Supplementary data

Supplementary Appendix 1. Study design and population

Patients were enrolled in the registry from January 2009 to December 2019. We included patients with clinical presentation compatible with acute coronary syndrome and meeting criteria for SCAD [1,2]. Patients with significant (≥50%) atherosclerotic disease in other coronary arterial segments or with an underlying complicated plaque as revealed by intracoronary imaging were excluded. Data on demographics, clinical presentation, treatment modality, angiographic findings, management, and early and late outcomes were extracted from clinical source documents or collected via medical records, patient interviews, and follow-up visits. A dedicated data manager (L. Lo Savio) was in charge of source verification, quality control, and queries generation from the coordinating centre to the participating sites to minimise bias. Follow-up data were collected by each centre through review of medical records or during outpatient visits and/or telephone contacts. The study was conducted in accordance with the Declaration of Helsinki.

Supplementary Appendix 2. Angiographic analysis and classification

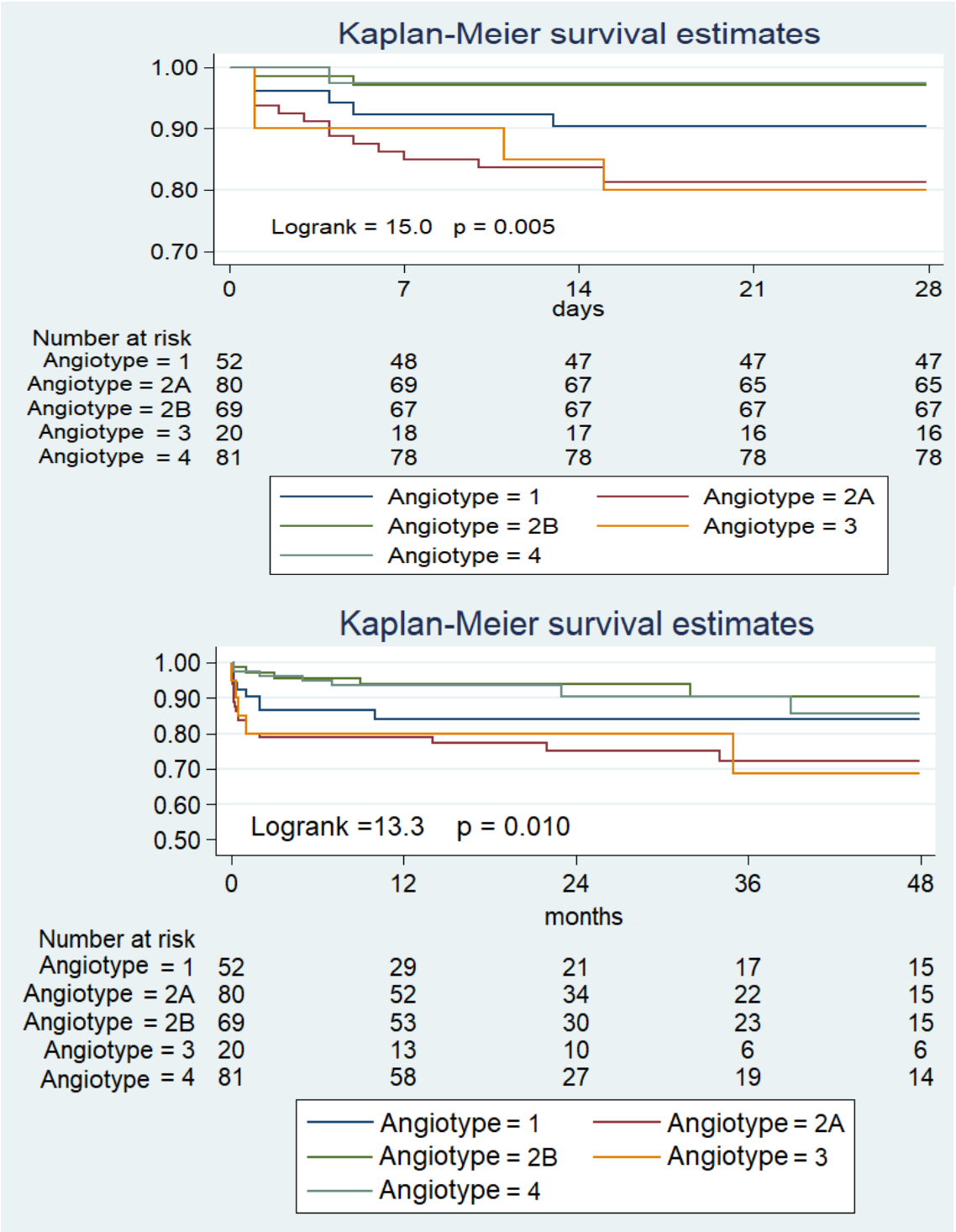
All coronary angiograms were sent to the coordinating centre and reviewed by two experienced interventional cardiologists (G. Quadri, C. Rolfo) for diagnostic confirmation. In case of disagreement, consensus was achieved after discussion with a third interventional cardiologist (F. Tomassini). Diagnostic criteria were based on angiography and intracoronary imaging data (whenever available) as previously described [1,2]. For the classification of SCAD, we followed the one proposed by Adlam et al [2] in the ESC-ACCA position paper on SCAD using five categories **(Supplementary Figure 1)**.

After diagnosis corroboration of SCAD at the coordinating centre, the angiographic classification was performed in a second stage by both the registry coordinating centre (G. Quadri, C. Rolfo, E. Cerrato) and the study leading centre (R. Mori, F. Macaya, J. Escaned) with a previous consensus agreement on the specific criteria to be used, as well as subsequent online meetings to discuss unclear cases. The angiographic classification criteria used were as follows: angiotype 1 is the classic angiographic radiolucent flap or linear double lumen, often associated with contrast hold-up. Angiotype 2 is characterised by a long diffuse (≥20 mm by quantitative coronary angiography) and smooth stenosis, corresponding to an angiographically contained intramural haematoma (small fenestrations of the intimomedial lamina cannot be excluded solely on the grounds of angiography). This angiotype is further divided into angiotype 2A, in which there is recrudescence of normal distal vessel calibre, and angiotype 2B, where the stenosis (haematoma) involves angiographically the entire distal segment. Angiotype 3 consists of ambiguous stenoses shorter than 20 mm (by quantitative coronary angiography), angiographically indistinguishable from a focal atherosclerotic stenosis, that require diagnostic confirmation by means of intracoronary imaging or a scheduled surveillance angiogram confirming vessel healing. This angiotype also corresponds to an angiographically contained intramural haematoma. Finally, angiotype 4 SCAD corresponds to a total occlusion of the main dissected vessel or large branches with TIMI 0 flow. For diagnosing angiotype 4, the presence of other typical angiographic characteristics (angiotypes 1 and 2), visible at the time of the baseline injections, during PCI or in surveillance angiograms, was necessary to establish the diagnosis of SCAD when intracoronary imaging was not used. A sixth category, the angiotype 1/2 (comprising features of both angiotypes 1 and 2 in the same lesion), was dismissed for the sake of simplicity and classified as angiotype 1.

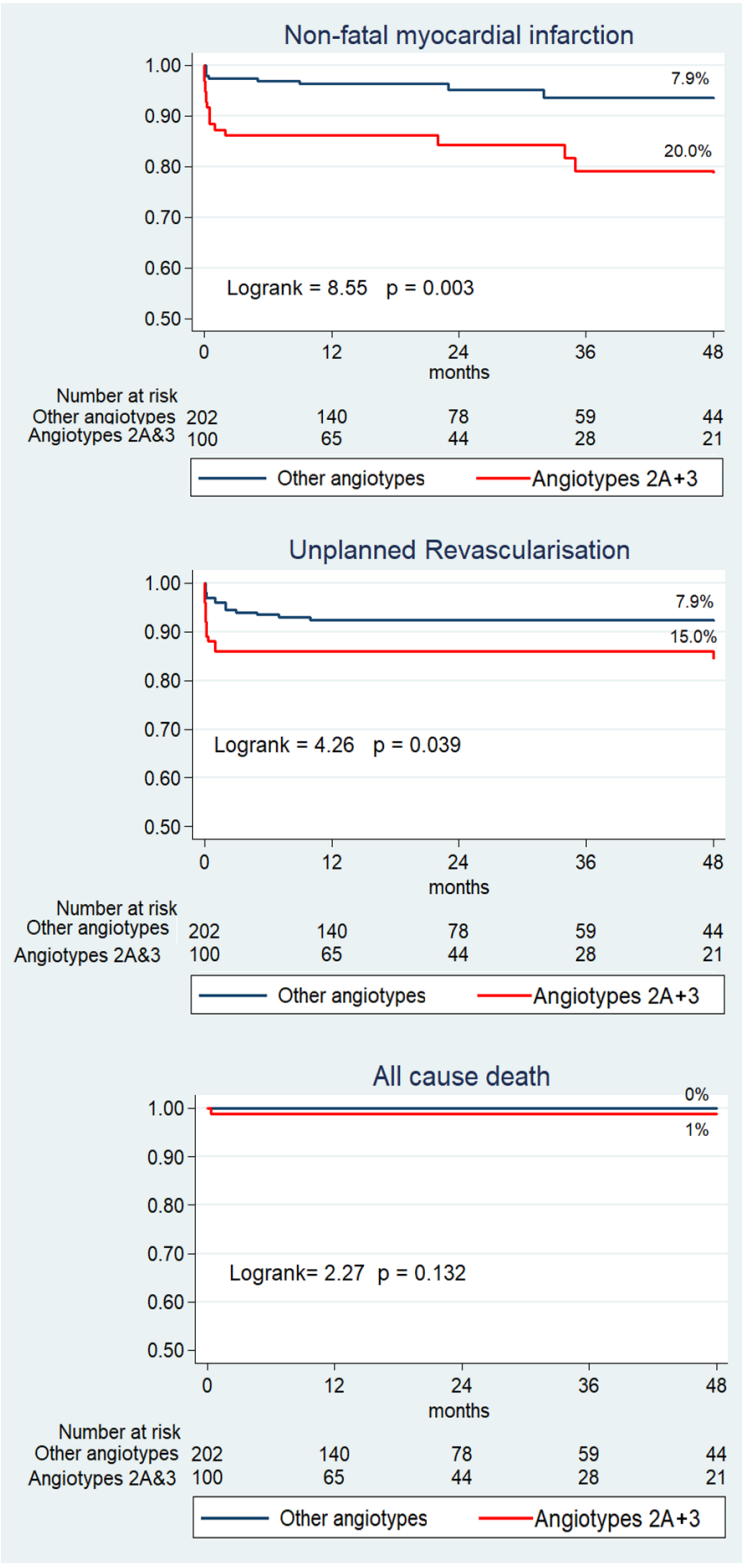
Supplementary Appendix 3. Statistical analysis

Angiographic type was the grouping variable (five groups). Non-categorical variables are summarised using means and were compared using ANOVA or Kruskal-Wallis tests according

to normality of distributions. Categorical variables are expressed as percentages and were compared using the chi-square or Fisher's exact tests if required. Kaplan-Meier curves were plotted for the time to occurrence of MACE by each angiographic type and were compared using the log-rank test, as it is the recommended test for infrequent events where the compared curves do not intersect. Multivariate adjustment was conducted using Cox regression including covariables with a significance level below 0.20 in the univariate analysis. Statistical significance was established at $p \leq 0.05$ (two-tailed) for all tests. All statistical analyses were conducted using Stata IC 14.1 (StataCorp, College Station, TX, USA).



Supplementary Figure 1. Kaplan-Meier curves for MACE in all angiotypes (Adlam's classification) during the first 28 days and long-term follow-up.



Supplementary Figure 2. Breakdown of the components of the composite major adverse cardiovascular events (MACE) in angiotypes 2A and 3 versus other angiotypes.

Supplementary Table 1. **Pharmacologic treatment in the studied population according to the initial therapeutic strategy.**

Medical treatment	Total (n=302)	Conservative strategy (n=198)	Revascularisation strategy (n=104)	*p*-value
Single antiplatelet therapy	74 (24.5)	67 (33.8)	7 (6.7)	<0.001
Dual antiplatelet therapy	228 (75.5)	131 (66.1)	97 (93.3)	<0.001
At least 12-month DAPT length	141 (46.7)	77 (38.9)	64 (61.5)	0.001
Beta-blockers	246 (81.3)	159 (80.3)	87 (83.7)	0.118
ACE inhibitors/ARBs	171 (56.6)	111 (56.1)	60 (57.7)	0.671
Statins	213 (70.5)	140 (70.7)	73 (70.2)	0.589
Calcium channel blockers	29 (9.6)	21 (10.6)	8 (7.7)	0.752

ACE: angiotensin-converting enzyme; ARBs: angiotensin receptor blockers; DAPT: dual antiplatelet therapy

Supplementary Table 2. MACE predictor analysis.

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Predictor	Univariate analysis		Multivariate analysis	
	HR	*p*-value	HR	*p*-value
Age, years	0.97 (0.94-0.99)	0.043	0.98 (0.95-1.02)	0.527
Men	1.16 (0.49-2.73)	0.732		
Arterial hypertension	0.67 (0.36-1.25)	0.215		
Diabetes mellitus	0.71 (0.09-5.20)	0.742		
Smoking	1.42 (0.80-2.54)	0.227		
Recent pregnancy	1.75 (0.24-13.04)	0.583		
Post-menopausal	0.66 (0.32-1.37)	0.265		
Hormonal therapy	1.64 (0.79-3.40)	0.178	1.08 (0.32-3.66)	0.901
Hypothyroidism	0.58 (0.18-1.87)	0.365		
STEMI	0.98 (0.55-1.72)	0.937		
Cardiac arrest	1.80 (0.56-5.81)	0.323		
Initial TIMI flow 0	0.49 (0.21-1.17)	0.110	0.57 (0.20-1.65)	0.303
Proximal segment affected	0.52 (0.10-2.53)	0.418		
LAD as culprit vessel	1.12 (0.64-1.97)	0.671		
Adlam type 2A & 3	2.34 (1.34-4.08)	0.003	2.44 (1.24-4.80)	0.010
PCI as first treatment	1.45 (0.79-2.66)	0.229		
OCT use	0.68 (0.24-1.94)	0.480		
Beta-blocker treatment	0.83 (0.40-1.72)	0.616		
SAP	0.38 (0.16-0.91)	0.029	0.31 (0.11-0.87)	0.027
Anticoagulation	1.51 (0.59-3.84)	0.383		
New $P2Y_{12}$ inhibitor	1.94 (1.03-3.68)	0.040	2.07 (0.98-4.36)	0.056

LAD: left anterior descending artery; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; SAP: single antiplatelet therapy; STEMI: ST-elevation myocardial infarction; TIMI: Thrombolysis In Myocardial Infarction

Supplementary Table 3. MACE during 48 months of follow-up according to the initial therapeutic strategy in each angiotype.

Adlam`s classification	Total	Conservative strategy		Total	Revascularisation strategy		*p*-value *
		MACE -	MACE+		MACE -	MACE +	
Type 1, n=52	**27 (51.9)**	19 (70.4)	8 (29.6)	**25 (48.1)**	22 (88)	3 (12.0)	0.177
Type 2A, n=80	**61 (76.2)**	48 (78.7)	13 (21.3)	**19 (23.8)**	12 (63.2)	7 (36.8)	0.226
Type 2B, n=69	**59 (85.5)**	54 (91.5)	5 (8.5)	**10 (14.5)**	9 (90)	1 (10.0)	1
Type 3, n=20	**13 (65)**	10 (76.9)	3 (23.1)	**7 (35)**	5 (71.5)	2 (28.5)	1
Type 4, n=81	**38 (46.9)**	38 (100)	0 (0)	**43 (53.1)**	37 (86.1)	6 (13.9)	0.027
Total, n=302	**198 (65.6)**	168 (85.4)	29 (14.6)	**104 (34.4)**	85 (81.7)	19 (18.3)	0.426

* p-value (for MACE+) comparing conservative strategy versus revascularisation strategy.