BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016169
Article Type:	Research
Date Submitted by the Author:	31-Jan-2017
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diagnostics
Keywords:	Ischaemic heart disease < CARDIOLOGY, Myocardial perfusion imaging, Functional ischaemia test, Survival benefit, All-cause death

Stable coronary artery disease without ischaemia:

Can exceptional revascularization be a good choice?

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Word count : 2,692

ABSTRACT

Objectives In stable coronary artery disease (CAD), coronary revascularization may reduce mortality of patients with a certain amount of left ventricular myocardial ischaemia. However, revascularization does not always follow the guidance suggested by ischaemia testing. We compared outcomes in patients without ischaemia who had either revascularization or medical treatment.

Design and population Based on registries, 1,327 consecutive patients with normal myocardial perfusion scintigraphy (MPS) and 278 with fixed perfusion defects were followed for a median of 6.1 years. Most patients received medical therapy alone (**Med**), but 26 (2%) with a normal MPS and 15 (5%) with fixed perfusion defects underwent revascularization (**Revasc**).

Outcome measures Incidence rates of all-cause death (ACD) and rates of cardiac death/myocardial infarction (CD/MI).

Results With a normal MPS, the ACD rate was 6.2%/year in the **Revasc** group versus 1.9%/year in the **Med** group (p=0.01); the CD/MI rates were 6.9%/year and 0.6%/year, respectively (p<0.00001). Results persisted after adjustment for predictors of revascularization, in particular angina score, and in comparisons of matched **Revasc** and **Med** patients. With fixed defects, the ACD rate was 9.1%/year in the **Revasc** group and 6.7%/year in the **Med** group (p=0.44); the CD/MI rate was 5.0%/year versus 4.2%/year, respectively (p=0.69). If adjusted for angiographic variables or analyzed in matched subsets differences remained insignificant.

Conclusions With normal MPS, revascularization conferred a higher risk, even after adjustment for predictors of revascularization. With fixed defects, the **Revasc** versus **Med** difference was close to equipoise. Hence, in patients with stable CAD without ischaemia, we could not find evidence to justify exceptional revascularization.

Strengths and limitations of this study

- The study was observational, and endpoints were collected from comprehensive national registries
- MPS results were open to referring clinicians
- Rationales for the choice of post-MPS treatment were found in medical records
- Careful adjustment was undertaken in order to achieve a fair comparison of subgroups, and a matching approach was also used
- We focused on hard events.

INTRODUCTION

In stable angina pectoris patients at low to intermediate risk of coronary artery disease (CAD), it is recommended to use non-invasive testing as a gatekeeper to coronary angiography[1 2]. Myocardial perfusion scintigraphy (MPS) is an ischaemia test that effectively stratifies patients with an intermediate pre-test risk into groups with low or high post-test risk and, hence, identifies potential candidates for coronary revascularization[3-5]. Revascularization is often performed with the intention to improve symptoms or prognosis; however, a survival benefit over optimal medical therapy has not been documented in stable CAD patients[6-8]. Data from registry-based studies suggest that only in the presence of a certain amount of ischaemia is the prognosis with respect to hard events better with coronary revascularization than with conservative therapy[9 10]. Nevertheless, in daily routine a small proportion of patients with normal MPS or fixed defects still undergoes revascularization. It remains an open question whether this reflects a clinically justified exception to the rule. Addressing this question is a non-trivial task, as a potential inferior prognosis in the revascularized patients may simply reflect a proper clinical selection of high-risk patients with a real need for revascularization, regardless of the MPS result. Comparison of patients with similar risk profiles as regards potential prognostic factors related to the treatment decision might allow for an answer. In an observational design we compared the outcome with and without coronary revascularization in consecutive patients with symptoms of stable CAD but without ischaemia in a setting, where the MPS results were open to the treating physicians.

MATERIALS AND METHODS

Study population and design

From a consecutive series of 2,157 MPS performed 2002-2007 at Odense University Hospital for suspected or known CAD in patients who did not participate in a research project, 1,327 patients had normal scintigraphic findings while 278 demonstrated fixed perfusion defects. Results were analyzed for all patients and for subsets undergoing early revascularization (**Revasc**) or receiving pure medical therapy (**Med**). Early revascularization was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 180 days from MPS, while performed >180 days later was termed late revascularization. Trial design and methods were published previously[11]. The study was approved by the local data protection committee.

MPS

MPS was performed as single photon emission computed tomography (SPECT) with technetium-99m sestamibi using a standard maximum exercise test or pharmacological stress by adenosine, dipyridamol, or dobutamine. In the early study period non-gated acquisitions were used. Later, gated studies were used with at-rest left ventricular ejection fraction (LVEF) being available in 648 patients (49%) with normal MPS and 147 patients (53%) with fixed defects. For post-stress LVEF, the numbers were 687 (52%) and 123 (44%), respectively. Scans were interpreted semi-quantitatively and deemed normal in case of normal radionuclide distribution throughout the myocardium in the presence also of normalcy with respect to available non-perfusion markers like wall thickening/motion and LVEF. All abnormal scans were reviewed by an experienced reader (AJ) blinded to clinical data. Extent and severity of perfusion defects at stress imaging were converted to percentage myocardium and categorized as small (5-9% of the myocardium), moderate (10-14%), or large (>14%) [12].

Follow-up

History of CAD and medication at the time of MPS were retrieved from medical records and MPS reports. Follow-up ran from the date of the MPS until 31st December 2011. Events during follow-up were appointed by means of regional and national registers as previously described[11]. Medical records were examined for treatment decision, and angiographic data were obtained from the Western Denmark Heart Registry comprising records on all coronary angiographies and revascularization procedures performed in Western Denmark, including angina score according to the Canadian Cardiovascular Society (CCS)[13].

Statistics

Continuous and categorical variables are shown by means of descriptive statistics and frequency counts including percentages, respectively. Inter-group differences in continuous variables were tested by the Wilcoxon rank-sum test; frequencies were compared by Fisher's exact test or the chi-squared test. Main endpoints were all-cause death (ACD) and cardiac death (defined as death from ischaemic heart disease, congestive heart failure, or malignant arrhythmia) or non-fatal myocardial infarction (CD/MI). Time until event is illustrated with cumulative incidence functions. Cause-specific hazard ratios (CSHR) based on a Cox proportional hazard model as well as subdistribution hazard ratios (SDHR) based on the Fine and Gray regression model[14] were used to assess the difference between **Revasc** and **Med**. The HRs were adjusted for main predictors of revascularization, which were identified by comparison of the two treatment groups and an analysis of the reasons given in the medical records of revascularized patients. Adjustment was performed for one covariate at a time as well as in multivariate models. When considering ACD, late revascularization was regarded as a competing event in order not to bias the natural course. When considering CD/MI, non-

cardiac death and late revascularization were regarded as competing events. Following the general advice to consider all competing events in the statistical analysis [15 16], we present cumulative incidence functions for all four events but restrict reporting of HRs to the two main endpoints.

Furthermore, a matching approach was used. For each revascularized patient we found a medically treated match with identical or nearly identical values for the variables predictive of revascularization. Event incidences for the revascularized patients and their matches were compared by cumulative incidence curves, CSHRs and SDHRs.

The significance level was set to 5%. Statistical analyses were performed with STATA (©StataCorp LP, Texas, USA). Matching was performed with the 'optmatch' program[17] and incidence rates were compared with the 'stir' command.

RESULTS

Early revascularization was performed in 26 patients (2%) with normal MPS and in 15 patients (5%) with fixed defects. Characteristics are given in table 1.

Table 1 Patient characteristics

a) Patients with normal MPS

	All	**Revasc**	**Med**	p
N	1327	26	1301	
Age, years (mean±SD)	59.5±11.8	62.1±12.2	59.5±11.8	0.29
Male	574 (43)	17 (65)	557 (43)	0.03
Known CAD	248 (19)	15 (58)	233 (18)	<0.0001
History				
MI	87 (7)	6 (23)	81 (6)	0.005
PCI	149 (11)	12 (46)	137 (11)	<0.0001
CABG	59 (4)	2 (8)	57 (4)	0.32
Diabetes mellitus	202 (15)	5 (19)	197 (15)	0.58
Medication				
Aspirin	797 (60)	23 (88)	774 (59)	0.001
Beta blocker	462 (35)	20 (77)	442 (34)	<0.0001
Calcium channel blocker	325 (24)	9 (35)	316 (24)	0.25
Nitrates	279 (21)	8 (31)	271 (21)	0.23

Lipid-lowering agents	481 (36)	16 (62)	465 (36)	0.01
LVEF, rest, N	648	15	633	1.00
<30%	0	0	0	
30≤ LVEF<50 %	34 (5)	0	34 (5)	
≥50%	614 (95)	15 (100)	599 (95)	
LVEF, stress, N	687	16	671	0.63
<30%	0	0	0	
30≤ LVEF<50%	41 (6)	0	41 (6)	
≥50%	646 (94)	16 (100)	630 (94)	
Family history of CAD, N	216	23	193	0.83
Positive	113 (52)	13 (57)	100 (52)	
CCS score, N	223	26	197	0.01
1	122 (55)	10 (38)	112 (57)	
2	76 (34)	8 (31)	68 (35)	
3	24 (11)	8 (31)	16 (8)	
4	1 (0.4)	0	1 (0.5)	
Smoking, N	203	22	181	0.41
Current	56 (28)	8 (36)	48 (27)	
Never	79 (39)	6 (27)	73 (40)	
Ceased	68 (34)	8 (36)	60 (33)	
Number of stenotic vessels, N	210	26	184	<0.0001
0 vessels	101 (48)	2 (8)	99 (54)	
1 vessel	59 (28)	10 (38)	49 (27)	
2 vessels	30 (14)	7 (27)	23 (13)	
3 vessels	20 (10)	7 (27)	13 (7)	

b) Patients with fixed perfusion defects

	All	**Revasc**	**Med**	p
N	278	15	263	
Age, years (mean±SD)	62.5±10.2	61.6±11.5	62.6±10.1	0.63
Male	214 (77)	14 (93)	200 (76)	0.20
Known CAD	196 (71)	11 (73)	185 (70)	1.00
History				
MI	152 (55)	8 (53)	144 (55)	1.00
PCI	101 (36)	6 (40)	95 (36)	0.79
CABG	76 (27)	3 (20)	73 (28)	0.77
Diabetes mellitus	59 (21)	5 (33)	54 (21)	0.33
Medication				
Aspirin	233 (84)	12 (80)	221 (84)	0.72
Beta blocker	177 (64)	9 (60)	168 (64)	0.79
Calcium channel blocker	76 (27)	6 (40)	70 (27)	0.25
Nitrates	75 (27)	4 (27)	71 (27)	1.00
Lipid-lowering agents	169 (61)	8 (53)	161 (61)	0.59
Size of defects				0.62
Small (5-9%)	92 (33)	4 (27)	88 (33)	
Medium (10-14%)	60 (22)	2 (13)	58 (22)	
Large (>14%)	126 (45)	9 (60)	117 (45)	
LVEF, rest, N	147	4	143	0.79
<30%	20 (14)	0	20 (14)	
30≤LVEF<50%	57 (39)	1 (25)	56 (39)	
≥50%	70 (48)	3 (75)	67 (47)	
LVEF, stress, N	123	5	118	0.84
<30%	21 (17)	0	21 (18)	
30≤LVEF<50%	48 (39)	2 (40)	46 (39)	
≥50%	54 (44)	3 (60)	51 (43)	
Family history of CAD, N	106	14	92	0.77
Positive	45 (42)	5 (36)	40 (43)	

CCS score, N	115	15	100	0.13
1	73 (63)	7 (47)	66 (66)	
2	25 (22)	3 (20)	22 (22)	
3	16 (14)	5 (33)	11 (11)	
4	1 (1)	0	1 (1)	
Smoking, N	102	13	89	1.00
Current	36 (35)	5 (38)	31 (35)	
Never	19 (19)	2 (15)	17 (19)	
Ceased	47 (46)	6 (46)	41 (46)	
Number of stenotic vessels, N	108	15	93	0.002
0 vessels	15 (14)	0	15 (16)	
1 vessel	26 (24)	3 (20)	23 (25)	
2 vessels	34 (31)	11 (73)	23 (25)	
3 vessels	33 (31)	1 (7)	32 (34)	

The decision to revascularize was clearly associated with symptoms and angiographic findings but less with MPS results (table 2). In four cases of normal MPS, revascularization was performed following a new incident independent of the symptoms prompting MPS.

Table 2 Reasons for revascularization according to medical records

a) Patients with normal MPS

DM	History	Angio findings*	CCS score	Time from MPS to revasc. (days)	Type of revasc.	Reasoning to decide for revascularization was based on
		0-VD	3	83	PCI	Angio, sympt, EET
	PCI	2-VD	2	72	PCI	Angio, sympt, ECG changes during dobutamine stress
+		2-VD	2	159	CABG	Angio, sympt, IVUS
	MI, PCI	2-VD	2	127	PCI	Angio, EET, history of MI
+		1-VD	1	157	PCI	MI, i.e., recurrent event
		3-VD	3	5	PCI	Angio
+		1-VD	3	71	PCI	Angio, sympt
	PCI, CABG	3-VD	1	169	PCI	Angio, sympt
		0-VD	1	49	PCI	Angio, IVUS, EET
		1-VD	1	93	PCI	MI, i.e., recurrent event
		1-VD	2	149	PCI	Angio, IVUS, sympt
	PCI	2-VD	1	131	PCI	MI, i.e., recurrent event
	PCI	1-VD	1	116	PCI	Angio, sympt
+	MI, PCI	3-VD	3	43	PCI	Angio, sympt
		1-VD	3	170	CABG	Angio, IVUS, persistent sympt
		1-VD	2	43	PCI	Angio, persistent sympt
		1-VD	1	145	PCI	Angio, sympt
	MI, PCI	3-VD	3	95	PCI	Angio, sympt
+	MI, PCI	2-VD	2	104	PCI	Angio, sympt
	MI, PCI	3-VD	3	104	CABG	Angio, sympt
	PCI	1-VD	3	37	PCI	Angio, sympt
	MI, PCI, CABG	3-VD	1	16	PCI	MI, i.e., recurrent event
	PCI	3-VD	1	43	PCI	Angio, sympt
		1-VD	2	76	PCI	Angio, sympt
		2-VD	1	49	PCI	Angio, sympt

		2-VD	2	53	PCI	Angio, ECG changes during adenosine stress	

b) Patients with fixed defects

DM	History	Size of defect	Angio findings*	CCS score	Time from MPS to revasc. (days)	Type of revasc.	Reasoning to decide for revascularization was based on
	MI, CABG, PCI	Large	3-VD	3	36	PCI	Sympt, angio
+	MI, CABG	Large	2-VD	3	49	PCI	Angio
		Mod.	1-VD	3	105	PCI	Sympt, angio
	PCI	Large	2-VD	3	158	PCI	Sympt, angio
	MI, PCI	Small	3-VD	2	98	CABG	Sympt, angio
	PCI	Small	2-VD	3	64	PCI	Sympt, angio
		Small	2-VD	1	60	PCI	Angio
	MI, PCI	Large	2-VD	1	70	CABG	Sympt, angio
	MI, PCI	Large	2-VD	1	72	PCI	Angio
	MI	Large	2-VD	1	25	CABG	Angio
+	PCI	Large	2-VD	1	148	PCI	Reduced LVEF, viability, angio
+	MI, CABG	Large	2-VD	2	71	PCI	Sympt, angio
+	MI	Large	2-VD	1	16	CABG	Angio
+		Mod.	1-VD	1	85	PCI	Sympt, angio
		Small	1-VD	2	77	PCI	Angio

*None had stenosis of the left main stem. Degree and appearance of stenoses were not reported

Angio = angiography; DM = diabetes mellitus; ECG = electrocardiogram; EET = exercise ECG testing; IVUS = intravascular ultrasound; mod. = moderate; MPS = myocardial perfusion scintigraphy; sympt = symptoms; VD = vessel disease

Median follow-up (range) was 6.1 years (0.02-9.96). Table 3 shows the cumulative numbers of events during follow-up. With normal MPS, the number of MIs was higher than the number of CDs (3% versus 1%, p<0.0001), whereas in the patients with fixed defects, the disparity, albeit insignificant, was the reverse (10% versus 14%, p=0.19). In none of the MPS groups did the CD/ACD ratio differ between subgroups; being 2/7 and 14/150, respectively (p=0.15) in normal MPS and 3/7 versus 35/88 (p=1.00) in patients with fixed defects (table 3).

Table 3 Cumulative number of events during follow-up

	Normal MPS				Fixed defects			
Events	All N (% of 1,327)	**Revasc** N (% of 26)	**Med** N (% of 1,301)	p	All N (% of 278)	**Revasc** N (% of 15)	**Med** N (% of 263)	p
No event	1,079 (81)	14 (54)	1,065 (82)	0.001	140 (50)	7 (47)	133 (51)	0.80

Any event (death/MI/revasc.)	248 (19)	12 (46)	236 (18)		138 (50)	8 (53)	130 (49)	
Death	157 (12)	7 (27)	150 (12)	0.03	95 (34)	7 (47)	88 (33)	0.40
Cardiac death	16 (1)	2 (8)	14 (1)	0.04	38 (14)	3 (20)	35 (13)	0.44
MI	43 (3)	5 (19)	38 (3)	0.001	27 (10)	1 (7)	26 (10)	1.00
MI or death	191 (14)	10 (38)	181 (14)	0.002	111 (40)	8 (53)	103 (39)	0.29
MI or cardiac death	57 (4)	7 (27)	50 (4)	<0.0001	58 (21)	4 (27)	54 (21)	0.53
PCI	81 (6)	1 (4)	80 (6)	1.00	48 (17)	1 (7)	47 (18)	0.48
CABG	15 (1)	2 (8)	13 (1)	0.03	6 (2)	0	6 (2)	1.00
PCI/CABG	92 (7)	3 (12)	89 (7)	0.42	50 (18)	1 (7)	49 (19)	0.49
MI/cardiac death/revasc.	124 (9)	9 (35)	115 (9)	<0.0001	87 (31)	4 (27)	83 (32)	0.78

Cumulative incidence functions shown in figure 1 indicated no difference in the incidence of non-cardiac deaths between the two treatment groups for neither patients with normal MPS, nor patients with fixed defects. As regards late revascularization, the **Med** curve tended to run above the **Revasc** curve in case of fixed defects; however, the difference was not significant. With normal MPS, substantially different incidence rates of the main endpoints could be observed. The ACD rate was 6.2%/year in the **Revasc** group compared with 1.9%/year in the **Med** group (p=0.01) and the CD/MI rate was 6.9%/year versus 0.6%/year, respectively (p<0.00001). In case of fixed defects there were no significant inter-group differences, and **Revasc**/**Med** ratios were similar for both endpoints: The ACD rate was 9.1%/year in the **Revasc** group and 6.7%/year in the **Med** group (p=0.44) and the CD/MI rate was 5.0%/year versus 4.2%/year, respectively (p=0.69).

Quantification of effects and adjustment

Judged from tables 1 and 2, variables CAD, previous MI, previous PCI, CCS score, and number of stenotic coronary arteries were associated with the decision to revascularize despite normal MPS. The use of aspirin, beta blockers, and lipid lowering agents was unequally distributed and, hence, could be a surrogate for a disease state also predictive of revascularization. Gender was also unevenly distributed and, therefore, considered in the

models. In patients with fixed effects, the only significant association found was for the number of stenotic arteries. The lack of significance for the other variables may, however, mainly reflect lack of power due to the small number of revascularized patients. It seems reasonable to assume that variables predictive of the treatment decision in patients with normal MPS would also be potential predictors in patients with fixed effects. Hence, we used the same list of (potential) predictors.

Unadjusted and adjusted CSHRs and SDHRs comparing the **Revasc** and **Med** groups are shown in table 4. Adjustment for clinical and/or angiographic variables did not change the HRs with normal MPS, which were always in the magnitude of 3-5 for ACD and >9 for CD/MI, all being significantly different from 1. With fixed defects, the HR was never significantly different from 1. Adjusted for clinical variables, the HRs for both outcomes stayed in the magnitude of 1.2 to 1.8. However, with adjustment for angiographic variables the HR changed more substantially to values around 2 for ACD and between 0.7 and 0.9 for CD/MI.

Table 4 Cause-specific hazard ratios and subdistribution hazard ratios of the **Revasc** versus **Med** difference

a) Patients with normal MPS

	ACD				CD/MI			
	CSHR	p	SDHR	p	CSHR	p	SDHR	p
Univariate analysis	3.85	0.001	3.42	0.002	15.44	<0.0001	14.09	<0.0001
Adjusted for clinical variables								
Age	3.22	0.003	3.12	0.005	12.93	<0.0001	11.75	<0.0001
Gender	3.58	0.001	3.17	0.003	15.11	<0.0001	13.85	<0.0001
Age, gender	2.89	0.007	2.80	0.01	12.37	<0.0001	11.26	<0.0001
DM	3.81	0.001	3.39	0.002	15.30	<0.0001	13.99	<0.0001
Known CAD	3.76	0.001	3.47	0.002	13.04	<0.0001	12.29	<0.0001
Previous MI	3.97	<0.0001	3.52	0.002	12.76	<0.0001	12.01	<0.0001
Previous PCI	4.27	<0.0001	3.87	0.001	14.42	<0.0001	13.45	<0.0001
CAD category*	3.71	0.001	3.45	0.003	13.02	<0.0001	12.26	<0.0001
CAD category*, previous MI	3.68	0.001	3.42	0.004	12.87	<0.0001	12.48	<0.0001
CAD category*, previous MI, aspirin, beta blocker, lipid lowering	4.22	<0.0001	3.81	0.001	11.86	<0.0001	11.43	<0.0001
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering	4.08	0.001	3.66	0.002	11.76	<0.0001	11.34	<0.0001
Adjusted for angiographic variables								
CCS score (N=223/115)	4.27	0.003	3.77	0.006	12.06	<0.0001	11.03	<0.0001
Number of stenotic vessels (N=210/108)	4.62	0.005	4.52	0.006	9.19	0.001	9.28	0.001
CCS score, number of stenotic vessels (N=210/108)	4.52	0.007	4.18	0.007	9.89	0.001	9.49	0.002

Adjusted for scintigraphic variables								
At-rest LVEF (N=648/147)	2.87	0.08	2.97	0.08	12.78	<0.0001	12.86	<0.0001
Post-stress LVEF (N=687/123)	2.70	0.09	2.80	0.10	12.74	<0.0001	12.93	<0.0001
Adjusted for selected variables of all types								
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, CCS score (N=223/115)	4.55	0.004	3.48	0.009	29.29	<0.0001	26.69	<0.0001
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, number of stenotic vessels (N=210/108)	4.30	0.02	3.79	0.03	11.70	0.001	11.80	0.001
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, CCS score, number of stenotic vessels (N=210/108)	4.14	0.02	3.31	0.06	20.86	0.001	20.23	0.001

b) Patients with fixed perfusion defects

	ACD				CD/MI			
	CSHR	p	SDHR	p	CSHR	p	SDHR	p
Univariate analysis	1.49	0.31	1.68	0.18	1.24	0.72	1.29	0.66
Adjusted for clinical variables								
Age	1.50	0.30	1.75	0.16	1.26	0.70	1.28	0.67
Gender	1.41	0.39	1.60	0.22	1.22	0.74	1.30	0.66
Age, gender	1.44	0.36	1.69	0.19	1.26	0.71	1.30	0.66
DM	1.42	0.39	1.63	0.23	1.19	0.78	1.26	0.40
Known CAD	1.49	0.31	1.68	0.17	1.20	0.76	1.28	0.67
Previous MI	1.50	0.31	1.69	0.17	1.24	0.72	1.29	0.66
Previous PCI	1.52	0.29	1.70	0.16	1.26	0.70	1.29	0.65
CAD category*	1.55	0.27	1.76	0.15	1.28	0.68	1.31	0.64
CAD category*, previous MI	1.56	0.26	1.77	0.14	1.29	0.67	1.32	0.64
CAD category*, previous MI, aspirin, beta blocker, lipid lowering	1.39	0.41	1.58	0.25	1.28	0.69	1.31	0.66
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering	1.34	0.47	1.51	0.30	1.27	0.69	1.32	0.65
Adjusted for angiographic variables								
CCS score (N=223/115)	1.61	0.27	1.93	0.09	0.82	0.75	0.87	0.80
Number of stenotic vessels (N=210/108)	2.35	0.09	2.67	0.06	0.74	0.65	0.77	0.69
CCS score, number of stenotic vessels (N=210/108)	1.76	0.28	2.27	0.07	0.64	0.51	0.73	0.58
Adjusted for scintigraphic variables								
At-rest LVEF (N=648/147)	0.85	0.87	1.00	1.00	-§	-§	-§	-§
Post-stress LVEF (N=687/123)	0.59	0.61	0.72	0.73	-§	-§	-§	-§
Size of defects	1.23	0.61	1.38	0.43	1.00	1.00	1.08	0.90
Adjusted for selected variables of all types								
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, CCS score (N=223/115)	1.54	0.38	1.99	0.13	0.89	0.86	0.94	0.93
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, number of stenotic vessels (N=210/108)	3.68	0.06	4.31	0.10	0.90	0.90	0.85	0.89
Gender, CAD category*,	3.05	0.11	4.37	0.07	0.84	0.83	0.92	0.94

	previous MI, aspirin, beta blocker, lipid lowering, CCS score, number of stenotic vessels (N=210/108)

*In order to reduce the number of covariates, and because of correlation between CAD and previous revascularization, a CAD category variable was generated, taking into account the history of both CAD and previous revascularization: 1 = suspected CAD; 2 = known CAD with no previous revascularization; 3 = known CAD with previous revascularization
§Fitting of Cox-model indicated complete separation; hence, no results could be presented

Scintigraphic variables, available only in a subgroup of all patients, were also to some degree associated with treatment decisions. All the **Revasc** patients with normal MPS had LVEF ≥50%, whereas some of the **Med** patients had 30≤LVEF<50%, cf. table 1a. Adjustment for LVEF category slightly reduced the HRs for ACD but not for CD/MI (table 4a). One out of four of the **Revasc** patients with fixed defects had a moderately reduced at-rest LVEF (30≤LVEF<50%), but no one had a severely reduced LVEF (<30%), which was the case in 14% of the **Med** patients (table 1b). Adjustment for LVEF category reduced the HRs for ACD, whereas for CD/MI, numbers were too small for an estimation. Similarly, in spite of no significant inter-group difference in size of perfusion defects, adjustment for defect size slightly reduced the HR for both endpoints (table 4b).

For matched subsets, results were similar to those from the entire groups; in case of normal MPS the CSHR was 7.97 (p=0.05) for ACD, 4.12 (p=0.08) for CD/MI. With fixed defects, the CSHR was 1.00 (p=1.00) for ACD and 0.70 (p=0.67) for CD/MI, respectively. Cumulative incidence functions resembled those for the entire groups. Detailed results are given in the Supplementary material.

DISCUSSION

In this study, 2% of patients with normal MPS and 5% with fixed perfusion defects underwent early coronary revascularization; i.e., exceptional revascularization. With normal MPS, **Revasc** patients had significantly higher event rates than **Med** patients. With fixed defects, no significant inter-group differences were observed. Results persisted after

adjustment for predictors of revascularization as well as after matching. Noteworthy, MPS was conducted as a part of the routine diagnostic work-up and results were open to the referring clinicians. Still, revascularization was undertaken in some patients, probably primarily based on angiographic and clinical findings.

The use of MPS

In patients with stable angina, an ischaemia test is far from always performed before angiography[18 19]. An anatomical approach to the CAD diagnosis and quantification typically leads to more revascularization procedures than a functional approach[20-22]. However, strategies involving MPS have a greater prognostic power than those without functional testing[23 24].

Optimal risk stratification derives from the ability of a normal MPS to identify patients at exceedingly low risk, and that of an abnormal scan to identify patients at greater risk, thus rendering a number of catheterization and invasive interventions superfluous[25-27]. Following a normal MPS, the annual death rate is generally <2% and the annual rate of hard cardiac events <1%, a little higher in risk groups[28 29]. We and others previously found a general warranty period following a normal MPS of 5 years[11 30]. Thus, under usual conditions, cardiac catheterization is not warranted in the presence of a normal study, unless there is a change in symptoms.

A small percentage of patients with normal scans do have events within the warranty period. In our population of 1,327 patients with normal MPS, four patients (0.3%) underwent revascularization within 6 months from MPS because of an acute MI. One had diabetes, one had chronic kidney disease, and two had known CAD. This supports previous findings of a poorer prognosis for high-risk subgroups and underscores the additional prognostic value of clinical findings to MPS results. It also illustrates the fact that MI – more

than death – is hard to anticipate[31]. MIs can break out in vessels with a normal appearance[32] [33], whereas stenotic and occluded arteries often come with collaterals, preventing MI or at least limiting its size[34]. Hence, although the occurrence of MI is associated with the presence of atherosclerosis, it may not be correlated to its severity, and therefore, MPS – like other imaging techniques – cannot predict specific lesions but patients at risk[35 36].

Left ventricular function in the shape of LVEF has an independent prognostic and predictive value[3 10]. However, decision to perform revascularization in our patients was in general not based on the presence of a reduced LVEF as all **Revasc** patients with normal MPS had preserved LVEFs, and far from all patients with a LVEF below 50% underwent revascularization.

Dominant MPS parameters driving subsequent resource utilization are extent and severity of reversible perfusion defects[12]. In addition, a variety of clinical elements, most importantly anginal symptoms, further influence referral rates[20]. Thus, when patients with normal scans or scans showing only mild ischaemia are referred to angiography, this is typically based on clinical symptoms[37]. In former reports from the US, 3% of patients without ischaemia were referred to angiography, and revascularization was performed in one fifth of these[38-40]. The numbers in our series were higher.

Strengths and limitations

Contrary to previous reports on post-MPS assignment in which the authors were left to speculate on possible reasons for paradoxical treatments [20], we went through medical records describing rationales for the choice of treatment, well aware that it is difficult to find specific information on the reason for a clinical decision in retrospect. Careful adjustment was undertaken in order to achieve a fair comparison of subgroups.

Subsets treated exceptionally, given the MPS findings, constituted a minority of our patients. Considering the small number of **Revasc** patients compared to **Med** patients it was not equitable to estimate a propensity score. However, results from Cox models adjusted for individual covariates are comparable to results from propensity score-adjusted Cox models[41]. Adjustment for different predictors of revascularization did not change our results; specifically, differences persisted after adjustment for angina score, one of the most important predictors of revascularization. In addition, results of the matching approach were comparable to those from Cox modelling, i.e., effects observed in univariate analyses did not vanish. An indicator of an even distribution of non-cardiac health problems affecting prognosis as well as treatment decision was the fact that in none of the subgroups of our patients did we observe a significant difference between the CD/ACD ratios.

In analyzing outcome, we focused on hard events. Just like observational studies have indicated that at least 10% of the left ventricular myocardium should be ischaemic in order for the patient to gain a survival benefit[42-44], the same amount seems to be a prerequisite of an improvement in symptoms and exercise capacity [45 46]. Hence, revascularization is unlikely to benefit stable CAD patients unless there is objective evidence of ischaemia.

CONCLUSIONS

In our consecutive series of patients undergoing MPS for stable angina pectoris in the clinical routine, 2% of those with normal MPS and 5% of those with fixed perfusion defects underwent revascularization, contrary to established rules. With normal MPS, **Revasc** was associated with significantly more cardiac events and shorter survival than **Med**, even after adjustment for clinical, angiographic, and scintigraphic variables. With fixed defects, there

were no significant differences. Thus, our findings could not justify deviations from the rule to avoid coronary revascularization in the absence of myocardial ischemia in stable angina pectoris patients.

ACKNOWLEDGMENTS

Thanks to Statistician Sonja Wehberg for assistance with computations.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

FUNDING

This work was part of a PhD project. The first author received a PhD scholarship from The PhD Research Fund at Odense University Hospital, Odense, Denmark.

DATA SHARING STATEMENT

There are no unpublished data from this study.

CONTRIBUTORSHIP STATEMENT

There are ten authors. The corresponding author is Jane Angel Simonsen.

Poul Flemming Hoilund-Carlsen, Jane Angel Simonsen, Allan Johansen, Oke Gerke, Anders Thomassen, Søren Hess, Hans Mickley, and Werner Vach contributed to the conception and design. Jane Angel Simonsen, Werner Vach, Oke Gerke, Poul Flemming Hoilund-Carlsen, Lisette Okkels Jensen, and Jesper Hallas were involved in data analysis. All authors were actively involved in collecting and interpreting data, in drafting or revising of the manuscript, and all read and approved the final manuscript submitted. Professor Werner Vach was the driving force in applying the statistical analyses as Professor Poul Flemming Hoilund-Carlsen was in most aspects of nuclear cardiologic imaging. Therefore, we propose that these two share the last authorship.

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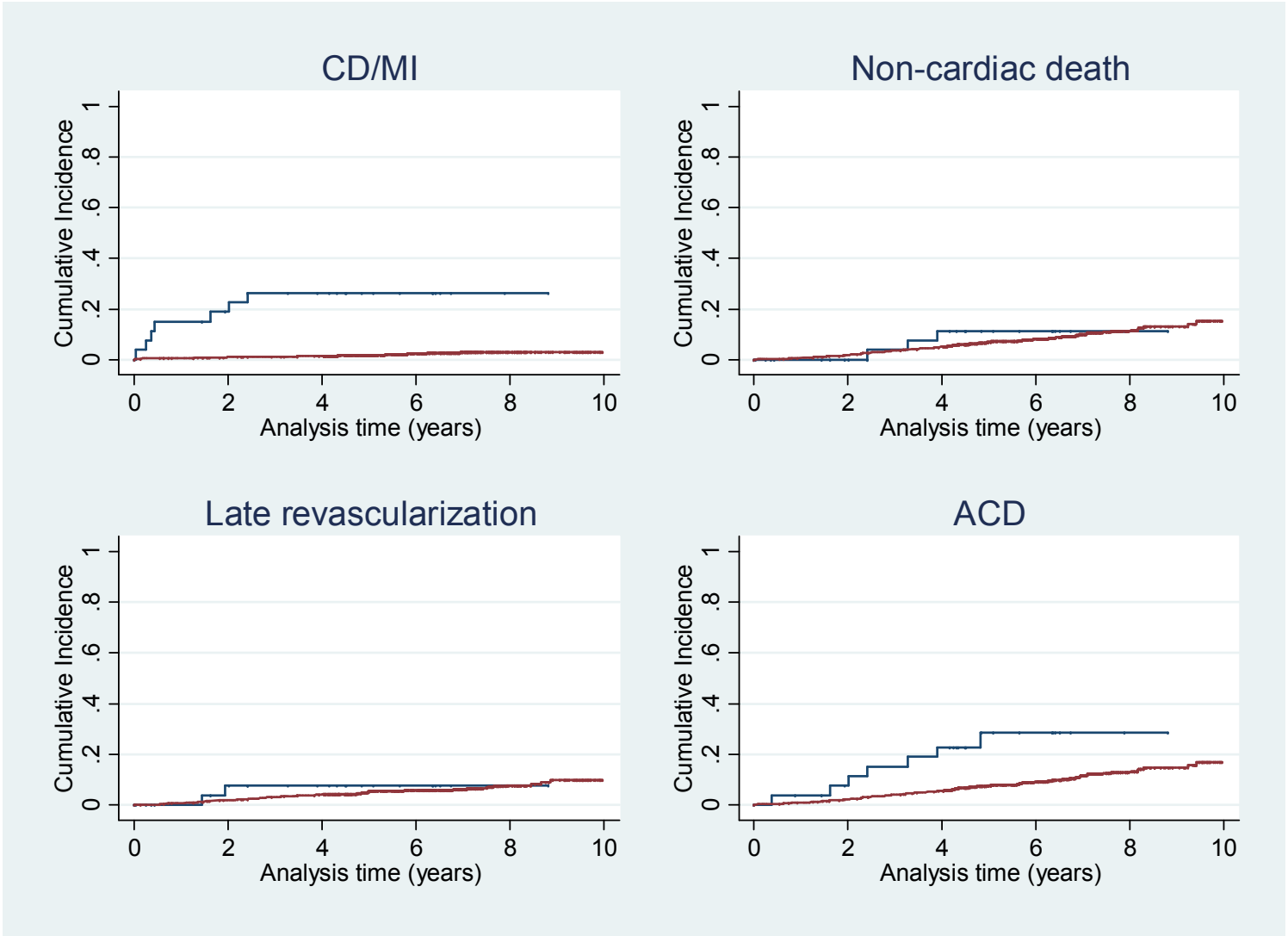
LEGENDS

Figure 1 Cumulative incidence functions. Blue lines: **Revasc**, red lines: **Med**

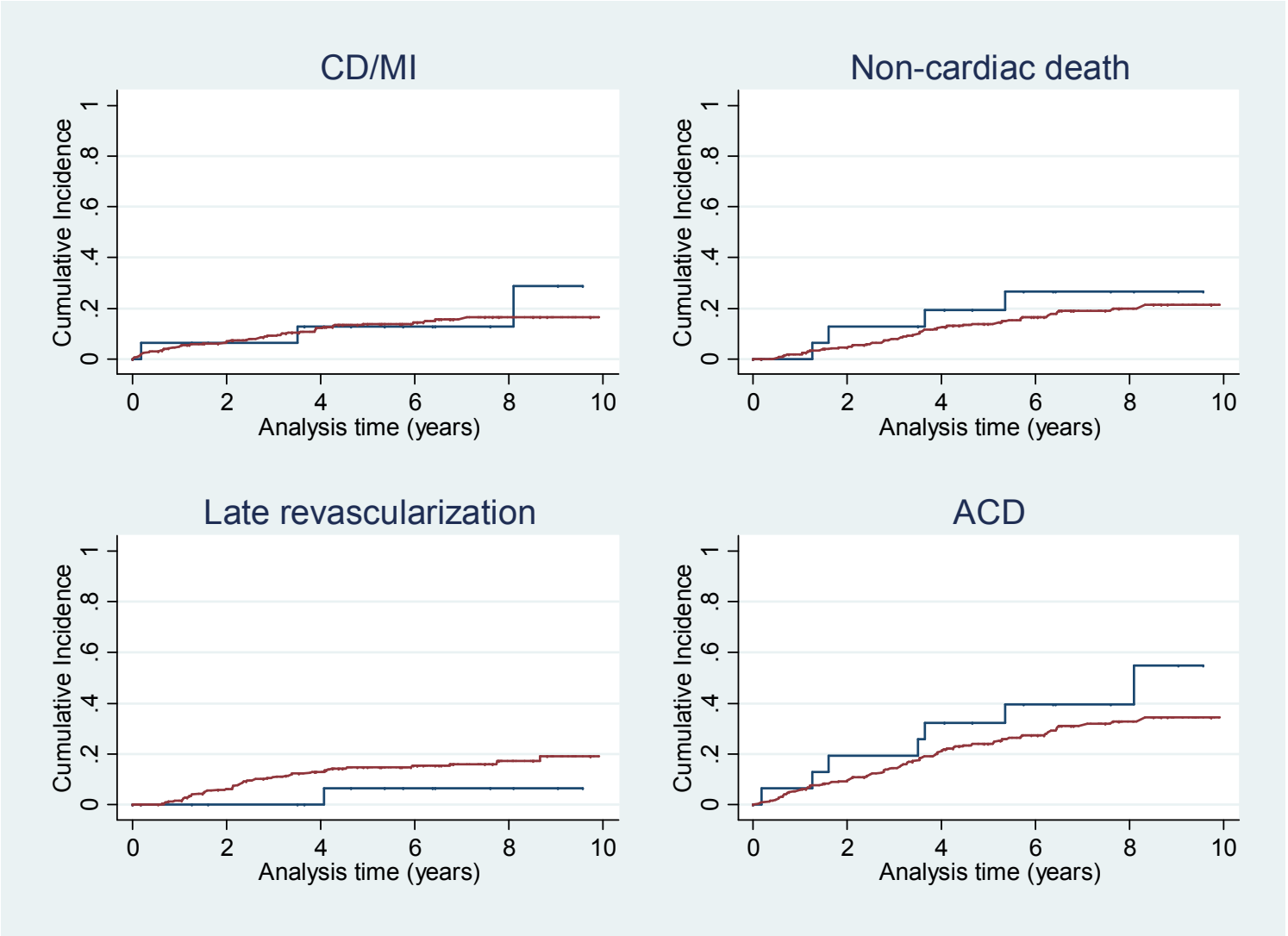
a) Patients with normal MPS

b) Patients with fixed perfusion defects

a)


CD/MI
Non-cardiac death
Late revascularization
ACD
Cumulative Incidence
0
.2
.4
.6
.8
1
0
2
4
6
8
10
Analysis time (years)

b)

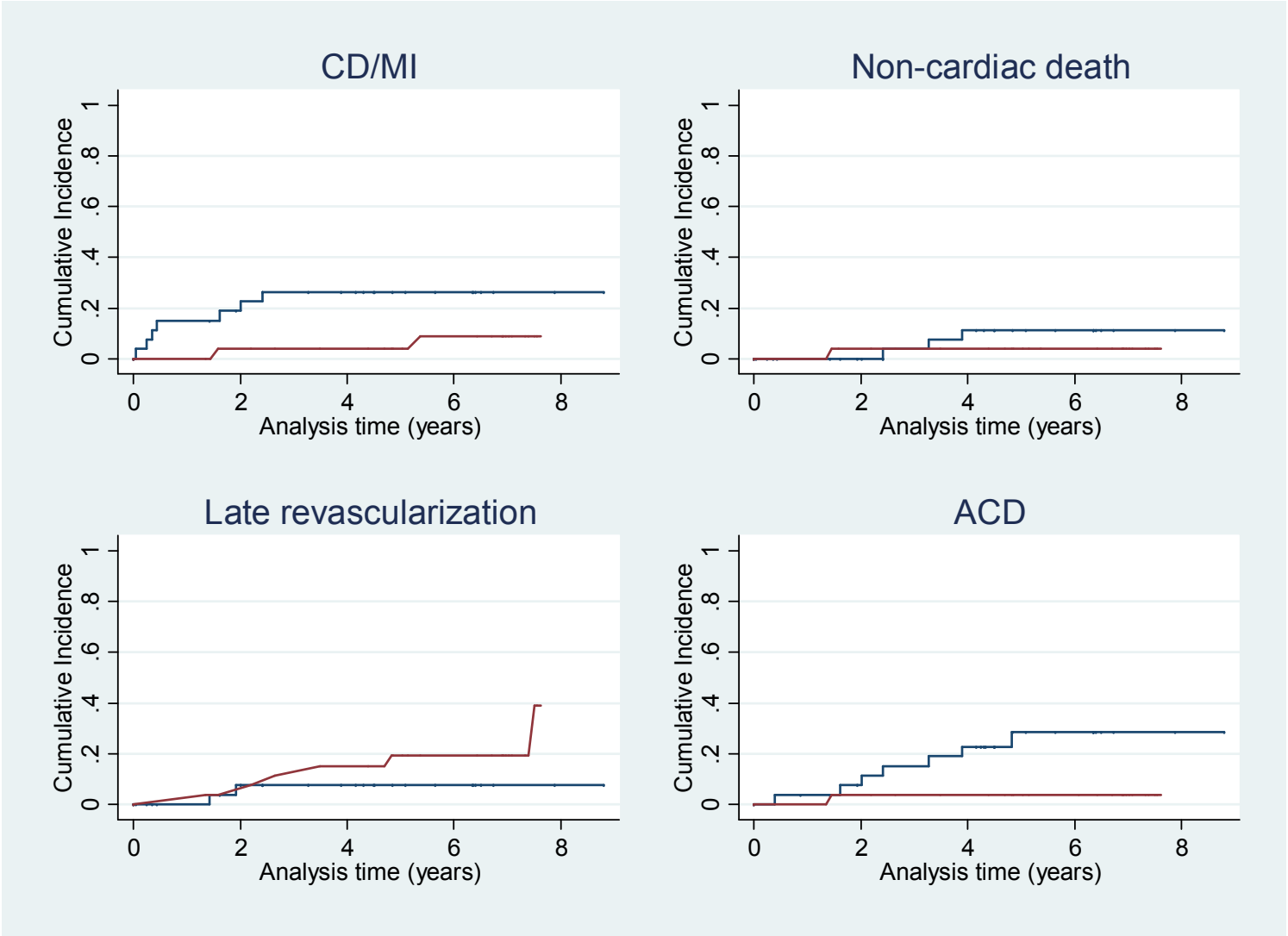

CD/MI
Non-cardiac death
Late revascularization
ACD
Cumulative Incidence
0
.2
.4
.6
.8
1
0
2
4
6
8
10
Analysis time (years)

Supplementary Table Cause-specific hazard ratios and subdistribution hazard ratios of the **Revasc** versus **Med** difference for matched subgroups

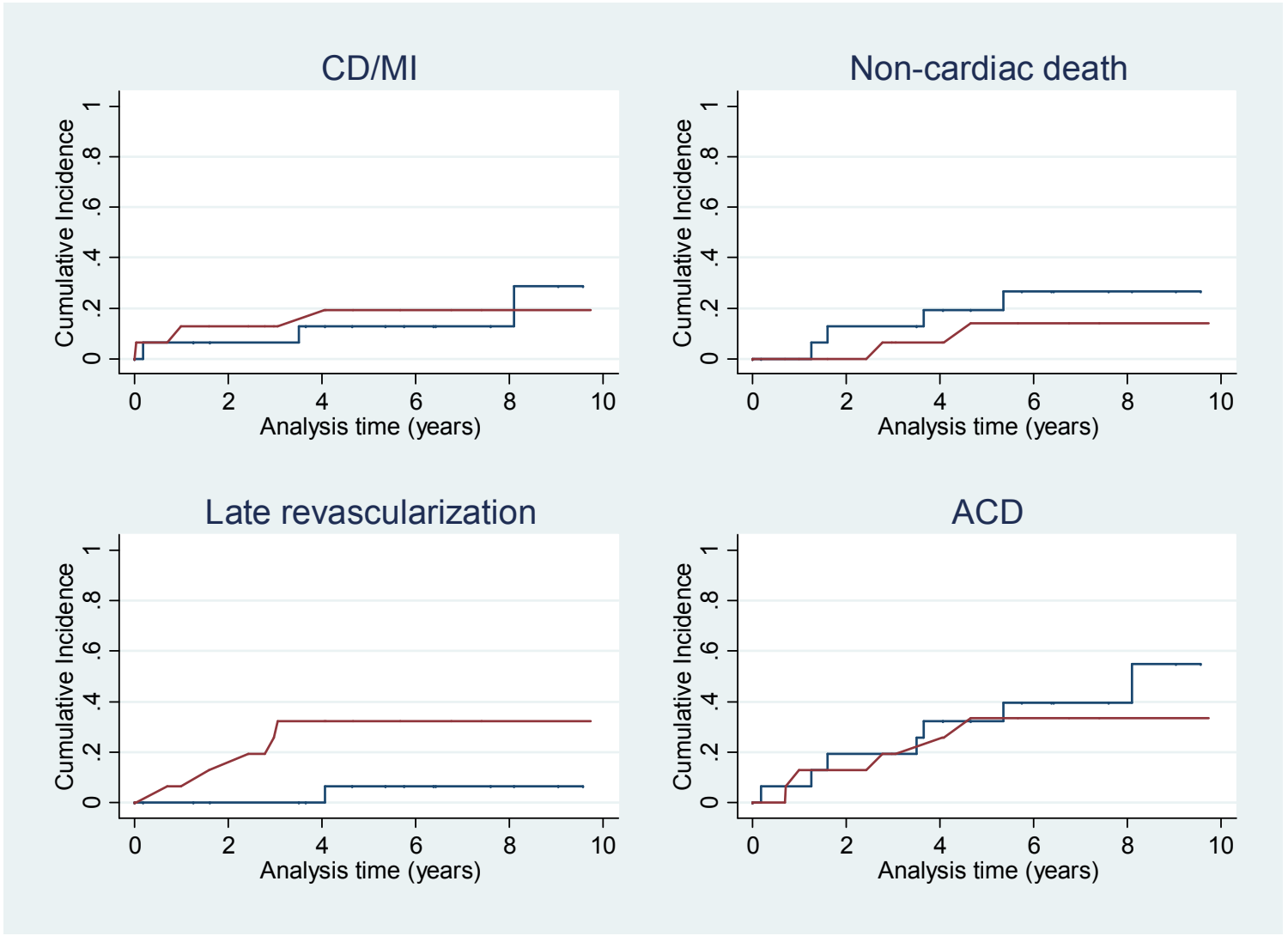
Normal MPS (N=52)								Fixed defects (N=30)							
ACD				CD/MI				ACD				CD/MI			
CSHR	p	SDHR	p	CSHR	p	SDHR	p	CSHR	p	SDHR	p	CSHR	p	SDHR	p
7.97	0.05	7.97	0.06	4.12	0.08	4.11	0.07	1.00	1.00	1.41	0.55	0.70	0.67	0.92	0.92

Supplementary figure. Cumulative incidence functions in matched groups. Blue line: **Revasc**, red line: **Med**
a) Patients with normal MPS (N=52)
b) Patients with fixed perfusion defects (N=30)

a)



b)


CD/MI
Non-cardiac death
Late revascularization
ACD
Cumulative Incidence
0
.2
.4
.6
.8
1
0
2
4
6
8
10
Analysis time (years)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract p 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p 4
Objectives	3	State specific objectives, including any prespecified hypotheses p 4
Methods		
Study design	4	Present key elements of study design early in the paper p 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up pp 5-6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (p 7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable pp 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group pp 5-7
Bias	9	Describe any efforts to address potential sources of bias pp 5-7
Study size	10	Explain how the study size was arrived at p 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why pp 5-7, 11-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding pp 6-7
		(*b*) Describe any methods used to examine subgroups and interactions pp 6-7
		(*c*) Explain how missing data were addressed pp 11-12
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses p 7

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed pp 7-11
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders pp 7-11
		(b) Indicate number of participants with missing data for each variable of interest p 7-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time p 10-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included p 11-14
		(*b*) Report category boundaries when continuous variables were categorized p 5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p 14
Discussion		
Key results	18	Summarise key results with reference to study objectives p 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias pp 16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p 14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results p 16-17
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Outcome of revascularization in stable coronary artery disease without ischaemia: a Danish registry-based follow-up study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-016169.R1
Article Type:	Research
Date Submitted by the Author:	23-Jun-2017
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Primary Subject Heading:	Cardiovascular medicine
Secondary Subject Heading:	Diagnostics
Keywords:	Ischaemic heart disease < CARDIOLOGY, Myocardial perfusion imaging, Functional ischaemia test, Survival benefit, All-cause death

Outcome of revascularization in stable coronary artery disease without ischaemia: a Danish registry-based follow-up study

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Word count : 2,805

ABSTRACT

Objectives In stable coronary artery disease (CAD), coronary revascularization may reduce mortality of patients with a certain amount of left ventricular myocardial ischaemia. However, revascularization does not always follow the guidance suggested by ischaemia testing. We compared outcomes in patients without ischaemia who had either revascularization or medical treatment.

Design and population Based on registries, 1,327 consecutive patients with normal myocardial perfusion scintigraphy (MPS) and 278 with fixed perfusion defects were followed for a median of 6.1 years. Most patients received medical therapy alone (**Med**), but 26 (2%) with a normal MPS and 15 (5%) with fixed perfusion defects underwent revascularization (**Revasc**).

Outcome measures Incidence rates of all-cause death (ACD) and rates of cardiac death/myocardial infarction (CD/MI).

Results With a normal MPS, the ACD rate was 6.2%/year in the **Revasc** group versus 1.9%/year in the **Med** group (p=0.01); the CD/MI rates were 6.9%/year and 0.6%/year, respectively (p<0.00001). Results persisted after adjustment for predictors of revascularization, in particular angina score, and in comparisons of matched **Revasc** and **Med** patients. With fixed defects, the ACD rate was 9.1%/year in the **Revasc** group and 6.7%/year in the **Med** group (p=0.44); the CD/MI rate was 5.0%/year versus 4.2%/year, respectively (p=0.69). If adjusted for angiographic variables or analyzed in matched subsets differences remained insignificant.

Conclusions With normal MPS, revascularization conferred a higher risk, even after adjustment for predictors of revascularization. With fixed defects, the **Revasc** versus **Med** difference was close to equipoise. Hence, in patients with stable CAD without ischaemia, we could not find evidence to justify exceptional revascularization.

Strengths and limitations of this study

- The observational design gave a rare chance to study outcome in a clinical setting, where MPS results were open to referring clinicians
- Endpoints were collected from comprehensive national registries ensuring a high validity
- Rationales for the choice of post-MPS treatment were found in medical records, which may have reduced the ability to address explanatory factors
- The major limitation was the small material with small subsets of patients revascularized
- However, careful adjustment was undertaken in order to achieve a fair comparison of subgroups, and a matching approach was also used
- We focused on hard events, which are indisputable. On the other side, we cannot tell from the present material whether revascularization yielded an amelioration of symptoms.

INTRODUCTION

In stable angina pectoris patients at low to intermediate risk of coronary artery disease (CAD), it is recommended to use non-invasive testing as a gatekeeper to coronary angiography[1 2]. Myocardial perfusion scintigraphy (MPS) is an ischaemia test that effectively stratifies patients with an intermediate pre-test risk into groups with low or high post-test risk and, hence, identifies potential candidates for coronary revascularization[3-5]. Revascularization is often performed with the intention to improve symptoms or prognosis; however, a survival benefit over optimal medical therapy has not been documented in stable CAD patients[6-8]. Data from registry-based studies suggest that only in the presence of a certain amount of ischaemia is the prognosis with respect to hard events better with coronary revascularization than with conservative therapy[9 10]. Nevertheless, in daily routine a small proportion of patients with normal MPS or fixed defects still undergoes revascularization. It remains an open question whether this reflects a clinically justified exception to the regular practice. Addressing this question is a non-trivial task, as a potential inferior prognosis in the revascularized patients may simply reflect a proper clinical selection of high-risk patients with a real need for revascularization, regardless of the MPS result. Comparison of patients with similar risk profiles as regards potential prognostic factors related to the treatment decision might allow for an answer. In an observational design we compared the outcome with and without coronary revascularization in consecutive patients with symptoms of stable CAD but without ischaemia in a setting, where the MPS results were open to the treating physicians.

MATERIALS AND METHODS

Study population and design

From a consecutive series of 2,157 MPS performed 2002-2007 at Odense University Hospital for suspected or known CAD in patients who did not participate in a research project, 1,327 patients had normal scintigraphic findings while 278 demonstrated fixed perfusion defects. Results were analyzed for all patients and for subsets undergoing early revascularization (**Revasc**) or receiving pure medical therapy (**Med**). Early revascularization was defined as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 180 days from MPS, while performed >180 days later was termed late revascularization. Trial design and methods were published previously[11]. The study was approved by the local data protection committee.

MPS

MPS was performed as single photon emission computed tomography (SPECT) with technetium-99m sestamibi using a standard maximum exercise test or pharmacological stress by adenosine, dipyridamol, or dobutamine. In the early study period non-gated acquisitions were used. Later, gated studies were used with at-rest left ventricular ejection fraction (LVEF) being available in 648 patients (49%) with normal MPS and 147 patients (53%) with fixed defects. For post-stress LVEF, the numbers were 687 (52%) and 123 (44%), respectively. Scans were interpreted semi-quantitatively and deemed normal in case of normal radionuclide distribution throughout the myocardium in the presence also of normalcy with respect to available non-perfusion markers like wall thickening/motion, ventricular size, and LVEF. All abnormal scans were reviewed by an experienced reader (AJ) blinded to clinical data. Extent and severity of perfusion defects at stress imaging were converted to

percentage myocardium and categorized as small (5-9% of the myocardium), moderate (10-14%), or large (>14%) [12].

Follow-up

History of CAD and medication at the time of MPS were retrieved from medical records and MPS reports. Follow-up ran from the date of the MPS until 31st December 2011. Events during follow-up were appointed by means of regional and national registers as previously described[11]. Medical records were examined for treatment decision, and angiographic data were obtained from the Western Denmark Heart Registry comprising records on all coronary angiographies and revascularization procedures performed in Western Denmark, including angina score according to the Canadian Cardiovascular Society (CCS)[13].

Statistics

Continuous and categorical variables are shown by means of descriptive statistics and frequency counts including percentages, respectively. Inter-group differences in continuous variables were tested by the Wilcoxon rank-sum test; frequencies were compared by Fisher's exact test or the chi-squared test. Main endpoints were all-cause death (ACD) and cardiac death (defined as death from ischaemic heart disease, congestive heart failure, or malignant arrhythmia) or non-fatal myocardial infarction (CD/MI). Time until event is illustrated with cumulative incidence functions. Cause-specific hazard ratios (CSHR) based on a Cox proportional hazard model as well as subdistribution hazard ratios (SDHR) based on the Fine and Gray regression model[14] were used to assess the difference between **Revasc** and **Med**. The HRs were adjusted for main predictors of revascularization, which were identified by comparison of the two treatment groups and an analysis of the reasons given in the medical

records of revascularized patients. Adjustment was performed for one covariate at a time as well as in multivariate models. When considering ACD, late revascularization was regarded as a competing event in order not to bias the natural course. When considering CD/MI, non-cardiac death and late revascularization were regarded as competing events. Following the general advice to consider all competing events in the statistical analysis [15 16], we present cumulative incidence functions for all four events but restrict reporting of HRs to the two main endpoints.

Furthermore, a matching approach was used. For each revascularized patient we found a medically treated match with identical or nearly identical values for the variables predictive of revascularization. Event incidences for the revascularized patients and their matches were compared by cumulative incidence curves, CSHRs and SDHRs.

The significance level was set to 5%. Statistical analyses were performed with STATA (©StataCorp LP, Texas, USA). Matching was performed with the 'optmatch' program[17] and incidence rates were compared with the 'stir' command.

RESULTS

Early revascularization was performed in 26 patients (2%) with normal MPS and in 15 patients (5%) with fixed defects. Characteristics are given in table 1.

Table 1 Patient characteristics

a) Patients with normal MPS

	All	**Revasc**	**Med**	p
N	1327	26	1301	
Age, years (mean±SD)	59.5±11.8	62.1±12.2	59.5±11.8	0.29
Male	574 (43)	17 (65)	557 (43)	0.03
Known CAD	248 (19)	15 (58)	233 (18)	<0.0001
History				
MI	87 (7)	6 (23)	81 (6)	0.005
PCI	149 (11)	12 (46)	137 (11)	<0.0001

CABG	59 (4)	2 (8)	57 (4)	0.32
Diabetes mellitus	202 (15)	5 (19)	197 (15)	0.58
Medication				
Aspirin	797 (60)	23 (88)	774 (59)	0.001
Beta blocker	462 (35)	20 (77)	442 (34)	<0.0001
Calcium channel blocker	325 (24)	9 (35)	316 (24)	0.25
Nitrates	279 (21)	8 (31)	271 (21)	0.23
Lipid-lowering agents	481 (36)	16 (62)	465 (36)	0.01
LVEF, rest, N	648	15	633	1.00
<30%	0	0	0	
30≤ LVEF<50 %	34 (5)	0	34 (5)	
≥50%	614 (95)	15 (100)	599 (95)	
LVEF, stress, N	687	16	671	0.63
<30%	0	0	0	
30≤ LVEF<50%	41 (6)	0	41 (6)	
≥50%	646 (94)	16 (100)	630 (94)	
Family history of CAD, N	216	23	193	0.83
Positive	113 (52)	13 (57)	100 (52)	
CCS score, N	223	26	197	0.01
1	122 (55)	10 (38)	112 (57)	
2	76 (34)	8 (31)	68 (35)	
3	24 (11)	8 (31)	16 (8)	
4	1 (0.4)	0	1 (0.5)	
Smoking, N	203	22	181	0.41
Current	56 (28)	8 (36)	48 (27)	
Never	79 (39)	6 (27)	73 (40)	
Ceased	68 (34)	8 (36)	60 (33)	
Number of stenotic vessels, N	210	26	184	<0.0001
0 vessels	101 (48)	2 (8)	99 (54)	
1 vessel	59 (28)	10 (38)	49 (27)	
2 vessels	30 (14)	7 (27)	23 (13)	
3 vessels	20 (10)	7 (27)	13 (7)	

b) Patients with fixed perfusion defects

	All	**Revasc**	**Med**	p
N	278	15	263	
Age, years (mean±SD)	62.5±10.2	61.6±11.5	62.6±10.1	0.63
Male	214 (77)	14 (93)	200 (76)	0.20
Known CAD	196 (71)	11 (73)	185 (70)	1.00
History				
MI	152 (55)	8 (53)	144 (55)	1.00
PCI	101 (36)	6 (40)	95 (36)	0.79
CABG	76 (27)	3 (20)	73 (28)	0.77
Diabetes mellitus	59 (21)	5 (33)	54 (21)	0.33
Medication				
Aspirin	233 (84)	12 (80)	221 (84)	0.72
Beta blocker	177 (64)	9 (60)	168 (64)	0.79
Calcium channel blocker	76 (27)	6 (40)	70 (27)	0.25
Nitrates	75 (27)	4 (27)	71 (27)	1.00
Lipid-lowering agents	169 (61)	8 (53)	161 (61)	0.59
Size of defects				0.62
Small (5-9%)	92 (33)	4 (27)	88 (33)	
Medium (10-14%)	60 (22)	2 (13)	58 (22)	
Large (>14%)	126 (45)	9 (60)	117 (45)	
LVEF, rest, N	147	4	143	0.79
<30%	20 (14)	0	20 (14)	
30≤LVEF<50%	57 (39)	1 (25)	56 (39)	

≥50%	70 (48)	3 (75)	67 (47)	
LVEF, stress, N	123	5	118	0.84
<30%	21 (17)	0	21 (18)	
30≤LVEF<50%	48 (39)	2 (40)	46 (39)	
≥50%	54 (44)	3 (60)	51 (43)	
Family history of CAD, N	106	14	92	0.77
Positive	45 (42)	5 (36)	40 (43)	
CCS score, N	115	15	100	0.13
1	73 (63)	7 (47)	66 (66)	
2	25 (22)	3 (20)	22 (22)	
3	16 (14)	5 (33)	11 (11)	
4	1 (1)	0	1 (1)	
Smoking, N	102	13	89	1.00
Current	36 (35)	5 (38)	31 (35)	
Never	19 (19)	2 (15)	17 (19)	
Ceased	47 (46)	6 (46)	41 (46)	
Number of stenotic vessels, N	108	15	93	0.002
0 vessels	15 (14)	0	15 (16)	
1 vessel	26 (24)	3 (20)	23 (25)	
2 vessels	34 (31)	11 (73)	23 (25)	
3 vessels	33 (31)	1 (7)	32 (34)	

The decision to revascularize was clearly associated with symptoms and angiographic findings but less with MPS results (table 2). In four cases of normal MPS, revascularization was performed following a new incident independent of the symptoms prompting MPS.

Table 2 Reasons for revascularization according to medical records

a) Patients with normal MPS

DM	History	Angio findings*	CCS score	Time from MPS to revasc. (days)	Type of revasc.	Reasoning to decide for revascularization was based on
		0-VD	3	83	PCI	Angio, sympt, EET
	PCI	2-VD	2	72	PCI	Angio, sympt, ECG changes during dobutamine stress
+		2-VD	2	159	CABG	Angio, sympt, IVUS
	MI, PCI	2-VD	2	127	PCI	Angio, EET, history of MI
+		1-VD	1	157	PCI	MI, i.e., recurrent event
		3-VD	3	5	PCI	Angio
+		1-VD	3	71	PCI	Angio, sympt
	PCI, CABG	3-VD	1	169	PCI	Angio, sympt
		0-VD	1	49	PCI	Angio, IVUS, EET
		1-VD	1	93	PCI	MI, i.e., recurrent event
		1-VD	2	149	PCI	Angio, IVUS, sympt
	PCI	2-VD	1	131	PCI	MI, i.e., recurrent event
	PCI	1-VD	1	116	PCI	Angio, sympt
+	MI, PCI	3-VD	3	43	PCI	Angio, sympt
		1-VD	3	170	CABG	Angio, IVUS, persistent sympt
		1-VD	2	43	PCI	Angio, persistent sympt
		1-VD	1	145	PCI	Angio, sympt
	MI, PCI	3-VD	3	95	PCI	Angio, sympt
+	MI, PCI	2-VD	2	104	PCI	Angio, sympt

	MI, PCI	3-VD	3	104	CABG	Angio, sympt
	PCI	1-VD	3	37	PCI	Angio, sympt
	MI, PCI, CABG	3-VD	1	16	PCI	MI, i.e., recurrent event
	PCI	3-VD	1	43	PCI	Angio, sympt
		1-VD	2	76	PCI	Angio, sympt
		2-VD	1	49	PCI	Angio, sympt
		2-VD	2	53	PCI	Angio, ECG changes during adenosine stress

b) Patients with fixed defects

DM	History	Size of defect	Angio findings*	CCS score	Time from MPS to revasc. (days)	Type of revasc.	Reasoning to decide for revascularization was based on
	MI, CABG, PCI	Large	3-VD	3	36	PCI	Sympt, angio
+	MI, CABG	Large	2-VD	3	49	PCI	Angio
		Mod.	1-VD	3	105	PCI	Sympt, angio
	PCI	Large	2-VD	3	158	PCI	Sympt, angio
	MI, PCI	Small	3-VD	2	98	CABG	Sympt, angio
	PCI	Small	2-VD	3	64	PCI	Sympt, angio
		Small	2-VD	1	60	PCI	Angio
	MI, PCI	Large	2-VD	1	70	CABG	Sympt, angio
	MI, PCI	Large	2-VD	1	72	PCI	Angio
	MI	Large	2-VD	1	25	CABG	Angio
+	PCI	Large	2-VD	1	148	PCI	Reduced LVEF, viability, angio
+	MI, CABG	Large	2-VD	2	71	PCI	Sympt, angio
+	MI	Large	2-VD	1	16	CABG	Angio
+		Mod.	1-VD	1	85	PCI	Sympt, angio
		Small	1-VD	2	77	PCI	Angio

*None had stenosis of the left main stem. Degree and appearance of stenoses were not reported

Angio = angiography; DM = diabetes mellitus; ECG = electrocardiogram; EET = exercise ECG testing; IVUS = intravascular ultrasound; mod. = moderate; MPS = myocardial perfusion scintigraphy; sympt = symptoms; VD = vessel disease

Median follow-up (range) was 6.1 years (0.02-9.96). Table 3 shows the cumulative numbers of events during follow-up. With normal MPS, the number of MIs was higher than the number of CDs (3% versus 1%, p<0.0001), whereas in the patients with fixed defects, the disparity, albeit insignificant, was the reverse (10% versus 14%, p=0.19). In none of the MPS groups did the CD/ACD ratio differ between subgroups; being 2/7 and 14/150, respectively (p=0.15) in normal MPS and 3/7 versus 35/88 (p=1.00) in patients with fixed defects (table 3).

Table 3 Cumulative number of events during follow-up

	Normal MPS				Fixed defects			
Events	All N (% of 1,327)	**Revasc** N (% of 26)	**Med** N (% of 1,301)	p	All N (% of 278)	**Revasc** N (% of 15)	**Med** N (% of 263)	p
No event	1,079 (81)	14 (54)	1,065 (82)	0.001	140 (50)	7 (47)	133 (51)	0.80
Any event (death/MI/revasc.)	248 (19)	12 (46)	236 (18)		138 (50)	8 (53)	130 (49)	
Death	157 (12)	7 (27)	150 (12)	0.03	95 (34)	7 (47)	88 (33)	0.40
Cardiac death	16 (1)	2 (8)	14 (1)	0.04	38 (14)	3 (20)	35 (13)	0.44
MI	43 (3)	5 (19)	38 (3)	0.001	27 (10)	1 (7)	26 (10)	1.00
MI or death	191 (14)	10 (38)	181 (14)	0.002	111 (40)	8 (53)	103 (39)	0.29
MI or cardiac death	57 (4)	7 (27)	50 (4)	<0.0001	58 (21)	4 (27)	54 (21)	0.53
PCI	81 (6)	1 (4)	80 (6)	1.00	48 (17)	1 (7)	47 (18)	0.48
CABG	15 (1)	2 (8)	13 (1)	0.03	6 (2)	0	6 (2)	1.00
PCI/CABG	92 (7)	3 (12)	89 (7)	0.42	50 (18)	1 (7)	49 (19)	0.49
MI/cardiac death/revasc.	124 (9)	9 (35)	115 (9)	<0.0001	87 (31)	4 (27)	83 (32)	0.78

Cumulative incidence functions shown in figure 1 indicated no difference in the incidence of non-cardiac deaths between the two treatment groups for neither patients with normal MPS, nor patients with fixed defects. As regards late revascularization, the **Med** curve tended to run above the **Revasc** curve in case of fixed defects; however, the difference was not significant. With normal MPS, substantially different incidence rates of the main endpoints could be observed. The ACD rate was 6.2%/year in the **Revasc** group compared with 1.9%/year in the **Med** group (p=0.01) and the CD/MI rate was 6.9%/year versus 0.6%/year, respectively (p<0.00001). In case of fixed defects there were no significant inter-group differences, and **Revasc**/**Med** ratios were similar for both endpoints: The ACD rate was 9.1%/year in the **Revasc** group and 6.7%/year in the **Med** group (p=0.44) and the CD/MI rate was 5.0%/year versus 4.2%/year, respectively (p=0.69).

Quantification of effects and adjustment

Judged from tables 1 and 2, variables CAD, previous MI, previous PCI, CCS score, and number of stenotic coronary arteries were associated with the decision to revascularize

despite normal MPS. The use of aspirin, beta blockers, and lipid lowering agents was unequally distributed and, hence, could be a surrogate for a disease state also predictive of revascularization. Gender was also unevenly distributed and, therefore, considered in the models. In patients with fixed effects, the only significant association found was for the number of stenotic arteries. The lack of significance for the other variables may, however, mainly reflect lack of power due to the small number of revascularized patients. It seems reasonable to assume that variables predictive of the treatment decision in patients with normal MPS would also be potential predictors in patients with fixed effects. Hence, we used the same list of (potential) predictors.

Unadjusted and adjusted CSHRs and SDHRs comparing the **Revasc** and **Med** groups are shown in table 4. Adjustment for clinical and/or angiographic variables did not change the HRs with normal MPS, which were always in the magnitude of 3-5 for ACD and >9 for CD/MI, all being significantly different from 1. With fixed defects, the HR was never significantly different from 1. Adjusted for clinical variables, the HRs for both outcomes stayed in the magnitude of 1.2 to 1.8. However, with adjustment for angiographic variables the HR changed more substantially to values around 2 for ACD and between 0.7 and 0.9 for CD/MI.

Table 4 Cause-specific hazard ratios and subdistribution hazard ratios of the **Revasc** versus **Med** difference

a) Patients with normal MPS

	ACD				CD/MI			
	CSHR	p	SDHR	p	CSHR	p	SDHR	p
Univariate analysis	3.85	0.001	3.42	0.002	15.44	<0.0001	14.09	<0.0001
Adjusted for clinical variables								
Age	3.22	0.003	3.12	0.005	12.93	<0.0001	11.75	<0.0001
Gender	3.58	0.001	3.17	0.003	15.11	<0.0001	13.85	<0.0001
Age, gender	2.89	0.007	2.80	0.01	12.37	<0.0001	11.26	<0.0001
DM	3.81	0.001	3.39	0.002	15.30	<0.0001	13.99	<0.0001
Known CAD	3.76	0.001	3.47	0.002	13.04	<0.0001	12.29	<0.0001
Previous MI	3.97	<0.0001	3.52	0.002	12.76	<0.0001	12.01	<0.0001
Previous PCI	4.27	<0.0001	3.87	0.001	14.42	<0.0001	13.45	<0.0001
CAD category*	3.71	0.001	3.45	0.003	13.02	<0.0001	12.26	<0.0001
CAD category*, previous MI	3.68	0.001	3.42	0.004	12.87	<0.0001	12.48	<0.0001
CAD category*, previous MI, aspirin, beta blocker, lipid lowering	4.22	<0.0001	3.81	0.001	11.86	<0.0001	11.43	<0.0001
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering	4.08	0.001	3.66	0.002	11.76	<0.0001	11.34	<0.0001

Adjusted for angiographic variables								
CCS score (N=223/115)	4.27	0.003	3.77	0.006	12.06	<0.0001	11.03	<0.0001
Number of stenotic vessels (N=210/108)	4.62	0.005	4.52	0.006	9.19	0.001	9.28	0.001
CCS score, number of stenotic vessels (N=210/108)	4.52	0.007	4.18	0.007	9.89	0.001	9.49	0.002
Adjusted for scintigraphic variables								
At-rest LVEF (N=648/147)	2.87	0.08	2.97	0.08	12.78	<0.0001	12.86	<0.0001
Post-stress LVEF (N=687/123)	2.70	0.09	2.80	0.10	12.74	<0.0001	12.93	<0.0001
Adjusted for selected variables of all types								
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, CCS score (N=223/115)	4.55	0.004	3.48	0.009	29.29	<0.0001	26.69	<0.0001
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, number of stenotic vessels (N=210/108)	4.30	0.02	3.79	0.03	11.70	0.001	11.80	0.001
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, CCS score, number of stenotic vessels (N=210/108)	4.14	0.02	3.31	0.06	20.86	0.001	20.23	0.001

b) Patients with fixed perfusion defects

	ACD				CD/MI			
	CSHR	p	SDHR	p	CSHR	p	SDHR	p
Univariate analysis	1.49	0.31	1.68	0.18	1.24	0.72	1.29	0.66
Adjusted for clinical variables								
Age	1.50	0.30	1.75	0.16	1.26	0.70	1.28	0.67
Gender	1.41	0.39	1.60	0.22	1.22	0.74	1.30	0.66
Age, gender	1.44	0.36	1.69	0.19	1.26	0.71	1.30	0.66
DM	1.42	0.39	1.63	0.23	1.19	0.78	1.26	0.40
Known CAD	1.49	0.31	1.68	0.17	1.20	0.76	1.28	0.67
Previous MI	1.50	0.31	1.69	0.17	1.24	0.72	1.29	0.66
Previous PCI	1.52	0.29	1.70	0.16	1.26	0.70	1.29	0.65
CAD category*	1.55	0.27	1.76	0.15	1.28	0.68	1.31	0.64
CAD category*, previous MI	1.56	0.26	1.77	0.14	1.29	0.67	1.32	0.64
CAD category*, previous MI, aspirin, beta blocker, lipid lowering	1.39	0.41	1.58	0.25	1.28	0.69	1.31	0.66
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering	1.34	0.47	1.51	0.30	1.27	0.69	1.32	0.65
Adjusted for angiographic variables								
CCS score (N=223/115)	1.61	0.27	1.93	0.09	0.82	0.75	0.87	0.80
Number of stenotic vessels (N=210/108)	2.35	0.09	2.67	0.06	0.74	0.65	0.77	0.69
CCS score, number of stenotic vessels (N=210/108)	1.76	0.28	2.27	0.07	0.64	0.51	0.73	0.58
Adjusted for scintigraphic variables								
At-rest LVEF (N=648/147)	0.85	0.87	1.00	1.00	-§	-§	-§	-§
Post-stress LVEF (N=687/123)	0.59	0.61	0.72	0.73	-§	-§	-§	-§
Size of defects	1.23	0.61	1.38	0.43	1.00	1.00	1.08	0.90
Adjusted for selected variables of all types								
Gender, CAD category*, previous MI, aspirin, beta	1.54	0.38	1.99	0.13	0.89	0.86	0.94	0.93

blocker, lipid lowering, CCS score (N=223/115)								
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, number of stenotic vessels (N=210/108)	3.68	0.06	4.31	0.10	0.90	0.90	0.85	0.89
Gender, CAD category*, previous MI, aspirin, beta blocker, lipid lowering, CCS score, number of stenotic vessels (N=210/108)	3.05	0.11	4.37	0.07	0.84	0.83	0.92	0.94

*In order to reduce the number of covariates, and because of correlation between CAD and previous revascularization, a CAD category variable was generated, taking into account the history of both CAD and previous revascularization: 1 = suspected CAD; 2 = known CAD with no previous revascularization; 3 = known CAD with previous revascularization
§Fitting of Cox-model indicated complete separation; hence, no results could be presented

Scintigraphic variables, available only in a subgroup of all patients, were also to some degree associated with treatment decisions. All the **Revasc** patients with normal MPS had LVEF ≥50%, whereas some of the **Med** patients had 30≤LVEF<50%, cf. table 1a. Adjustment for LVEF category slightly reduced the HRs for ACD but not for CD/MI (table 4a). One out of four of the **Revasc** patients with fixed defects had a moderately reduced at-rest LVEF (30≤LVEF<50%), but no one had a severely reduced LVEF (<30%), which was the case in 14% of the **Med** patients (table 1b). Adjustment for LVEF category reduced the HRs for ACD, whereas for CD/MI, numbers were too small for an estimation. Similarly, in spite of no significant inter-group difference in size of perfusion defects, adjustment for defect size slightly reduced the HR for both endpoints (table 4b).

Results from the matching procedure can be seen from the Supplementary material. For matched subsets, results were similar to those from the entire groups; in case of normal MPS the CSHR was 7.97 (p=0.05) for ACD, 4.12 (p=0.08) for CD/MI. With fixed defects, the CSHR was 1.00 (p=1.00) for ACD and 0.70 (p=0.67) for CD/MI, respectively. Cumulative incidence functions resembled those for the entire groups. Detailed results are given in the Supplementary table and figure.

DISCUSSION

In this study, 2% of patients with normal MPS and 5% with fixed perfusion defects underwent early coronary revascularization; i.e., exceptional revascularization. With normal MPS, **Revasc** patients had significantly higher event rates than **Med** patients. With fixed defects, no significant inter-group differences were observed. Results persisted after adjustment for predictors of revascularization as well as after matching. Noteworthy, MPS was conducted as a part of the routine diagnostic work-up and results were open to the referring clinicians. Still, revascularization was undertaken in some patients, probably primarily based on angiographic and clinical findings.

The use of MPS

In patients with stable angina, an ischaemia test is far from always performed before angiography[18 19]. An anatomical approach to the CAD diagnosis and quantification typically leads to more revascularization procedures than a functional approach[20-22]. However, strategies involving MPS have a greater prognostic power than those without functional testing[23 24].

Optimal risk stratification derives from the ability of a normal MPS to identify patients at exceedingly low risk, and that of an abnormal scan to identify patients at greater risk, thus rendering a number of catheterization and invasive interventions superfluous[25-27]. Following a normal MPS, the annual death rate is generally <2% and the annual rate of hard cardiac events <1%, a little higher in risk groups[28 29]. We and others previously found a general warranty period following a normal MPS of 5 years[11 30]. Thus, under usual conditions, cardiac catheterization is not warranted in the presence of a normal study, unless there is a change in symptoms.

A small percentage of patients with normal scans do have events within the warranty period. In our population of 1,327 patients with normal MPS, four patients (0.3%)

underwent revascularization within 6 months from MPS because of an acute MI. One had diabetes, one had chronic kidney disease, and two had known CAD. This supports previous findings of a poorer prognosis for high-risk subgroups and underscores the additional prognostic value of clinical findings to MPS results. It also illustrates the fact that MI – more than death – is hard to anticipate[31]. MIs can break out in vessels with a normal appearance[32] [33], whereas stenotic and occluded arteries often come with collaterals, preventing MI or at least limiting its size[34]. Hence, although the occurrence of MI is associated with the presence of atherosclerosis, it may not be correlated to its severity, and therefore, MPS – like other imaging techniques – cannot predict specific lesions but patients at risk[35 36].

The risk of false negative MPS results caused by balanced ischaemia was reduced as non-perfusion scan markers were also taken into consideration. Left ventricular function in the shape of LVEF has an independent prognostic and predictive value[3 10]. However, decision to perform revascularization in our patients was in general not based on the presence of a reduced LVEF as all **Revasc** patients with normal MPS had preserved LVEFs, and far from all patients with a LVEF below 50% underwent revascularization.

Dominant MPS parameters driving subsequent resource utilization are extent and severity of reversible perfusion defects[12]. In addition, a variety of clinical elements, most importantly anginal symptoms, further influence referral rates[20]. Thus, when patients with normal scans or scans showing only mild ischaemia are referred to angiography, this is typically based on clinical symptoms[37]. In former reports from the US, 3% of patients without ischaemia were referred to angiography, and revascularization was performed in one fifth of these[38-40]. The numbers in our series were higher.

Strengths and limitations

Contrary to previous reports on post-MPS assignment in which the authors were left to speculate on possible reasons for paradoxical treatments [20], we went through medical records describing rationales for the choice of treatment, well aware that it is difficult to find specific information on the reason for a clinical decision in retrospect. Careful adjustment was undertaken in order to achieve a fair comparison of subgroups. Due to a low number of revascularizations, PCI and CABG were looked at together. This may, however, be inappropriate as several studies have shown that CABG treated patients have a lower MI rate compared to PCI treated patients.

Subsets treated exceptionally, given the MPS findings, constituted a minority of our patients. Considering the small number of **Revasc** patients compared to **Med** patients it was not equitable to estimate a propensity score. However, results from Cox models adjusted for individual covariates are comparable to results from propensity score-adjusted Cox models[41]. Adjustment for different predictors of revascularization did not change our results; specifically, differences persisted after adjustment for angina score, one of the most important predictors of revascularization. In addition, results of the matching approach were comparable to those from Cox modelling, i.e., effects observed in univariate analyses did not vanish. An indicator of an even distribution of non-cardiac health problems affecting prognosis as well as treatment decision was the fact that in none of the subgroups of our patients did we observe a significant difference between the CD/ACD ratios.

In analyzing outcome, we focused on hard events. Just like observational studies have indicated that at least 10% of the left ventricular myocardium should be ischaemic in order for the patient to gain a survival benefit[42-44], the same amount seems to be a prerequisite of an improvement in symptoms and exercise capacity [45 46]. Hence, revascularization is unlikely to benefit stable CAD patients unless there is objective evidence of ischaemia.

CONCLUSIONS

In our consecutive series of patients undergoing MPS for stable angina pectoris in the clinical routine, 2% of those with normal MPS and 5% of those with fixed perfusion defects underwent revascularization against theguidelines. With normal MPS, **Revasc** was associated with significantly more cardiac events and shorter survival than **Med**, even after adjustment for clinical, angiographic, and scintigraphic variables. With fixed defects, there were no significant differences. Thus, our findings could not justify deviations from the rule to avoid coronary revascularization in the absence of myocardial ischemia in stable angina pectoris patients.

ACKNOWLEDGMENTS

Thanks to Statistician Sonja Wehberg for assistance with computations.

COMPETING INTERESTS

The authors declare that they have no conflict of interest.

FUNDING

This work was part of a PhD project. The first author received a PhD scholarship from The PhD Research Fund at Odense University Hospital, Odense, Denmark.

DATA SHARING STATEMENT

There are no unpublished data from this study.

CONTRIBUTORSHIP STATEMENT

There are ten authors. The corresponding author is Jane Angel Simonsen.

Poul Flemming Hoilund-Carlsen, Jane Angel Simonsen, Allan Johansen, Oke Gerke, Anders Thomassen, Søren Hess, Hans Mickley, and Werner Vach contributed to the conception and design. Jane Angel Simonsen, Werner Vach, Oke Gerke, Poul Flemming Hoilund-Carlsen, Lisette Okkels Jensen, and Jesper Hallas were involved in data analysis. All authors were actively involved in collecting and interpreting data, in drafting or revising of the manuscript, and all read and approved the final manuscript submitted. Professor Werner Vach was the driving force in applying the statistical analyses as Professor Poul Flemming Hoilund-Carlsen was in most aspects of nuclear cardiologic imaging. Therefore, we propose that these two share the last authorship.

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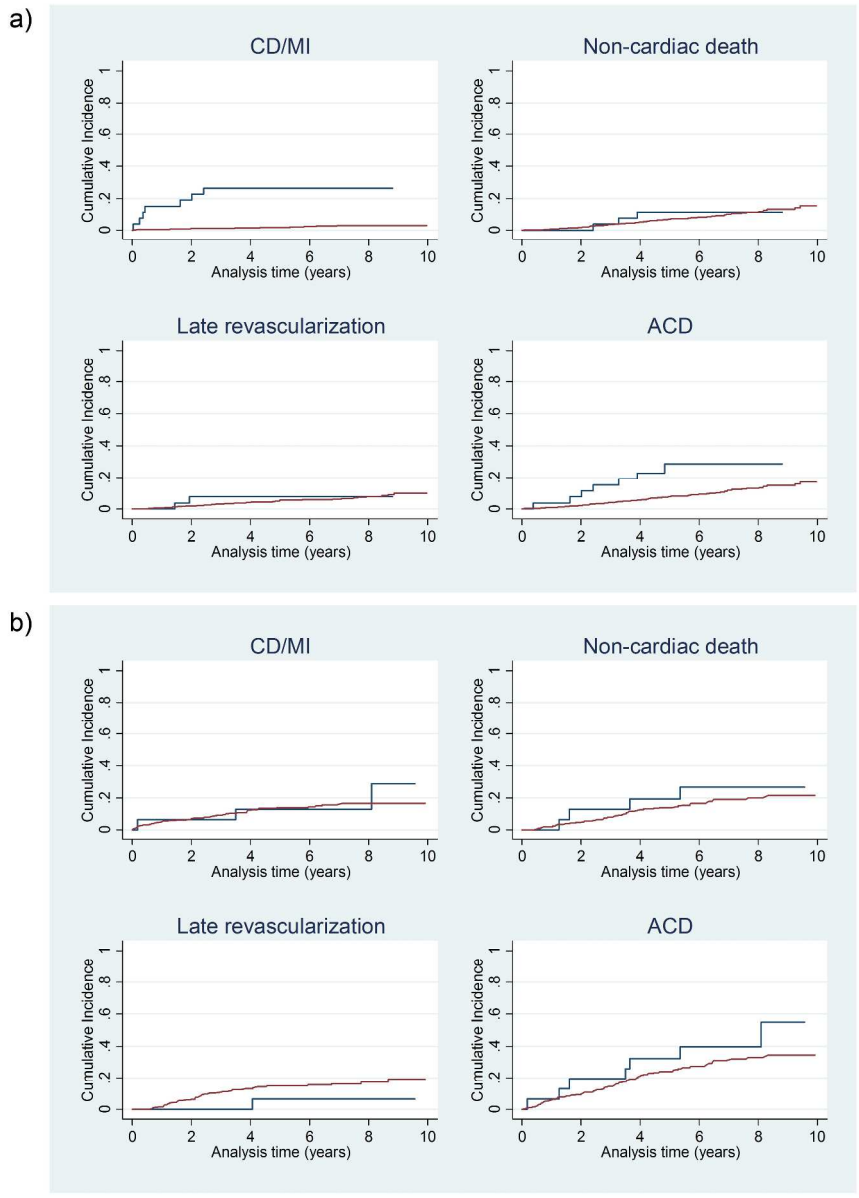
LEGENDS

Figure 1 Cumulative incidence functions. Blue lines: **Revasc**, red lines: **Med**

a) Patients with normal MPS

b) Patients with fixed perfusion defects



Cumulative incidence functions. Blue lines: **Revasc**, red lines: **Med**. a) Patients with normal MPS, b) Patients with fixed perfusion defects.

306x415mm (300 x 300 DPI)

SUPPLEMENT TO THE MATCHING SECTION

For normal MPS, complete matching of **Revasc** patients with **Med** patients was obtained with respect to CAD, use of aspirin, beta blockers, and lipid lowering agents as well as dichotomized values of CCS score (1: CCS score 1-2; 2: CCS score 3-4) and number of stenotic coronary arteries (1: 0-1 vessels; 2: 2-3 vessels). Age and gender did not differ between **Revasc** patients and **Med** matches (age: 62.1±12.2 years versus 61.3±10.4 years, p=0.78; gender: 65% versus 50% male, p=0.40). Since among patients with known CAD, there was no inter-group difference with regard to previous MI, previous PCI, or previous CABG (p=0.78, p=0.17, and p=0.53, respectively), we did not match according to CAD category (CAD with or without previous revascularization) and previous MI.

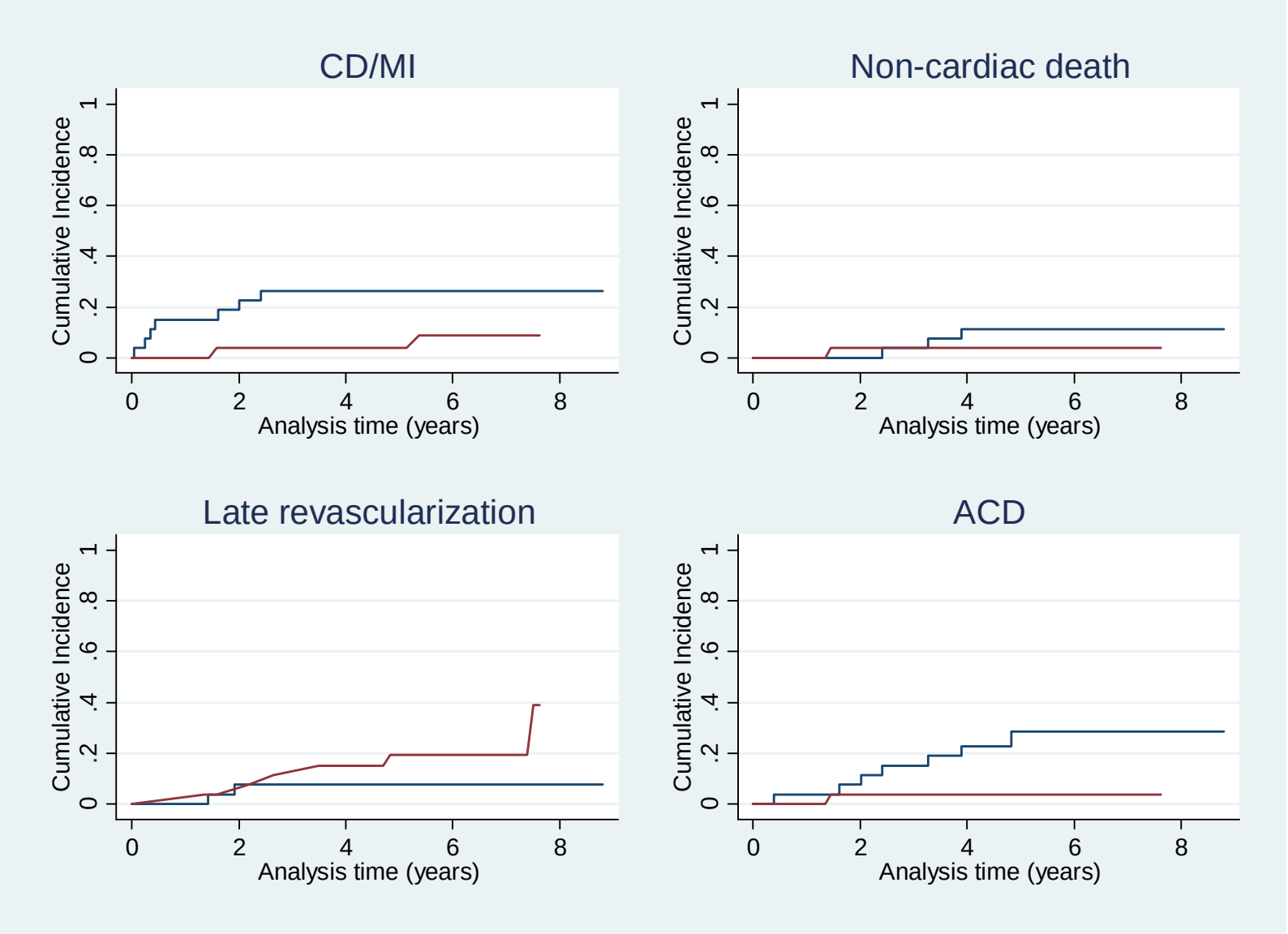
For fixed defects, perfect matches were obtained with regard to CAD, use of aspirin, beta blockers, lipid lowering agents, and number of arteries. Addition of CCS score always resulted in one mismatch; involving different pairs in each run, though. Again, age and gender did not differ between **Revasc** patients and **Med** matches (age: 61.6±11.5 years versus 64.3±8.7 years, p=0.37; gender: 93% versus 73% male, p=0.33). Using CAD category instead and including also previous MI still yielded perfect matches; however, among patients with known CAD, there was no inter-group difference pertaining to previous MI, previous PCI, or previous CABG (p=0.71, p=1.00, and p=0.54). Matching according to LVEF category was also feasible; yet, addition of angiographic variables then yielded three mismatches or more; hence, LVEF was not included in the final matching.

Supplementary Table Cause-specific hazard ratios and subdistribution hazard ratios of the **Revasc** versus **Med** difference for matched subgroups

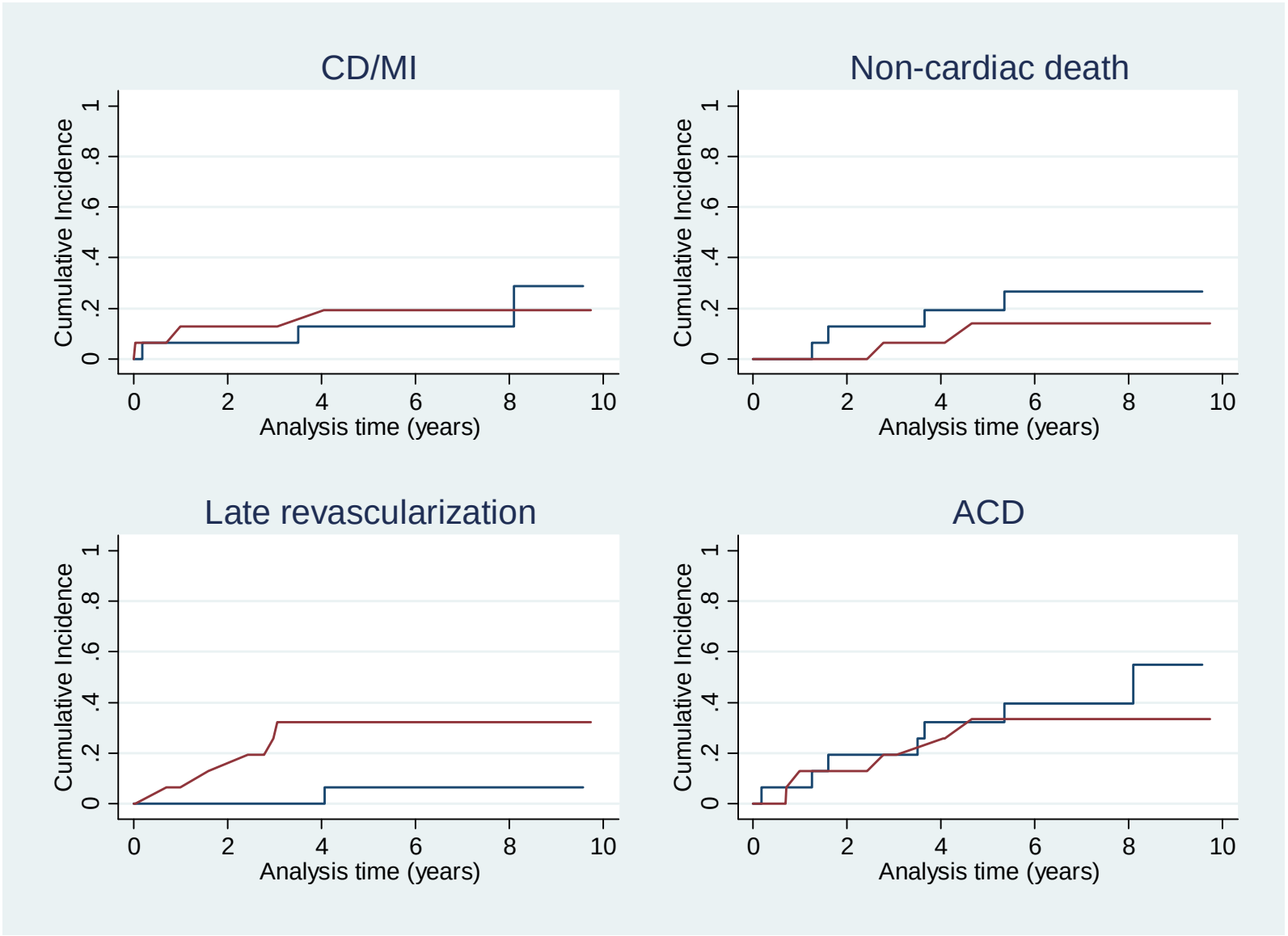
Normal MPS (N=52)								Fixed defects (N=30)							
ACD				CD/MI				ACD				CD/MI			
CSHR	p	SDHR	p	CSHR	p	SDHR	p	CSHR	p	SDHR	p	CSHR	p	SDHR	p
7.97	0.05	7.97	0.06	4.12	0.08	4.11	0.07	1.00	1.00	1.41	0.55	0.70	0.67	0.92	0.92

Supplementary Figure Cumulative incidence functions in matched groups. Blue line: **Revasc**, red line: **Med**
a) Patients with normal MPS (N=52)
b) Patients with fixed perfusion defects (N=30)

a)



b)


CD/MI
Non-cardiac death
Late revascularization
ACD
Cumulative Incidence
0
.2
.4
.6
.8
1
0
2
4
6
8
10
Analysis time (years)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract p 2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found p 2
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported p 4
Objectives	3	State specific objectives, including any prespecified hypotheses p 4
Methods		
Study design	4	Present key elements of study design early in the paper p 5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection p 5
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up pp 5-6 *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed (p 7) *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable pp 5-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group pp 5-7
Bias	9	Describe any efforts to address potential sources of bias pp 5-7
Study size	10	Explain how the study size was arrived at p 5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why pp 5-7, 11-12
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding pp 6-7
		(*b*) Describe any methods used to examine subgroups and interactions pp 6-7
		(*c*) Explain how missing data were addressed pp 11-12
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses p 7

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed pp 7-11
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders pp 7-11
		(b) Indicate number of participants with missing data for each variable of interest p 7-11
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time p 10-11
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included p 11-14
		(*b*) Report category boundaries when continuous variables were categorized p 5
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses p 14
Discussion		
Key results	18	Summarise key results with reference to study objectives p 14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias pp 16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence p 14-17
Generalisability	21	Discuss the generalisability (external validity) of the study results p 16-17
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based p 18

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.