

## Supplementary Online Content

Vergallo R, Porto I, D'Amario D, et al. Coronary atherosclerotic phenotype and plaque healing in patients with recurrent acute coronary syndromes compared with patients with long-term clinical stability: in vivo optical coherence tomography study. *JAMA Cardiol*. Published online March 13, 2019. doi:10.1001/jamacardio.2019.0275

### **eMethods.**

**eTable 1.** Inclusion and Exclusion Criteria

**eTable 2.** Segment-Based OCT Analysis.

**eTable 3.** Clinical Follow-up

**eTable 4.** Univariate Cox Regression Analysis

**eTable 5.** Multivariate Cox Regression Analysis

### **eReferences.**

**eFigure.** Major Adverse Cardiac Event (MACE) Rates and Kaplan-Meier Survival Curves in Patients With and Without Healed Coronary Plaques

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

## **eMethods**

### **Angiographic analysis**

Severity and extent of coronary artery disease were assessed by using the Bogaty and the Gensini scores, as previously described (1,2). According to the Bogaty score, the severity of coronary artery disease was assessed by considering the following three parameters: 1) number of diseased vessels, including the number of major epicardial vessels with at least one lesion with a diameter stenosis >70%. A left main stem stenosis >50% was considered as two diseased vessels; 2) number of stenoses, represented by the total number of >50% narrowings in all the vessels of the angiogram. A maximum of three stenoses was allowed per coronary segment; 3) number of occlusions, which included the number of lesions with TIMI flow grade 0-1 (1). The extent of coronary artery disease was quantified by assigning a score of 0-3 to each coronary segment, where a score 0 was given to an angiographically normal segment, a score 1 to a coronary segment with <10% of its length appearing abnormal (narrowed and/or irregular), a score 2 to a coronary segment with 10% to 50% of its length appearing abnormal, and a score 3 to a coronary segment with >50% of its length appearing abnormal. In case of occluded or suboccluded segments (TIMI flow grade 0-1), these were assigned a score of 2 (or 3 if there were abnormalities proximal to the occlusion involving >50% of the nonoccluded part of the segment), and the corresponding distal segments were not scored. An extent score was calculated as the sum of each segment's score (varying from 0 to 45), and it was normalized by dividing the total extent score by the number of coronary segments (i.e., 15), obtaining an extend index, varying from 0 to 3 (1). Of note, the American Heart Association (AHA) classification was used to define the coronary artery segments on the angiogram, as previously described (3).

The Gensini score quantifies coronary artery disease severity by weighting the degree of luminal narrowing of each lesion for its specific coronary tree location (2). In particular, based on the severity of luminal narrowing, lesions with 25% stenosis are given 1 point, lesions with 50% stenosis 2 points, lesions with 75% stenosis 4 points, lesions with 90% stenosis 8 points, subocclusive lesions (i.e., 99% stenosis) 16 points, and total occlusions (100% stenosis) 32 points. Region multiplying factors for coronary segments, which takes into account the relative amount of myocardium supplied by the diseased segment, are 5 for lesions located at the left main stem, 2.5 for those located at the proximal left anterior descending (LAD) or left circumflex (LCx) segments, 1.5 for those located at the mid LAD or LCx segments, 1 for those located at the distal LAD or LCx segments, first diagonal branch, first obtuse marginal branch, right coronary artery (RCA), posterior descending artery, and intermediate branch, 0.5 for lesions located at the second diagonal or second obtuse marginal branches, and 0.25 for those located at the third diagonal or third obtuse marginal branches. The sum of each adjusted lesion score represents the Gensini score (2).

### **OCT image acquisition**

OCT imaging was performed after intracoronary administration of nitroglycerin (100-200  $\mu$ g), using an FD-OCT system (C7-XR or ILUMIEN OPTIS, St. Jude Medical, St. Paul, MN). An automated pullback was initiated at a speed of 20 mm/sec (C7-XR, 100 frames/sec) or 36 mm/sec (ILUMIEN OPTIS, 180 frames/sec), in concordance with blood clearance using contrast medium.

**eTable 1. Inclusion and exclusion criteria**

Inclusion criteria	Exclusion criteria
<i>All patients</i>	
1. OCT imaging during coronary angiography and/or PCI	1. Incomplete clinical information related to the history of previous AMI and/or duration of clinical stability
<i>rACS group</i>	
1. History of $\geq 3$ AMIs or $\geq 4$ ACS [AMI or UAP] with at least 1 AMI.	1. AMI due to stent thrombosis
2. At least 1 month between two AMI or ACS	
<i>Is-SAP group</i>	
1. At least 3-year history of stable angina	1. Any episode suggestive of an acute coronary event
2. Myocardial ischemia documented by a functional test (i.e., exercise treadmill testing and/or myocardial perfusion imaging)	2. Q-waves on 12-leads EKG
	3. Abnormal echocardiogram (i.e., LVEF <50%, and/or wall motion abnormalities)
<i>sAMI group</i>	
1. History of a single episode of AMI, followed by a minimum 3-year period of clinical stability	1. Any episode suggestive of an acute coronary event after the first AMI
2. Myocardial ischemia documented by a functional test (i.e., exercise treadmill testing and/or myocardial perfusion imaging)	

OCT, optical coherence tomography; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction; ACS, acute coronary syndrome; UAP, unstable angina pectoris; EKG, electrocardiogram; LVEF, left ventricular ejection fraction.

**eTable 2. Segment-based OCT analysis.**

	rACS [1] (n=407)	ls-SAP [2] (n=640)	sAMI [3] (n=562)	p value		
				[1] vs. [2]	[1] vs. [3]	[2] vs. [3]
Lipid-rich plaque	167 (41.0)	130 (20.3)	217 (38.6)	<0.001	0.447	<0.001
TCFA	32 (7.9)	6 (0.9)	29 (5.2)	<0.001	0.090	<0.001
Fibrous plaque	170 (41.8)	381 (59.5)	241 (42.9)	<0.001	0.729	<0.001
Healed coronary plaque	1 (0.2)	27 (4.2)	32 (5.7)	0.005	0.002	0.239
Macrophage accumulation	61 (15.0)	18 (2.8)	15 (2.7)	<0.001	<0.001	0.879
Intimal vasculature	90 (22.1)	106 (16.6)	83 (14.8)	0.025	0.003	0.394
Calcification	109 (26.8)	305 (47.7)	212 (37.7)	<0.001	<0.001	0.001
Spotty calcification	88 (21.6)	57 (8.9)	45 (8.0)	<0.001	<0.001	0.577

Data are expressed as counts (percentages) or median (interquartile range). TCFA, thin-cap fibroatheroma;

**eTable 3. Clinical follow-up**

	<b>Overall (n=101)</b>	<b>rACS (n=29)</b>	<b>Is-SAP (n=36)</b>	<b>sAMI (n=36)</b>	<b>p value</b>
MACE, n (%)	26 (25.7)	15 (51.7)	6 (16.7)	5 (13.9)	<0.001
CARDIAC DEATH, N (%)	5 (5.0)	3 (10.3)	1 (2.8)	1 (2.8)	0.113
NON-FATAL MI, N (%)	10 (9.9)	7 (24.1)	2 (5.6)	1 (2.8)	<0.001
RE-HOSPITALIZATION DUE TO UAP, N (%)	11 (10.9)	5 (17.2)	3 (8.3)	3 (8.3)	0.023
NON-TVR, N (%)	18 (17.8)	9 (31.0)	5 (13.9)	4 (11.1)	0.001

P values are Kaplan-Meier estimates. MACE, major adverse cardiovascular events; MI, myocardial infarction; UAP, unstable angina pectoris; non-TVR, non-target vessel revascularization.

**eTable 4. Univariate Cox regression analysis.**

		<b>HR</b>	<b>95% CI</b>	<b>p value</b>
Age > 68 years <sup>§</sup>		1.26	0.58–2.76	0.564
Male sex		0.57	0.25–1.31	0.186
Hypertension		0.89	0.40–2.01	0.785
Dyslipidemia		1.11	0.38–3.25	0.845
Diabetes		1.22	0.56–2.67	0.619
Current smoking		1.40	0.42–4.68	0.583
rACS		7.63	3.14–18.54	<b>&lt;0.001</b>
Prior PCI		2.98	0.88–10.10	0.080
Prior CABG		0.81	0.19–3.46	0.774
DAPT at discharge		0.90	0.39–2.07	0.796
Beta-blockers at discharge		0.64	0.24–1.71	0.373
ACE-i/ARBs at discharge		0.83	0.30–2.25	0.709
Statins at discharge		0.88	0.40–1.95	0.756
Lipid-rich plaque		1.20	0.54–2.66	0.658
TCFA		2.55	1.17–5.56	<b>0.019</b>
Fibrous plaque		0.32	0.14–0.73	<b>0.007</b>
Macrophage accumulation		3.12	1.43–6.80	<b>0.004</b>
Intimal vasculature		0.77	0.35–1.68	0.506
Calcification		0.60	0.27–1.31	0.201
Spotty calcification		2.47	1.07–5.71	<b>0.034</b>
Healed coronary plaque		0.19	0.04–0.80	<b>0.024</b>
Bogaty score		3.12	1.07–9.06	<b>0.037</b>
Gensini score		1.46	0.61–3.48	0.392

Data are expressed as HR (95% CI). Bogaty score and Gensini score correspond to intermediate-to-high vs. low tertiles. rACS, recurrent acute coronary syndromes; PCI, percutaneous coronary intervention; CABG, coronary artery bypass graft; DAPT, dual antiplatelet therapy; ACE-

i/ARBs, angiotensin converting enzyme inhibitor/angiotensin receptor blockers; TCFA, thin-cap fibroatheroma; HR, hazard ratio; CI, confidence interval.



**eTable 5. Multivariate Cox regression analysis.**

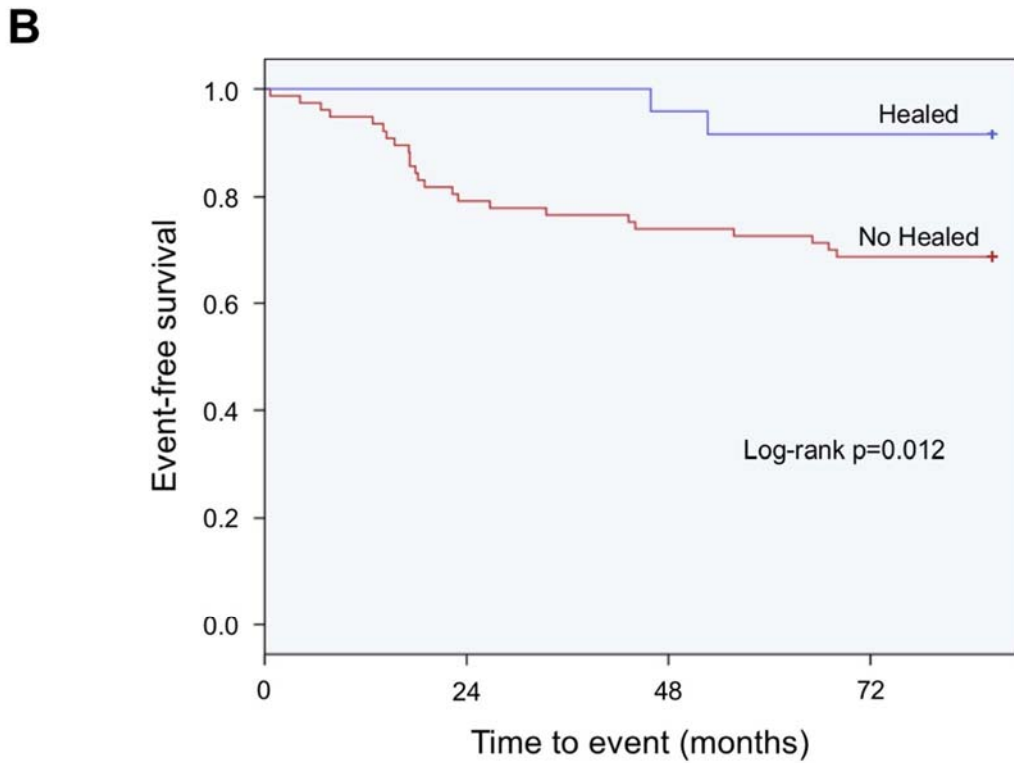
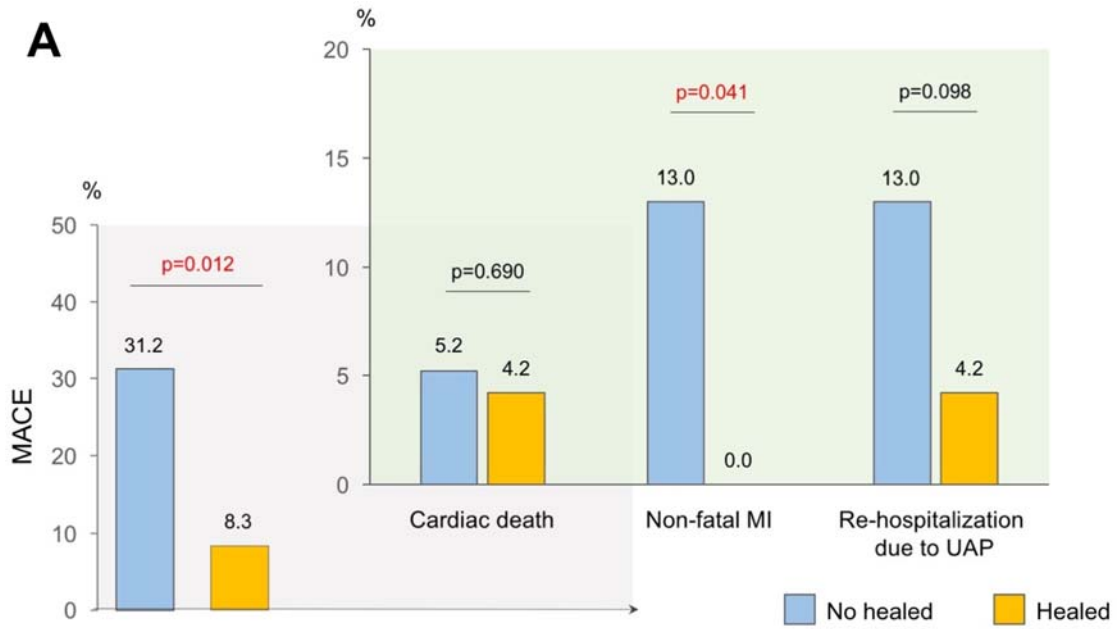
		<b>HR</b>	<b>95% CI</b>	<b>p value</b>
Age>68 years <sup>§</sup>		1.34	0.54–3.27	0.528
Male sex		0.52	0.19–1.47	0.220
rACS		3.09	1.04–9.20	<b>0.043</b>
Prior PCI		1.08	0.23–5.07	0.923
TCFA		2.80	1.04–7.54	<b>0.041</b>
Fibrous plaque		0.51	0.19–1.41	0.197
Macrophage accumulation		2.78	1.13–6.86	<b>0.026</b>
Spotty calcification		1.66	0.60–4.62	0.331
Healed coronary plaque		0.17	0.03–0.85	<b>0.031</b>
Bogaty score		3.21	0.83–12.43	0.092

Data are expressed as HR (95% CI). <sup>§</sup> corresponds to the median value of age. Bogaty score corresponds to intermediate-to-high vs. low tertiles. rACS, recurrent acute coronary syndromes; PCI, percutaneous coronary intervention; TCFA, thin-cap fibroatheroma; HR, hazard ratio; CI, confidence interval.

## References

1. Bogaty P, Brecker SJ, White SE, et al. Comparison of coronary angiographic findings in acute and chronic first presentation of ischemic heart disease. *Circulation*. 1993;87(6):1938-1946.
2. Gensini G. *Coronary arteriography*. New York, NY Futura Publishing Co 1975.
3. Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51(4 Suppl):5-40.

eFigure 1



No. at risk	0	24	48	72
Overall	101	85	80	75
Healed	24	24	23	22
No healed	77	61	57	53

**eFigure 1. Major adverse cardiac event (MACE) rates and Kaplan-Meier survival curves in patients with and without healed coronary plaques.** The rate of cardiac death, non-fatal myocardial infarction, and re-hospitalization due to unstable angina pectoris (UAP) in patients with and without healed coronary plaques (A). MACE-free survival curves in patients with and without healed coronary plaques (B). P values are based on the log-rank test. Survival rates represent Kaplan-Meier estimates.