ORIGINAL ARTICLE
Vascular and cardiac imaging

Coronary morphological features in women with non-ST-segment elevation MINOCA and MI-CAD as assessed by optical coherence tomography

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Aims	We aimed to use optical coherence tomography (OCT) to identify differences in atherosclerotic culprit lesion morphology in women with myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) compared with MI with obstructive coronary artery disease (MI-CAD).
Methods and results	Women with an OCT-determined atherosclerotic aetiology of non-ST segment elevation (NSTE)-MINOCA (angiographic diameter stenosis <50%) who were enrolled in the multicentre Women's Heart Attack Research Program (HARP) study were compared with a consecutive series of women with NSTE-MI-CAD who underwent OCT prior to coronary intervention at a single institution. Atherosclerotic pathologies identified by OCT included plaque rupture, plaque erosion, intraplaque haemorrhage (IPH, a region of low signal intensity with minimum attenuation adjacent to a lipidic plaque without fibrous cap disruption), layered plaque (superficial layer with clear demarcation from the underlying plaque indicating early thrombus healing), or eruptive calcified nodule.
	We analysed 58 women with NSTE-MINOCA and 52 women with NSTE-MI-CAD. Optical coherence tomography features of underlying vulnerable plaque (thin-cap fibroatheroma) were less common in MINOCA (3 vs. 35%) than in MI-CAD. Intraplaque haemorrhage (47 vs. 2%) and layered plaque (31 vs. 12%) were more common in MINOCA than MI-CAD,

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whereas plaque rupture (14 vs. 67%), plaque erosion (8 vs. 14%), and calcified nodule (0 vs. 6%) were less common in MINOCA. The angle of ruptured cavity was smaller and thrombus burden was lower in MINOCA.

Conclusion

The prevalence of atherothrombotic culprit lesion subtype varied substantially between MINOCA and MI-CAD. A majority of culprit lesions in MINOCA had the appearance of IPH or layered plaque.

Clinical Trial Registration Information

Clinical Trial Name: Heart Attack Research Program- Imaging Study (HARP); *ClinicalTrial.gov Identifier*: NCT02905357; *URL*: https://clinicaltrials.gov/ct2/show/NCT02905357
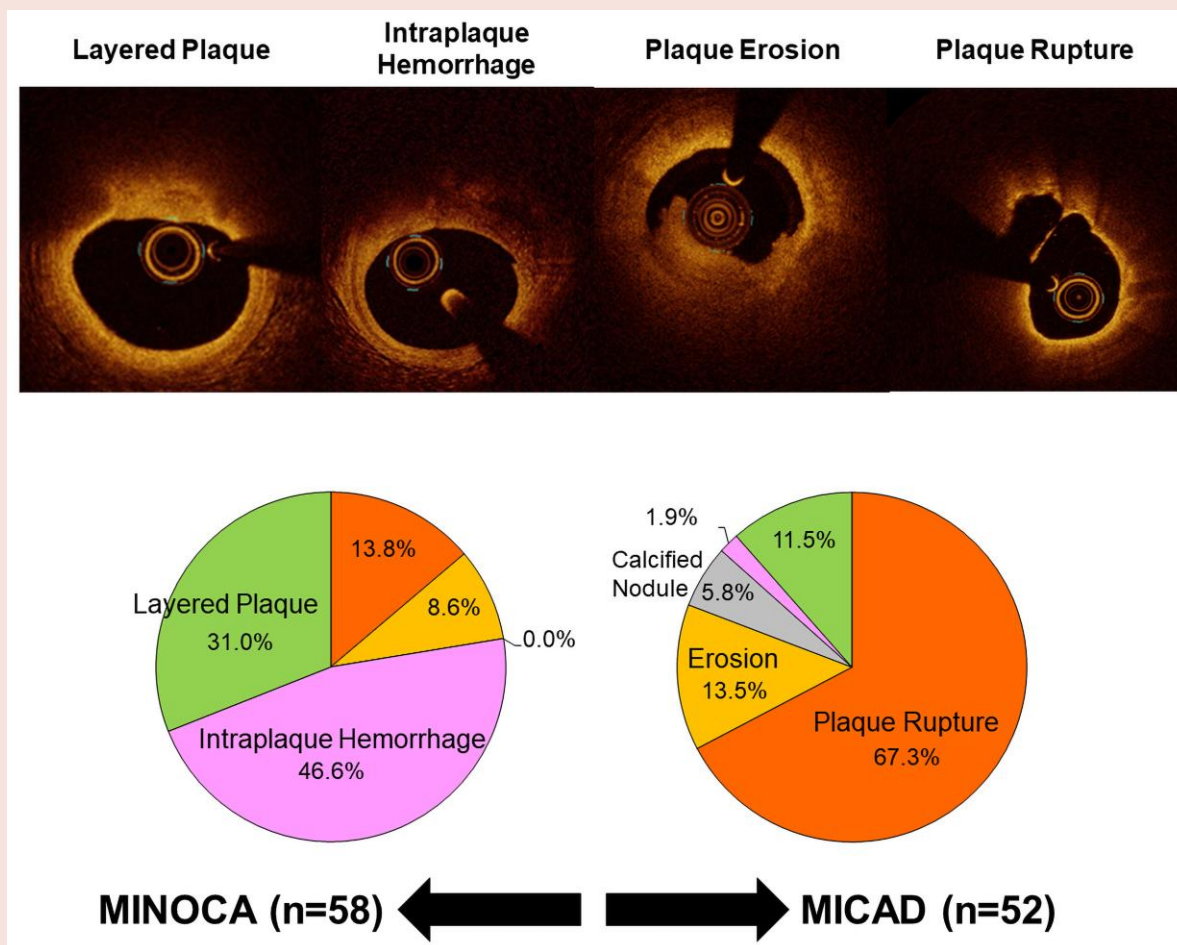
Graphical Abstract

Translational perspective

Plaque rupture and plaque erosion are the major causes of atherosclerotic thrombotic events in patients presenting with both myocardial infarction and non-obstructive disease (MINOCA) or MI with obstructive disease coronary artery disease (MI-CAD). Compared with MI-CAD, plaque rupture in MINOCA was smaller in size with preserved lumen area and more likely to be in an early healing stage based on imaging, meeting OCT criteria for intraplaque haemorrhage (intraplaque thrombus with sealed fibrous cap), or layered plaque (early healing thrombus). Along with on-going investigation of pathophysiology of MINOCA in men, future studies will investigate platelet activity and genetics in patients with MINOCA and MI-CAD, to determine how thrombotic tendency relates to OCT findings.

Introduction

Myocardial infarction (MI) with non-obstructive coronary arteries (MINOCA) is observed in ~6% of patients presenting with an MI and is more frequent in women.[1–4] Previous optical coherence tomography (OCT) studies have reported that plaque rupture (14–35%) and plaque erosion (11–38%) can be observed in infarct-related arteries in patients with MINOCA.[5–8] On the other hand, based on autopsy studies[9–13] and intracoronary imaging studies[14–17] of MI and obstructive thrombotic coronary artery disease (MI-CAD), plaque rupture or erosion is the most common cause of MI-CAD. However, *in vivo* studies have not compared atherosclerotic culprit lesion morphology between MINOCA vs. MI-CAD.

Pathologic studies have previously demonstrated that plaque rupture can manifest as an intimal cavity with luminal communication or, in the early healing stages, as intraplaque haemorrhage (IPH) or healing thrombus.[9,10] These early healing stages have been observed in some cases of sudden death at a time early after infarction, as based on pathologic dating of MI,[12] or in the extracted tissue by thrombectomy during MI.[18] Intraplaque haemorrhage may also precede luminal narrowing and MI through rapid plaque expansion. In the multicentre Women's Heart Attack Research Program (HARP),[8] we identified culprit lesions using OCT in almost half of the 145 women enrolled, considering morphologies of the early healing stages along with traditional rupture and erosion. This study aimed to use OCT to compare underlying morphological characteristics between women with MINOCA and women with MI-CAD.

Methods

Study population

The HARP was a multicentre observational study in which the primary objective was to determine the prevalence of various causes of MINOCA by OCT and cardiac magnetic resonance (CMR) (see Supplementary material online, *Figure S1*). The primary study findings have been reported previously.[8] Given that 98.6% of women with MINOCA enrolled in the HARP study presented with non-ST segment elevation (NSTE)-MI, as a comparator cohort, we retrospectively identified consecutive women who presented with NSTE-MI-CAD and underwent OCT-guided percutaneous coronary intervention (PCI) for *de novo* culprit lesions (angiographic diameter stenosis >50%) from an OCT database (1209 patients) at Tsuchiura Kyodo General Hospital, Ibaraki, Japan from February 2009 to May 2018, and excluded patients without MI, with STEMI, men, and those with insufficient OCT image quality (see Supplementary material online, *Figure S2*). Culprit lesions of control group were identified clinically from angiographic findings that correlated with the ischaemic myocardial territory by electrocardiography or echocardiography and OCT of culprit lesion was performed. Thrombectomy was performed in two MI-CAD patients before OCT examination at the operator's discretion. All OCT were analysed at the core laboratory at Cardiovascular Research Foundation (New York, NY, USA) blinded to clinical, angiographic, and CMR data. CMR was analysed at the core laboratory at Brigham and Women's Hospital (Boston, MA, USA) blinded to clinical, angiographic, and OCT data. Subsequently, OCT

and CMR findings were integrated to determine the most likely underlying cause of MINOCA for each participant.[8] CMR was not available in the MI-CAD cohort.

The study complied with the Declaration of Helsinki, and the research protocol was approved by the institutional ethics committee. In HARP, all patients provided written informed consent before participation. In the comparator group with MI-CAD, all patients provided written informed consent before procedures and permitted data use in future studies. Heart Attack Research Program was funded by the American Heart Association Go Red for Women Strategically Focused Research Network.

Optical coherence tomography imaging acquisition and analysis

In the MINOCA cohort, frequency-domain OCT (ILUMIEN OPTIS, Abbott Vascular, Santa Clara, CA, USA) was used. In the MI-CAD cohort, either time-domain OCT (M3 Cardiology Imaging System, LightLab Imaging Inc., Westford, MA, USA) or frequency-domain OCT (ILUMIEN OPTIS or LUNAWAVE, Terumo Corporation, Tokyo, Japan) was used. Additional details of OCT image acquisition are described in the Supplementary material online.

Plaque rupture was defined as disruption of the fibrous cap overlying lipidic plaque. The angle of rupture cavity (angle between the lateral ends of the rupture cavity, using the centre of coronary lumen as the vertex) was measured as a marker of severity in all cases with rupture.[19] Intraplaque haemorrhage was defined as a region of low signal intensity with minimum attenuation adjacent to a lipidic plaque without fibrous cap disruption, presumably representing red blood cells or organized thrombus in the ruptured cavity followed by sealing of rupture site.[19–21] Of note, in our prior manuscript reporting the primary results of the HARP study, the term 'intraplaque cavity' was used to differentiate blood or thrombus in the plaque (as a consequence of plaque rupture) vs. IPH due to leaky vasa vasorum.[21] However, after considering the prior pathological literature, we have changed our terminology from 'intraplaque cavity' to 'IPH.' Layered plaque (presumably indicating organization of thrombus and early plaque healing in the current cohort) was defined as a superficial layer adjacent to the blood pool with a different optical intensity and clear demarcation from the underlying plaque.[22] Thrombus was defined as a mass protruding into the lumen or adherent to the intima (i.e. mural thrombus).[14,16,17,19] Plaque erosion was defined according to the absence of fibrous cap disruption and the presence of overlying thrombus.[14] Eruptive calcified nodule was defined as the accumulation of small calcium fragments with an irregular surface and adjacent proximal or distal calcification, with or without thrombus.[23] More details and definitions can be found in the Supplementary material online and representative images are shown in *Figure 1*.

When more than one potential culprit lesion was present on OCT, we chose a primary culprit lesion according to the following hierarchy of culprit lesions: (i) plaque rupture, (ii) plaque erosion (thrombus without rupture), (iii) IPH, (iv) layered plaque, and (v) calcified nodule (*Figure 1*). All OCT images were analysed using proprietary software (Abbott or Terumo). For IPH and layered plaque, additional features indicating acute morphology have been considered to choose a primary culprit lesion: (i) IPH with thinner fibrous cap and superficial location and accompanying lipid-rich plaque and (ii) relatively thin layered plaque with heterogeneous and low intensity overlying lipid-rich plaque.
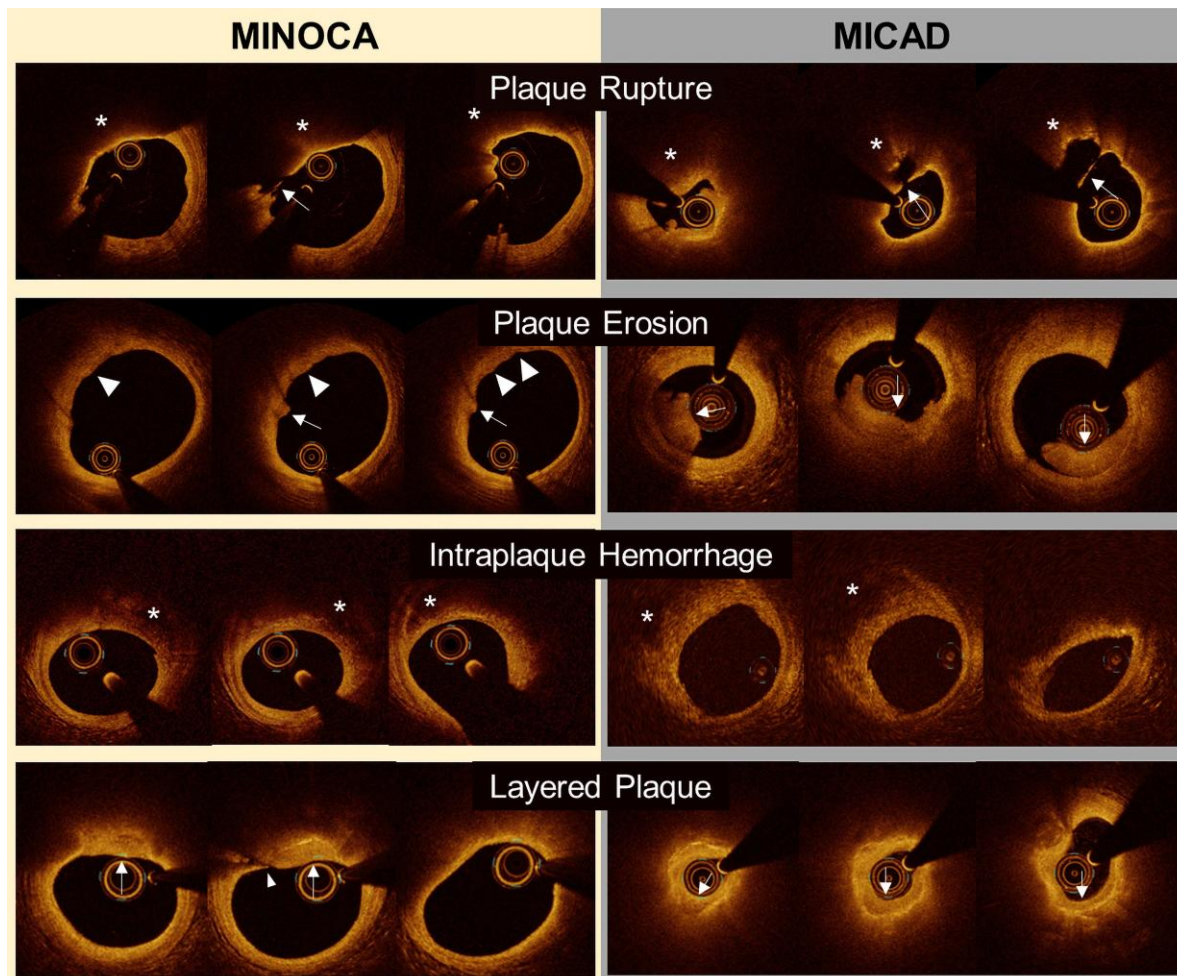
Figure 1 Representative optical coherence tomography images. Plaque rupture: In both MINOCA and MI-CAD, the fibrous cap disruption was observed (arrows) in the lipidic plaque (asterisks). Ruptured cavity size was smaller and lumen area was larger in MINOCA than those in MI-CAD. Plaque erosion (thrombus without plaque rupture): In both MINOCA and MI-CAD, thrombi (arrows) were observed with underlying non-lipidic plaque. Thrombi was smaller in MINOCA than those in MI-CAD. In MINOCA, there is a luminal irregularity, which may indicate mural thrombus (white triangles). Intraplaque haemorrhage: In both MINOCA and MI-CAD, similar low intensity regions without attenuation (asterisks), but with an overlying fibrous cap were observed. Layered plaque: In both MINOCA and MI-CAD, there was a layered plaque having heterogeneous and low intensity signal (arrows) on top of the lipidic plaque. Lumen area was larger in MINOCA than those in MI-CAD. A tangential artefact mimicking rupture was observed (an arrowhead). MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary artery disease.

Integrated optical coherence tomography and CMR diagnosis in Heart Attack Research Program

Heart Attack Research Program study participants with MINOCA underwent CMR with cine imaging for left ventricular function, late gadolinium enhancement (LGE) with phase-sensitive inversion recovery reconstruction and, where available, T2-weighted fat-suppressed fast-spin echo imaging and/or T1 mapping using a modified look-locker inversion sequence. CMR ischaemic findings included infarction (defined as ischaemic LGE with associated oedema or wall motion abnormalities), or regional myocardial injury (defined as prolonged T1, increased extracellular volume, increased T2-weighted signal and/or wall motion abnormality, in a myocardial territory subtended by a single coronary territory, without LGE). The territory associated with a coronary artery was based on the American Heart Association (AHA) 16-segment model.[24]

Tissue characterization of layered plaques

In order to characterize the maturity of layered plaques, we compared mean signal intensity and normalized standard deviation of layered plaques in patients with MINOCA or MI-CAD vs. 38 layered plaques in patients with stable coronary artery disease who underwent OCT at the Tsuchiura Kyodo General Hospital.[20] Detailed methods are described in the Supplementary material online. Comparator lesions with stable coronary artery disease were matched to MINOCA or MI-CAD patients based on the distance from the OCT catheter to the surface of layered plaque, which affects measured signal intensity.

Statistical analysis

Categorical variables were presented as frequencies and compared with χ^2 statistics or the Fisher exact test. Normally distributed continuous variables were presented as mean $\pm$ standard deviation and compared using

Student's *t*-test. Non-normally distributed continuous variables were presented as median and first and third quartiles and compared using the Mann–Whitney *U* test. A two-sided *P*-value < 0.05 was considered statistically significant. Statistical analysis was performed with R statistics version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Population

In MINOCA cohort, among 301 women with a clinically diagnosed MI who consented to participate, 170 were diagnosed with MINOCA (angiographic diameter stenosis <50%) and 147 underwent OCT of at least one coronary artery, of whom 145 had evaluable OCT (three vessels in 59%, two vessels in 32%) (see Supplementary material online, Figure S1). Among these 145 women, 116 underwent CMR at a median of 6 days after the diagnosis of MI. Multimodality imaging with OCT and CMR identified ischaemic cause of MINOCA in 63.8%, a non-ischaemic cause in 20.7%, and no mechanism was identified in the remaining 15.5%.[8] Among 145 women in the HARP with analysable OCT images, a culprit lesion was identified by OCT in 46% (67/145). Out of these 67 women, seven had non-atherosclerotic findings (three with intimal bumping suggesting spasm, one with spontaneous coronary artery dissection, and three cases of myocarditis) and two presented

with ST-segment elevation MI (STEMI). No provocative testing for spasm or fractional flow reserve was performed. After excluding these nine women, 58 women with NSTE-MINOCA comprised the final cohort (see Supplementary material online, Figure S1). In the comparator group of 55 women with NSTE-MI-CAD, we excluded three women with insufficient OCT image quality, leaving 52 women in the MI-CAD cohort (see Supplementary material online, Figure S2).

Clinical characteristics and luminal stenosis

Women with MINOCA were younger, presented with lower LDL cholesterol and peak troponin concentrations, and tended to have

Table 1 Baseline clinical characteristics

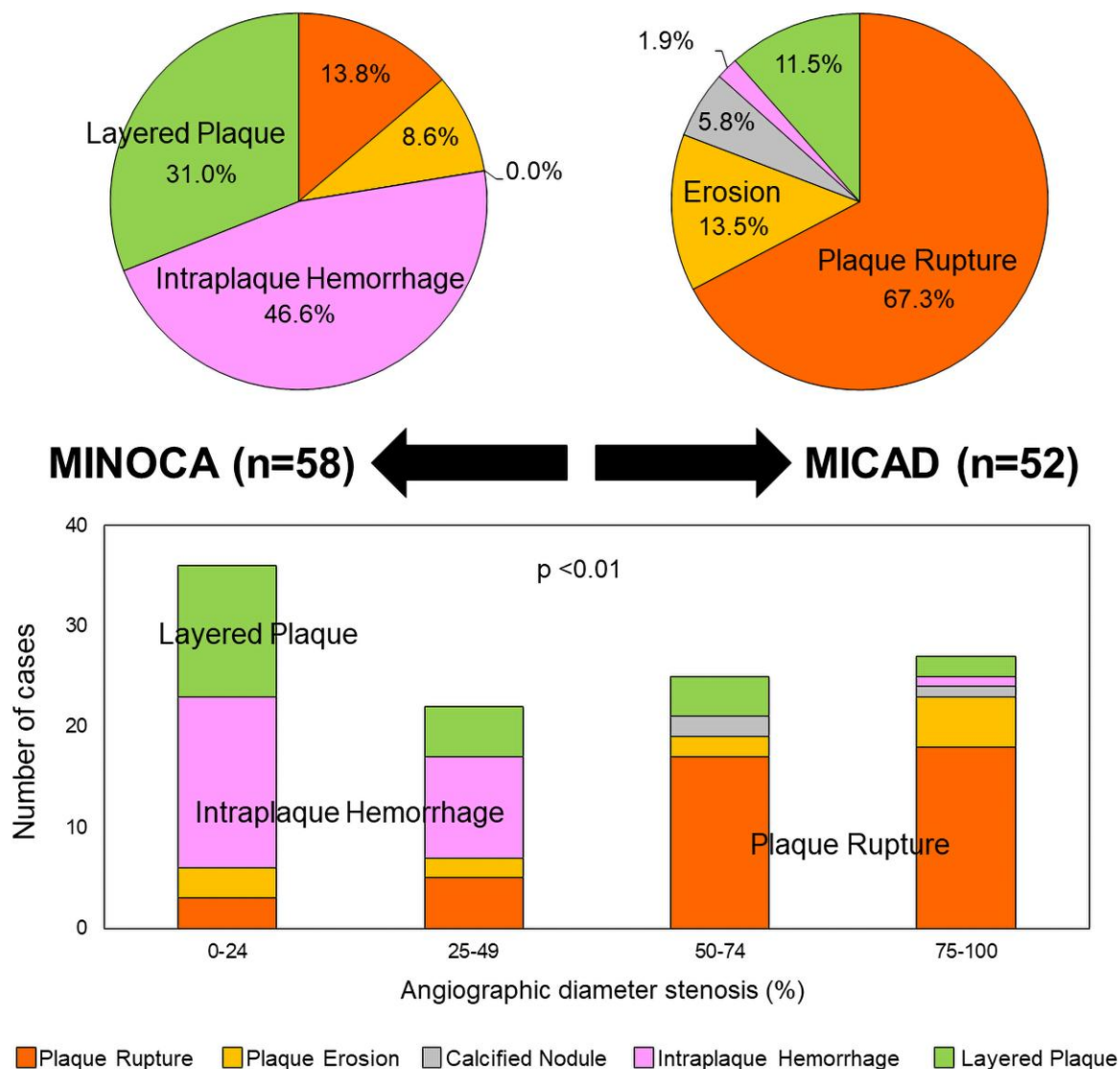|	MINOCA (*n* = 58)	MI-CAD (*n* = 52)	*P*-value
Age, years	65.5 (57.3, 71.8)	72.0 (65.8, 79.0)	<0.01
<65 years old	27 (46.6)	12 (23.1)	0.01
Female	58 (100.0)	52 (100.0)	—
NSTEMI presentation	58 (100.0)	52 (100.0)	—
Hypertension	30 (51.7)	35 (67.3)	0.14
Diabetes mellitus	15 (25.9)	22 (42.3)	0.11
Dyslipidaemia	30 (51.7)	28 (53.8)	0.98
Current smoking	8 (13.8)	10 (19.2)	0.61
Renal insufficiency[a]	6 (10.3)	7 (13.5)	0.83
Prior myocardial infarction	8 (13.8)	3 (5.8)	0.28
Total cholesterol, mg/dL	175 (151, 196)	199 (159, 233)	0.01
LDL cholesterol, mg/dL	101 (82, 114)	127 (90, 156)	<0.01
HDL cholesterol, mg/dL	51 (39, 58)	46 (38, 54)	0.21
Triglycerides, mg/dL	118 (75, 151)	100 (70, 132)	0.18
Peak troponin, ng/mL	0.68 (0.28, 2.50)	3.62 (0.73, 7.40)	<0.01
Peak troponin/local ULN	16.4 (4.7, 52.9)	26.8 (5.0, 81.8)	0.22
Aspirin on admission	22/48 (45.8)	10 (19.2)	<0.01
Statin on admission	36 (62.1)	15 (28.8)	<0.01

Vales are *n* (%) or median (1st quartile, 3rd quartile).
[a]Estimated glomerular filtration rate <60 mL/min/1.73 m^2 using the Modification of Diet in Renal Disease study equation. MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary artery disease; NSTEMI, non-ST-segment elevation myocardial infarction; ULN, upper limit normal.

Table 2 Angiographic and optical coherence tomography findings

	MINOCA (*n* = 58)	MI-CAD (*n* = 52)	*P*-value
Angiographic findings			
Culprit vessel			0.12
Left anterior descending artery	30 (51.7)	23 (44.2)	
Left circumflex artery	7 (12.0)	14 (26.9)	
Right coronary artery	1 (1.7)	0 (0.0)	
Diameter stenosis, %	21 (17, 28)	75 (65, 82)	<0.01
Optical coherence tomography findings			
Minimum lumen area, mm^2	5.79 (4.07, 8.18)	0.80 (0.67, 1.17)	<0.01
Area stenosis, %	33.7 (23.2, 44.9)	86.2 (80.8, 91.2)	<0.01
Plaque rupture	8 (13.8)	35 (67.3)	
Angle of rupture cavity, °	78 (30, 91)	100 (64, 142)	0.05
Thrombus	11 (19.0)	37 (71.2)	<0.01
Red	2 (3.4)	14 (26.9)	<0.01
White	9 (15.5)	34 (65.4)	<0.01
Maximum thrombus area, mm^2	0.08 (0.02, 0.12)	0.22 (0.13, 0.49)	<0.01
Lipid-rich plaque	20 (34.5)	41 (78.8)	<0.01
Maximum lipid angle, °	86 (73, 109)	256 (220, 360)	<0.01
Fibrous cap thickness, mm	0.15 (0.11, 0.24)	0.07 (0.06, 0.11)	<0.01
Thin-cap fibroatheroma	2 (3.4)	18 (34.6)	<0.01
Macrophage	43 (74.1)	38 (73.1)	1.00
Cholesterol crystal	12 (20.7)	26 (50.0)	<0.01
Calcification	19 (32.8)	38 (73.1)	<0.01
Maximum calcium angle <90°	15 (25.9)	27 (51.9)	0.01

Values are *n* (%) or median (1st quartile, 3rd quartile). MI-CAD, myocardial infarction with obstructive coronary artery disease; MINOCA, myocardial infarction with non-obstructive coronary artery disease.

increase in the frequency of plaque rupture and a decrease in the frequency of IPH and layered plaque at the culprit lesion ($P < 0.01$) (*Figure 2*).

Angle of plaque rupture cavities was smaller in MINOCA compared with MI-CAD (*Table 2*). Thrombus, both red and white, was less prevalent in women with MINOCA than women with MI-CAD (19 vs. 71%, $P < 0.01$). When thrombus was present, the maximum thrombus area was smaller in women with MINOCA than women with MI-CAD. Lesion morphologies indicating high-risk plaque were less common in patients with MINOCA than those with MI-CAD. Thin-cap fibroatheroma (3 vs. 34%, $P < 0.01$) and lipid-rich plaques (35 vs. 79%, $P < 0.01$) were less frequent in MINOCA than MI-CAD. Median fibrous cap thickness was greater in culprit plaques for women with MINOCA than MI-CAD [median 0.15 mm, first and third quartiles (0.11–0.24) vs. 0.07 (0.06–0.11), $P < 0.01$]. Cholesterol crystals and calcification were also less frequent in women with MINOCA than in women with MI-CAD.

Evidence of myocardial ischaemic pattern corresponding to optical coherence tomography culprit lesions in the MINOCA cohort

In the final analysed MINOCA cohort, 74% (43/58) of patients underwent CMR (7 plaque ruptures, 4 plaque erosions, 18 IPHs, and 14 layered plaques) (see Supplementary material online, *Figure S1*). Among 18 patients with IPH, 13 patients (72%) had a CMR myocardial ischaemic pattern that matched the vascular territory of the culprit vessel as defined by OCT using the AHA 16-segment model; three patients (17%) had an CMR ischaemic pattern that did not match the territory of the OCT culprit vessel; and two patients (11%) had normal CMR without evidence of infarction or regional oedema.

Among 14 patients with layered plaque, six patients (43%) had a CMR ischaemic pattern that matched the territory of the culprit vessel as defined by OCT; three patients (21%) had a CMR ischaemic pattern that did not match the territory of the OCT culprit vessel; and five patients (36%) had normal CMR.

Among seven patients with plaque rupture, two patients (29%) had a CMR ischaemic pattern that matched the territory of the culprit vessel as defined by OCT; five patients (71%) had normal CMR. Among four patients with plaque erosions, all patients had a CMR ischaemic pattern that matched the territory of the culprit vessel as defined by OCT.

Although we kept the original diagnosis from each independent core laboratory, cases with mismatched OCT- and CMR-suggested culprits were re-evaluated. Four out of 6 cases showed OCT culprit morphologies explaining CMR in culprit vessels, while two were indeterminate due to the lack of OCT images in CMR-culprit vessels (see Supplementary material online, *Table S1*). Thus, in 31 women with LGE or ischemic injury by CMR, 94% (29/31) of them had at least one plaque morphologies (2 plaque rupture, 4 plaque erosion, 15 intraplaque hemorrhage, or 8 layered plaque) by OCT possibly led to CMR-detected LGEs or ischemic injuries.

Signal intensity of layered plaque in MINOCA or MI-CAD vs. in patients with stable coronary artery disease

In order to assess the maturity of layered plaque in MINOCA or MI-CAD, 14 layered plaques in MINOCA patients and 5 patients in MI-CAD were compared with 38 layered plaques in stable patients (see Supplementary material online, *Tables S2 and S3*). Compared with layered plaque in stable patients, layered plaques in MINOCA or MI-CAD showed lower signal intensity [78.9 (67.0,

88.2) vs. 91.4 (85.0, 104.3), $P < 0.01$] with greater heterogeneity [normalized standard deviation = 0.20 (0.17, 0.25) vs. 0.16 (0.14, 0.19), $P = 0.02$], indicating that the layered plaques in MINOCA or MI-CAD were possibly less mature compared with patients with stable lesions (see Supplementary material online, *Table S3 and Figure S3*).[25]

Long-term clinical outcome

None of the women in the MINOCA cohort underwent PCI. At discharge, 80% (44/55) had aspirin, 34% (19/56) had $P2Y_{12}$ inhibitor, and 84% (47/56) had statin. During 1-year follow-up, two women died (one sudden cardiac death and one non-cardiac death); and other two women had recurrent MI without revascularization. All women in the MI-CAD cohort underwent PCI. At discharge, all women in the MI-CAD cohort had both aspirin and $P2Y_{12}$ inhibitor, and 75% (39/52) had statin. During 1-year follow-up, no cardiac death or MI occurred; but two patients required target lesion revascularization.

Discussion

This is the first analysis of culprit lesion characteristics on OCT comparing women with MINOCA to women with MI-CAD. The major findings of this study were as follows: (i) prevalence of various culprit lesion types differed significantly between MINOCA and MI-CAD; (ii) women with MINOCA had a smaller burden of thrombus and a smaller size of rupture cavity than women with MI-CAD; (iii) across all patients, increasing angiographic diameter stenosis of the culprit vessel was associated with greater frequency of plaque rupture or plaque erosion (acute phase of thrombotic event) and a lower prevalence of OCT-defined IPH or layered plaque (early healing phase); (iv) over 90% of women with NSTE-MINOCA having CMR-detected regional LGE or ischemic injury showed possible corresponding culprit plaque morphologies by OCT.

Optical coherence tomography diagnosis of plaque morphology in women with MINOCA

MINOCA is known to have various mechanisms including atherosclerotic plaque rupture, erosion, embolization, coronary artery spasm (epicardial or microvascular), and spontaneous coronary artery dissection.[4] The prevalence of plaque erosion among patients with MINOCA was similar to two prior studies including patients with MINOCA with similar eligibility criteria, whereas the prevalence of plaque rupture (14%) was lower in the current study.[5,6] Opolski et al.[5] included 38 patients with MINOCA (55% women, 61% NSTE-MI); OCT culprit lesion morphology was 21% plaque rupture, 11% plaque erosion, and 3% calcified nodule. Taruya et al.[6] included 82 patients with MINOCA (30% women); OCT culprit lesion morphology was 16% plaque rupture, 10% thrombus without rupture (plaque erosion), and 11% calcified nodule. Differences to our cohort may be relate to our restriction to women with NSTE-MI, and lower angiographic diameter stenosis (median 21% overall) than in the Opolski cohort (median diameter stenosis 45% in lesions with rupture and 30% in lesions without rupture).[5] Our frequency of plaque rupture and erosion was far lower than in a study by Gerbaud et al.[7] including 40 highly selected patients (37% women, 67% NSTEMI) with MINOCA who had electrocardiographic features of ischaemia associated with corresponding wall motion abnormalities (thus highly suspicious of vascular MI); OCT culprit lesion morphology was 35% plaque rupture, 38% plaque erosion, and 3% calcified nodule.

Culprit intraplaque haemorrhage or layered plaque in patients presenting with NSTE-MINOCA or NSTE-MI-CAD

Our finding that over 90% of women with NSTE-MINOCA having CMR-detected LGE or ischaemic injury showed possible corresponding culprit plaque morphologies by OCT, of which most of them formed IPH or layered plaque. These findings strongly support the concept that IPH or layered plaque may be responsible for myocardial injury subtended by the culprit artery.

Pathologic studies have shown consistently that both IPH and layered plaque are culprit lesions for some fatal cases of MI. In a study by Falk[9] of patients with fatal MI, 61% (63/103) of plaque ruptures had sealed, with small thrombus only visible by microscopy, consistent with the OCT finding of IPH. Similarly, Davies *et al.*[10] reported coronary pathology in 100 subjects with sudden death due to ischaemic heart disease, of whom 19 had only *intra-intimal* fresh thrombus with a sealed rupture site indicating IPH. Healing thrombus is also common in acute coronary syndromes. In 211 STEMI patients who underwent thrombectomy and primary PCI within 6 h of symptom-onset, Rittersma *et al.*[18] reported that 9% of thrombi were organized (>5 days old). In an autopsy study of 65 culprit lesions with plaque rupture in sudden death victims, Kramer *et al.*[12] showed that 19% (12/65) of thrombi were 4–7 days old (infiltrating stage), and 9% (6/65) were in the final healing stage (>7 days). These studies indicate that symptom-onset might represent the final phase in a series of nonocclusive atherothrombotic events in the preceding days or even weeks. During thrombus healing, mural thrombus can be interspersed among smooth muscle cells and endothelial cells with proteoglycan-collagen matrix, and this pathology is seen as layered plaque by OCT.[12,22] Among women with MINOCA in the current study, layered plaques may have been more immature, as defined by lower OCT signal intensity, than layered plaques in a cohort of stable patients.[25] This supports the hypothesis that layered plaque represents a recent coronary culprit with mural thrombus in early stage of healing. Because MINOCA has heterogeneous pathophysiology,[4] identifying the aetiology in each patient may be helpful to select treatment. Complementary imaging (OCT and CMR) makes a specific diagnosis in most cases (85%). At present, the OCT finding of a culprit plaque may lead to more intensive antiplatelet therapy or lipid lowering based on extrapolation from studies in MI-CAD populations. Further prospective clinical trials will be needed to evaluate the optimal strategy to improve patient outcomes, including antiplatelet therapies and, perhaps, mechanical therapies.

The smaller proportion of culprit lesions associated with ischaemic injury in a territory that did not match the culprit lesion on the 16-segment AHA model, may relate to variability in coronary anatomy and myocardial blood supply from person to person, and is consistent with a prior publication in NSTE-MI-CAD.[26] The limited spatial resolution of current CMR LGE could result in overlooking of a small myocardial scar. Unfortunately, CMR was not performed in the NSTE-MI-CAD comparator cohort.

Study limitations

This study combined data from a prospective multicentre diagnostic study of women with MINOCA in North America and a retrospective observational database of OCT findings in women with MI-CAD from a single centre in Japan and was limited to NSTEMI. A relatively small number of patients was available for analysis, and the ethnicities of the cohorts differed considerably, although in a previous OCT study the underlying pathophysiology in Caucasians and Asians was similar.[27] Optical coherence tomography-detected IPH has not yet been validated by direct pathological comparison. The temporal course of plaque healing remains uncertain. Thus, the results of the present study are hypothesis-generating and require validation. The sensitivity of

myocardial oedema on CMR for pathologic evidence of ischaemic injury is unclear. CMR was not performed in 26% of the MINOCA cohort or any of the MI-CAD cohort. We did not perform provocative testing for spasm and may have underestimated MI due to vasospasm. We included both time-domain and frequency-domain OCT imaging in the cohort of patients with MI-CAD.

Conclusion

Prevalence of atherothrombotic culprit lesion subtypes varied substantially between MINOCA and MI-CAD. Plaque rupture with a persistent cavity, and thrombus, were less frequent in MINOCA, and recently ruptured plaques in MINOCA most commonly had the appearance of IPH or layered plaque, suggesting that MINOCA and MI-CAD may lie on a spectrum of atherosclerotic disease.

Lead author biography

Eisuke Usui graduated from Tokyo Medical and Dental University and completed the MD course in 2010. After his cardiovascular interventional fellowship at Department of Cardiovascular Medicine, Tsuchiura Kyodo General Hospital, he is currently working as an intravascular imaging fellow at Cardiovascular Research Foundation and Columbia University Medical Center in New York, NY, USA.

Data availability

The data that support the findings of this study are available from the corresponding authors on reasonable request.

Supplementary material

Supplementary material is available at *European Heart Journal Open* online.

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