize as:
    - Q-wave
    - Non-Q-wave
    - Unknown (no ECG or ECG not interpretable)
- Unknown (no ECG or ECG not interpretable)

Unplanned hospitalization leading to an urgent revascularization procedure

This component of the primary end-point will be present only if the patient is hospitalized unexpectedly because of persisting or increasing complaints of chest pain (with or without ST-T changes, with or without elevated biomarkers) AND a revascularization is performed within the same hospitalization. This event should be clearly distinguished from the cross-over revascularization procedure (secondary endpoint) which is performed on non-urgent basis. A complete and detailed narrative of this event by the investigator will be needed.

Data and Safety Monitoring Board Stopping Rules

The DSMB charter specifies that the recommendation of stopping the study would be based on safety concerns as evidenced by statistical and clinical judgment to the rate of serious adverse events. There were no pre-specified formal statistical stopping rules for the study. The reason that the DSMB decided against a formal stopping rule was to be able to continue the trial even if formal rules would have been satisfied. The DSMB met to review study data by treatment group in April 2011, August 2011 and November 2011. An independent third party CRO was responsible for the data analysis and the CRO statistician provided the interface with DSMB members. The DSMB also received twice monthly reports of enrolment and events. The DSMB received listings, figures, and reports including events as reported by the site and as adjudicated by the CEC and had full access to the data.

III. Supplementary Results

1. Procedural results

Among the 447 patients assigned to PCI plus OMT, FFR-guided PCI was performed in 435 patients (97.3%). The success rate of stenting in attempted PCI cases 99.1%. A total of 728 stents were implanted in these patients: 416 everolimus-eluting stents (57.1% of stents), 117 zotarolimus-eluting (16.1%), 113 biolimus-eluting (15.5%), 38 sirolimus-eluting (5.2%), 24 paclitaxel-eluting (3.3%) and 20 bare-metal stents (2.7%). 421 patients received only DES, 3 patients received at least one DES and one bare-metal stent, 11 patients received only bare-metal stents. The remaining 12 patients did not receive any stent: 3 underwent successful balloon angioplasty, 4 underwent bypass surgery rather than PCI, one did not receive a PCI since FFR was >0.8 in all lesions, one had an unsuccessful PCI because of severe calcification, and 3 were foreseen for staged procedure, 2 of these subsequently received a DES and one a drug-eluting balloon. Among the 441 patients assigned to OMT alone, 439 received OMT alone as assigned, whereas 2 patients received DES, one everolimus-eluting, the other biolimus-eluting stents. Among the 166 registry patients randomly selected for follow-up, 1 patient received an everolimus-eluting stent.

IV. Supplementary Tables

Table S1: Medications in randomized and registry patients at baseline, and 1 month, 6 months and 1 year of follow-up.

	Randomized Trial				
	PCI+OMT	OMT	p-value*	Registry	p-value for trial vs. registry
BASELINE	n=447	n=441		n=166	
Aspirin	390 (87.2)	395 (89.6)	0.28	143 (86.1)	0.41
Clopidogrel/Prasugrel	221 (49.4)	199 (45.1)	0.20	72 (43.4)	0.35
Statin	370 (82.8)	361 (81.9)	0.72	128 (77.1)	0.11
Beta blocker	338 (75.6)	343 (77.8)	0.45	122 (73.5)	0.38
ACE-inhibitors/AT-II antagonist	307 (68.7)	308 (69.8)	0.71	127 (76.5)	0.060
Calcium entry blocker	103 (23.0)	99 (22.4)	0.83	50 (30.1)	0.041
30 DAYS	n=414	n=415		n=151	
Aspirin	408 (98.6)	399 (96.1)	0.031	138 (92.0)	0.001
Clopidogrel/Prasugrel	404 (97.6)	182 (43.9)	<0.0001	52 (34.7)	<0.0001
Statin	397 (95.9)	400 (96.4)	0.71	143 (95.3)	0.64
Beta blocker	353 (85.3)	375 (90.4)	0.025	118 (78.7)	0.003
ACE-inhibitors/AT-II antagonist	329 (79.5)	335 (80.7)	0.65	119 (79.3)	0.83
Calcium entry blocker	100 (24.2)	133 (32.0)	0.011	52 (34.7)	0.11
6 MONTHS	n=238	n=240		n=93	
Aspirin	235 (98.7)	225 (93.8)	0.004	86 (93.5)	0.23
Clopidogrel/Prasugrel	231 (97.1)	110 (45.8)	<0.0001	24 (26.1)	<0.0001
Statin	230 (96.6)	228 (95.0)	0.37	87 (94.6)	0.59
Beta blocker	192 (80.7)	197 (82.1)	0.69	68 (73.9)	0.10
ACE-inhibitors/AT-II antagonist	195 (81.9)	206 (85.8)	0.25	71 (77.2)	0.12
Calcium entry blocker	60 (25.2)	73 (30.4)	0.20	39 (42.4)	0.005
1 YEAR	n=41	n=37		n=7	
Aspirin	37 (90.2)	34 (91.9)	1.00	7 (100.0)	1.00
Clopidogrel/Prasugrel	26 (63.4)	13 (35.1)	0.023	2 (28.6)	0.44
Statin	37 (90.2)	37 (100.0)	0.12	7 (100.0)	1.00
Beta blocker	28 (68.3)	31 (83.8)	0.12	6 (85.7)	1.00
ACE-inhibitors/AT-II antagonist	32 (78.0)	32 (86.5)	0.39	6 (85.7)	1.00
Calcium entry blocker	12 (29.3)	11 (29.7)	1.00	2 (28.6)	1.00

p-value using chi square test; when cells are <15 Fisher's test was used.

Number of patients eligible for follow up was 414, 417 and 151 at 30 days in respective groups, 238, 241 and 92 at 6 months and 41, 38 and 7 at 1 year.

Table S2: Clinical events in randomized trial and registry patients

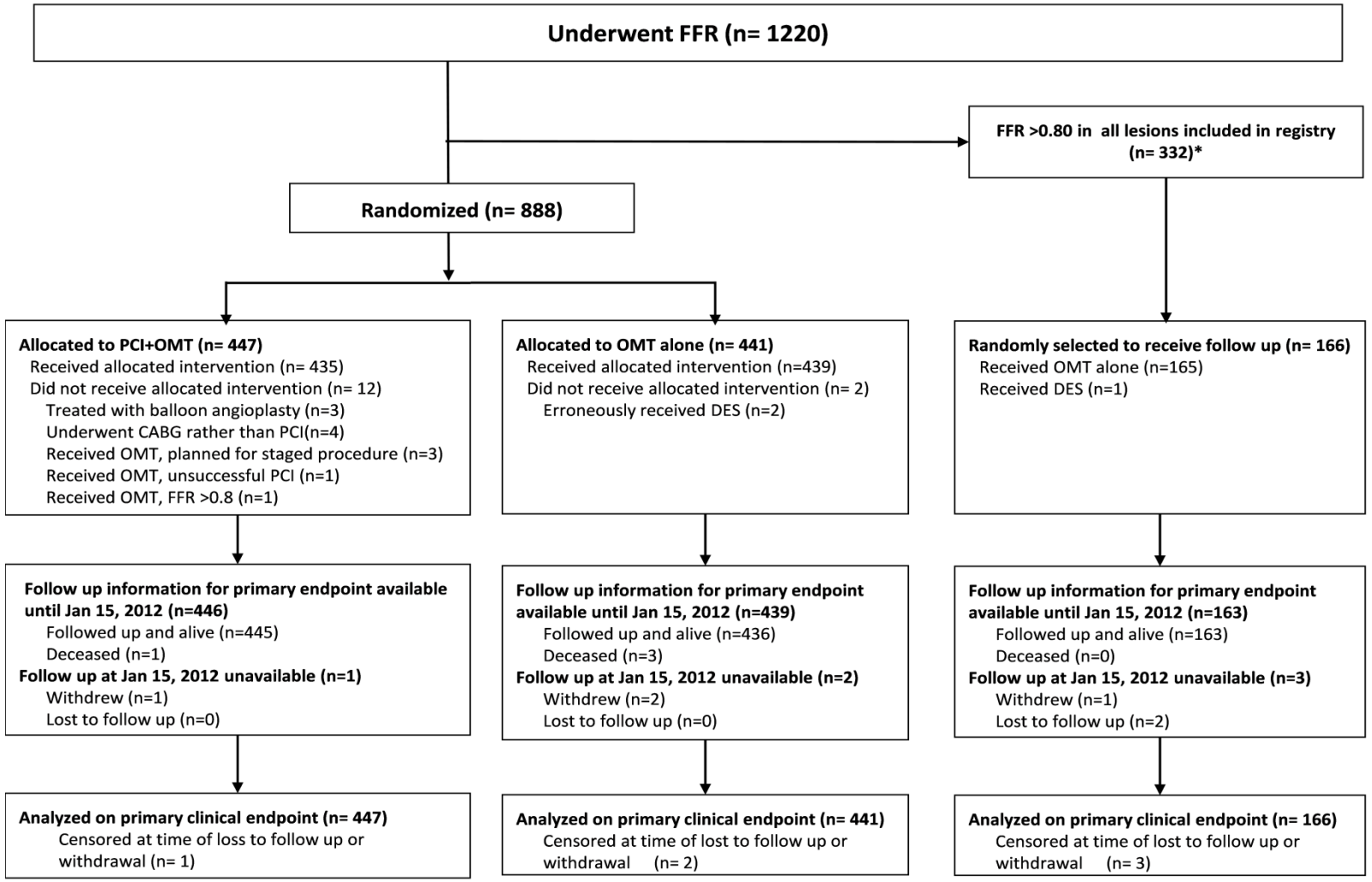
				PCI+OMT vs. Registry		OMT vs. Registry	
	PCI+OMT	**OMT**	**Registry**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Number of patients	*447*	*441*	*166*				
Primary endpoint*	19 (4.3)	56 (12.7)	5 (3.0)	1.29 (0.49 to 3.39)	0.61	4.32 (1.75 to 10.66)	0.001
All-cause death	1 (0.2)	3 (0.7)	0 (0)	1.12 (0.05 to 27.33)	0.54	2.66 (0.14 to 51.18)	0.30
MI	15 (3.4)	14 (3.2)	3 (1.8)	1.61 (0.48 to 5.37)	0.41	1.65 (0.50 to 5.47)	0.41
Urgent revascularization	7 (1.6)	49 (11.1)	4 (2.4)	0.63 (0.19 to 2.03)	0.43	4.65 (1.72 to 12.62)	0.001
Death or myocardial infarction	15 (3.4)	17 (3.9)	3 (1.8)	1.03 (0.29 to 3.62)	0.97	1.88 (0.57 to 6.16)	0.29
Cardiac death	1 (0.2)	1 (0.2)	0 (0)	0.84 (0.06 to 11.63)	0.54	0.85 (0.06 to 11.78)	0.54
Any revascularization	14 (3.1)	86 (19.5)	6 (3.6)	0.84 (0.33 to 2.14)	0.72	5.76 (2.54 to 13.07)	<0.0001
Non-urgent revascularization	7 (1.6)	38 (8.6)	2 (1.2)	1.28 (0.26 to 6.23)	0.76	7.24 (1.74 to 30.15)	0.001
Stroke	1 (0.2)	2 (0.5)	1 (0.6)	0.37 (0.02 to 5.95)	0.47	0.75 (0.07 to 8.22)	0.81
Definite or probable ST	5 (1.1)	1 (0.2)	1 (0.6)	1.68 (0.19 to 14.46)	0.64	0.32 (0.02 to 5.54)	0.40

Relative risk using continuity correction if events are zero

*Primary end point= Death or Myocardial infarction or Urgent revascularization

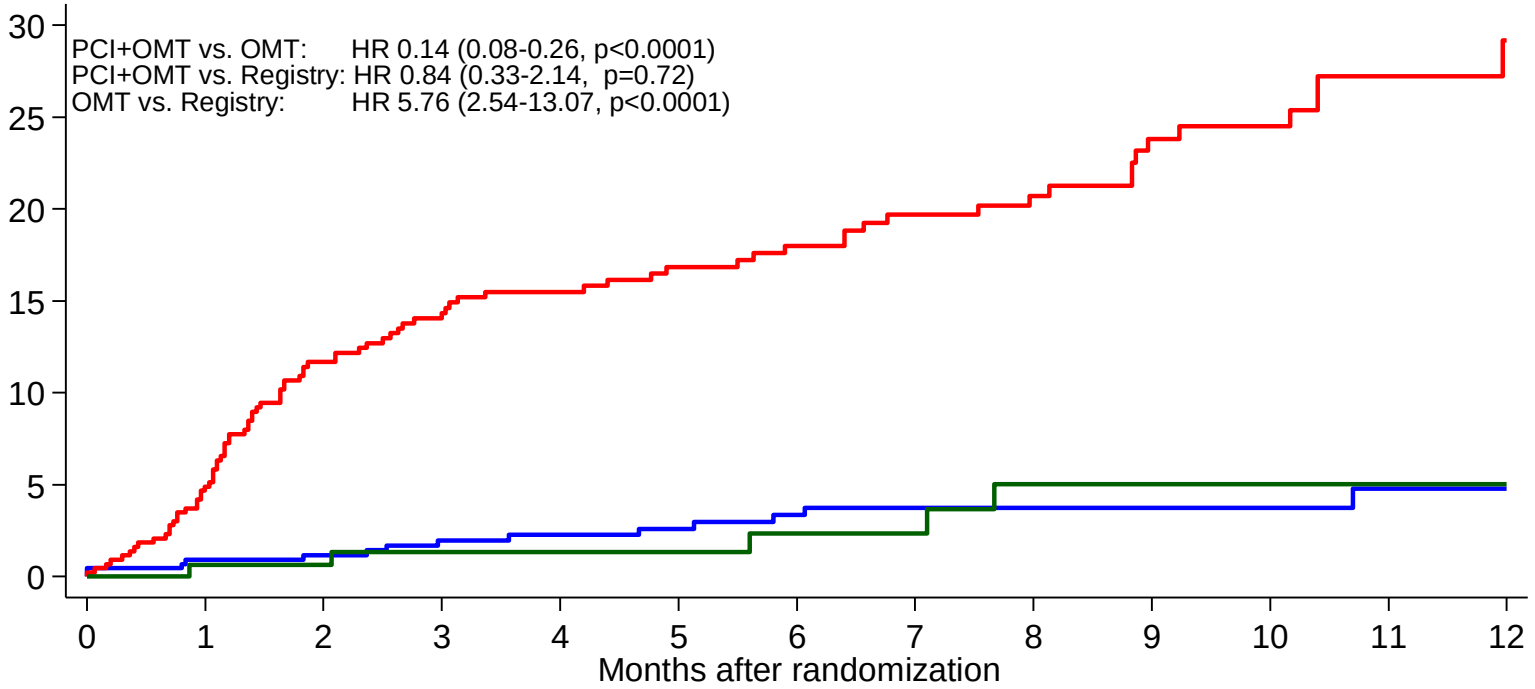
V. Supplementary Figures

Supplementary Figure S1: Flow Chart



* Note that 6 patients had total occlusions supplying akinetic myocardium and were therefore not considered for PCI; 1 patient had 2 FFR –ve lesions and was therefore included in the registry, however a subsequently detected total occlusion was eventually treated with DES.

Supplementary Figure S2: (Panel A) Kaplan-Meier plots of total revascularization in randomized and registry patients

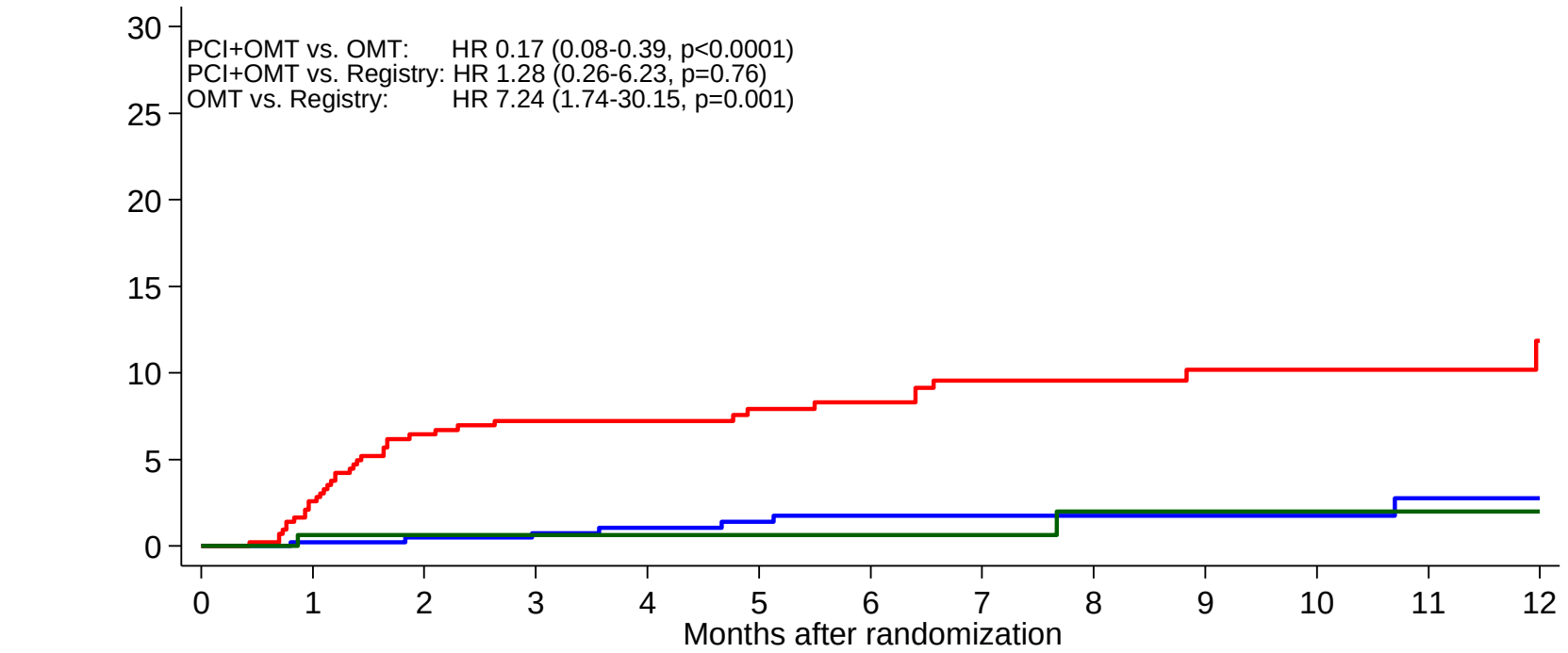


No. at risk

OMT	441	404	348	302	267	236	203	175	150	118	91	63	35
PCI+OMT	447	420	393	353	311	280	243	212	176	156	116	89	52
Registry	166	155	144	132	117	106	94	75	64	53	42	26	13

One event in registry occurred after 12 months of follow up

Supplementary Figure S2: (Panel B) Kaplan-Meier plots of non-urgent revascularization in randomized and registry patients

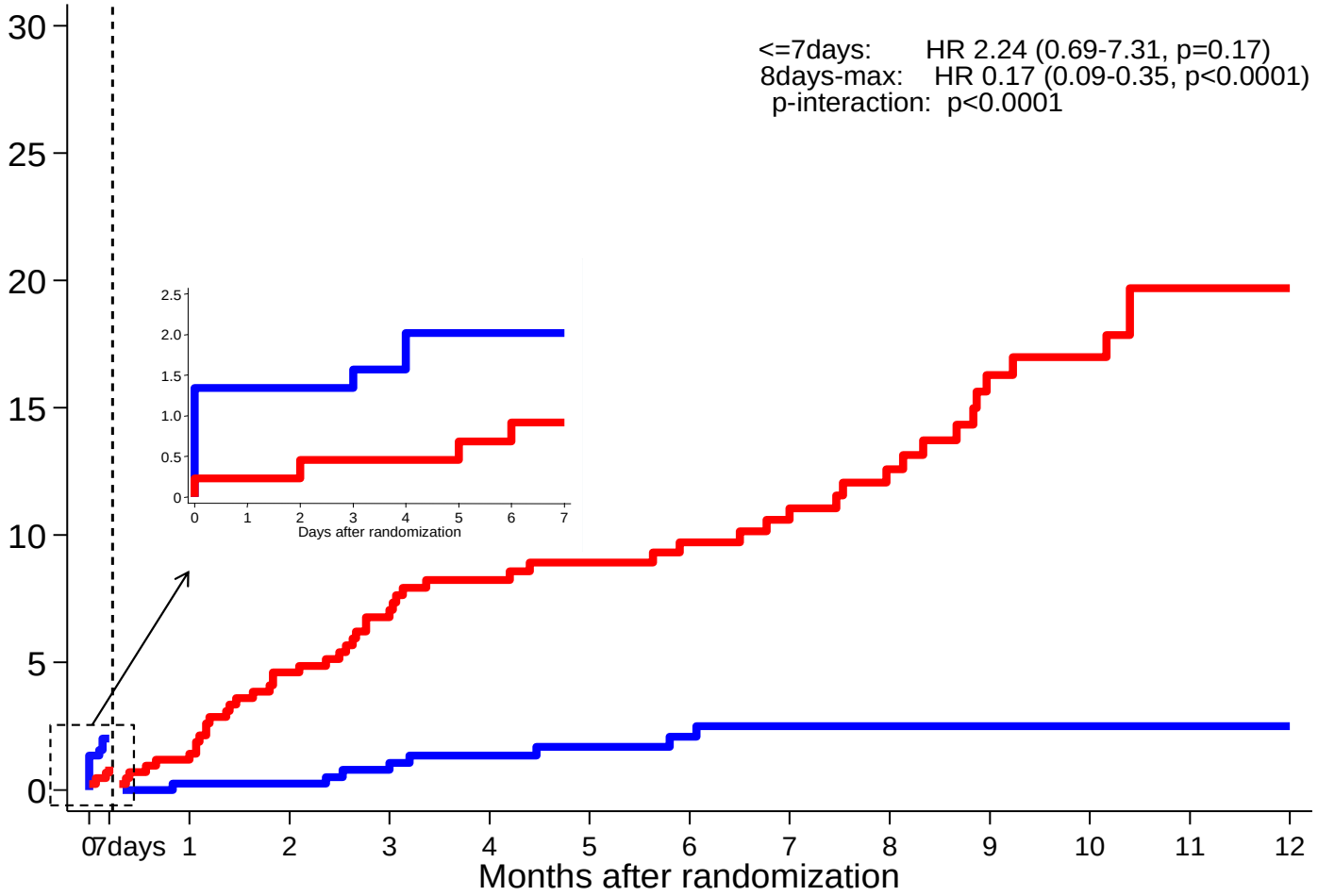


No. at risk

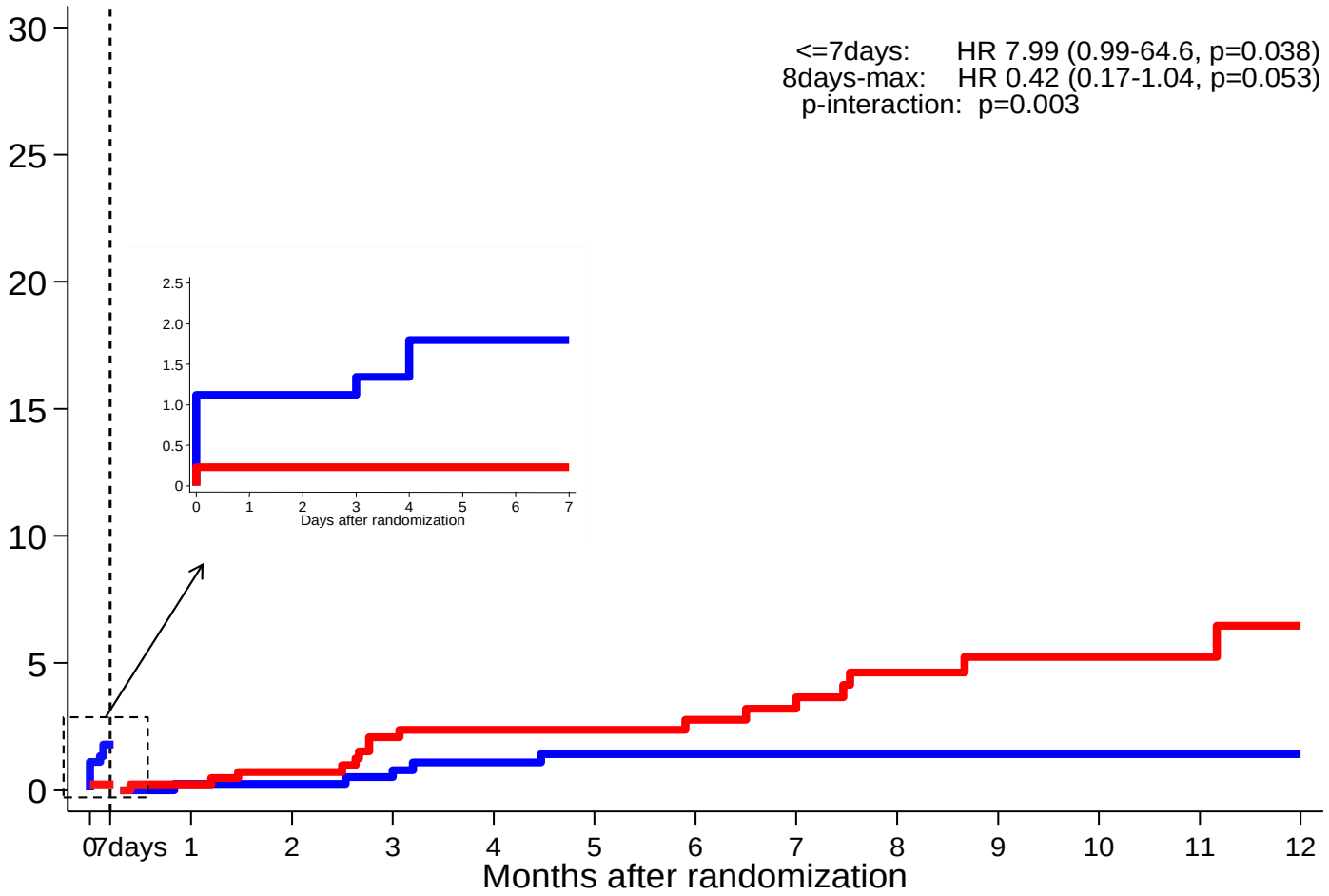
OMT	441	413	367	327	293	261	227	199	174	142	111	82	51
PCI+OMT	447	422	394	356	314	283	245	215	179	159	119	91	53
Registry	166	155	144	133	118	107	96	76	66	55	43	27	13

No events occurred after 12 months of follow up

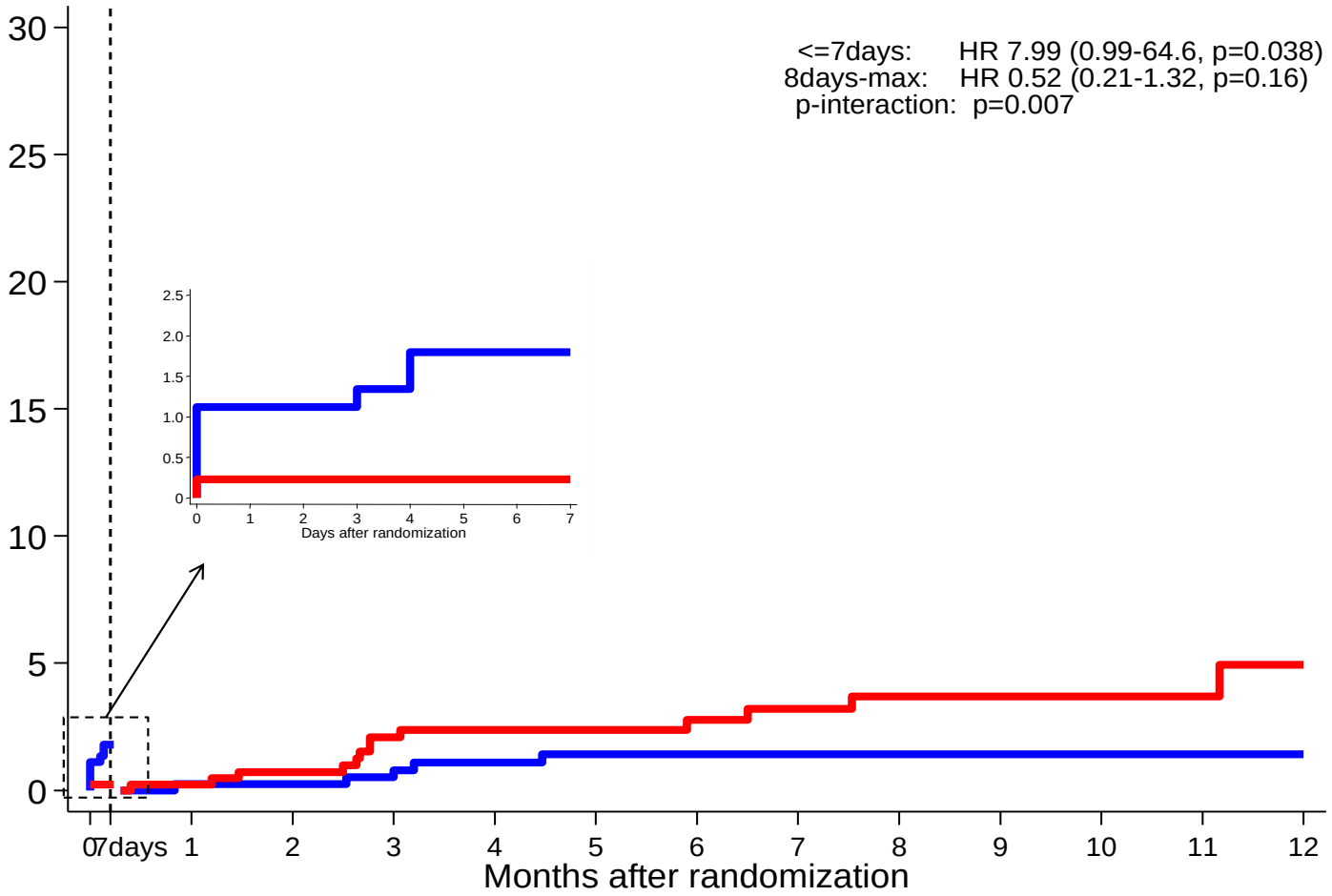
Supplementary Figure S3: (Panel A) Kaplan-Meier plots of landmark analysis of Primary outcome (Death or MI or Urgent Revascularization)



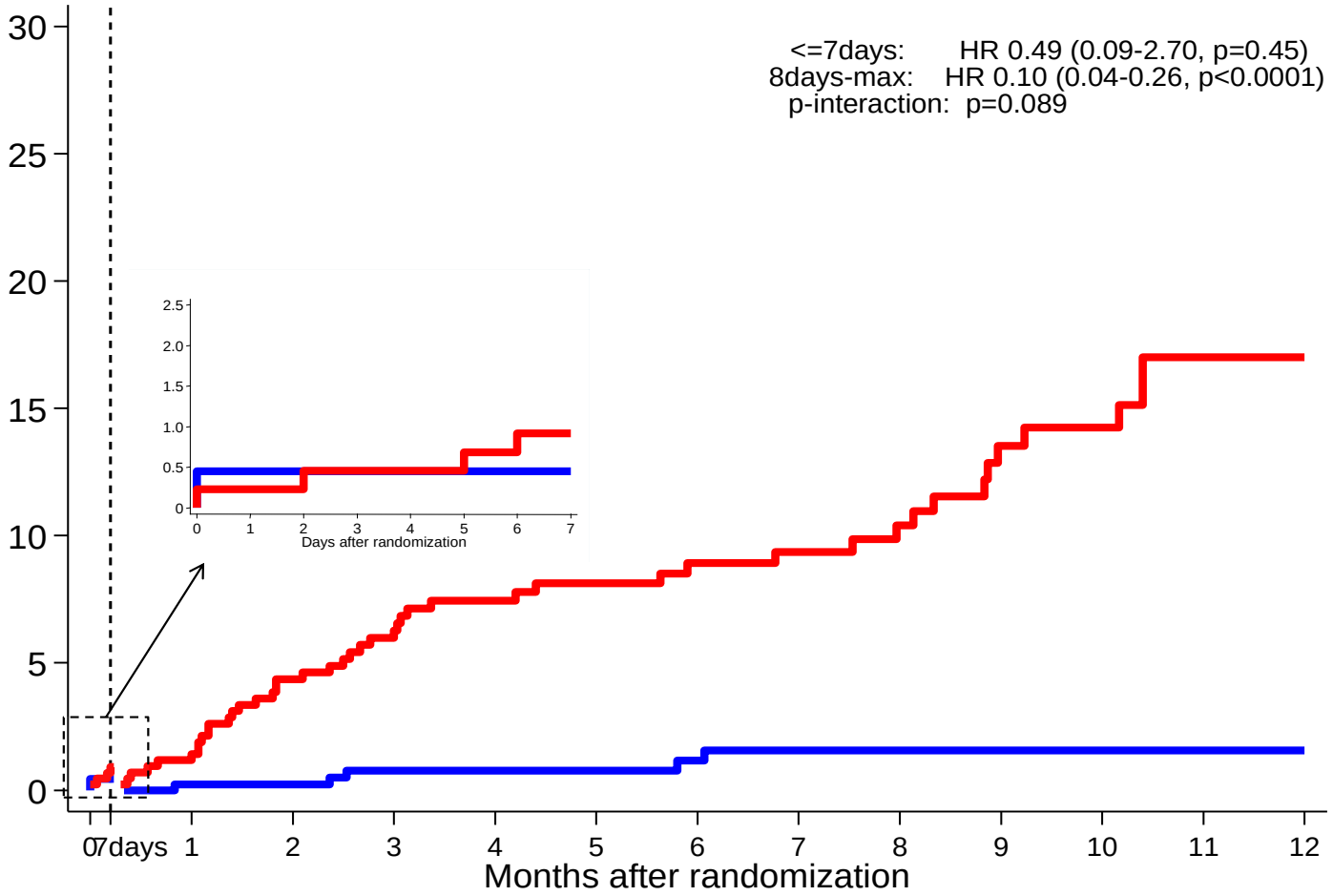
Supplementary Figure S3: (Panel B) Kaplan-Meier plots of landmark analysis of Death or MI



Supplementary Figure S3: (Panel C) Kaplan-Meier plots of landmark analysis of MI



Supplementary Figure S3: (Panel D) Kaplan-Meier plots of landmark analysis of Urgent Revascularization



Supplementary Figure S4: Stratified analysis of the primary endpoint

	PCI+OMT	OMT	HR (95% CI)	p-value for interaction
Age				0.22
>60	9 (3.2)	33 (11.8)	0.14 (0.05 to 0.37)	
≤60	10 (6.1)	23 (14.2)	0.31 (0.13 to 0.71)	
Gender				0.33
male	12 (3.4)	42 (12.4)	0.18 (0.08 to 0.38)	
female	7 (7.7)	14 (13.6)	0.34 (0.12 to 1.02)	
Diabetes				0.33
Yes	7 (5.7)	17 (14.5)	0.31 (0.13 to 0.75)	
No	12 (3.7)	39 (12.0)	0.17 (0.08 to 0.39)	
History of Stroke/ TIA				0.34
Yes	2 (8.3)	2 (14.3)	0.52 (0.07 to 3.82)	
No	17 (4.0)	54 (12.6)	0.20 (0.10 to 0.38)	
History of MI				0.85
Yes	7 (4.3)	24 (14.5)	0.20 (0.08 to 0.53)	
No	12 (4.3)	32 (11.8)	0.23 (0.10 to 0.51)	
History of PCI				0.56
Yes	4 (5.0)	12 (15.8)	0.29 (0.10 to 0.87)	
No	15 (4.1)	44 (12.1)	0.20 (0.10 to 0.41)	
LVEF				0.99
≤50	2 (2.4)	6 (10.7)	0.22 (0.05 to 1.08)	
>50	16 (4.7)	48 (13.6)	0.23 (0.12 to 0.44)	
FFR				0.010
<0.65	7 (3.1)	35 (17.1)	0.08 (0.03 to 0.26)	
≥0.65	12 (5.4)	21 (8.9)	0.46 (0.21 to 1.01)	
Diameter Stenosis				0.98
≥70%	16 (4.6)	45 (14.2)	0.21 (0.11 to 0.42)	
<70%	3 (3.0)	11 (8.9)	0.21 (0.05 to 0.91)