Supplemental Material to Coronary Optical Coherence Tomography and Cardiac Magnetic Resonance Imaging to Determine Underlying Causes of MINOCA in Women, by Reynolds HR et al.

Supplemental Methods

Coronary Angiography Interpretation

The angiographic core laboratory, at Cardiovascular Research Foundation, determined maximal severity of stenosis (qualitative and quantitative), which coronary artery supplied each myocardial territory, and whether there were any complications of OCT, such as spasm, slow flow or dissection.

OCT Image Interpretation

Plaque rupture was defined as disruption of the fibrous cap overlying lipidic plaque. Intra-plaque cavity was defined as an area of low signal intensity with minimal attenuation adjacent to a lipidic plaque without fibrous cap disruption, with the cavity presumably due to recent plaque rupture and sealing. Layered plaque was defined as a homogeneous, superficial layer of atheroma with a different optical intensity and clear demarcation from underlying plaque. Plaque erosion was defined as OCT evidence of luminal thrombus superimposed on non-ruptured plaque. Thrombus was defined as a floating or protruding mass into the lumen, subcategorized as red cell-rich if characterized by strong attenuation, platelet-rich if there was no attenuation, or mixed. Calcified nodule was defined as accumulation of small calcium fragments on a calcified plate, with or without thrombus. Intimal bumping suggestive of coronary artery spasm was defined as intimal projections into the lumen, particularly with thickening of the arterial media, corresponding as previously reported at locations where spasm was provoked. Spontaneous coronary artery dissection was defined as intramural hematoma with or without communication between hematoma and true lumen.

Cardiac Magnetic Resonance Image Analysis

CMR was interpreted at the core laboratory at Brigham and Women's Hospital, Images were analyzed for myocardial extent and segmental distribution of LGE. Patterns of LGE were classified as subendocardial, transmural, subepicardial, midwall, focal, subsegmental or diffuse. Infarction was defined as subendocardial and/or transmural LGE in a segmental pattern that conformed to a coronary distribution. Native T1, extracellular volume (ECV), and T2-weighted images were quantified. Maps were generated to identify regions of increased signal intensity indicating myocardial edema. An regional pattern of injury was defined as wall motion abnormality, prolonged T1, increased ECV and/or increased T2-weighted signal (by either T2-weighted fast spin echo imaging or post-contrast cine SSFP imaging) in a myocardial territory subtended by a single coronary artery. Myocarditis was defined as LGE in a non-ischemic distribution (e.g., epicardial and/or midwall LGE in >1 coronary territory, with or without associated wall motion abnormalities and/or edema). Takotsubo syndrome was defined as abnormal left ventricular wall motion of the apical, midventricular or basal type, without LGE evidence of MI or myocarditis. Non-ischemic cardiomyopathy was defined as global LV dysfunction without infarct-pattern LGE or myocardial edema.

Supplemental Table I. Clinical Characteristics of Enrolled Women with MINOCA and Excluded Women with MI-CAD.

	MI-CAD Screen Failures (n=120)	MINOCA (n=145)	p
Age, mean(SD)	62.5 (11.8)	59.8 (11.5)	0.063
Race, n (%)			
American Indian or Alaska Native	0 (0%)	2 (1.4%)	
Asian	3 (2.8%)	12 (8.3%)	
Black or African American	23 (21.3%)	17 (11.7%)	
Mixed-Race	0 (0%)	1 (0.7%)	
Native Hawaiian or Other Pacific Island	0 (0%)	1 (0.7%)	
Other	11 (10.2%)	16 (11.0%)	
White	71 (65.7%)	96 (66.2%)	0.101
Hispanic/Latino Ethnicity (%)	22 (20.4%)	35 (24.1%)	0.577
Medical History			
Diabetes (%)	42 (48.3%)	23 (15.9%)	<0.001
Hypertension (%)	54 (62.1%)	66 (45.5%)	0.021
Dyslipidemia (%)	49 (57.0%)	51 (35.2%)	0.002
Prior Stroke/TIA (%)	6 (7.0%)	9 (6.2%)	>0.99
Depression (%)	17 (20.0%)	34 (23.8%)	0.619
Anxiety (%)	15 (17.4%)	31 (21.7%)	0.545
Prior MI (%)	5 (6.0%)	13 (9.0%)	0.574
Smoking Status (%)			
Current	28 (32.9%)	16 (11.1%)	
Former	16 (18.8%)	31 (21.5%)	
Never	41 (48.2%)	97 (67.4%)	<0.001
STEMI presentation	2 (2.2%)	5 (3.5%)	0.708
Laboratory Findings			
Peak Troponin, ng/mL (median [IQR])	1.23 [0.24, 5.33]	0.94 [0.34, 4.38]	0.715
Peak Troponin, multiple of upper limit of normal (median [IQR])	31.25 [9.50, 94.46]	17.25 [7.00, 61.00]	0.116
Angiographic Findings (Site Reported)			
Maximum % stenosis (median [IQR])	90% [80%, 99%]	0% [0%, 30%]	<0.001
Revascularization performed			
Coronary artery bypass grafting	11 (12.9%)	0 (0%)	
Percutaneous coronary intervention	56 (65.9%)	1 (0.7%)	
Neither	18 (21.2%)	144 (99.3%)	<0.001

MI-CAD = myocardial infarction with obstructive coronary artery disease; MINOCA = myocardial infarction with non-obstructive coronary artery disease.

Supplemental Table II. OCT and CMR Findings in Women with Normal Angiography vs. Non-Obstructive CAD as Determined by Sites.

	Non-Obstructive Disease (Site Reported) N=68	Angiographically Normal (Site Reported) N=77	p-value
OCT culprit findings, n (%)			
Plaque rupture	8 (11.8%)	0 (0%)	0.076 for comparison of type of culprit lesion when present <0.001 for any vs. no culprit lesion
Intra-plaque cavity	21 (30.9%)	10 (13.0%)	
Layered plaque	10 (14.7%)	9 (11.7%)	
Thrombus without plaque rupture, intimal bumping or coronary dissection	5 (7.4%)	4 (5.2%)	
No culprit lesion	24 (35.3%)	54 (70.1%)	
CMR findings (n=116)	N=57	N=59	
Myocardial infarction (ischemic pattern LGE)	15 (26.3%)	23 (39.0%)	0.284 for type of abnormality when present 0.242 for comparison of any CMR abnormalities to normal CMR
Regional edema without LGE (ischemic injury)	15 (26.3%)	9 (15.3%)	
Myocarditis	7 (12.3%)	10 (16.9%)	
Takotsubo syndrome	1 (1.8%)	3 (5.1%)	
Non-ischemic cardiomyopathy	1 (1.8%)	2 (3.4%)	
Normal	18 (31.6%)	12 (20.3%)	

Supplemental Table III. Characteristics of women with definite, possible or no culprit lesion on OCT.

	Definite Culprit Lesion N=26	Possible Culprit Lesion N=41	No Culprit Lesion N=78	p value
Age, mean(SD)				
Race(%)				
American Indian or Alaska Native	1 (3.8%)	1 (2.4%)	0 (0%)	
Asian	0 (0%)	3 (7.3%)	9 (11.5%)	
Black or African American	3 (11.5%)	7 (17.1%)	7 (9.0%)	
Native Hawaiian or Other Pacific Islander	1 (3.8%)	0 (0%)	0 (0%)	
Other	6 (23.1%)	3 (7.3%)	8 (10.3%)	
White	15 (57.7%)	27 (65.9%)	54 (69.2%)	0.084
Hispanic/Latino Ethnicity (%)	3 (11.5%)	13 (31.7%)	19 (24.4%)	0.165
Medical History				
Diabetes (%)	7 (26.9%)	11 (26.8%)	5 (6.4%)	0.004
Hypertension (%)	14 (53.8%)	21 (51.2%)	31 (39.7%)	0.315
Dyslipidemia (%)	12 (46.2%)	21 (51.2%)	18 (23.1%)	0.004
Depression (%)	7 (26.9%)	7 (17.1%)	20 (26.3%)	0.489
Anxiety (%)	6 (23.1%)	9 (22.0%)	16 (21.1%)	0.976
Prior MI (%)	3 (11.5%)	5 (12.2%)	5 (6.4%)	0.451
Smoking Status (%)				
Current	2 (7.7%)	6 (15.0%)	8 (10.3%)	
Former	10 (38.5%)	9 (22.5%)	12 (15.4%)	0.142

Never	14 (53.8%)	25 (62.5%)	58 (74.4%)	
STEMI presentation	0 (0%)	2 (5.0%)	3 (3.9%)	0.708
Laboratory Findings				
Peak Troponin, ng/mL (median [IQR])	0.72 [0.23, 3.24]	0.79 [0.46, 3.63]	1.18 [0.40, 4.55]	0.569
Peak Troponin, multiple of upper limit of normal (median [IQR])	17.6 [7.1, 51.8]	17.3 [10.0, 73.2]	16.8 [5.1, 60.5]	0.808
Angiographic Findings				
Maximum % stenosis (median [IQR])	34% [26%, 38%]	29% [26%, 35%]	29% [26%, 38%]	0.384
Site determined normal angiogram, n (%)	5 (19.2%)	19 (46.3%)	54 (69.2%)	<0.001
OCT number of vessels imaged, n (%)				
1	0 (0%)	3 (7.3%)	9 (11.5%)	
2	8 (30.8%)	8 (19.5%)	31 (39.7%)	
3	18 (69.2%)	30 (73.2%)	38 (48.7%)	0.038
CMR findings (n=116)				
Myocardial infarction (ischemic pattern LGE)	5 (33.3%)	22 (81.5%)	11 (55.0%)	
Regional edema without LGE (ischemic injury)	10 (66.7%)	5 (18.5%)	9 (45.0%)	
Myocarditis	1 (3.8%)	3 (7.3%)	13 (16.7%)	
Takotsubo syndrome	0 (0%)	0 (0%)	4 (6.2%)	
Non-ischemic cardiomyopathy	0 (0%)	0 (0%)	3 (4.6%)	0.182

Supplemental Table IV. Results of Multivariable Analysis of OCT and CMR Findings

Correlates of the Presence of an OCT Culprit Lesion		
	OR [95% CI]	p
Diabetes Yes vs No	5.41 [1.77, 19.22]	0.005
Abnormal Angiography vs Normal Angiography (Site-Determined)	5.43 [2.50, 12.41]	<0.001
Age	1.05 [1.02, 1.09]	0.004
Correlates of the Presence of Any CMR Abnormality		
	OR [95% CI]	p
Diastolic blood pressure	1.05 [1.00, 1.10]	0.047
Peak troponin*	1.61 [1.20, 2.27]	0.003
Creatinine*	0.52 [0.31, 0.86]	0.012

*peak troponin and creatinine are log-transformed.

Supplemental Table V. Native T1 Values

	MI with abnormal ECV or T1 Mapping (n=37)			MI with normal ECV and T1 Mapping Or Non-MI with Normal CMR (n=34)		
	Abnormal Segments	Comparator Segments		All Segments	P-value *	P-value †
Extracellular volume (ECV) %, mean (SD)	34.2 (4.9)	31.6 (4.2)		30.9 (4.9)	0.02	0.012
Native T1 (ms), mean (SD)	1182.8 (165.4)	1110.4 (141.0)		1079.7 (135.0)	0.046	0.01

* Abnormal versus comparator segments in patients with abnormal native T1 mapping or ECV (n=37). † Abnormal segments in patients with abnormal native T1 mapping or ECV (n=37) compared to global measures in patients with MI and normal ECV and T1 Mapping and patients without a diagnosis of MI with normal CMR, for whom T1 mapping and ECV was available (n=34).

Supplemental Table VI. Definite and Probable MI as Final Diagnosis in Women with MINOCA (OCT and CMR cohort, N = 116)

Myocardial Infarction as Final Diagnosis in MINOCA	**74 (63.8%)**
***Definite AMI in MINOCA**:*	***56 (76% of MI)***
CMR: LGE in ischemic pattern with associated myocardial edema indicating acute MI, with or without any OCT culprit lesion	36† (4 with OCT showing plaque rupture or thrombus without rupture)
OCT: plaque rupture, thrombus without plaque rupture	12
OCT: intra-plaque cavity without thrombus, layered plaque or evidence of recent coronary spasm* **and** CMR: regional myocardial edema in a coronary territory subtended by an artery with an OCT culprit	12†
***Probable AMI in MINOCA**:*	***18 (24% of MI)***
OCT: intra-plaque cavity without thrombus, layered plaque or evidence of recent coronary spasm* **and** CMR: ischemic abnormalities on CMR in a different coronary territory or normal CMR	11†
CMR: regional myocardial edema in a coronary territory without an OCT culprit lesion	5
CMR: LGE in ischemic pattern without associated myocardial edema (MI may not be acute), without an OCT culprit lesion	2
Non-Ischemic Alternate Diagnosis to MI:	**24 (20.7%)**
CMR: myocarditis, takotsubo syndrome or non-ischemic cardiomyopathy**	24
Unclear Diagnosis	**18 (15.5%)**
No abnormalities on OCT or CMR	18

* On OCT, intimal bumping is evidence of recent coronary spasm.

**Myocarditis: LGE in a non-ischemic pattern, in more than one coronary territory, with or without associated wall motion abnormalities and/or myocardial edema; takotsubo syndrome: abnormal left ventricular wall motion meeting criteria for takotsubo syndrome of the apical, midventricular or basal type, in the absence of LGE evidence of MI or myocarditis; non-ischemic cardiomyopathy: global LV dysfunction in the absence of infarct-pattern LGE or myocardial edema.

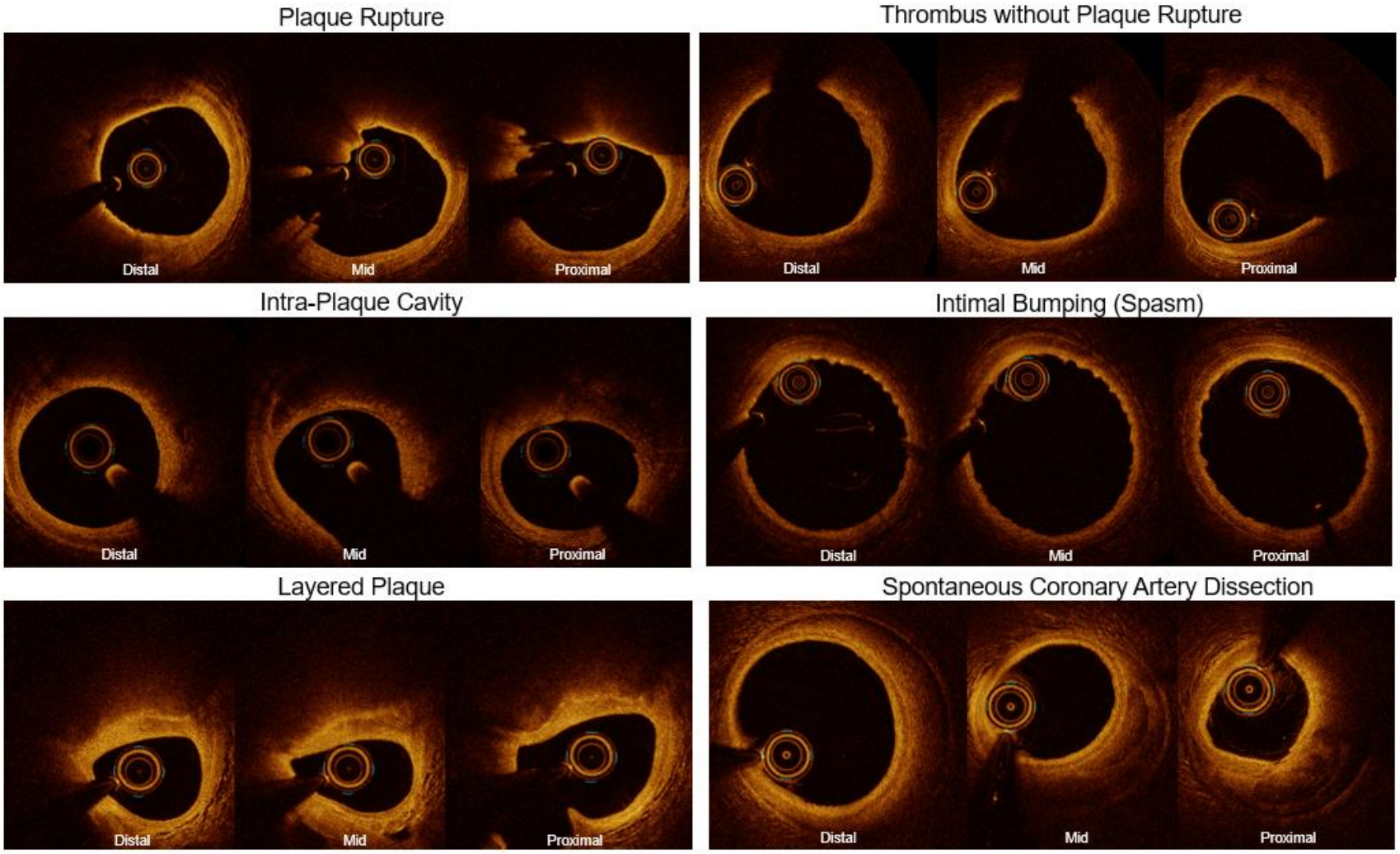
†OCT findings in women with CMR showing LGE with associated myocardial edema: 2 plaque rupture, 2 thrombus without rupture, 6 intra-plaque cavity without OCT evidence of thrombus, 5 layered plaque, 1 dissection, 20 no culprit lesion identified.

OCT findings in women with CMR showing regional myocardial edema without LGE in a matching territory: 7 intra-plaque cavity without OCT evidence of thrombus, 4 layered plaque, 1 intimal bumping (and also 2 thrombus without rupture, captured in the category “OCT with plaque rupture or thrombus without plaque rupture”).

OCT culprit lesions in women with probable AMI: 5 intra-plaque cavity without OCT evidence of thrombus, 6 layered plaque.

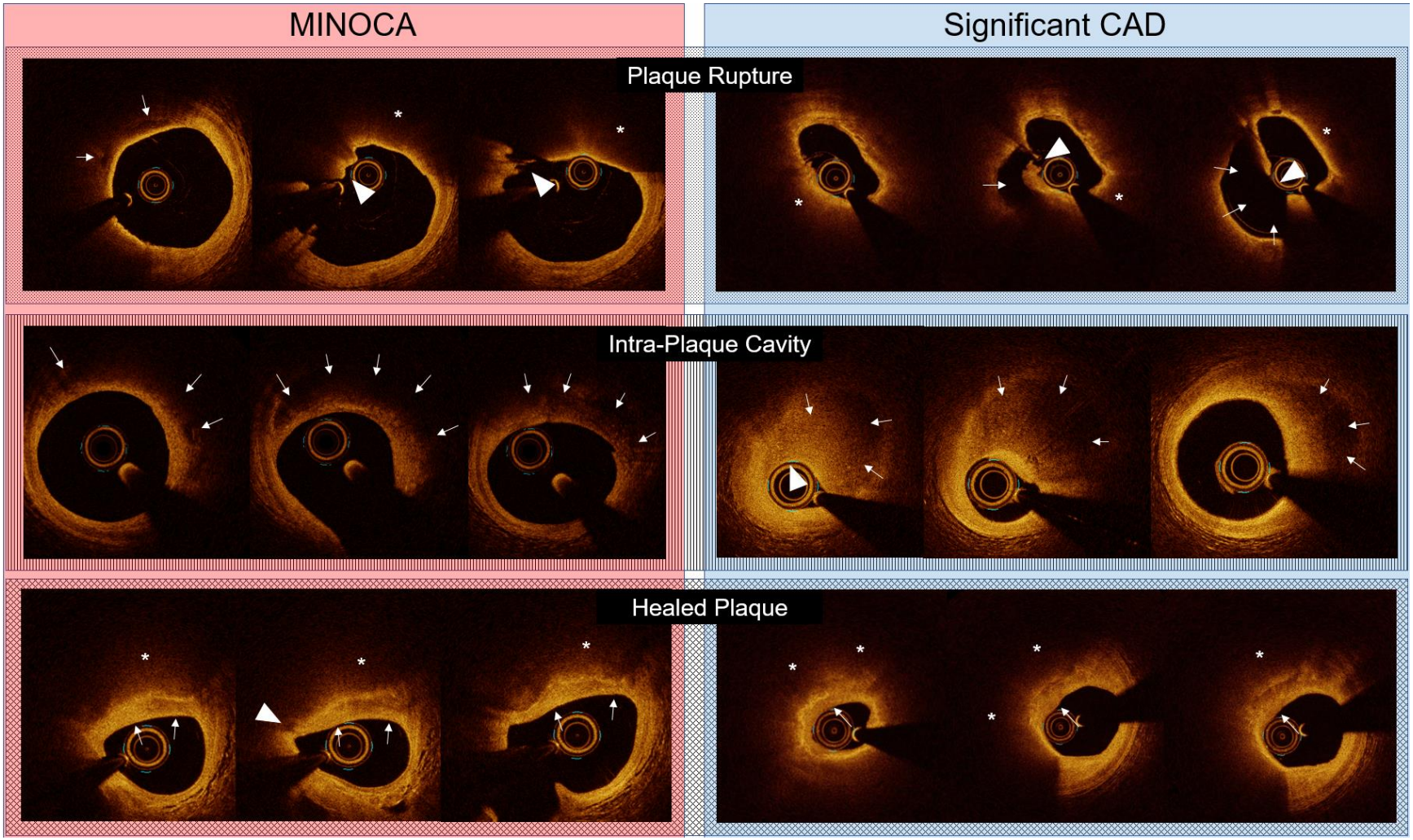
Note that not all participants underwent 3-vessel OCT.

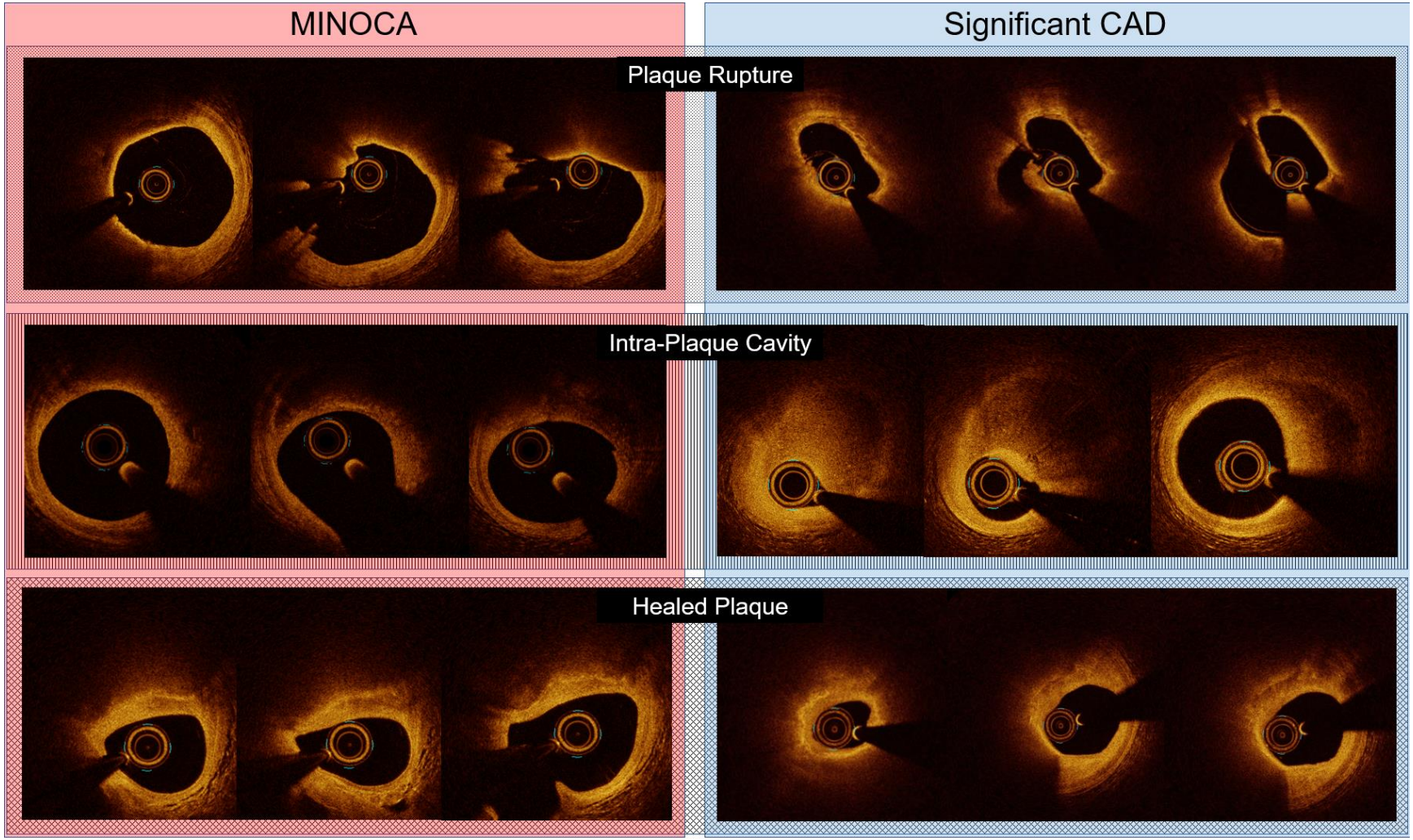
Supplemental Figure I. Representative OCT findings as in Figure 3, without annotation.



Supplemental Figure II. Comparison between lesion characteristics between MINOCA versus significant coronary artery disease.

Supplemental Figure II-A and II-B are the same images. Supplemental Figure II-A has annotation.





MINOCA cases are taken from the present study. MI-CAD lesions are taken from a cohort at Tsuchiura Kyodo Hospital (Ibaraki, Japan)[34] and are provided for comparison, illustrating that findings are similar in MINOCA and MI-CAD, with the main difference being the larger plaque volume in MI-CAD cases.

Plaque rupture: In both MINOCA and significant coronary artery disease (CAD) lesions, the rupture of fibrous cap was observed (arrowheads) in the lipidic plaque (*). A ruptured cavity (arrows) in MINOCA is smaller than opened evacuated cavity (arrows) in the significant CAD lesion.

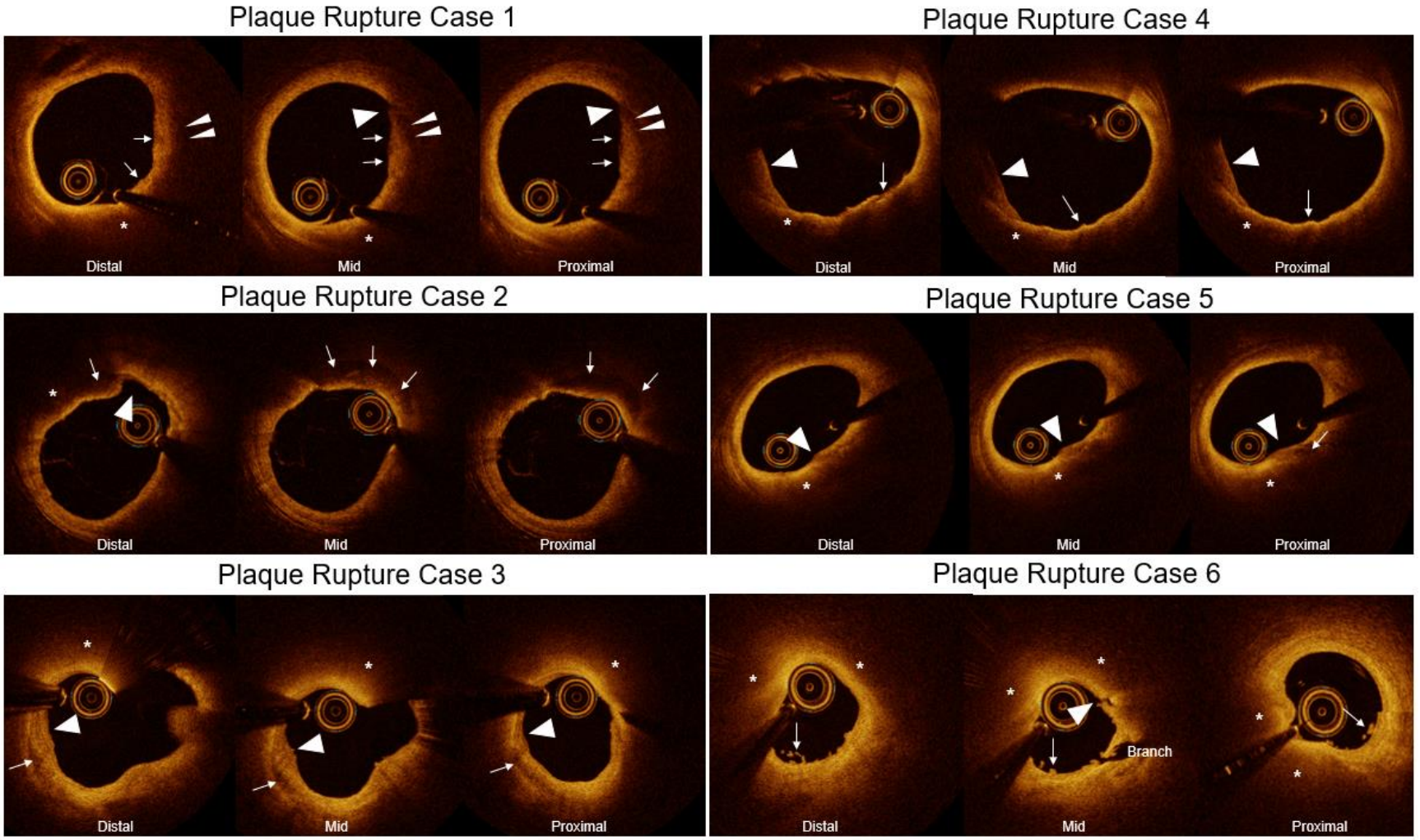
Intra-plaque cavity: In both MINOCA and significant CAD lesions, similar low intensity regions without attenuation (arrows), but with an overlying fibrous cap were observed. The size of the cavity was smaller in MINOCA than those in significant CAD lesions.

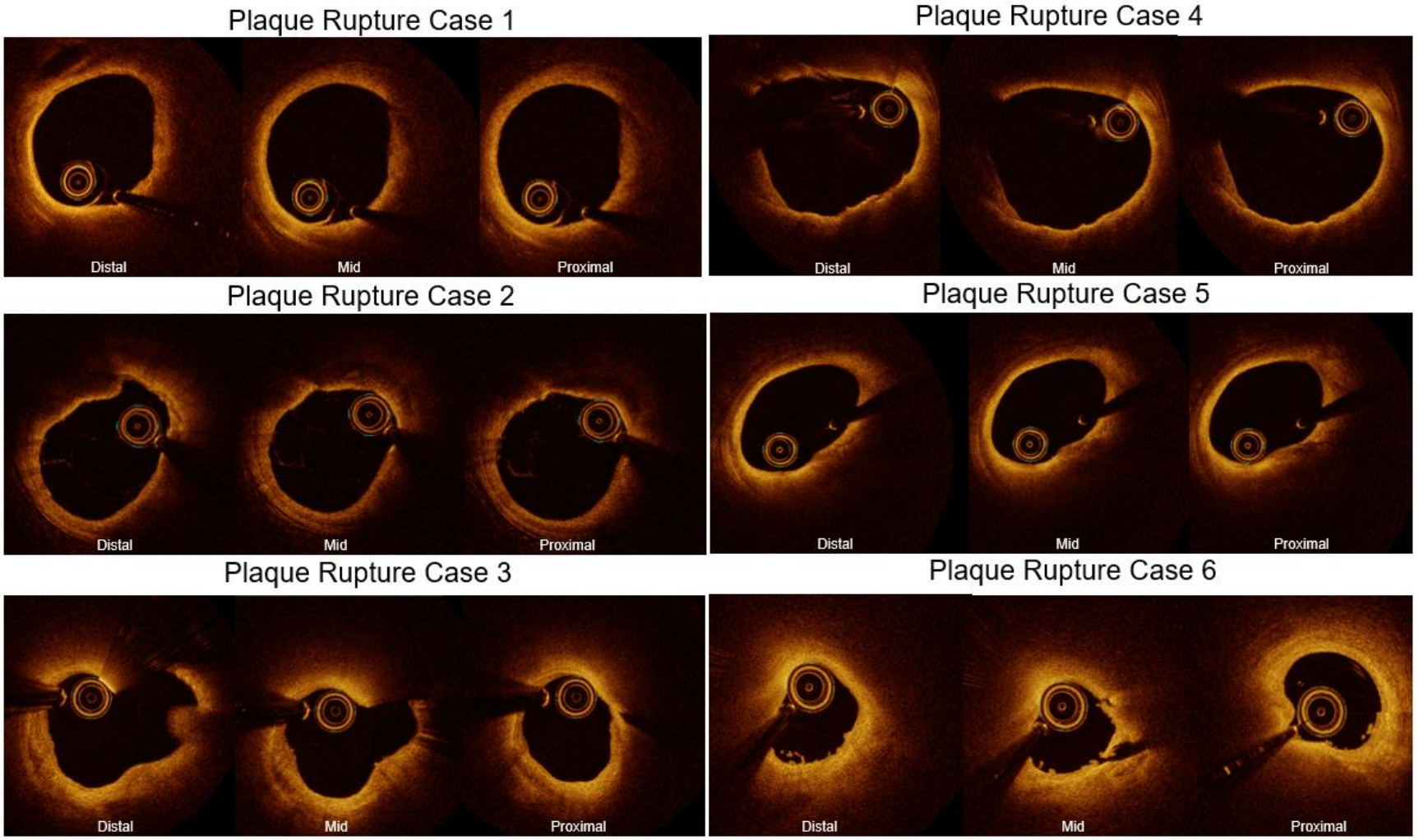
Layered plaque: In both MINOCA and significant CAD lesions, there was a similar homogeneous layered plaque (arrows) on top of the lipidic plaque (*). The residual lumen was larger in MINOCA than those in significant CAD lesion.

MI-CAD = myocardial infarction with obstructive coronary artery disease; MINOCA = myocardial infarction with non-obstructive coronary artery disease.

Supplemental Figure III. Additional plaque rupture cases.

Supplemental Figures III-A and III-B are the same images. Supplemental Figure 3A has annotation.





Case 1: There is a local linear low intensity region (double arrowhead in proximal and mid frames) connected to the lumen along with low intensity region (double arrowheads in distal frame) in the lipidic plaque indicating organized thrombus in the ruptured plaque. There is an irregularity of plaque surface indicating possible platelet rich mural thrombus.

Case 2: There is a low intensity region without attenuation (arrows) at proximal and mid frames indicating organized thrombus and/or injected contrast, and at the adjacent distal frame, a disruption of fibrous cap was observed (arrowhead). Underlying plaque is a lipidic plaque (*).

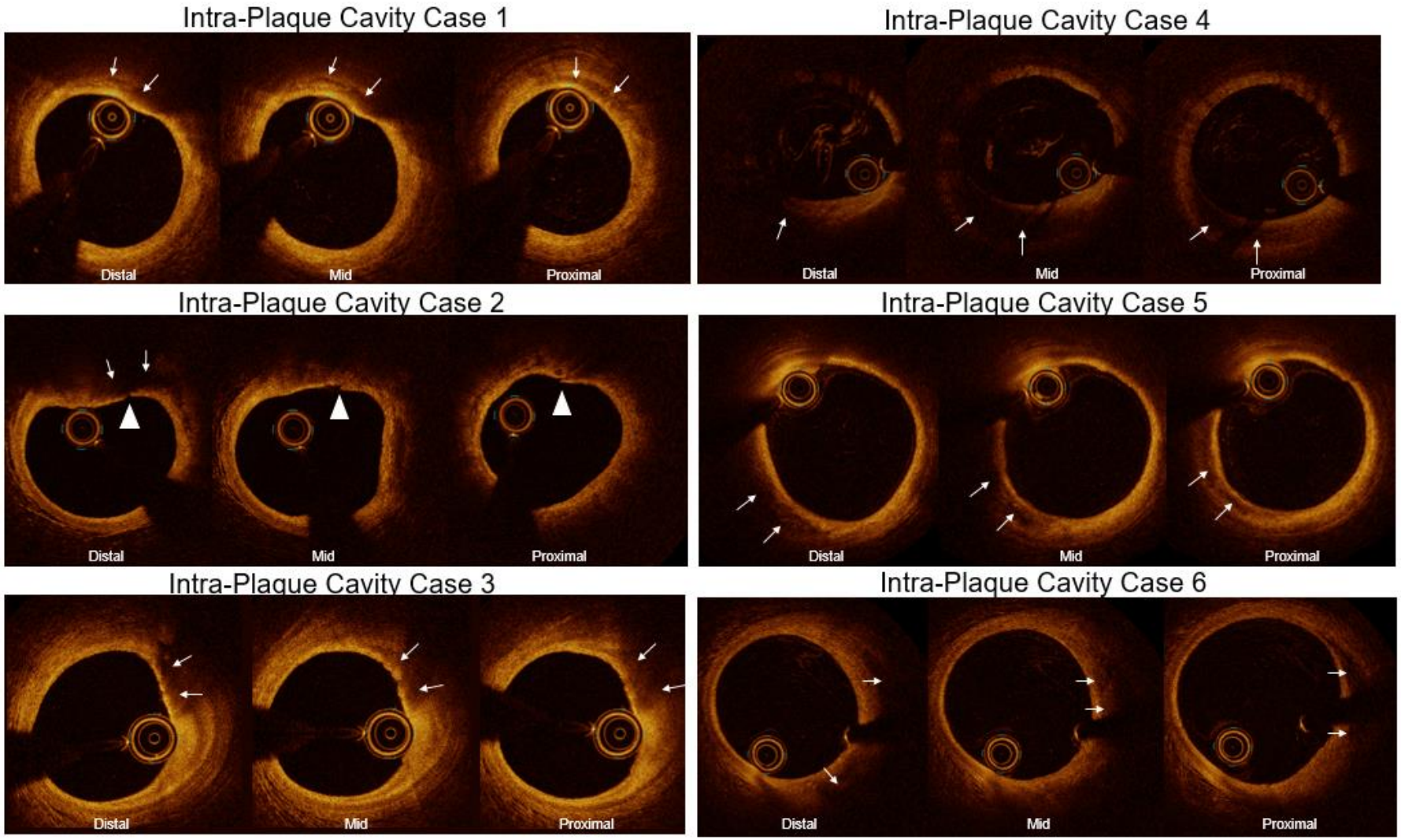
Case 3: There is a homogeneous low intensity thin region with irregular surface indicating mural platelet rich thrombus (arrowheads) along with underlying low intensity region (either organized thrombus and/or injected contrast) indicating recent plaque rupture. Underlying plaque is a lipidic plaque (*).

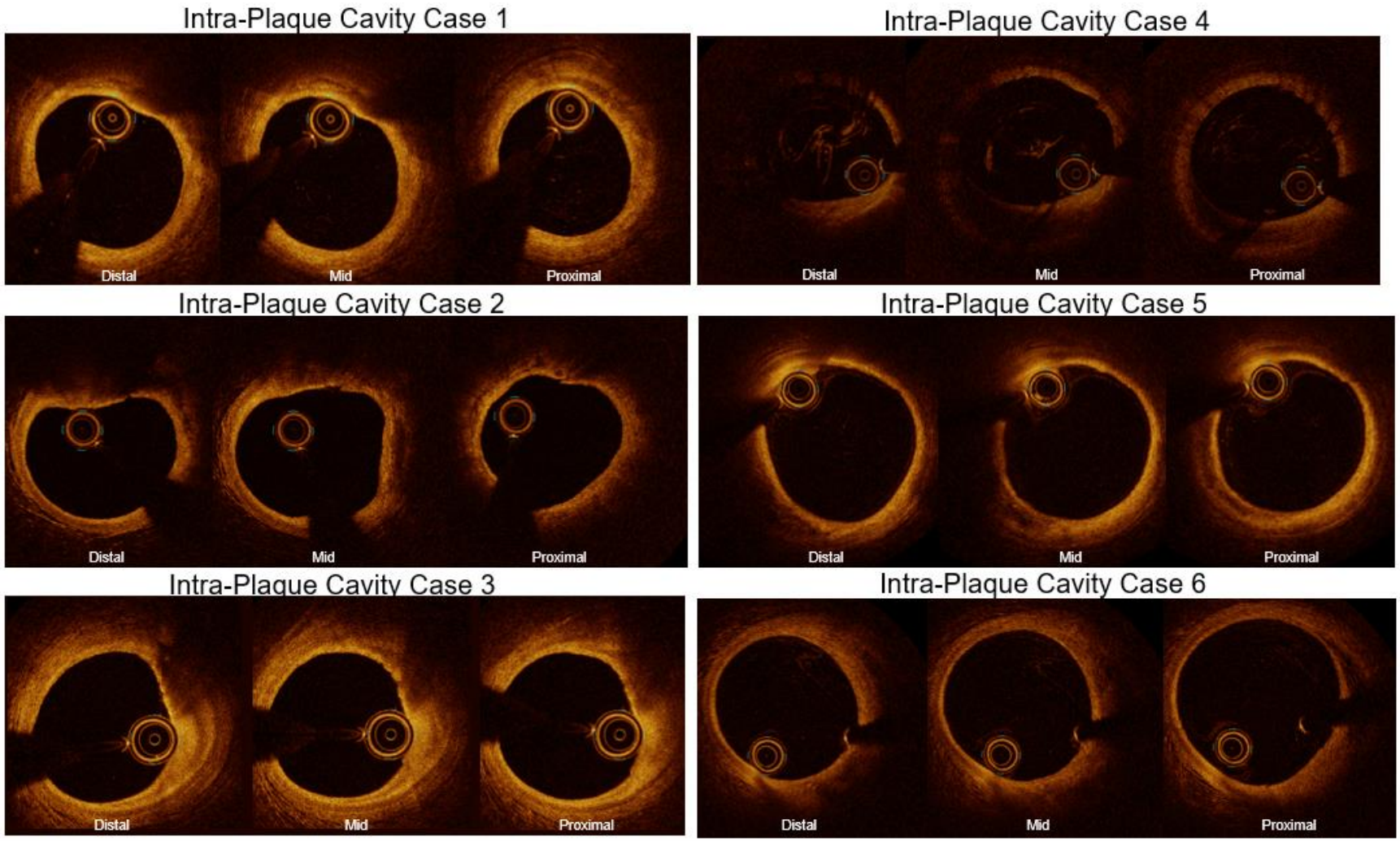
Case 4: At the distal frame, there is a small disruption of fibrous cap (arrow) along with an irregular surface (possible mural thrombus) at mid and proximal fames. Mural platelet rich thrombus (arrowheads) was observed. Underlying plaque is a lipidic plaque (*).

Case 5: There is a small disruption of the fibrous cap (arrowhead) that is sealed with mural thrombus overlaying lipidic plaque (*).

Case 6: At the mid frame, there is a side branch, and a disruption of fibrous cap (arrowhead) was observed overlaying lipidic plaque (*). Small amount of platelet rich thrombus was observed (arrows).

Supplemental Figure IV. Additional intra-plaque cavity cases.





Supplemental Figures IV-A and IV-B are the same images. Supplemental Figure 4A has annotation.

Case 1: There is a low intensity region with limited attenuation (arrows) within the plaque without clear disruption of the fibrous cap.

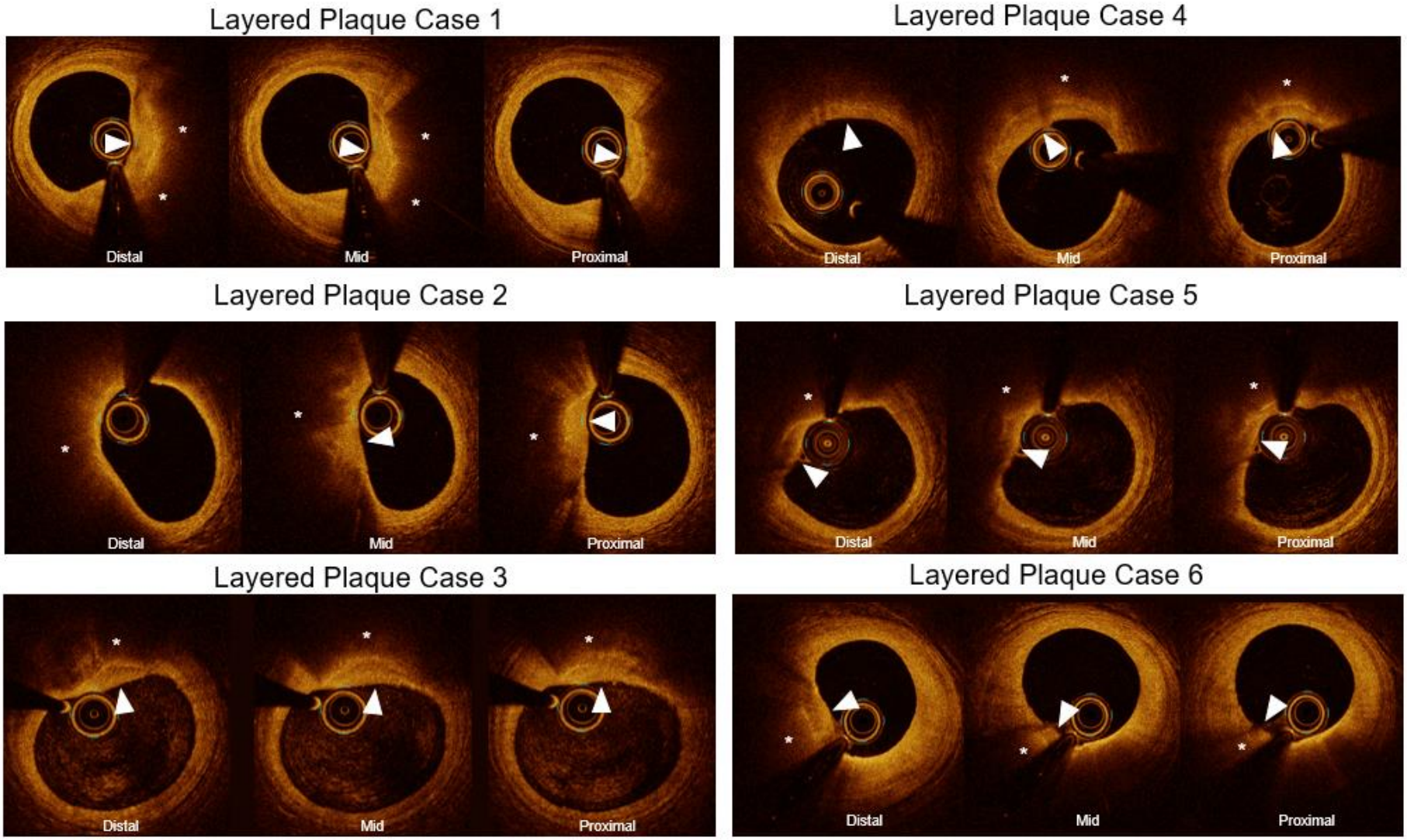
Case 2: There is a low intensity region with limited attenuation (arrows) within the plaque without clear disruption of fibrous cap. Though the apparent discontinuity of the fibrous cap (arrowheads) in proximal and mid frames are motion artifact, discontinuity of fibrous cap (arrowhead) in the distal frame may indicate real disruption of fibrous cap.

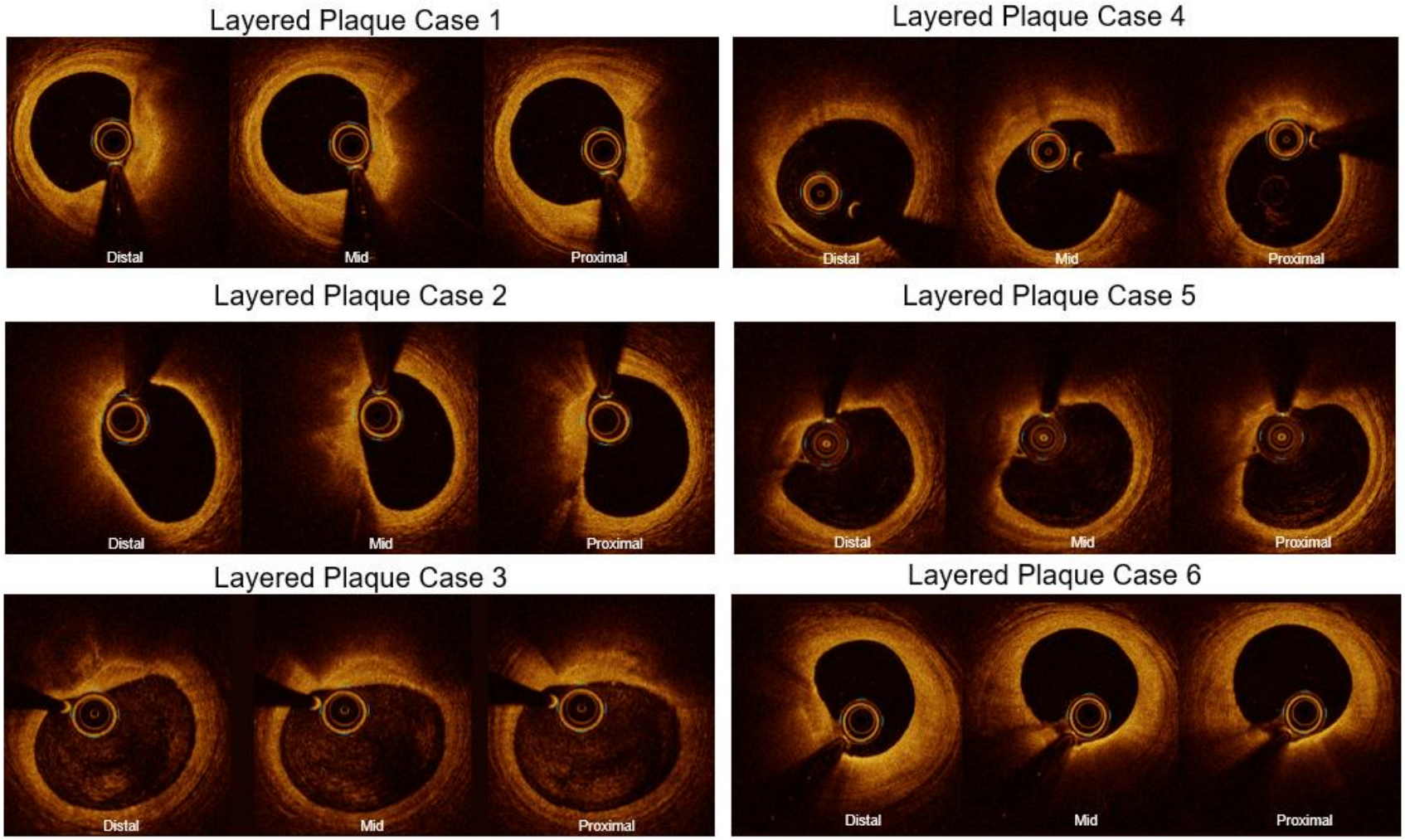
Case 3: There is a low intensity region with limited attenuation (arrows) within the plaque with surface irregularity.

Case 4-6: A crescent moon shape low intensity region without attenuation indicating evacuated cavity (arrows) filled with organized thrombus and/or contrast without clear disruption of fibrous cap.

Supplemental Figure V. Layered plaque on lipidic plaque.

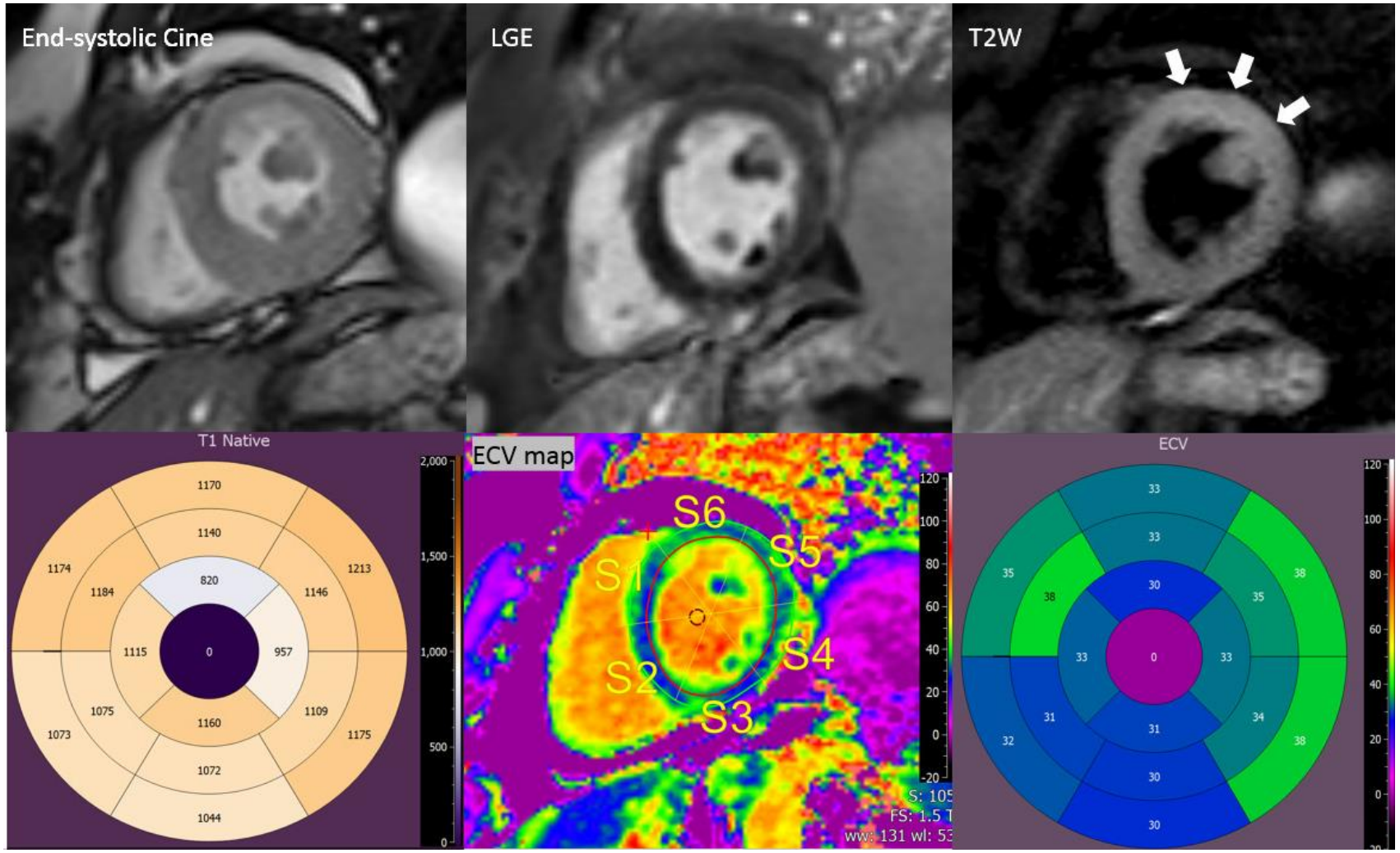
Supplemental Figures V-A and V-B are the same images. Supplemental Figure V-A has annotation.





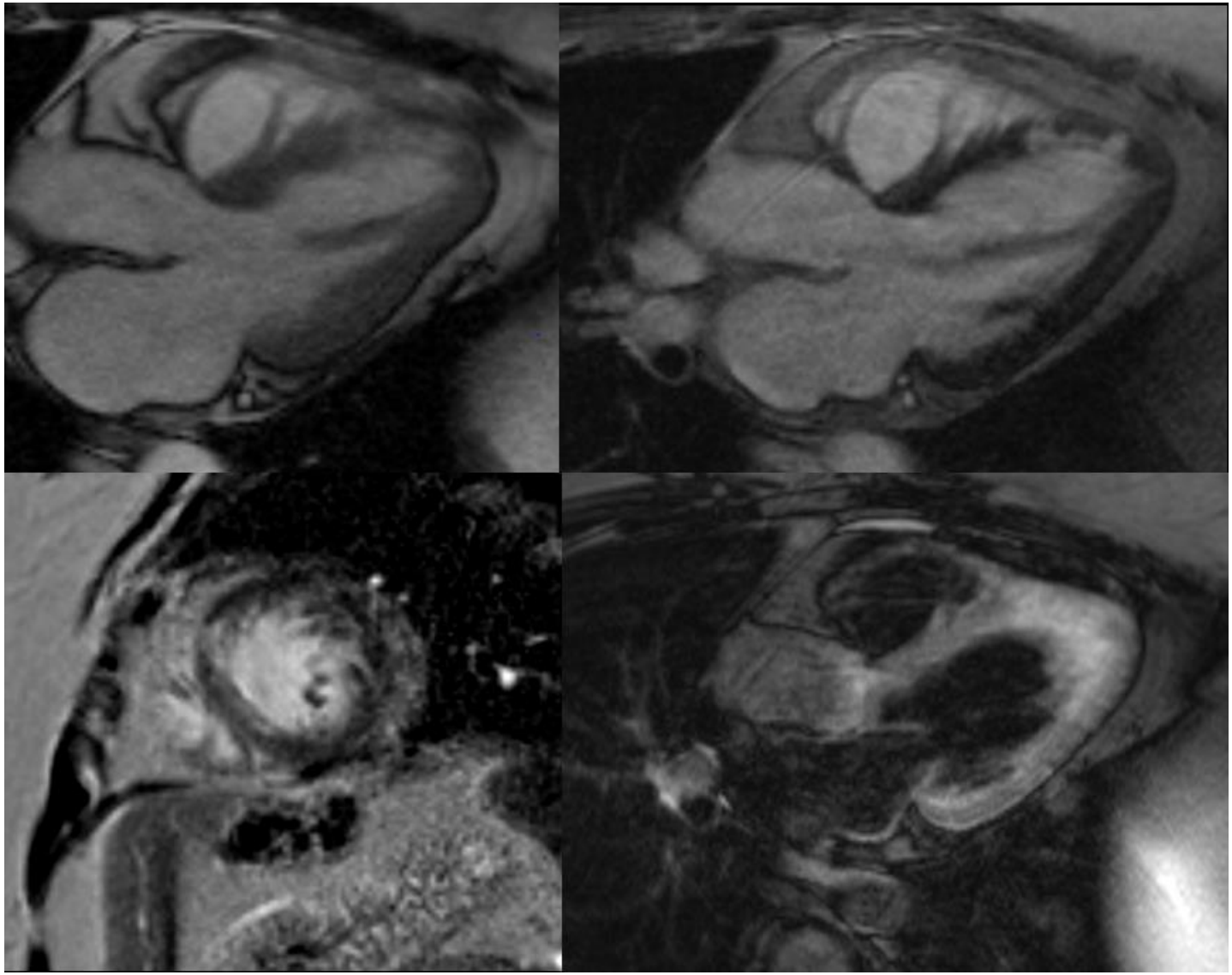
Cases 1-6 show similar characteristics. There is a heterogeneous or homogeneous layer (triangles) with clear demarcation compared to underlying lipidic plaque (asterisks), indicating layered plaque. Based on a previous pathology study showing diverse phases of healing thrombi in the sudden death victims,[23] this may represent a sequela of plaque rupture that occurred days before imaging.

Supplemental Figure VI. Regional Myocardial Edema without Late Gadolinium Enhancement.



A case of acute ischemic injury without LGE. In this case, the mid and distal anterior wall was hypokinetic (upper left) but has no LGE (upper mid) to indicate myocardial scar. However, there is a) evidence of myocardial edema by enhanced signal on T2W imaging (arrows, upper right), and b) elevated native T1 (segments with native T1 elevated > 1100 msec, lower left panel) and increased ECV (ECV values>32%, lower mid and right) in the anterior and anterolateral wall.

Supplemental Figure VII. Myocardial Infarction on CMR, Additional Example.



Upper left and right, lower left panels. Subendocardial to transmural infarction of the septum on late gadolinium enhanced imaging. Lower right panel. Increased T2 signal intensity in the apical septum and apex.

Supplemental References

23. Kramer MC, Rittersma SZ, de Winter RJ, Ladich ER, Fowler DR, Liang YH, Kutys R, Carter-Monroe N, Kolodgie FD, van der Wal AC and Virmani R. Relationship of thrombus healing to underlying plaque morphology in sudden coronary death. Journal of the American College of Cardiology. 2010;55:122-32.

34. Usui E, Mintz GS, Lee T, Matsumura M, Zhang Y, Hada M, Yamaguchi M, Hoshino M, Kanaji Y, Sugiyama T, et al. Prognostic impact of healed coronary plaque in non-culprit lesions assessed by optical coherence tomography. Atherosclerosis. 2020;309:1-7.