Portuguese Society of CARDIOLOGY

ORIGINAL ARTICLE

Multivessel vs. culprit-only revascularization in patients with non-ST-elevation acute coronary syndromes and multivessel coronary disease[☆]

CrossMark

César Correia[a], Carlos Galvão Braga[b,*], Juliana Martins[b], Carina Arantes[b], Glória Abreu[b], Catarina Quina[b], Alberto Salgado[b], Miguel Álvares Pereira[b], João Costa[b], Jorge Marques[b]

[a] *Escola de Ciências da Saúde, Universidade do Minho, Braga, Portugal*
[b] *Serviço de Cardiologia, Hospital de Braga, Braga, Portugal*

Abstract
Introduction: There have been no prospective randomized trials that enable the best strategy and timing to be determined for revascularization in patients with non-ST-segment elevation acute coronary syndrome (NSTE-ACS) and multivessel coronary artery disease (CAD).
Objectives: To compare short- and long-term adverse events following multivessel vs. culprit-only revascularization in patients with NSTE-ACS and multivessel CAD.
Methods: This was a retrospective observational study that included all patients diagnosed with NSTE-ACS and multivessel CAD who underwent percutaneous coronary intervention (PCI) between January 2010 and June 2013 (n=232). After exclusion of patients with previous coronary artery bypass grafting (n=30), a multivessel revascularization strategy was adopted in 35.1% of patients (n=71); in the others (n=131, 64.9%), only the culprit artery was revascularized. After propensity score matching (PSM), two groups of 66 patients were obtained, matched according to revascularization strategy.
Results: During follow-up (1543±545 days), after PSM, patients undergoing multivessel revascularization had lower rates of reinfarction (4.5% vs. 16.7%; log-rank p=0.018), unplanned revascularization (6.1% vs. 16.7%; log-rank p=0.048), unplanned PCI (3.0% vs. 13.6%; log-rank p=0.023) and the combined endpoint of death, reinfarction and unplanned revascularization (16.7 vs. 31.8%; log-rank p=0.046).

Conclusions: In real-world patients presenting with NSTE-ACS and multivessel CAD, a multivessel revascularization strategy was associated with lower rates of reinfarction, unplanned revascularization and unplanned PCI, as well as a reduction in the combined endpoint of death, reinfarction and unplanned revascularization.

Revascularização multivaso *versus* revascularização da artéria *culprit* em pacientes com síndrome coronária aguda sem supradesnivelamento do segmento ST e doença coronária multivaso

Resumo
Introdução: Atualmente, não existem estudos prospetivos aleatorizados que permitam definir a estratégia de revascularização ideal quanto ao tipo e *timing* da sua realização, em doentes com síndrome coronária aguda (SCA) sem supradesnivelamento do segmento ST (SCAsSST) e doença coronária multivaso (DCMV).
Objetivos: Comparar os eventos adversos a curto e a longo prazo da revascularização multivaso *versus* revascularização apenas da artéria *culprit* em doentes com SCAsSST e DCMV.
Métodos: Este estudo observacional retrospetivo incluiu todos os doentes com SCAsSST e DCMV submetidos a intervenção coronária percutânea (ICP), entre janeiro de 2010 e junho de 2013 (n=232). Após exclusão dos doentes com história de cirurgia de revascularização miocárdica (n=30), a estratégia de revascularização multivaso foi adotada em 35,1% (n=71) dos doentes; nos restantes 64,9% (n=131) procedeu-se à revascularização apenas da artéria *culprit*. Após *propensity score matching* (PSM), obtiveram-se dois grupos de 66 doentes, emparelhados de acordo com a estratégia de revascularização.
Resultados: Durante o seguimento (1543±545dias), após PSM, os pacientes submetidos a revascularização multivaso tiveram menores taxas de reenfarte (4,5 *versus* 16,7%; *log-rank* p=0,018), revascularização não planeada (RVNP; 6,1 *versus* 16,7%; *log-rank* p=0,048), ICP não planeada (3,0 *versus* 13,6%; *log-rank* p=0,023) e do *endpoint* combinado de morte, *reenfarte* e RVNP (16,7 *versus* 31,8%; *log-rank* p=0,046).
Conclusão: Nesta população de pacientes do mundo real com SCAsSST e DCMV, a revascularização multivaso associou-se a menores taxas de reenfarte, RVNP e ICP não planeada, bem como a uma redução do *endpoint* combinado de morte, reenfarte e RVNP.

Introduction

The prevalence of significant multivessel coronary artery disease (CAD) in patients with non-ST-segment elevation acute coronary syndrome (ACS) (NSTE-ACS) has been reported as around 50%.[1] According to current guidelines, patients with NSTE-ACS and multivessel CAD should preferably undergo complete revascularization, although the consensus that incomplete revascularization has a negative prognostic impact is only based on observational studies.[2–4] In patients with complex coronary anatomy, complete revascularization, whether percutaneous or surgical, may carry excessive risk and the patient's age, comorbidities and general clinical status should therefore be taken into consideration.

There have been no prospective randomized trials that enable the best strategy (multivessel vs. culprit-only, complete vs. incomplete) and timing (one-stage vs. multi-staged) to be determined for revascularization in patients with NSTE-ACS and multivessel CAD.[2] Although it is not possible to make a direct association, recently published randomized clinical trials have shown a beneficial effect of complete revascularization compared to culprit-only revascularization in patients with ST-elevation acute coronary syndrome (STE-ACS) and multivessel CAD,[5–8] which suggests that this strategy should at least be assessed prospectively in patients with NSTE-ACS.

The main objective of this study was to compare prognosis and short- and long-term adverse events following multivessel vs. culprit-only revascularization before and after propensity score matching (PSM) in a real-world population of patients with NSTE-ACS and multivessel CAD.

Methods

This was a retrospective, longitudinal and observational study that included all patients (n=1052) with a diagnosis of ACS who underwent percutaneous coronary intervention (PCI) in the catheterization laboratory of Braga Hospital

and who were registered in the Portuguese Registry of Acute Coronary Syndromes between January 2010 and June 2013, enabling a clinical follow-up of at least three years. Patients' clinical presentation was divided more or less evenly between NSTE-ACS (n=500, 47.5%) and STE-ACS (n=552, 52.5%). Of the patients with NSTE-ACS, about 94% (n=470) presented with non-ST-segment elevation myocardial infarction (MI), and the other 6% (n=30) presented with unstable angina. Among patients with NSTE-ACS, the prevalence of multivessel CAD was 46.4% (n=232); the other 53.6% (n=268) had single-vessel disease.

Study population and follow-up

In order to analyze the impact of multivessel vs. culprit-only or single-vessel revascularization, patients with multivessel CAD and a previous history of coronary artery bypass grafting (CABG) (n=30) were excluded due to their excessive anatomical complexity (Figure 1). The study population consisted of 202 patients with NSTE-ACS and multivessel CAD, of whom 35.1% (n=71) underwent multivessel revascularization (70 by PCI and only one by CABG) and 64.9% (n=131) underwent culprit-only revascularization (all by PCI). The decision to perform non-culprit revascularization and its timing were determined by the interventional cardiologist and the clinical cardiologist, or by the heart team when appropriate.

PCI was performed according to the guidelines of the European Society of Cardiology and the clinical practice of the interventional clinicians and included administration of low molecular weight or unfractionated heparin, use of glycoprotein IIb/IIIa inhibitors and, in a few cases, aspiration thrombectomy. Antiplatelet therapy included aspirin and a $P2Y_{12}$ inhibitor (clopidogrel in most cases).

Information regarding the revascularization strategy was collected, including the type (multivessel vs. single-vessel; complete vs. incomplete), ischemia testing, the reasons for deciding whether to perform multivessel revascularization, the timing of revascularization, and arteries revascularized or to be revascularized.

Demographic, clinical, laboratory, echocardiographic and angiographic data were collected and entered into an electronic database. This information was obtained from patients' medical records, using medical information management software (Glintt®, SimmaCardio®, SClínico® and PDS®). Data on short-term (in-hospital mortality, residual or new-onset angina, reinfarction, second degree or higher atrioventricular block, stroke, in-stent thrombosis, and mechanical complications) and long-term (mortality, reinfarction, unplanned revascularization, unplanned PCI, stroke and heart failure) prognosis and adverse events were also obtained and flagged.

Follow-up was conducted by reviewing patients' medical records, using the above software. All medical assessments and hospital records were reviewed. The mean follow-up was 1542±554 days, median 1520 days and interquartile range 704 days.

Definitions

The diagnosis of NSTE-ACS was made in accordance with the current guidelines.[2] Multivessel CAD was defined as the presence of at least two lesions deemed angiographically significant ($\geq$50% stenosis of the intraluminal diameter) in different coronary artery territories. The culprit artery was defined by the interventional cardiologist according to a combination of clinical, electrocardiographic, echocardiographic and angiographic data. Culprit-only or single-vessel revascularization was defined as an intervention on the culprit artery only, while multivessel revascularization was defined as intervention (percutaneous or surgical) on two
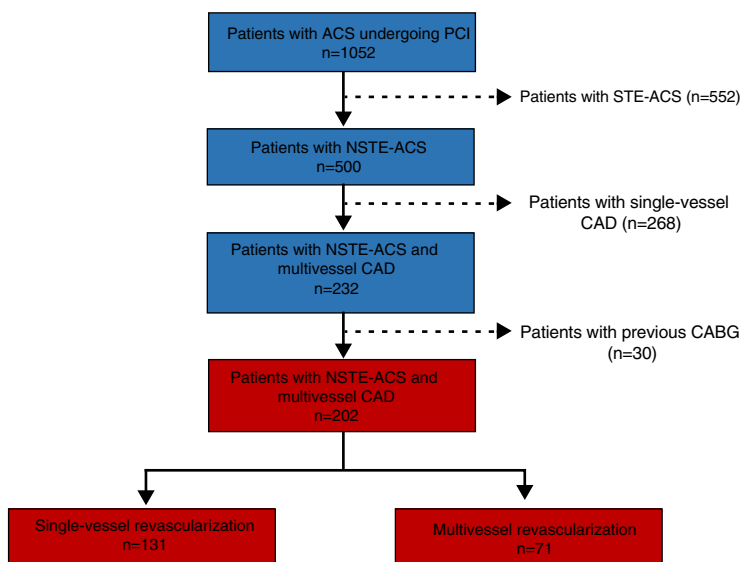

Figure 1 Study flowchart. ACS: acute coronary syndrome; CAD: coronary disease; NSTE-ACS: non-ST-segment elevation acute coronary syndrome; PCI: percutaneous coronary intervention; STE-ACS: ST-segment elevation acute coronary syndrome.

or more lesions in different coronary artery territories, during the initial procedure (first stage) or planned in the next 30 days (second stage). Heart failure during follow-up was defined by the presence of dyspnea on exertion corresponding to New York Heart Association (NYHA) functional class II or higher[9] or hospital admission due to heart failure. The Killip classification and the Global Registry of Acute Coronary Events (GRACE) and Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines (CRUSADE) risk scores were used, according to the definitions described in the literature.[10–13] Creatinine clearance was calculated by the Cockcroft-Gault formula. Major adverse cardiovascular events (MACE) were defined as mortality, MI, heart failure and stroke.

Statistical analysis

The statistical analysis was performed using IBM SPSS® version 23.0. A p-value ≤0.05 was considered to indicate statistically significant differences.

Frequencies and respective percentages were calculated for categorical variables. The chi-square test was used, continuity correction factors being reported in 2×2 contingency tables, and the Pearson's chi-square was used for contingency tables larger than 2×2. Fisher's exact test was used whenever the proportion of cells in the table with expected frequency less than five was higher than 20%.[14]

For continuous variables, medians and standard deviation were calculated using a parametric test and medians and interquartile range were calculated with a non-parametric test. In order to compare continuous variables between the two groups (multivessel vs. culprit-only revascularization), the following tests were performed: the t test for independent samples (parametric) and the Mann-Whitney test (non-parametric), respectively, depending on whether or not the dependent variable showed a normal distribution.

Given that this was a non-randomized, observational, single-center study, and considering the multiple factors that can influence the choice of revascularization type in patients with NSTE-ACS and multivessel CAD, it was decided that PSM should be performed to match the study populations (patients undergoing multivessel vs. culprit-only revascularization) and to reduce bias caused by confounding variables that could have influenced treatment decisions and clinical outcomes. The propensity score was used to assess the likelihood of each individual being selected for a revascularization strategy according to their baseline characteristics. This was followed by propensity score matching, a statistical technique that matches the characteristics of the groups according to defined variables, thus enabling the effect of one variable to be analyzed, in this case revascularization strategy (multivessel vs. single-vessel). For this case, the nearest neighbor matching without replacement technique was used, setting the optimal standard deviation as 0.03. The analysis was performed using binary logistic regression, with revascularization strategy (multivessel vs. culprit artery) as the dependent variable and the following explanatory variables: age, gender, body mass index, diabetes, history of MI, previous PCI, left ventricular ejection fraction, peak troponin I, creatinine clearance (using the
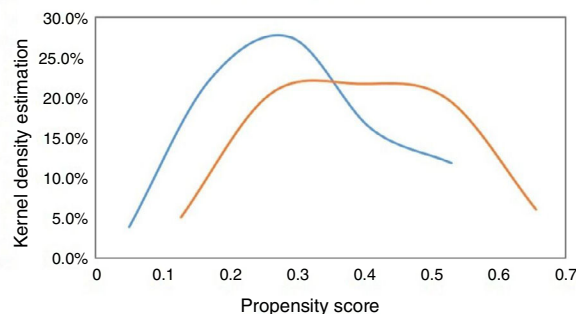

Figure 2 Degree of overlap of the propensity score according to revascularization strategy (multivessel vs. culprit artery).

Cockcroft-Gault formula), maximum Killip class, minimum hemoglobin, vascular access for coronary angiography, and significant left main, left anterior descending, circumflex, and right coronary artery disease. The degree of overlap of the propensity score between the two groups was high, as shown in Figure 2. Two groups of 66 patients matched for decision on revascularization type (multivessel vs. single-vessel) were thereby obtained. The predictive capacity of the model used to generate the propensity score was 0.69, with adequate calibration (Hosmer-Lemeshow p=0.81).

In the matched cohort, Kaplan-Meier curves were obtained comparing the groups with the log-rank test to analyze clinical event-free survival during follow-up (death, reinfarction, unplanned revascularization, unplanned PCI and MACE).

Results

Baseline population characteristics

The study population consisted of 202 patients with NSTE-ACS and multivessel CAD. Mean age was 65.3±12.5 years and 77.2% were male. Regarding cardiovascular risk factors, 34.7% had diabetes, 71.3% hypertension, 59.4% dyslipidemia, 23.3% were current smokers and 22.3% former smokers. With regard to history, 16.3% reported a previous history of MI, 20.3% angina and 12.4% PCI.

Patients who underwent multivessel revascularization tended to be younger than those who underwent culprit-only revascularization (64.1±12.5 vs. 66.0±12.4 years), with no statistically significant difference (p=0.639) (Table 1). In addition, those who underwent multivessel revascularization tended to have a higher body mass index than those undergoing culprit-only revascularization (28.9±3.9 vs. 27.7±4.2 kg/m²), at the threshold of statistical significance (p=0.051) and with a small effect.

There were no statistically significant differences between the study groups in terms of clinical characteristics (Table 1).

Regarding laboratory characteristics, there were no significant differences between the groups before matching with the exception of pro-B-type natriuretic peptide levels, which differed significantly between patients undergoing

Table 1 Demographic, clinical, laboratory, echocardiographic and angiographic characteristics of the study groups before and after matching.

Characteristics	Before matching			After matching		
	Multivessel RV (n=71)	Culprit-only RV (n=131)	p	Multivessel RV (n=66)	Culprit-only RV (n=66)	p
Demographic						
Age, years	64.1±12.5	66.0±12.4	0.304	64.6±12.3	65.6±12.5	0.639
Male	78.9% (56)	76.3% (100)	0.814	77.3% (51)	72.7% (48)	0.668
BMI, kg/m^2	28.9±3.9	27.7±4.2	0.051	28.6±3.82	28.8±4.50	0.725
Clinical						
CV risk factors						
Diabetes	36.6% (26)	33.6% (44)	0.781	36.4% (24)	36.4 (24)	1.000
Hypertension	74.6% (53)	69.5% (91)	0.539	74.2% (49)	75.8% (50)	1.000
Dyslipidemia	56.3% (40)	61.1% (80)	0.615	57.6% (38)	60.6% (40)	0.859
Smoking	19.7% (14)	25.2% (33)	0.481	18.2% (12)	22.7% (15)	0.666
History						
CRF	7.0% (5)	6.1% (8)	0.772[a]	6.1% (4)	7.6% (5)	1.000[a]
MI	11.3% (8)	19.1% (25)	0.217	12.1% (8)	12.1% (8)	1.000
Angina	19.7% (14)	20.6% (27)	1.000	19.7% (13)	21.2% (14)	1.000
Stroke/TIA	5.6% (4)	7.6% (10)	0.774[a]	4.5% (3)	9.1% (6)	0.492[a]
PAD	2.8% (2)	3.8% (5)	1.000[a]	1.5% (1)	3.0% (2)	1.000[a]
Carotid disease	0% (0)	2.3% (3)	0.553[a]	0% (0)	4.5% (3)	0.244[a]
PCI	11.3% (8)	13.0% (17)	0.898	10.6% (7)	12.1% (8)	1.000
Previous medication						
Aspirin	32.4% (23)	29.0% (38)	0.734	33.3% (22)	28.8% (19)	0.707
ACEI/ARB	52.1% (37)	51.1% (67)	1.000	54.5% (36)	42.4% (28)	0.223
Beta-blocker	23.9% (17)	27.5% (36)	0.705	24.2% (16)	25.8% (17)	1.000
Statin	36.6% (26)	43.5% (57)	0.423	37.9% (25)	42.4% (28)	0.723
Diuretic	22.5% (16)	22.1% (29)	1.000	22.7% (15)	24.2% (16)	1.000
Max. Killip class			0.751			0.496
I	73.2% (52)	74.0% (97)		74.2% (49)	66.7% (44)	
II	18.3% (13)	19.8% (26)		16.7% (11)	25.8% (17)	
III	7.0% (5)	3.8% (5)		7.6% (5)	4.5% (3)	
IV	1.4% (1)	2.3% (3)		1.5% (1)	3.0% (2)	
CRUSADE score	25.9±18.4	28.4±18.7	0.547	25.5±18.1	27.2±19.0	0.713
GRACE score	127±40.8	134±44.8	0.247	128±41.3	134±45.2	0.446
Laboratory						
Peak TnI, ng/ml	4.88 (22.65)	6.56 (15.46)	0.571	5.32 (21.90)	6.56 (10.96)	0.915
Peak Cr, mg/dl	0.90 (0.40)	0.90 (0.40)	0.882	0.90 (0.40)	0.90 (0.40)	0.579
ClCr, ml/min	93.7±38.6	86.3±36.2	0.181	91.6±37.5	90.8±37.2	0.909
proBNP, pg/ml	691 (1966)	1088 (2108)	0.024	729 (2029)	937 (2074)	0.187
Min. Hb, g/dl	14.1±1.67	13.7±1.66	0.183	14.1±1.66	13.8±1.57	0.217
Echocardiographic						
LVEF, %	50.1±9.6	48.7±9.3	0.293	50.0±9.83	50.0±9.67	0.831
Angiographic						
Vascular access			0.499[a]			1.000[a]
Radial	97.2% (69)	93.9% (123)		97.0% (64)	95.5% (63)	
Femoral	2.8% (2)	6.1% (8)		3.0% (2)	4.5% (3)	
Significant CAD						
LM	2.8% (2)	3.8% (5)	1.000[a]	3.0% (2)	1.5% (1)	1.000[a]
LAD	88.7% (63)	80.2% (105)	0.174	87.9% (58)	87.9% (58)	1.000
Cx	81.7% (58)	76.3% (100)	0.483	80.3% (53)	78.8% (52)	1.000
RCA	76.1% (54)	71.0% (93)	0.544	74.2% (49)	74.2% (49)	1.000

[a] Fisher's exact test.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; CAD: coronary artery disease; Cr: creatinine; CrCl: creatinine clearance; CRF: chronic renal failure; CV: cardiovascular; Cx: circumflex artery; Hb: hemoglobin; LAD: left anterior descending; LM: left main; LVEF: left ventricular ejection fraction; Max.: maximum; Min.: minimum; PAD: peripheral arterial disease; proBNP: pro-B-type natriuretic peptide; RCA: right coronary artery; RV: revascularization; TIA: transient ischemic attack; TnI: troponin I.

multivessel revascularization and those undergoing culprit-only revascularization (1088 [2108] vs. 691 [1966], p=0.024).

There were also no statistically significant differences between the groups with regard to echocardiographic and angiographic characteristics (Table 1).

No significant differences were found between the groups in any of the above characteristics after matching.

Revascularization strategy

As can be seen in Table 2, multivessel revascularization was most often performed percutaneously during the same procedure (first stage) (66.2%, n=47), while 32.4% of the patients underwent second-stage percutaneous revascularization. Only one patient underwent CABG, although seven were rejected for surgery due to high surgical risk. In 18.3% (n=13) of the cases, the decision to revascularize more than one vessel was based on ischemia testing. Complete revascularization was achieved in 52.1% (n=37) of patients undergoing multivessel revascularization. Among the main reasons for incomplete revascularization were diffuse disease, small vessels or high anatomical complexity (e.g. chronic occlusions). The decision not to perform PCI of non-culprit arteries was influenced by various factors, the most common being the presence of moderate lesions, i.e. with less than 70% stenosis (n=46, 35.1%). The most commonly revascularized arteries in patients undergoing culprit-only revascularization were the circumflex (35.9%, n=47) and anterior descending artery (n=35.1%, n=46); in 35.9% (n=47) of these patients, more than one artery remained to be revascularized (Table 2).

Adverse clinical events during hospital stay

There were no statistically significant differences between the multivessel and culprit-only revascularization groups with regard to in-hospital adverse clinical events before and after PSM, as seen in Table 3.

Adverse clinical events during follow-up

Adverse clinical events during follow-up are shown in Table 4. After PSM, patients undergoing multivessel revascularization had a lower incidence of reinfarction (4.5% vs. 16.7%; log-rank p=0.018; Figure 3), unplanned revascularization (6.1% vs. 16.7%; log-rank p=0.048; Figure 3), unplanned PCI (3.0% vs. 13.6%; log-rank p=0.023; Figure 3), the composite endpoint of reinfarction and unplanned revascularization (7.6% vs. 21.2%; log-rank p=0.031; Figure 4) and the composite endpoint of death, reinfarction and unplanned revascularization (16.7% vs. 31.8%; log-rank p=0.046; Figure 4). The incidence of MACE in these patients was significantly lower before, but not after, matching, although it also tended to be lower after matching (39.4% vs. 53.0%; log-rank p=0.056; Figure 4).

Discussion

The prevalence of multivessel CAD in patients with NSTE-ACS in this study was 46.4%. This result is comparable to those of other studies and meta-analyses, in which the prevalence was about 50% for those undergoing angiography.[15–20]

The present study shows a protective effect of multivessel revascularization compared with culprit-only revascularization with regard to occurrence of long-term adverse clinical events, after adjustment of baseline characteristics by PSM. In this study of real-world patients, significant reductions are reported in reinfarction, unplanned revascularization, unplanned PCI, and the composite endpoints of reinfarction and unplanned revascularization and of death, reinfarction and unplanned revascularization. Other studies[21–25] and a meta-analysis[26] have also shown a reduction in need for revascularization during follow-up, and in some cases there has also been a reduction in MACE. In a PSM analysis of 1240 patients with ACS and multivessel CAD, Shishehbor et al.[27] observed that complete revascularization was associated with a lower rate of the composite endpoint of death, reinfarction or revascularization. However, a recent meta-analysis[20] does not confirm the reduction in revascularization during follow-up and even suggests that in some cases there is increased mortality, reinfarction or MACE with a multivessel revascularization strategy, which conflicts with our results and those of other studies.

In this study, the decision whether to perform multivessel revascularization was taken by the clinical cardiologist and the interventional cardiologist or by the heart team, as appropriate. This reflects real-world practice, in which decisions on how, when and which coronary arteries should be revascularized is individualized on the basis of the anatomical characteristics of the lesions themselves, symptoms, the results of ischemia testing, the myocardial territory at risk, left ventricular systolic function, the risk of complications, the experience of the site and operator, and the patient's age, comorbidities and preferences.[28]

Higher morbidity and mortality in patients with NSTE-ACS and multivessel CAD compared with those with single-vessel disease only[29,30] may be due to various mechanisms, including multiple unstable plaques and abnormalities in myocardial perfusion or contractility, which may result in MI, arrhythmias and death. The potential advantages of multivessel revascularization in this context include preventing ischemia or reinfarction and associated complications, reducing the myocardial territory at risk, and improving myocardial function by increasing blood flow to the peri-infarct area.

However, there may also be disadvantages in multivessel revascularization, including more prolonged procedures, requiring greater use of contrast and higher radiation dose, and more stent-associated complications (in-stent thrombosis and restenosis) due to more stents being implanted. Nonetheless, the use of new antiplatelet agents, radial access and new-generation drug-eluting stents may help enhance the safety of the procedure for experienced operators. In this study, patients undergoing multivessel revascularization showed a similar in-stent thrombosis rate to those undergoing single-vessel revascularization, as well as similar rates for other in-hospital adverse events. Therefore, in our study, multivessel revascularization was not associated with worse short-term prognosis relative to culprit-only revascularization, as also seen in other studies, in which there were no statistically significant differences between the groups (multivessel vs. single-vessel) in terms

Table 2 Factors associated with revascularization strategy.

	Unmatched groups		
	Multivessel RV (n=71)	Single-vessel RV (n=131)	p
Type of RV			
Single-vessel PCI	0% (0)	100% (131)	
1st-stage multivessel PCI	66.2% (47)	0% (0)	
2nd-stage multivessel PCI	32.4% (23)	0% (0)	
Planned CABG	1.4% (1)	0% (0)	
Ischemia testing			0.013
Positive	18.3% (13)	5.3% (7)	
Negative	1.4% (1)	2.3% (3)	
Not performed	80.3% (57)	92.4% (121)	
Reason not to perform multivessel revascularization			
Negative ischemia test		3.8% (5)	
Moderate lesions (<70%)		35.1% (46)	
Anatomical complexity		17.6% (23)	
Chronic occlusion		8.4% (11)	
Age and comorbidities		2.3% (3)	
More than one of the above		32.8% (43)	
Reason to perform multivessel revascularization			
Positive ischemia test	18.3% (13)		
Anatomical	81.7% (58)		
Complete revascularization			<0.001
No	47.9% (34)	100% (131)	
Yes	52.1% (37)	0% (0)	
1st-stage artery revascularized			<0.001
LM	0% (0)	2.3% (3)	
LAD	9.9% (7)	35.1% (46)	
Cx	8.5% (6)	35.9% (47)	
RCA	15.5% (11)	24.4% (32)	
More than one	66.2% (47)	0% (0)	
2nd-stage artery revascularized			
LM	0% (0)		
LAD	12.7% (9)		
Cx	7.0% (5)		
RCA	7.0% (5)		
More than one	7.0% (5)		
Artery or branch to be revascularized			<0.001
LM	0% (0)	0% (0)	
LAD	12.7% (9)	26.2% (34)	
Cx	9.9% (7)	17.6% (23)	
RCA	14.1% (10)	21.5% (28)	
More than one	0% (0)	35.1% (46)	
Stent characteristics			
No. of stents per patient	2.3±0.9	1.0±0.4	<0.001
Total length (mm)	48±23	18±8	<0.001
% DES	81.6%	55.2%	<0.001

CABG: coronary artery bypass grafting; Cx: circumflex artery; DES: drug-eluting stents; LAD: left anterior descending; LM: left main; PCI: percutaneous coronary intervention; RCA: right coronary artery; RV: revascularization.

of periprocedural complications. It can thus be stated that multivessel revascularization is as safe as, and in some cases safer than, culprit-only revascularization.[29,31,32]

In this study, multivessel revascularization was mainly performed during the initial procedure (66.2%). Intervention on a non-culprit lesion during the initial procedure can result in unnecessary hemodynamic compromise, at a time when the patient may have significant regional myocardial dysfunction due to the infarction. Moreover, non-culprit lesions may be overestimated and their physiological significance

Table 3 In-hospital adverse clinical events before and after propensity score matching.

Events	Before matching			After matching		
	Multivessel RV (n=71)	Culprit-only RV (n=131)	p	Multivessel RV (n=66)	Culprit-only RV (n=66)	p
Death	0% (0)	1.5% (2)	0.542[a]	0% (0)	1.5% (1)	1.000[a]
Angina[b]	7.0% (5)	8.4% (11)	0.946	7.6% (5)	6.1% (4)	1.000[a]
Reinfarction	7.0% (5)	4.6% (6)	0.522[a]	7.6% (5)	4.5% (3)	0.718[a]
≥2 AV block	4.2% (3)	3.1% (4)	0.698[a]	4.5% (3)	3.0% (2)	1.000[a]
Stroke	2.8% (2)	0% (0)	0.122[a]	3.0% (2)	0% (0)	0.496[a]

[a] Fisher's exact test.
[b] residual or new-onset.
≥2 AV block: second degree or higher atrioventricular block; RV: revascularization.
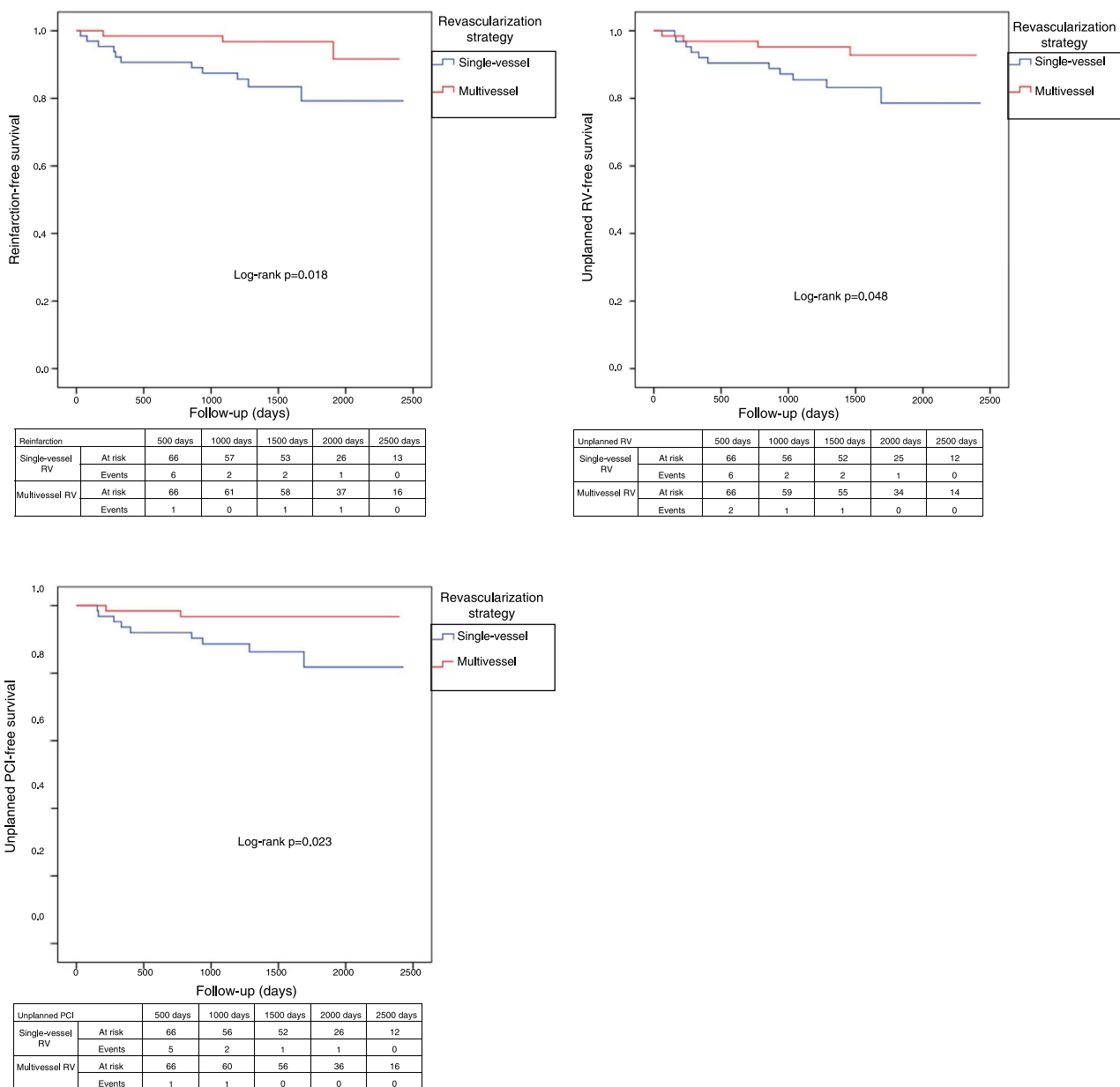

Figure 3 Kaplan-Meier curves for survival free of reinfarction, unplanned revascularization, and unplanned PCI, after matching. RV: revascularization.

Table 4 Adverse clinical events during follow-up before and after propensity score matching.

Events	Before matching			After matching		
	Multivessel RV (n=71)	Culprit-only RV (n=131)	Log-rank p	Multivessel RV (n=66)	Culprit-only RV (n=66)	Log-rank p
Death	11.3% (8)	16.0% (21)	0.307	12.1% (8)	18.2% (12)	0.248
Reinfarction	5.6% (4)	16.8% (22)	0.018	4.5% (3)	16.7% (11)	0.018
Stroke	5.6% (4)	3.8% (5)	0.619	6.1% (4)	3.0% (2)	0.495
HF	29.6% (21)	34.4% (45)	0.426	30.3% (20)	31.8% (21)	0.767
Unplanned RV	5.6% (4)	15.3% (20)	0.040	6.1% (4)	16.7% (11)	0.048
Unplanned PCI	2.8% (2)	12.2% (16)	0.022	3.0% (2)	13.6% (9)	0.023
Unplanned CABG	2.8% (2)	3.1% (4)	0.900	3.0% (2)	3.0% (2)	0.945
Reinfarction or unplanned RV	8.5% (6)	19.8% (26)	0.027	7.6% (5)	21.2% (14)	0.031
Death, reinfarction or unplanned RV	16.9% (12)	31.3% (41)	0.034	16.7% (11)	31.8% (21)	0.046
MACE	39.4% (28)	53.4% (70)	0.031	39.4% (26)	53.0% (35)	0.056

CABG: coronary artery bypass grafting; HF: heart failure; MACE: major adverse cardiovascular events (mortality, myocardial infarction, heart failure and stroke); PCI: percutaneous coronary intervention; RV: revascularization.
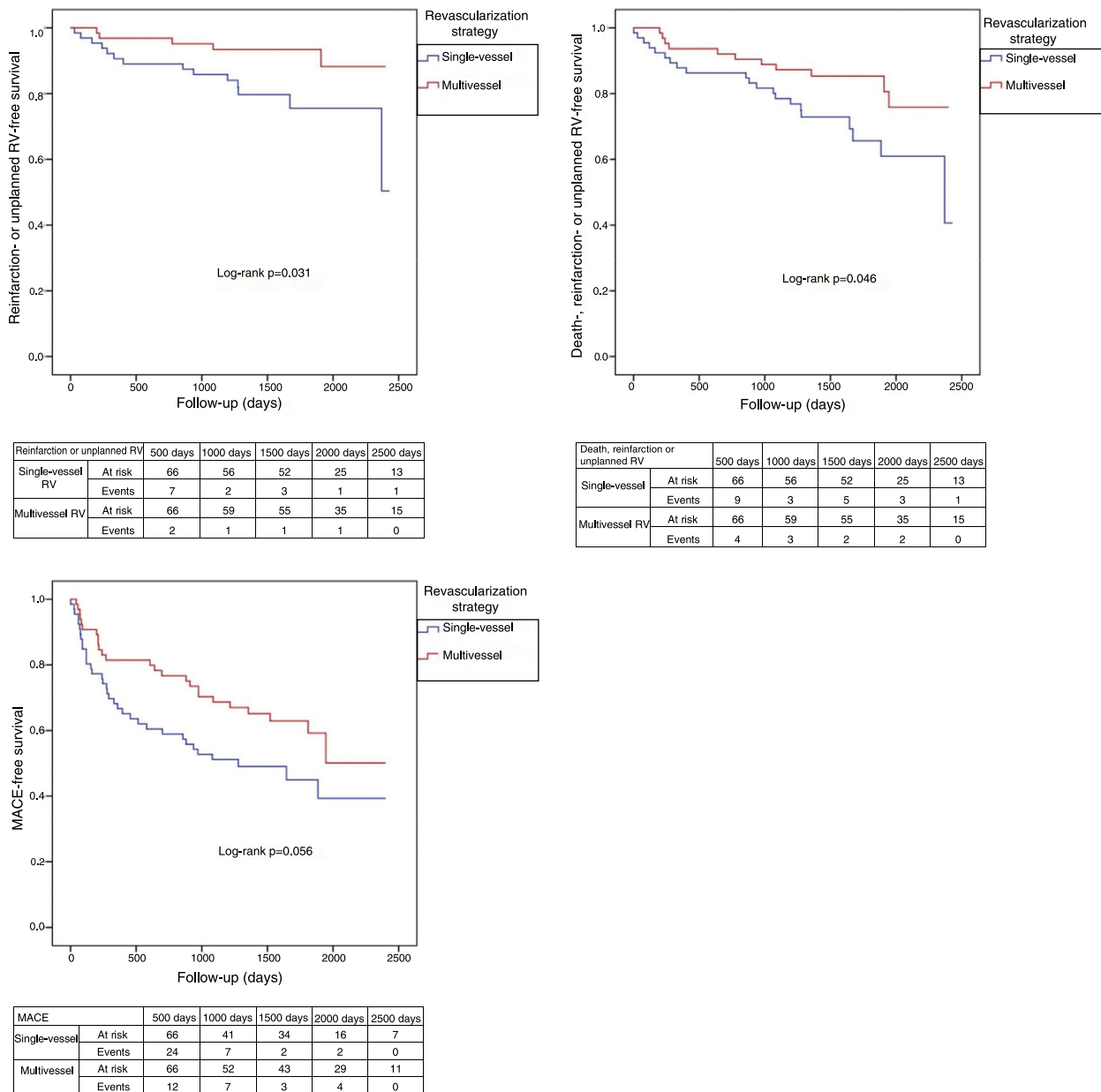
Reinfarction or unplanned RV		500 days	1000 days	1500 days	2000 days	2500 days
Single-vessel RV	At risk	66	56	52	25	13
	Events	7	2	3	1	1
Multivessel RV	At risk	66	59	55	35	15
	Events	2	1	1	1	0

Death, reinfarction or unplanned RV		500 days	1000 days	1500 days	2000 days	2500 days
Single-vessel	At risk	66	56	52	25	13
	Events	9	3	5	3	1
Multivessel RV	At risk	66	59	55	35	15
	Events	4	3	2	2	0

MACE		500 days	1000 days	1500 days	2000 days	2500 days
Single-vessel	At risk	66	41	34	16	7
	Events	24	7	2	2	0
Multivessel	At risk	66	52	43	29	11
	Events	12	7	3	4	0

Figure 4   Kaplan-Meier curves for survival free from the composite endpoints of reinfarction or unplanned revascularization and of death, reinfarction or unplanned revascularization and MACE. MACE: major adverse cardiovascular events; RV: revascularization.

may be difficult to assess, which may lead to PCI being performed unnecessarily.[33] Elective revascularization enables better assessment of the physiological significance of non-culprit lesions, through invasive and non-invasive ischemia tests, and gives more time to discuss the revascularization strategy, which may thus be safer. However, in a recent randomized trial (SMILE[34]) comparing multivessel revascularization during the initial procedure with a staged revascularization strategy, a reduction in major cardiovascular events was found with the former, mainly due to fewer unplanned revascularizations.

In summary, data from articles published in this field suggest that assessment of the risk-benefit balance associated with future invasive procedures should be based on analysis of the patient's general status and cardiovascular risk factors, the possibility of identifying the culprit artery, the technical feasibility of performing multivessel revascularization, and the location, degree of stenosis and severity of lesions. In addition, the patient's clinical stability, operator experience, the decisions of the heart team, and the availability of cardiac surgery facilities are also relevant to the choice of strategy[32] (Figure 5).

In view of the conflicting results obtained in meta-analyses and observational studies, prospective randomized studies with large patient populations are needed to be able to identify the most appropriate revascularization strategy for patients with NSTE-ACS and multivessel CAD.
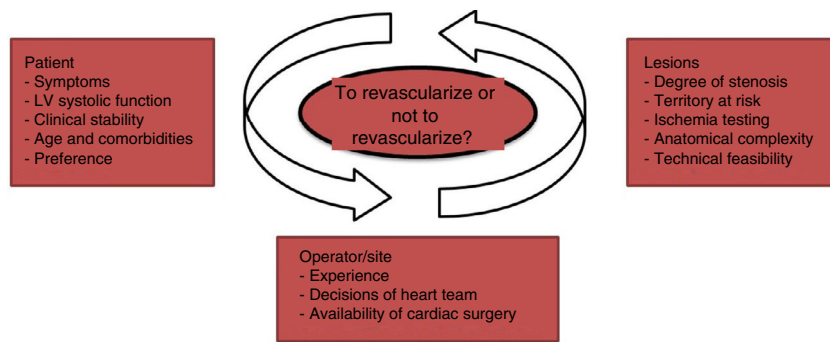
Figure 5 Factors that may influence the decision to revascularize. LV: left ventricular.

Limitations

There are several limitations to be considered when interpreting this study. First, this was a retrospective, non-randomized observational study conducted at a single hospital, involving a relatively small number of patients, and thus presents the limitations and biases inherent to retrospective single-center studies. Although PSM was carried out between the groups, which increases the power of the statistical analysis, it is impossible to correct for unmeasured confounding factors and all the selection biases related to treatment decisions, which means definitive conclusions cannot be drawn. Second, definition of the type of lesion (culprit vs. non-culprit) did not follow a protocol, and it is therefore likely that this decision varied according to how the interventional cardiologist interpreted the angiographic results at the time of coronary angiography. Given how difficult it can be to identify the culprit artery, it cannot be ruled out that incorrect identification may have influenced the results, such as the culprit lesion being more likely to be erroneously identified in the group undergoing single-vessel revascularization. Third, there is no simple way to identify the factors that led to the decision to perform multivessel revascularization in each case, and so it is impossible to establish a standard approach for patients with NSTE-ACS and multivessel CAD. Fourth, data on the functional assessment of coronary stenoses were not collected for all patients undergoing multivessel revascularization. In practice, most of the non-culprit lesions were identified as significant using coronary angiography alone. Fifth, the treatment groups were defined after patients underwent PCI, and some patients who had been initially allocated to the multivessel revascularization group may have undergone culprit-only revascularization, due to technical or anatomical factors that may have precluded more complete revascularization.

Conclusion

The decision to perform multivessel vs. culprit-only revascularization in patients with NSTE-ACS and multivessel CAD is still the subject of heated debate and there is as yet no consensus.

However, this study supports the hypothesis that multivessel revascularization in patients with NSTE-ACS and multivessel CAD reduces the occurrence of adverse clinical events during follow-up, including reinfarction, unplanned revascularization, unplanned PCI, and the composite endpoints of reinfarction and unplanned revascularization and of death, reinfarction and unplanned revascularization, both before and after performing PSM.

Conflicts of interest

The authors have no conflicts of interest to declare.

References

1. Bajraktari G, Henein MY. Treatment strategies of NSTEMI-ACS with multivessel disease. Int Cardiovasc F J. 2016;6:3–5.
2. Roffi M, Patrono C, Collet JP, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37:267–315.
3. Jneid H, Anderson JL, Wright RS, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/Non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2012;126:875–910.
4. Moreira D, Marmelo B, Delgado A, et al. A conservative strategy in non ST segment elevation myocardial infarction – constraints and prognosis: the situation in Portugal. Rev Port Cardiol. 2015;34:315–28.
5. Wald DS, Morris JK, Wald NJ, et al. Randomized trial of preventive angioplasty in myocardial infarction. N Engl J Med. 2013;369:1115–23.
6. Gershlick AH, Khan JN, Kelly DJ, et al. Randomized trial of complete versus lesion-only revascularization in patients undergoing primary percutaneous coronary intervention for STEMI and multivessel disease: the CvLPRIT trial. J Am Coll Cardiol. 2015;65:963–72.
7. Engstrøm T, Kelbæk H, Helqvist S, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015;386:665–71.
8. Sousa Almeida M. ''Unsuitable for PCI..'' Multivessel primary PCI. But for whom? Rev Port Cardiol. 2014;33:75–7.
9. Ponikowski P, Voors AA, Anker SD, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of

acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129--200.

10. Granger CB, Goldberg RJ, Dabbous O, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163:2345--53.

11. Eagle KA, Lim MJ, Dabbous OH, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. JAMA. 2004;291:2727--33.

12. Ariza-Solé A, Sánchez-Elvira G, Sánchez-Salado JC, et al. CRUSADE bleeding risk score validation for ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention. Thromb Res. 2013;132:652--8.

13. Killip T, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967;20:457--64.

14. Field A. Discovering statistics using SPPS. 3rd edition London: SAGE Publications, Ltd; 2009.

15. Davies MJ. The pathophysiology of acute coronary syndromes. Heart. 2000;83:361--70.

16. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. N Engl J Med. 2009;360:2165--75.

17. Lee HJ, Song YB, Hahn JY, et al. Multivessel vs single-vessel revascularization in patients with non-ST-segment elevation acute coronary syndrome and multivessel disease in the drug-eluting stent era. Clin Cardiol. 2011;34:160--5.

18. Henriques JP, Claessen BE. A SMILE and a frown: one-stage or multistage PCI in NSTEMI patients with multivessel disease. J Am Coll Cardiol. 2016;26:273--4.

19. Hassanin A, Brener SJ, Lansky AJ, et al. Prognostic impact of multivessel versus culprit vessel only percutaneous intervention for patients with multivessel coronary artery disease presenting with acute coronary syndrome. EuroIntervention. 2015;11:293--300.

20. Mariani J, Macchia A, de Abreu M, et al. Multivessel versus single vessel angioplasty in non-ST elevation acute coronary syndromes: a systematic review and metaanalysis. PLoS One. 2016;11:e0148756.

21. Bhatt DL, Topol EJ. Does creatinine kinase-MB elevation after percutaneous coronary intervention predict outcomes in 2005? Periprocedural cardiac enzyme elevation predicts adverse outcomes. Circulation. 2005;112:906--15.

22. Brener SJ, Milford-Beland S, Roe MT, et al. American College of Cardiology National Cardiovascular Database Registry Culprit-only or multivessel revascularization in patients with acute coronary syndromes: an American College of Cardiology National Cardiovascular Database Registry report. Am Heart J. 2008;155:140--6.

23. Zapata GO, Lasave LI, Kozak F, et al. Culprit-only or multivessel percutaneous coronary stenting in patients with non-ST-segment elevation acute coronary syndromes: one-year follow-up. J Interv Cardiol. 2009;22:329--35.

24. Brener SJ, Murphy SA, Gibson CM, et al. Efficacy and safety of multivessel percutaneous revascularization and tirofiban therapy in patients with acute coronary syndromes. Am J Cardiol. 2002;90:631--3.

25. Palmer ND, Causer JP, Ramsdale DR, et al. Effect of completeness of revascularization on clinical outcome in patients with multivessel disease presenting with unstable angina who undergo percutaneous coronary intervention. J Invasive Cardiol. 2004;16:185--8.

26. Jang JS, Jin HY, Seo JS, et al. Meta-analysis of multivessel versus culprit-only percutaneous coronary intervention in patients with non-ST-segment elevation acute coronary syndrome and multivessel coronary disease. Am J Cardiol. 2015;115:1027--32.

27. Shishehbor MH, Lauer MS, Singh IM, et al. In unstable angina or non-ST-segment acute coronary syndrome, should patients with multivessel coronary artery disease undergo multivessel or culprit-only stenting? J Am Coll Cardiol. 2007;49:849--54.

28. Galvão Braga C, Cid-Álvarez AB, Redondo Diéguez A, et al. Multivessel versus culprit-only percutaneous coronary intervention in ST-segment elevation acute myocardial infarction: analysis of an 8-year registry. Rev Esp Cardiol (Engl Ed). 2017;70:425--32.

29. Salem M, Farag S, Atia AI, et al. Multivessel stenting versus culprit-only stenting in multivessel coronary artery disease patients presented with non-ST-segment elevation acute coronary syndrome (NSTE-ACS). J Cardiol Current Res. 2015;3.

30. Jaski B, Cohen J, Trusch J, et al. Outcome of urgent percutaneous transluminal coronary angioplasty in acute myocardial infarction: comparison of single-vessel versus multivessel coronary artery disease. Am Heart J. 1992;124:143--8.

31. Kim MC, Jeong MH, Ahn Y, et al. What is optimal revascularization strategy in patients with multivessel coronary artery disease in non-ST-elevation myocardial infarction? Multivessel or culprit-only revascularization. Int J Cardiol. 2011;153:148--53.

32. Gąsior P, Desperak P, Gierlaszyńska K, et al. Percutaneous coronary intervention in treatment of multivessel coronary artery disease in patients with non-ST-segment elevation acute coronary syndrome. Postepy Kardiol Interwencyjnej. 2013;9:136--45.

33. Hanratty CG, Koyama Y, Rasmussen HH, et al. Exaggeration of nonculprit stenosis severity during acute myocardial infarction: implications for immediate multivessel revascularization. J Am Coll Cardiol. 2002;40:911--6.

34. Sardella G, Lucisano L, Garbo R, et al. Single-staged compared with multi-staged PCI in multivessel NSTEMI patients: the SMILE trial. J Am Coll Cardiol. 2016;67:264--72.