Coronary Plaque Characteristics Affect No-Reflow During Primary Percutaneous Coronary Intervention: A Pooled Analysis of 14 Observational Studies Using Intravascular Ultrasound

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The association between coronary plaque composition and no-reflow during percutaneous coronary intervention (PCI) is still debated. We performed a systematic literature search using MEDLINE, Embase, Cochrane, and Ovid databases for intravascular ultrasound (IVUS) studies evaluating the relationship between coronary plague characteristics and no-reflow after PCI. Fourteen observational trials were included in the meta-analysis, including 1457 patients (237 in the no-reflow group, 1220 in the normal reflow group). Pooled analysis indicated that the no-reflow group had a significantly higher absolute volume of fibrofatty plague (weighted mean differences [WMD], 4.94 mm³; 95% confidence interval [CI], 1.83-8.06; P = .002), external elastic membrane cross-sectional area (EEM-CSA) (WMD, 3.40 mm²; 95% Cl, 2.22-4.58; *P* < .00001), plaque area (WMD, 4.06 mm²; 95% Cl, 2.24-5.89; *P* < .0001), and artery remodeling index (WMD, 0.09; 95% CI, 0.06-0.13; P < .00001), and a smaller percentage of fibrous plaque (WMD, -5.89 %; 95% Cl, -0.66 to -11.12; P = .03) than in the normal reflow group. There were no significant differences in the other plaque components between the two groups. This meta-analysis confirmed that high absolute volume of fibrofatty plague, EEM-CSA, plague area, and coronary artery remodeling index, and a decreased percentage of fibrous plague as detected by IVUS in culprit lesions, are linked with the development of the no-reflow phenomenon after PCI.

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KEY WORDS

No-reflow phenomenon • Plaque characteristics • Intravascular ultrasound • Coronary disease • Meta-analysis

The "no-reflow" phenomenon refers to the inability to reperfuse myocardial tissue despite the reopening of the infarct-related artery.¹ No-reflow often happens in acute myocardial infarction (MI) patients during primary percutaneous coronary intervention (PCI), which has a

in MI flow grade 3) without mechanical obstruction (Table 1).^{4,5}

The pathophysiology of no-reflow is likely multifactorial; the type of plaque may be an important predictor for no-reflow after PCI. A few observational studies have reported that the angiographic no-reflow phenomenon is asso-

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strong negative impact on clinical outcome, negating the potential benefit of primary PCI. No-reflow is associated with a higher rate of mortality and early postinfarction complications.² The occurrence of no-reflow can be evaluated first in the catheterization laboratory angiographic by the use of indexes, Doppler wire, and electrocardiographic assessment.³ On angiograms, the no-reflow phenomenon is defined as substantial coronary antegrade flow reduction (less than thrombolysis

ciated with atherosclerotic plaque characteristics detected by intravascular ultrasound (IVUS) before PCI in acute MI patients,^{6,7} however, with inconsistent results.⁸⁻¹⁶ Because of the small sample size, the power achieved in those studies was not sufficient to detect whether coronary plaque composition increased risk of no-reflow after PCI (Figure 1). Using all available published data to increase statistical power, meta-analysis is an efficient way of analytically combining the results of individual studies together

to detect and quantify an effect with more precision.

The purpose of this pooled analysis is to combine primary data from all relevant studies to produce reliable estimates of the associations of coronary plaque composition assessed by IVUS with the incidence of no-reflow after PCI among patients with acute coronary syndrome (ACS).

Methods

Search Strategy

We performed a computerized literature search in PubMed, Embase, Cochrane, and Ovid databases (up to November, 2014), using the key words *no-reflow*, *slow reflow*, *intravascular ultrasound*, *virtual histology*, *plaque characteristic*, *plaque composition*, and *percutaneous coronary intervention* along with a filter for studies in human beings. Citations were screened and evaluated using the established inclusion/exclusion criteria at the abstract level by two

TABLE 1

Definition	of TIMI Flow Grading
Grade	TIMI Myocardial Perfusion
0	No perfusion; no antegrade flow beyond the point of occlusion
1	Penetration without perfusion; incomplete clearance of dye between injections (at least 30 s)
2	Partial perfusion; slow entry and clearance of dye (strongly persistent opacification beyond 3 cardiac cycles after injection)
3	Complete perfusion; myocardial blush present with normal entry and exit of dye

TIMI, thrombolysis in myocardial infarction.

Adapted from The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. TIMI Study Group. N Engl J Med. 1985;312:932-936.

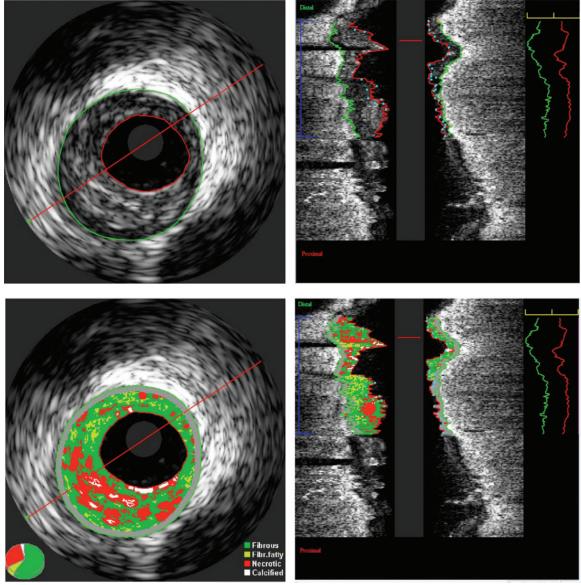


Figure 1. Information theoretic quantification of the absolute plaque volume. Grayscale intravascular ultrasound (IVUS) image (*top*). Virtual histology IVUS image (*bottom*). A region of interest is defined and analyzed by indicating the outlines of the lumen and the external elastic membrane in all frames. Out of this analysis, lumen, vessel, and plaque volumes are calculated together with virtual histology data such as fibrofatty and fibrous plaque volumes. Image courtesy of Jurgen M.R. Ligthart, BSc.

operators (Drs. Zhang and Wang), and relevant studies were retrieved as full manuscripts. There were no language restrictions. Our systematic review was conducted according to the Meta-analysis of Observational Studies in Epidemiology guidelines.¹²

Selection

Inclusion criteria were (1) grayscale and/or virtual histology (VH)-IVUS examination before PCI; and (2) direct comparison of lesion characteristics and/or plaque composition in patients with or without no reflow/slow reflow phenomenon after PCI. Studies were excluded from the meta-analyses if enrolled subjects without control group and IVUS measurements cannot provide appropriate quantitative results.

Data Extraction

Two independent investigators (Drs. Li and Zhou) reviewed each report to determine its eligibility and then extracted and tabulated all of the relevant data. Disagreement was

resolved by consensus between the two authors. The following basic information was obtained from each article: first author, year of publication, country of origin, sample size, mean age, distribution, sex hypertension, diabetes, clinical setting, definition of no-reflow, and IVUS type. In addition, we retrieved conventional IVUS data including the volume and percentage of each tissue component of plaque, plaque area, plaque burden, culprit lesions, external elastic membrane cross-sectional

areas (EEM-CSA) and lumen CSA, and coronary artery remodeling index from included trials.

Statistical Analysis

To ensure adequate statistical power, we only conducted pooled analysis for IVUS quantitative measurements with available data from at least three independent studies. All analyses were performed using Review Manager 5.0 software (available from The Cochrane Collaboration at http// www.cochrane.org) and software STATA version 11.2 (Stata Corporation, College Station, TX). The Mantel-Haenszel method for fixed effects and the DerSimonian-Laird method for random effects were used to estimate pooled weighted mean differences (WMD). We tested heterogeneity of the included studies with Q statistics and the extent of inconsistency between results with I² statistics.¹³ In the absence of heterogeneity between studies, the methods produced very similar results. We report fixed-effects estimates because fixed effects are more robust in meta-analysis calculations when there are small numbers of events. Possibility of publication bias was assessed by funnel plot analysis. Sensitivity analysis was also done by omitting one study at a time to examine influence of one study on the overall summary estimate. Data are presented as WMD with 95% confidence intervals (CIs). P < .05 was considered statistically significant.

Results

Description of Studies

Of 253 potentially relevant articles initially screened, 207 publications were excluded because they did not meet the inclusion criteria. Of the remaining 46 complete reports, 32 studies without appropriate IVUS measurements or a comparison of normal reflow were excluded. Finally, 14 observational trials^{8-11,14-23} met inclusion criteria and were included in the final meta-analysis, consisting of a total of 1457 patients (237 in the no-reflow group, 1220 in the normal reflow group). Five studies had a prospective design,^{9,10,14,15,18} and nine studies had a retrospective design.^{8,11,16,17,19-23}

Of the 14 studies, 9 studies involved acute MI patients,^{8-10,14,15,17-20} 4 studies enrolled ACS (including both acute MI and unstable angina) patients,^{11,16,21,22} and the remaining study involved unstable angina patients.23 In this pooled analysis, six used grayscale IVUS,^{8,14-17,19} two used both grayscale and VH-IVUS,^{10,20} five used VH-IVUS,9,11,18,21,23 and one study used grayscale and iMap-IVUS only.²² The baseline characteristics of patients and coronary plaque characteristics included in the meta-analysis are reported in Tables 2 through 4. All studies were published in English. The subject population was derived from three countries.

Relationship Between Coronary Plaque Characteristics and No-Reflow After Primary PCI

The Absolute Plaque Component Volume Findings. Four trials^{10,18,20,22} of 249 patients were included. The meta-analysis normal reflow group (Figure 2). There were no significant differences in absolute volume of fibrous, dense calcified, and necrotic core at the culprit lesions between the two groups. On sensitive analysis, the results remained unchanged by excluding any individual trial.

The Percentage of Plaque Composition Findings. Six trials^{9,11,18,20,22,23} of 457 patients were included. Pooled analysis showed the percentage of the fibrous plaque was significantly smaller in the no-reflow group (WMD, -5.89%; 95% CI, -0.66 to -11.12; P = .03) compared with the normal reflow group (Figure 3). No significant differences were noted in the percentage of fibrofatty, dense calcified, and necrotic core at the culprit lesions between the two groups. Substantial statistical heterogeneity was detected in all of the comparisons among the trials.

Sensitivity analysis for the percentage of the fibrous plaque, excluding the studies by Higashikuni and colleagues,¹⁶ Ohshima and colleagues,18 Utsunomiya and associates,22 and Zhao and colleagues²³ from the pooled analysis, resulted in a borderline statistical significance between the two groups (P = .06 for excluding either, and)P = .07 for excluding either). With regard to the percentage of necrotic core, sensitivity analysis showed that omitting one study by Nakamura and associates,14 it was significantly greater in the no-reflow group compared with the normal reflow

The meta-analysis showed the no-reflow group had a significantly higher absolute volume of fibrofatty plaque ... compared with the normal reflow group.

showed the no-reflow group had a significantly higher absolute volume of fibrofatty plaque (WMD, 4.94 mm³; 95% CI, 1.83-8.06; P = .002) compared with the group (WMD, 4.95%; 95% CI, 0.54-9.36; *P* = .03).

The Culprit Lesions EEM-CSA and Lumen CSA Findings. Four studies^{8,14,17,19} were used for the

TABLE 2					
Baseline Characteristics of the Included Studies	s of the Included	Studies			
Study	Study Design	Location	Clinical Setting	Definition of No-Reflow	IVUS type
Tanaka A et al ¹⁰	PSC	Japan	Acute MI	TIMI flow grade ≤ 2	Grayscale
Watanabe T et al ¹¹	PSC	Japan	Acute MI	TIMI flow grade ≤ 2	Grayscale
lijima R et al ¹²	RSC	Japan	ACS	TIMI flow grade ≤ 2	Grayscale
Katayama T et al ¹³	RSC	Japan	Acute MI	Decreased TIMI flow grade	Grayscale
Nakamura T et al ¹⁴	PSC	Japan	Acute MI	Decreased TIMI flow grade	VH-IVUS
Bae JH et al ¹⁵	PSC	South Korea	Acute MI	TIMI flow grade ≤ 2	Grayscale and VH
Higashikuni Y et al ¹⁶	RSC	Japan	ACS	Decrease of at least 1 grade in TIMI	VH-IVUS
Hong YJ et al ¹⁷	RSC	South Korea	Acute MI	TIMI flow grade ≤ 2	Grayscale
Ohshima K et al ¹⁸	PSC	Japan	Acute MI	TIMI flow grade ≤ 2	VH-IVUS
Endo M et al ¹⁹	RSC	Japan	Acute MI	TIMI flow grade ≤ 2	Grayscale
Ohshima K et al ²⁰	RSC	Japan	Acute MI	TIMI flow grade ≤ 2	Grayscale and VH
Hong YJ et al ²¹	RSC	South Korea	ACS	TIMI flow grade ≤ 2	VH-IVUS
Utsunomiya M et al ²²	RSC	Japan	ACS	TIMI flow grade ≤ 2	Grayscale and iMap-IVUS
Zhao XY 2013 ²³	RSC	China	Unstable angina	TIMI flow grade ≤ 2	VH-IVUS

baseline characteristics of the included studies (<i>continued</i>)	יא טו נוופ וווכוממפט אנמופי				
	Sample Size (n)	Age (y)	Male (%)	Diabetes (%)	Hypertension (%)
Study	No-Reflow/Reflow	No-Reflow/Reflow	No-Reflow/Reflow	No-Reflow/Reflow	No-Reflow/Reflow
Tanaka A et al ¹⁰	13/87	$62 \pm 8.0/64 \pm 11$	TTITT	31/25	53/47
Watanabe T et al ¹¹	21/60	65.2/64.7	76.2/70	28.5/25	61.9/41.7
lijima R et al ¹²	20/200	69 ± 10/65 ± 11	75/82	35/31	75/65
Katayama T et al ¹³	12/58	$65 \pm 10/63 \pm 11$	75/76	25/34	58/60
Nakamura T et al ¹⁴	8/42	$58.5 \pm 1.6/65.3 \pm 1.6$	87.5/85.7	37.5/23.8	25.0/42.9
Bae JH et al ¹⁵	12/45	$67.5 \pm 13.8/56.2 \pm 13.9$	66.7/82.2	33.3/13.3	27.3/31.1
Higashikuni Y et al ¹⁶	9/40	$60.6 \pm 13.5/66.6 \pm 11.4$	77.8/92.5	55.6/30.0	55.6/70.0
Hong YJ et al ¹⁷	17/95	63.1 ± 15.4/62.5 ± 13.4	59/59	47/41	88/59
Ohshima K et al ¹⁸	20/24	$74.0 \pm 14.0/66.0 \pm 14.0$	65/83	60/54	75/58
Endo M et al ¹⁹	30/140	$65 \pm 11/63 \pm 11$	70/81	20/26	53/61
Ohshima K et al ²⁰	19/34	73 ± 14/67 ± 11	68/85	26/38	79/71
Hong YJ et al^{21}	24/166	$60.1 \pm 14.4/60.5 \pm 12.2$	58/66	25/19	71/52
Utsunomiya M et al ²²	11/84	$65.1 \pm 14.0/67.9 \pm 10.9$	90.9/78.6	63.6/42.9	72.7/77.4
Zhao XY et al ²³	21/145	49 ± 7/51 ± 6	66.7/66.2	47.6/26.9	61.9/59.3

TABLE 3				
Plaque Characteristic	s of Included Studies Based or	א Absolute Volumetric Analys	Plaque Characteristics of Included Studies Based on Absolute Volumetric Analysis by Intravascular Ultrasound (No-Reflow/Reflow)	-Reflow/Reflow)
Study	Fibrous Volume (mm ³)	Fibrofatty Volume (mm³)	Dense Calcified Volume (mm ³)	Necrotic Core Volume (mm ³)
Bae JH et al ¹⁵	$119.6 \pm 61.7/83.8 \pm 66.8$	$36.7 \pm 25.5/18.0 \pm 18.6$	9.3 ± 8.9/12.7 ± 13.9	$26.1 \pm 21.0/28.8 \pm 26.0$
Ohshima K et al ¹⁸	$56.2 \pm 32.6/56.6 \pm 21.8$	$14.2 \pm 11.4/8.6 \pm 5.2$	$10.3 \pm 7.6/6.5 \pm 5.3$	$14.1 \pm 6.7/12.0 \pm 7.4$
Ohshima K et al ²⁰	$57.0 \pm 33.3/67.5 \pm 29.7$	$14.7 \pm 11.5/15.0 \pm 11.7$	$9.3 \pm 6.0/11.0 \pm 8.8$	$13.7 \pm 6.7/16.8 \pm 10.0$
Utsunomiya M et al ²²	$114.43 \pm 67.1/75.04 \pm 41.1$	$14.12 \pm 8.1/8.11 \pm 5.5$	$6.15 \pm 3.2/4.76 \pm 4.0$	$43.33 \pm 33.5/20.08 \pm 17.2$
Study	Fibrous (%)	Fibrofatty (%)	Dense Calcium (%)	Necrotic Core (%)
Nakamura T et al ¹⁴	$68.3 \pm 2.1/67.0 \pm 1.5$	$23.1 \pm 3.5/17.0 \pm 1.1$	$2.6 \pm 0.6/4.8 \pm 0.6$	$6.3 \pm 1.0/11.2 \pm 1.2$
Higashikuni Y et al ¹⁶	$59.6 \pm 11.2/68.3 \pm 10.2$	$12.0 \pm 9.7/15.5 \pm 7.1$	$4.7 \pm 3.3/4.8 \pm 3.6$	$22.1 \pm 9.3/11.7 \pm 7.9$
Ohshima K et al ¹⁸	$57.5 \pm 10.7/67.8 \pm 10.2$	$14.5 \pm 9.6/10.1 \pm 3.9$	$11.8 \pm 8.9/7.8 \pm 5.2$	$15.8 \pm 7.4/14.3 \pm 6.7$
Ohshima K et al ²⁰	$59.0 \pm 12.4/62.9 \pm 10.6$	17.7 ± 14.3/12.2 ± 7.1	$8.8 \pm 7.9/8.7 \pm 6.4$	$14.5 \pm 8.5/16.2 \pm 7.2$
Utsunomiya M et al ²²	$55.64 \pm 7.7/62.11 \pm 13.4$	$6.46 \pm 1.3/5.71 \pm 2.1$	$3.09 \pm 1.5/3.45 \pm 2.8$	$19.73 \pm 5.1/14.56 \pm 8.3$
Zhao XY et al ²³	$50.26 \pm 8.72/59.24 \pm 6.72$	15.29 ± 2.83/17.90 ± 3.21	9.53 ± 2.99/8.36 ± 3.13	$24.92 \pm 10.04/14.50 \pm 5.48$

TABLE 4					
Plaque Characteristi	Plaque Characteristics of Included Studies by Intravascular Ultrasound (No-Reflow/Reflow)	Intravascular Ultrasou	ind (No-Reflow/Reflow)		
Study	EEM CSA (mm ²)	Lumen CSA (mm²)	Remodeling Index	Plaque Area (mm²)	Plaque Burden (%)
Tanaka A et al ¹⁰	$18.4 \pm 4.3/13.3 \pm 4.1$	2.2 ± 1.4/2.3 ± 1.4	NP	NP	NP
lijima R et al ¹²	NP	NP	$1.2 \pm 0.2/1.1 \pm 0.3$	$18.7 \pm 5.3/14.0 \pm 6.0$	$0.90 \pm 0.03 / 0.83 \pm 0.08$
Katayama T et al ¹³	$20.1 \pm 6.5/16.4 \pm 4.3$	NP	$1.06 \pm 0.21/0.98 \pm 0.19$	$16.0 \pm 7.7/13.4 \pm 4.3$	$85.3 \pm 5.0/82.9 \pm 4.8$
Bae JH et al ¹⁵	NP	NP	$1.10 \pm 0.17 / 0.99 \pm 0.16$	$16.2 \pm 5.4/12.5 \pm 4.9$	$79.4 \pm 7.2/73.9 \pm 9.5$
Higashikuni Y et al ¹⁶	NP	NP	$1.20\pm0.26/1.03\pm0.22$	NP	$68.7 \pm 9.1/63.7 \pm 10.7$
Hong YJ et al ¹⁷	$16.2 \pm 4.7/13.4 \pm 4.6$	$2.7 \pm 1.5/2.6 \pm 1.2$	$1.14 \pm 0.17/1.03 \pm 0.20$	NP	$82.0 \pm 11.4/79.4 \pm 9.0$
Ohshima K et al ¹⁸	NP	NP	$1.26 \pm 0.17/1.12 \pm 0.19$	NP	$60.7 \pm 6.9/59.3 \pm 7.4$
Endo M et al ¹⁹	$17.4 \pm 4.6/14.6 \pm 3.9$	$2.3 \pm 0.7/2.4 \pm 1.0$	$1.11 \pm 0.23/1.07 \pm 0.23$	NP	NP
Hong YJ et al ²¹	NP	NP	$1.05 \pm 0.38/1.02 \pm 0.23$	NP	$70.4 \pm 7.9/76.9 \pm 55.4$
Utsunomiya M et al ²²	NP	NP	NP	NP	$79.26 \pm 6.87/82.83 \pm 5.53$
CSA, cross-sectional area; EEM, ex	CSA, cross-sectional area; EEM, external elastic membrane; NP, not reported	orted.			

Study	or Subaroup		No-ref	low Total	Mean	Refl		Weight	Mean Difference IV, Random, 95% Cl	Mean Difference IV. Random, 95% Cl
Bae JH		119.6		12	83.8		45		35.80 [-4.19, 75.79]	
	ma K 2009		32.6	20		21.8	43 24		-0.40 [-17.14, 16.34]	
	ma K 2009		33.3	19	67.5				-10.50 [-28.50, 7.50]	
	omiya M2011				75.04				39.39 [-1.23, 80.01]	
Otsum	01111ya 1112011	114.45	07.1		75.04	41.1	04	10.470	39.39 [⁻ 1.23, 60.01]	
	(95% CI)			62					8.84 [-11.96, 29.64]	
	ogeneity: Tau ²				df = 3	(P = .0)	05); I ²	= 62%		
lest fo	or overall effect	L: Z = 0.8	33 (P =	.40)						-50 -25 0 25 50
										Favors Favors Favors normal reflow no-reflow
		,	No-ref	low		Refl	ow		Mean Difference	Mean Difference
Study	or Subgroup			Total	Mean			Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
Bae JH	2008	36.7	25.5	12	18	18.6	45	4.1%	18.70 [3.28, 34.12]	
Ohshi	ma K 2009	14.2	11.4	20	8.6	5.2	24	33.1%	5.60 [0.19, 11.01]	
Ohshi	ma K 2011	14.7	11.5	19	15	11.7	34	23.0%	-0.30 [-6.80, 6.20]	
Utsun	omiya M2011	14.12	8.1	11	8.11	5.5	84	39.9 %	6.01 [1.08, 10.94]	B
Total	(95% CI)			62			107	100.0%	4 94 [1 93 9 64]	
	(95% CI) ogeneity: Chi ²	= 5.80 c	lf = 3		$2 \cdot l^2 = 4$	18%	107	100.0%	4.94 [1.83, 8.06]	
	or overall effect				-,, •	10 / 0				-50 -25 0 25 50
				,						Favors Favors
										normal reflow no-reflow
Study	or Subgroup		No-ref SD	low Total	Mean	Refi SD		Weight	Mean Difference IV, Fixed, 95% Cl	
Study Bae JH					Mean 12.7	SD		Weight 6.2%		normal reflow no-reflow Mean Difference
Bae JH		Mean	SD	Total		SD	Total		IV, Fixed, 95% CI	normal reflow no-reflow Mean Difference
Bae JH Ohshi	1 2008	Mean 9.3	SD 8.9	Total	12.7	SD 13.9	Total 45	6.2%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07]	normal reflow no-reflow Mean Difference
Bae JH Ohshi Ohshi	I 2008 ma K 2009	Mean 9.3 10.3	SD 8.9 7.6	Total 12 20	12.7 6.3	SD 13.9 5.3	Total 45 24	6.2% 16.8% 16.3%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75]	normal reflow no-reflow Mean Difference
Bae JH Ohshin Ohshin Utsun	I 2008 ma K 2009 ma K 2011 omiya M2011	Mean 9.3 10.3 9.3	SD 8.9 7.6 6	Total 12 20 19 11	12.7 6.3 11	SD 13.9 5.3 8.8	Total 45 24 34 84	6.2% 16.8% 16.3% 60.7%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47]	normal reflow no-reflow Mean Difference
Bae JH Ohshin Ohshin Utsun Total	I 2008 ma K 2009 ma K 2011	Mean 9.3 10.3 9.3 6.15	SD 8.9 7.6 6 3.2	Total 12 20 19 11 62	12.7 6.3 11 4.76	SD 13.9 5.3 8.8 4	Total 45 24 34 84	6.2% 16.8% 16.3%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30]	normal reflow no-reflow Mean Difference
Bae JH Ohshin Ohshin Utsun Total Hetero	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI)	Mean 9.3 10.3 9.3 6.15 = 5.59, c	SD 8.9 7.6 6 3.2 If = 3	Total 12 20 19 11 62 (<i>P</i> = .13	12.7 6.3 11 4.76	SD 13.9 5.3 8.8 4	Total 45 24 34 84	6.2% 16.8% 16.3% 60.7%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47]	normal reflow no-reflow Mean Difference
Bae JH Ohshin Ohshin Utsun Total Hetero	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ²	Mean 9.3 10.3 9.3 6.15 = 5.59, c	SD 8.9 7.6 6 3.2 If = 3	Total 12 20 19 11 62 (<i>P</i> = .13	12.7 6.3 11 4.76	SD 13.9 5.3 8.8 4	Total 45 24 34 84	6.2% 16.8% 16.3% 60.7%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI
Bae JH Ohshin Ohshin Utsun Total Hetero	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ²	Mean 9.3 10.3 9.3 6.15 = 5.59, c	SD 8.9 7.6 6 3.2 If = 3	Total 12 20 19 11 62 (<i>P</i> = .13	12.7 6.3 11 4.76	SD 13.9 5.3 8.8 4	Total 45 24 34 84	6.2% 16.8% 16.3% 60.7%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50
Bae JH Ohshin Ohshin Utsun Total Hetero Test fo	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² or overall effect	Mean 9.3 10.3 9.3 6.15 = 5.59, c t: Z = 1.2	SD 8.9 7.6 6 3.2 Hf = 3 20 (<i>P</i> =	Total 12 20 19 11 62 (P = .13 .23)	12.7 6.3 11 4.76 3); 1 ² = 4	SD 13.9 5.3 8.8 4 46% Refl	Total 45 24 34 84 187	6.2% 16.8% 16.3% 60.7% 100.0%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50 Favors Favors normal reflow no-reflow Mean Difference
Bae JH Ohshin Ohshin Utsun Total Hetero Test fo	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² for overall effect	Mean 9.3 10.3 9.3 6.15 = 5.59, c t: Z = 1.2	SD 8.9 7.6 6 3.2 If = 3 20 (<i>P</i> = 20 (<i>P</i> =	Total 12 20 19 11 62 (P = .13 .23) low Total	12.7 6.3 11 4.76 3); l ² = 4 Mean	SD 13.9 5.3 8.8 4 4 46% Refl SD	Total 45 24 34 84 187 ow Total	6.2% 16.8% 16.3% 60.7% 100.0% Weight	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl	normal reflow no-reflow Mean Difference IV, Fixed, 95% Cl -50 -25 0 25 50 Favors normal reflow Favors no-reflow
Bae JH Ohshin Ohshin Utsun Total Hetero Test fo Study Bae JH	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² or overall effect	Mean 9.3 10.3 9.3 6.15 = 5.59, c :: Z = 1.2 Mean 26.1	SD 8.9 7.6 6 3.2 Hf = 3 20 (P = 20 (P = No-refined SD 21	Total 12 20 19 11 62 (<i>P</i> = .13 .23) low Total 12	12.7 6.3 11 4.76 3); l ² = 4 <u>Mean</u> 28.8	SD 13.9 5.3 8.8 4 4 46% Refl SD 26	Total 45 24 34 84 187 0w Total 45	6.2% 16.8% 16.3% 60.7% 100.0% Weight 13.8%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl -2.70 [-16.80, 11.40]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50 Favors Favors normal reflow no-reflow Mean Difference
Bae JH Ohshin Ohshin Utsun Total Hetero Test fo Study Bae JH Ohshin	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² or overall effect or overall effect for Subgroup I 2008 ma K 2009	Mean 9.3 10.3 9.3 6.15 = 5.59, c t: Z = 1.2 Mean 26.1 14.1	SD 8.9 7.6 6 3.2 3.2 If = 3 20 (P = 20 (P = 5D 21 6.7	Total 12 20 19 11 62 (<i>P</i> = .13 (<i>P</i> = .13 (<i>D</i> = .13) (<i></i>	12.7 6.3 11 4.76 3); $l^2 = 2$ Mean 28.8 12	SD 13.9 5.3 8.8 4 46% Refi SD 26 7.4	Total 45 24 34 84 187 0w Total 45 24	6.2% 16.8% 16.3% 60.7% 100.0% Weight 13.8% 39.7%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl -2.70 [-16.80, 11.40] 2.10 [-2.07, 6.27]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50 Favors Favors normal reflow no-reflow Mean Difference
Bae JH Ohshin Utsun Total Hetero Test fo Study Bae JH Ohshin Ohshin	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² or overall effect or overall effect for Subgroup I 2008 ma K 2009 ma K 2011	Mean 9.3 10.3 9.3 6.15 = 5.59, c :: Z = 1.2 Mean 26.1 14.1 13.7	SD 8.9 7.6 6 3.2 3.2 if = 3 20 (P = 20 (P = 5D 21 6.7 6.7 6.7	Total 12 20 19 11 62 (<i>P</i> = .13 2.23) low Total 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 12 11 12 20 12 12 12 12 12 12 12 12 12 12	12.7 6.3 11 4.76 8); $l^2 = 2$ Mean 28.8 12 16.8	SD 13.9 5.3 8.8 4 46% Refi SD 26 7.4 10	Total 45 24 34 84 187 0w Total 45 24 34	6.2% 16.8% 16.3% 60.7% 100.0% Weight 13.8% 39.7% 38.5%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl -2.70 [-16.80, 11.40] 2.10 [-2.07, 6.27] -3.10 [-7.61, 1.41]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50 Favors Favors normal reflow no-reflow Mean Difference
Bae JH Ohshin Utsun Total Hetero Test fo Study Bae JH Ohshin Ohshin	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² or overall effect or overall effect for Subgroup I 2008 ma K 2009	Mean 9.3 10.3 9.3 6.15 = 5.59, c t: Z = 1.2 Mean 26.1 14.1	SD 8.9 7.6 6 3.2 3.2 if = 3 20 (P = 20 (P = 5D 21 6.7 6.7 6.7	Total 12 20 19 11 62 (<i>P</i> = .13 2.23) low Total 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 19 11 12 20 12 11 12 20 12 12 12 12 12 12 12 12 12 12	12.7 6.3 11 4.76 3); $l^2 = 2$ Mean 28.8 12	SD 13.9 5.3 8.8 4 46% Refi SD 26 7.4 10	Total 45 24 34 84 187 0w Total 45 24 34	6.2% 16.8% 16.3% 60.7% 100.0% Weight 13.8% 39.7% 38.5%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl -2.70 [-16.80, 11.40] 2.10 [-2.07, 6.27]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50 Favors Favors normal reflow no-reflow Mean Difference
Bae JH Ohshin Utsun Total Hetero Test fo Study Bae JH Ohshin Utsun Total	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² or overall effect or overall effect t 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI)	Mean 9.3 10.3 9.3 6.15 = 5.59, c :: Z = 1.2 Mean 26.1 14.1 13.7 43.33	SD 8.9 7.6 6 3.2 3.2 If = 3 20 (P = 20 (P = 50 21 6.7 6.7 33.5	Total 12 20 19 11 62 (P = .13 2.23) ow Total 12 20 19 11 220 19 11 62 12 12 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 62 19 11 10 10 10 10 10 10 10 10 10	12.7 6.3 11 4.76 3); $l^2 = 2$ Mean 28.8 12 16.8 20.08	SD 13.9 5.3 8.8 4 46% Reff SD 26 7.4 10 17.2	Total 45 24 34 84 187 ow Total 45 24 34 84 187	6.2% 16.8% 16.3% 60.7% 100.0% Weight 13.8% 39.7% 38.5% 7.9% 100.0%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl -2.70 [-16.80, 11.40] 2.10 [-2.07, 6.27] -3.10 [-7.61, 1.41]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50 Favors Favors normal reflow no-reflow Mean Difference
Bae JH Ohshin Utsun Total Hetero Test fo Study Bae JH Ohshin Utsun Total Hetero	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% Cl) ogeneity: Chi ² or overall effect for Subgroup I 2008 ma K 2009 ma K 2011 omiya M2011 (95% Cl) ogeneity: Tau ²	Mean 9.3 10.3 9.3 6.15 = 5.59, c :: Z = 1.2 Mean 26.1 14.1 13.7 43.33 = 20.61;	SD 8.9 7.6 6 3.2 1f = 3 20 (P = No-reff SD 21 6.7 33.5 Chi ² =	Total 12 20 19 11 62 (P = .13 2.23) low Total 12 20 19 11 12 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 19 10 10 10 10 10 10 10 10 10 10	12.7 6.3 11 4.76 3); $l^2 = 2$ Mean 28.8 12 16.8 20.08	SD 13.9 5.3 8.8 4 46% Reff SD 26 7.4 10 17.2	Total 45 24 34 84 187 ow Total 45 24 34 84 187	6.2% 16.8% 16.3% 60.7% 100.0% Weight 13.8% 39.7% 38.5% 7.9% 100.0%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl -2.70 [-16.80, 11.40] 2.10 [-2.07, 6.27] -3.10 [-7.61, 1.41] 23.25 [3.11, 43.39]	normal reflow Mean Difference IV, Fixed, 95% Cl
Bae JH Ohshin Utsun Total Hetero Test fo Study Bae JH Ohshin Utsun Total Hetero	I 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI) ogeneity: Chi ² or overall effect or overall effect t 2008 ma K 2009 ma K 2011 omiya M2011 (95% CI)	Mean 9.3 10.3 9.3 6.15 = 5.59, c :: Z = 1.2 Mean 26.1 14.1 13.7 43.33 = 20.61;	SD 8.9 7.6 6 3.2 1f = 3 20 (P = No-reff SD 21 6.7 33.5 Chi ² =	Total 12 20 19 11 62 (P = .13 2.23) low Total 12 20 19 11 12 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 2.0 19 11 62 19 10 10 10 10 10 10 10 10 10 10	12.7 6.3 11 4.76 3); $l^2 = 2$ Mean 28.8 12 16.8 20.08	SD 13.9 5.3 8.8 4 46% Reff SD 26 7.4 10 17.2	Total 45 24 34 84 187 ow Total 45 24 34 84 187	6.2% 16.8% 16.3% 60.7% 100.0% Weight 13.8% 39.7% 38.5% 7.9% 100.0%	IV, Fixed, 95% Cl -3.40 [-9.87, 3.07] 3.80 [-0.15, 7.75] -1.70 [-5.70, 2.30] 1.39 [-0.69, 3.47] 0.99 [-0.63, 2.61] Mean Difference IV, Random, 95% Cl -2.70 [-16.80, 11.40] 2.10 [-2.07, 6.27] -3.10 [-7.61, 1.41] 23.25 [3.11, 43.39]	normal reflow no-reflow Mean Difference IV, Fixed, 95% CI -50 -25 0 25 50 Favors Favors normal reflow no-reflow Mean Difference

Figure 2. Forest plot of weighted mean difference for absolute plaque component volume in the no-reflow and normal reflow groups. (A) Absolute fibrous volume comparison. (B) Absolute fibrofatty volume comparison. (C) Absolute dense calcium volume comparison. (D) Absolute necrotic core volume comparison. CI, confidence interval; IV, instrumental variable; SD, standard deviation.

		o-reflow			Reflow	_		Mean Difference	Mean Difference
Study or Subgroup	Mean		Total	Mean		Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Higashikuni Y 2008	59.6	11.2	9	68.3	10.2	40	13.8%	-8.70 [-16.67, -0.73]	-8-
Nakamura T 2007	68.3	2.1	8	67	1.5	42	20.0%	1.30 [-0.22, 2.82]	•
Ohshima K 2009	57.5	10.7	20	67.8	10.2	24	15.8%	-10.30 [-16.52, -4.08]	-8-
Ohshima K 2011	59	12.4	19	62.9	10.6	34	15.3%	-3.90 [-10.52, 2.72]	
Utsunomiya M2011	55.64	7.7	11	62.11	13.4	84	16.7%	-6.47 [-11.85, -1.09]	-@-
Zhao XY 2013	50.26	8.72	21	59.24	6.72	145	18.3%	-8.98 [-12.87, -5.09]	-
Total (95% CI)			88			369	100.0%	-5.89 [-11.12, -0.66]	♦
Heterogeneity: $Tau^2 = 3$	4.99; Chi ² =	41.68,	df = 5 (P	P < .00001)	; I ² = 88	%			-50 -25 0 25 50
Test for overall effect: Z	= 2.21 (P =	.03)							Favors Favors normal reflow no-reflo
	No	o-reflow	v		Reflow			Mean Difference	Mean Difference
Study or Subgroup	Mean	SD		Mean		Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Higashikuni Y 2008	12	9.7	9	15.5	7.1	40	10.4%	-3.50 [-10.21, 3.21]	
Nakamura T 2007	23.1	3.5	8	17	1.1	42	19.9%	6.10 [3.65, 8.55]	
Ohshima K 2009	14.5	9.6	20	10.1	3.9	24	14.9%	4.40 [-0.09, 8.89]	-
Ohshima K 2011	17.7	14.3	19	12.2	7.1	34	10.1%	5.50 [-1.36, 12.36]	
Utsunomiya M2011	6.46	1.3	11	5.71	2.1	84	22.6%	0.75 [-0.14, 1.64]	
Zhao XY 2013	15.29	2.83	21	17.9	3.21	145	22.1%	-2.61 [-3.93, -1.29]	
Total (95% CI)			88			369	100.0%	1.66 [-1.26, 4.57]	
Heterogeneity: $Tau^2 = 9$	$0.58: Chi^2 =$	47.89.0		< .00001):	$1^2 = 90\%$				
Test for overall effect: Z					,	•			-50 -25 0 25 50
rescrot overall effect. Z	- 1.11 (/ -	.27)							Favors Favors normal reflow no-reflo
	м.				D.(I			Marin D'ffammer	Mean Difference
	INC	o-reflow	v		Reflow			Mean Difference	Mean Difference
Study or Subaroun	Mean	SD	Total	Mean	SD	Total	Weight	IV Random 95% CI	
Study or Subgroup Higashikuni Y 2008	Mean 4.7	SD	Total 9	Mean 4.8	SD 3.6	Total 40	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Higashikuni Y 2008	4.7	3.3	9	4.8	3.6	40	15.7%	-0.10 [-2.53, 2.33]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007	4.7 2.6	3.3 0.6	9 8	4.8 4.8	3.6 0.6	40 42	15.7% 23.7%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009	4.7 2.6 11.8	3.3 0.6 8.9	9 8 20	4.8 4.8 7.8	3.6 0.6 5.2	40 42 24	15.7% 23.7% 8.7%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011	4.7 2.6 11.8 8.8	3.3 0.6 8.9 7.9	9 8 20 19	4.8 4.8 7.8 8.7	3.6 0.6 5.2 6.4	40 42 24 34	15.7% 23.7% 8.7% 9.4%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009	4.7 2.6 11.8	3.3 0.6 8.9	9 8 20	4.8 4.8 7.8	3.6 0.6 5.2	40 42 24	15.7% 23.7% 8.7%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013	4.7 2.6 11.8 8.8 3.09	3.3 0.6 8.9 7.9 1.5	9 8 20 19 11 21	4.8 4.8 7.8 8.7 3.45	3.6 0.6 5.2 6.4 2.8	40 42 24 34 84 145	15.7% 23.7% 8.7% 9.4% 21.8% 20.6%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI)	4.7 2.6 11.8 8.8 3.09 9.53	3.3 0.6 8.9 7.9 1.5 2.99	9 8 20 19 11 21 88	4.8 4.8 7.8 8.7 3.45 8.36	3.6 0.6 5.2 6.4 2.8 3.13	40 42 24 34 84 145 369	15.7% 23.7% 8.7% 9.4% 21.8%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² =	3.3 0.6 8.9 7.9 1.5 2.99	9 8 20 19 11 21 88	4.8 4.8 7.8 8.7 3.45 8.36	3.6 0.6 5.2 6.4 2.8 3.13	40 42 24 34 84 145 369	15.7% 23.7% 8.7% 9.4% 21.8% 20.6%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI)	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² =	3.3 0.6 8.9 7.9 1.5 2.99	9 8 20 19 11 21 88	4.8 4.8 7.8 8.7 3.45 8.36	3.6 0.6 5.2 6.4 2.8 3.13	40 42 24 34 84 145 369	15.7% 23.7% 8.7% 9.4% 21.8% 20.6%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> =	3.3 0.6 8.9 7.9 1.5 2.99 35.67, 0	9 8 20 19 11 21 88 If = 5 (P ·	4.8 4.8 7.8 8.7 3.45 8.36 < .00001);	3.6 0.6 5.2 6.4 2.8 3.13 $1^2 = 869$	40 42 24 34 84 145 369	15.7% 23.7% 8.7% 9.4% 21.8% 20.6%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62]	IV, Random, 95% Cl -50 -25 0 25 50 Favors normal reflow -50 -25 0 25 favors
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> =	3.3 0.6 8.9 7.9 1.5 2.99	9 8 20 19 11 21 88 85 1f = 5 (P ·	4.8 4.8 7.8 8.7 3.45 8.36 < .00001);	3.6 0.6 5.2 6.4 2.8 3.13 1 ² = 869 Reflow	40 42 24 34 84 145 369 %	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> = No	3.3 0.6 8.9 7.9 1.5 2.99 35.67, 0 .99)	9 8 20 19 11 21 88 85 1f = 5 (P ·	4.8 4.8 7.8 8.7 3.45 8.36 < .00001);	3.6 0.6 5.2 6.4 2.8 3.13 1 ² = 869 Reflow	40 42 24 34 84 145 369	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% Weight	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI	IV, Random, 95% Cl -50 -25 0 25 50 Favors normal reflow -50 -25 0 25 favors
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup Higashikuni Y 2008	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> = <u>Mean</u> 22.1	3.3 0.6 8.9 7.9 1.5 2.99 35.67, (.99) •-reflov SD	9 8 20 19 11 21 88 8f = 5 (<i>P</i> · V Total 9	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); <u>Mean</u> 11.7	$3.6 \\ 0.6 \\ 5.2 \\ 6.4 \\ 2.8 \\ 3.13 \\ l^2 = 869 \\ Reflow \\ SD \\ 7.9 \\ \hline$	40 42 24 34 84 145 369 6 Total 40	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% Weight 14.9%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> = <u>Mean</u> 22.1 6.3	3.3 0.6 8.9 7.9 1.5 2.99 35.67, 0 .99) 5-reflov SD 9.3 1	9 8 20 19 11 21 88 85 1f = 5 (P V Total 9 8	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); <u>Mean</u> 11.7 11.2	3.6 0.6 5.2 6.4 2.8 3.13 I2 = 869 Reflow SD 7.9 1.2	40 42 24 34 84 145 369 6 Total 40 42	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% Weight 14.9% 18.2%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95] -4.90 [-5.68, -4.12]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> = Note Mean 22.1 6.3 15.8	3.3 0.6 8.9 7.9 1.5 2.99 35.67, 0 .99) 5-reflow SD 9.3 1 7.4	9 8 20 19 11 21 88 85 1f = 5 (P V Total 9 8 20	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); Mean 11.7 11.2 14.3	$3.60.65.26.42.83.13l^2 = 869ReflowSD7.91.26.7$	40 42 24 34 84 145 369 6 Total 40 42 24	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% Weight 14.9% 18.2% 16.7%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95] -4.90 [-5.68, -4.12] 1.50 [-2.71, 5.71]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> = No <u>Mean</u> 22.1 6.3 15.8 14.5	3.3 0.6 8.9 7.9 1.5 2.99 35.67, 0 .99) 5-reflow SD 9.3 1 7.4 8.5	9 8 20 19 11 21 88 85 5 (P V Total 9 8 20 19	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); Mean 11.7 11.2 14.3 16.2	3.6 0.6 5.2 6.4 2.8 3.13 I2 = 869 Reflow SD 7.9 1.2 6.7 7.2	40 42 24 34 84 145 369 6 Total 40 42 24 34	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% 100.0% Weight 14.9% 18.2% 16.7% 16.5%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95] -4.90 [-5.68, -4.12] 1.50 [-2.71, 5.71] -1.70 [-6.22, 2.82]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (<i>P</i> = Note Mean 22.1 6.3 15.8	3.3 0.6 8.9 7.9 1.5 2.99 35.67, 0 .99) 5-reflov SD 9.3 1 7.4 8.5 5.1	9 8 20 19 11 21 88 85 1f = 5 (P V Total 9 8 20	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); Mean 11.7 11.2 14.3	$3.60.65.26.42.83.13l^2 = 869ReflowSD7.91.26.7$	40 42 24 34 84 145 369 6 Total 40 42 24	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% Weight 14.9% 18.2% 16.7%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95] -4.90 [-5.68, -4.12] 1.50 [-2.71, 5.71]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (P = No Mean 22.1 6.3 15.8 14.5 19.73	3.3 0.6 8.9 7.9 1.5 2.99 35.67, 0 .99) 5-reflov SD 9.3 1 7.4 8.5 5.1	9 8 20 19 11 21 88 8f = 5 (<i>P</i> · · Y Total 9 8 20 19 11 21	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); Mean 11.7 11.2 14.3 16.2 14.56	3.6 0.6 5.2 6.4 2.8 3.13 I2 = 869 Reflow SD 7.9 1.2 6.7 7.2 8.3	40 42 24 34 84 145 369 6 Total 40 42 24 34 84 145	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% 100.0% Weight 14.9% 18.2% 16.7% 16.5% 17.1% 16.6%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95] -4.90 [-5.68, -4.12] 1.50 [-2.71, 5.71] -1.70 [-6.22, 2.82] 5.17 [1.67, 8.67] 10.42 [6.03, 14.81]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI)	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (P = No Mean 22.1 6.3 15.8 14.5 19.73 24.92	3.3 0.6 8.9 7.9 1.5 2.99 35.67, (.99) 5-reflov 5D 9.3 1 7.4 8.5 5.1 10.04	9 8 20 19 11 21 88 df = 5 (<i>P</i> · · V Total 9 8 20 19 11 21 88	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); (Mean 11.7 11.2 14.3 16.2 14.56 14.5	3.6 0.6 5.2 6.4 2.8 3.13 l2 = 869 Reflow SD 7.9 1.2 6.7 7.2 8.3 5.48	40 42 24 34 84 145 369 6 Total 40 42 24 34 84 145 369	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% 100.0% Weight 14.9% 18.2% 16.7% 16.5% 17.1%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95] -4.90 [-5.68, -4.12] 1.50 [-2.71, 5.71] -1.70 [-6.22, 2.82] 5.17 [1.67, 8.67]	IV, Random, 95% Cl
Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013 Total (95% CI) Heterogeneity: Tau ² = 2 Test for overall effect: Z Study or Subgroup Higashikuni Y 2008 Nakamura T 2007 Ohshima K 2009 Ohshima K 2011 Utsunomiya M2011 Zhao XY 2013	4.7 2.6 11.8 8.8 3.09 9.53 2.89; Chi ² = = 0.02 (P = Note Mean 22.1 6.3 15.8 14.5 19.73 24.92 i0.34; Chi ² =	3.3 0.6 8.9 7.9 1.5 2.99 35.67, (.99) 9.3 5. 7.4 8.5 5.1 10.04	9 8 20 19 11 21 88 df = 5 (<i>P</i> · · V Total 9 8 20 19 11 21 88	4.8 4.8 7.8 8.7 3.45 8.36 < .00001); (Mean 11.7 11.2 14.3 16.2 14.56 14.5	3.6 0.6 5.2 6.4 2.8 3.13 l2 = 869 Reflow SD 7.9 1.2 6.7 7.2 8.3 5.48	40 42 24 34 84 145 369 6 Total 40 42 24 34 84 145 369	15.7% 23.7% 8.7% 9.4% 21.8% 20.6% 100.0% 100.0% Weight 14.9% 18.2% 16.7% 16.5% 17.1% 16.6%	-0.10 [-2.53, 2.33] -2.20 [-2.65, -1.75] 4.00 [-0.42, 8.42] 0.10 [-4.05, 4.25] -0.36 [-1.43, 0.71] 1.17 [-0.21, 2.55] - 0.02 [-1.65, 1.62] Mean Difference IV, Random, 95% CI 10.40 [3.85 16.95] -4.90 [-5.68, -4.12] 1.50 [-2.71, 5.71] -1.70 [-6.22, 2.82] 5.17 [1.67, 8.67] 10.42 [6.03, 14.81]	IV, Random, 95% Cl

Figure 3. Forest plot of weighted mean difference for percentage of plaque composition in the no-reflow and normal reflow groups. (A) Fibrous percentage comparison. (B) Fibrofatty percentage comparison. (C) Dense calcium percentage comparison. (D) Necrotic core percentage comparison. CI, confidence interval; IV, instrumental variable; SD, standard deviation.

analysis of the EEM-CSA, including 452 patients. As shown in Figure 4A, culprit lesions EEM-CSA of the no-reflow group were larger than in the normal reflow group (WMD, 3.40 mm²; 95% CI, 2.22-4.58; P < .00001). However, lumen CSA was not different between the two groups (Figure 4B). No evidence of statistical heterogeneity was identified (I² = 0%). Influence analysis demonstrated that no single study significantly altered the summary estimates.

The Plaque Area and Plaque Burden Findings. Data for

St	udy or Subgroup		lo-ref SD	low Total	Mean	Refl SD		Weight	Mean Difference IV. Fixed, 95% CI	Mean Difference IV. Fixed, 95% Cl
En	ndo M 2010	17.4	4.6	30	14.6	3.9	140	44.4%	2.80 [1.03, 4.57]	
Н	ong YJ 2009	16.2	4.7	17	13.4	4.6	95	23.8%	2.80 [0.38, 5.22]	•
Ka	atayama T 2006	20.1	6.5	12	16.4	4.3	58	9.4%	3.70 [-0.14, 7.54]	
Та	inaka A 2002	18.4	4.3	13	13.3	4.1	87	22.4%	5.10 [2.61, 7.59]	
He	otal (95% CI) eterogeneity: Chi ² =)%	380	100.0%	3.40 [2.22, 4.58]	
Те	est for overall effect:	: Z = 5.6	65 (P =	• .00001)					-50 -25 0 25 50 Favors normal reflow Favors no-reflov
			lo-ref	low		Refl	014/		Mean Difference	Mean Difference
St	udy or Subgroup			Total	Mean			Weight	IV. Fixed, 95% CI	IV. Fixed, 95% CI
En	ndo M 2010	2.3	0.7	30	2.4	1	140	77.2%	-0.10 [-0.40, 0.20]	
Н	ong YJ 2009	2.7	1.5	17	2.6	1.2	95	12.3%	0.10 [-0.65, 0.85]	
Та	inaka A 2002	2.2	1.4	13	2.3	1.4	87	10.5%	-0.10 [-0.92, 0.72]	+
То	otal (95% CI)			60			322	100.0%	-0.08 [-0.34, 0.19]	
He	eterogeneity: Chi ² =	= 0.24, d	lf = 2	(P = .89	9); I ² = (0%				-10 -5 0 5 10
Te	est for overall effect:	: Z = 0.5	6 (P =	.58)						Favors normal reflow Favors no-reflov
		N	lo-ref	low		Refle	ow		Mean Difference	Mean Difference
_	ae IH 2008	Mean	SD	Total		SD	Total	Weight	IV, Fixed, 95% CI	
Ba	ae JH 2008	Mean 16.2	SD 5.4	Total	12.5	SD 4.9	Total 45	29.1%	IV, Fixed, 95% Cl 3.70 [0.33, 7.07]	
Ba Iiji	ae JH 2008 ima R 2006	Mean	SD	Total		SD	Total		IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17]	
Ba liji Ka	ae JH 2008 ima R 2006 atayama T 2006	Mean 16.2 18.7	SD 5.4 5.3	Total 12 20 12	12.5 14	SD 4.9 6	Total 45 200 58	29.1% 54.5% 16.4%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09]	
Ba liji Ka To	ae JH 2008 ima R 2006 atayama T 2006 otal (95% CI)	Mean 16.2 18.7 16	SD 5.4 5.3 7.7	Total 12 20 12 44	12.5 14 13.4	SD 4.9 6 4.3	Total 45 200 58	29.1% 54.5%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17]	
Ba liji Ka To He	ne JH 2008 ima R 2006 atayama T 2006 otal (95% CI) eterogeneity: Chi ² =	Mean 16.2 18.7 16 = 0.71, d	SD 5.4 5.3 7.7	Total 12 20 12 44 (<i>P</i> = .70	12.5 14 13.4)); I ² = (SD 4.9 6 4.3	Total 45 200 58	29.1% 54.5% 16.4%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09]	
Ba liji Ka To He	ae JH 2008 ima R 2006 atayama T 2006 otal (95% CI)	Mean 16.2 18.7 16 = 0.71, d	SD 5.4 5.3 7.7	Total 12 20 12 44 (<i>P</i> = .70	12.5 14 13.4)); I ² = (SD 4.9 6 4.3	Total 45 200 58	29.1% 54.5% 16.4%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09]	IV, Fixed, 95% Cl □ □ □ □ □ □ □ □ □ □ □ □ □
— Ba Iiji Ka To He Te	ne JH 2008 ima R 2006 atayama T 2006 otal (95% CI) eterogeneity: Chi ² =	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3	SD 5.4 5.3 7.7 If = 2 87 (<i>P</i> <	Total 12 20 12 44 (<i>P</i> = .70 (2.0001)	12.5 14 13.4)); I ² = (SD 4.9 6 4.3 0% Refle	Total 45 200 58 303	29.1% 54.5% 16.4% 100.0%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09]	IV, Fixed, 95% CI □ □ -50 -25 0 25 50
Ba liji Ka To He St	ae JH 2008 ima R 2006 atayama T 2006 otal (95% CI) eterogeneity: Chi ² = est for overall effect:	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3	SD 5.4 5.3 7.7 If = 2 87 (<i>P</i> <	Total 12 20 12 44 (<i>P</i> = .70 (0001)	12.5 14 13.4)); I ² = (SD 4.9 6 4.3 0% Refle	Total 45 200 58 303	29.1% 54.5% 16.4% 100.0%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09] 4.06 [2.24, 5.89] Mean Difference	IV, Fixed, 95% Cl
Baa liji Kaa Too He Te St	ae JH 2008 ima R 2006 atayama T 2006 otal (95% Cl) eterogeneity: Chi ² = est for overall effect:	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3 Mean 79.4 68.7	SD 5.4 5.3 7.7 67 (<i>P</i> < SD 7.2 9.1	Total 12 20 12 44 (P = .70 4.0001) low Total	12.5 14 13.4)); 1 ² = (<u>Mean</u> 73.9	SD 4.9 6 4.3 0% Refl SD	Total 45 200 58 303	29.1% 54.5% 16.4% 100.0% Weight	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09] 4.06 [2.24, 5.89] Mean Difference IV, Random, 95% CI	IV, Fixed, 95% Cl
Ba liji Ka To He Te St Ba Hi	ae JH 2008 ima R 2006 atayama T 2006 otal (95% CI) eterogeneity: Chi ² = est for overall effect: cudy or Subgroup	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3 Mean 79.4 68.7	SD 5.4 5.3 7.7 If = 2 67 (<i>P</i> < No-ref SD 7.2	Total 12 20 12 44 (P = .70 (.0001) low Total 12	12.5 14 13.4)); 1 ² = (<u>Mean</u> 73.9	SD 4.9 6 4.3 0% Refl SD 9.5	Total 45 200 58 303 ow Total 45	29.1% 54.5% 16.4% 100.0% Weight 10.1%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09] 4.06 [2.24, 5.89] Mean Difference IV, Random, 95% CI 5.50 [0.57, 10.43]	IV, Fixed, 95% Cl
Baa liji Kaa Too He Te Baa Hi Ho	ae JH 2008 ima R 2006 atayama T 2006 otal (95% Cl) eterogeneity: Chi ² = est for overall effect: cudy or Subgroup ae JH 2008 igashikuni Y 2008	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3 Mean 79.4 68.7	SD 5.4 5.3 7.7 67 (<i>P</i> < SD 7.2 9.1	Total 12 20 12 44 (P = .70 0001) low Total 12 9	12.5 14 13.4)); l ² = (Mean 73.9 63.7 79.4 76.9	SD 4.9 6 4.3 0% Refl SD 9.5 10.7 9 55.4	Total 45 200 58 303 303 00W Total 45 40	29.1% 54.5% 16.4% 100.0% Weight 10.1% 6.3%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09] 4.06 [2.24, 5.89] Mean Difference IV, Random, 95% CI 5.50 [0.57, 10.43] 5.00 [-1.81, 11.81] 2.60 [-3.11, 8.31] -6.50 [-15.50, 2.50]	IV, Fixed, 95% Cl
Baa liji Ka To Ho Te St Baa Hi Ho Ho	ae JH 2008 ima R 2006 atayama T 2006 otal (95% Cl) eterogeneity: Chi ² = est for overall effect: audy or Subgroup ae JH 2008 igashikuni Y 2008 ong YJ 2009	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3 Mean 79.4 68.7 82 70.4	SD 5.4 5.3 7.7 i f = 2 (i 5.7 (<i>P</i> < i i i i f = 2 (i 5.7 (<i>P</i> < i i f = 2 (i 5.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.7 i 7.2 i 9.1 i 1.1.4	Total 12 20 12 44 (<i>P</i> = .7(.0001) low Total 12 9 17	12.5 14 13.4)); $l^2 = 0$ Mean 73.9 63.7 79.4	SD 4.9 6 4.3 0% Refl SD 9.5 10.7 9 55.4	Total 45 200 58 303 00W Total 45 40 95	29.1% 54.5% 16.4% 100.0% Weight 10.1% 6.3% 8.2% 4.0% 30.1%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09] 4.06 [2.24, 5.89] Mean Difference IV, Random, 95% CI 5.50 [0.57, 10.43] 5.00 [-1.81, 11.81] 2.60 [-3.11, 8.31] -6.50 [-15.50, 2.50] 0.07 [0.05, 0.09]	IV, Fixed, 95% Cl
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Baa Hiji Ka To Baa Hi Ho Hiji Ka Ol Ut	ae JH 2008 ima R 2006 atayama T 2006 otal (95% Cl) eterogeneity: Chi ² = est for overall effect: cudy or Subgroup ae JH 2008 igashikuni Y 2008 ong YJ 2009 ong YJ 2011 ima R 2006 atayama T 2006 hshima K 2009 tsunomiya M 2011 otal (95% Cl)	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3 Mean 79.4 68.7 82 70.4 0.9 85.3 60.7 79.26	SD 5.4 5.3 7.7 7 C P C C C C C C C C C C	Total 12 20 12 44 (<i>P</i> = .7(.0001) low Total 12 9 17 24 20 12 9 17 24 20 12 12 12 12 12 12 12 12 12 12	12.5 14 13.4)); $l^2 = 0$ Mean 73.9 63.7 79.4 76.9 0.83 82.9 59.3 82.83	SD 4.9 6 4.3 0% Refl SD 9.5 10.7 9 55.4 0.08 4.8 7.4 5.53	Total 45 200 58 303 303 45 40 95 166 200 58 24 84 24 84 712	29.1% 54.5% 16.4% 100.0% Weight 10.1% 6.3% 8.2% 4.0% 30.1% 16.9% 12.2% 12.2%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09] 4.06 [2.24, 5.89] Mean Difference IV, Random, 95% CI 5.50 [0.57, 10.43] 5.00 [-1.81, 11.81] 2.60 [-3.11, 8.31] -6.50 [-15.50, 2.50] 0.07 [0.05, 0.09] 2.40 [-0.69, 5.49] 1.40 [-2.83, 5.63]	IV, Fixed, 95% Cl
Baa Hiji Ka To Baa Hi Ho Hiji Ka Ol Ut	ae JH 2008 ima R 2006 atayama T 2006 otal (95% Cl) eterogeneity: Chi ² = est for overall effect: audy or Subgroup ae JH 2008 igashikuni Y 2008 ong YJ 2009 ong YJ 2011 ima R 2006 atayama T 2006 hshima K 2009 tsunomiya M 2011	Mean 16.2 18.7 16 = 0.71, d : Z = 4.3 Mean 79.4 68.7 82 70.4 0.9 85.3 60.7 79.26	SD 5.4 5.3 7.7 7 C P C C C C C C C C C C	Total 12 20 12 44 (<i>P</i> = .7(.0001) low Total 12 9 17 24 20 12 9 17 24 20 12 12 12 12 12 12 12 12 12 12	12.5 14 13.4)); $l^2 = 0$ Mean 73.9 63.7 79.4 76.9 0.83 82.9 59.3 82.83	SD 4.9 6 4.3 0% Refl SD 9.5 10.7 9 55.4 0.08 4.8 7.4 5.53	Total 45 200 58 303 303 45 40 95 166 200 58 24 84 24 84 712	29.1% 54.5% 16.4% 100.0% Weight 10.1% 6.3% 8.2% 4.0% 30.1% 16.9% 12.2% 12.2%	IV, Fixed, 95% CI 3.70 [0.33, 7.07] 4.70 [2.23, 7.17] 2.60 [-1.89, 7.09] 4.06 [2.24, 5.89] Mean Difference IV, Random, 95% CI 5.50 [0.57, 10.43] 5.00 [-1.81, 11.81] 2.60 [-3.11, 8.31] -6.50 [-15.50, 2.50] 0.07 [0.05, 0.09] 2.40 [-0.69, 5.49] 1.40 [-2.83, 5.63] -3.57 [-7.80, 0.66]	IV, Fixed, 95% Cl

Figure 4. Forest plot of weighted mean difference for the entire culprit lesion analysis in the no-reflow and normal reflow groups. (A) External elastic membrane crosssectional area comparison. (B) Lumen cross-sectional area comparison. (C) Plaque area comparison. (D) Plaque burden comparison. (E) Coronary artery remodeling index comparison. CI, confidence interval; IV, instrumental variable; SD, standard deviation.

	1	lo-ref	ow		Refle	w		Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% Cl
Bae JH 2008	1.1	0.17	12	0.99	0.16	45	13.3%	0.11 [0.00, 0.22]	- e -
Endo M 2010	1.11	0.23	30	1.07	0.23	140	18.5%	0.04 [-0.05, 0.13]	
Higashikuni Y 2008	1.2	0.26	9	1.03	0.22	40	4.5%	0.17 [-0.01, 0.35]	
Hong YJ 2009	1.14	0.17	17	1.03	0.2	95	18.7%	0.11 [0.02, 0.20]	-8-
Hong YJ 2011	1.05	0.38	24	1.02	0.23	166	6.2%	0.03 [-0.13, 0.19]	
lijima R 2006	1.2	0.2	20	1.1	0.3	200	16.2%	0.10 [0.00, 0.20]	
Katayama T 2006	1.06	0.21	12	0.98	0.19	58	9.2%	0.08 [-0.05, 0.21]	+
Ohshima K 2009	1.26	0.17	20	1.12	0.19	24	13.4%	0.14 [0.03, 0.25]	
Total (95% CI)			144			768	100.0%	0.09 [0.06, 0.13]	•
Heterogeneity: Chi ²	= 3.65, c	lf = 7	(<i>P</i> = .82	2); I ² = (0%				
Test for overall effect	: Z = 4.7	75 (P <	.00001)					-1-0.500.5Favors normal reflowFavors no-reflow

Figure 4. (Continued)

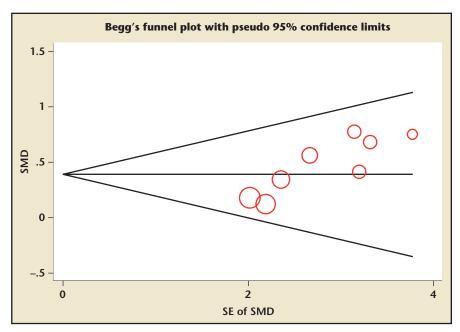


Figure 5. Funnel plots of the remodeling index for assessment of publication bias. SE, standard error; SMD, standardized mean difference.

plaque area were available from three studies^{8,10,16} including 347 patients, and are shown in Figure 4C. Overall, plaque area was significantly greater in the no-reflow group compared with the normal reflow group (WMD, 4.06 mm²; 95% CI, 2.24-5.89; P < .0001). A total of 837 patients were included in eight studies^{8,10,11,16-18,21,22} reporting plaque burden. There was no significant difference between the two groups (WMD, 0.99%; 95% CI, -0.93-2.91; P = .31) (Figure 4D). On sensitivity analyses, the results remained unchanged by omitting one study at a time. **Coronary Artery Remodeling Index Findings.** A total of 912 patients were included in eight studies^{8,10,11,16-19,21} reporting coronary artery remodeling index. It was significantly greater in the noreflow group compared with the normal reflow group (WMD, 0.09; 95% CI, 0.06-0.13; P < .00001) (Figure 4E). There was no evidence of heterogeneity (P = .82, $I^2 = 0\%$). Sensitivity analysis indicated that the results of the meta-analysis were reliable and stable.

Publication Bias Diagnostics

Because the coronary artery remodeling index comes from eight studies, funnel plots were performed for remodeling index data. The funnel plot did not show an asymmetric pattern (Figure 5).

Discussion

The present meta-analysis based on currently available published observational studies demonstrates that, among IVUS measurement parameters, absolute volume of fibrofatty plaque, EEM-CSA, plaque area, and coronary artery remodeling index in culprit lesions are significantly greater in patients with no-reflow after PCI compared with patients with normal reflow. However, the percentage of the fibrous plaque was significantly smaller in the patients with no-reflow.

The no-reflow phenomenon has been recognized as an uncommon complication after after PCI. Tanaka and associates¹⁰ demonstrated that lesion EEM-CSA, not lumen CSA, are independent predictive factors of no-reflow after reperfusion in patients with acute MI. In addition, our study is in accordance with previous studies,⁹ showing larger plaque volume (high fibrofatty plaque and plaque area) in the

[The no-reflow phenomenon] is a complex phenomenon and is caused by the variable combination of four pathogenetic components: distal atherothrombotic embolization, ischemic injury, reperfusion injury, and susceptibility of coronary microcirculation to injury.

reperfusion therapy (mechanical or thrombolytic) for acute MI and after PCI. It is a complex phenomenon and is caused by the variable combination of four pathogenetic components: distal atherothrombotic embolization, ischemic injury, reperfusion injury, no-reflow group. The fibrofatty plaque is also known as lipidrich plaque, which is associated with positive vascular remodeling via matrix metalloproteinase production.²⁶ With regard to the coronary artery remodeling index detected by IVUS in patients with

With regard to the coronary artery remodeling index detected by IVUS in patients with ACS, previous clinical studies have shown that preintervention findings, including remodeling index, are predictable risk factors for the angiographic no-reflow phenomenon.

and susceptibility of coronary microcirculation to injury.²⁴ As a consequence, early identification of a potent mechanism may prevent the occurrence of no-reflow.

The present study adds to the current literature confirming that plaque composition coronary culprit/target lesions based of on IVUS analysis is closely related to the development of impaired myocardial perfusion following primary angioplasty, which suggests the importance of evaluation of plaque volume and composition by IVUS prior to mechanical therapy.²⁵ Our data support most previous observations of an association between the culprit plaque composition and subsequent no-reflow phenomenon ACS, previous clinical studies have shown that preintervention findings, including remodeling index, are predictable risk factors for the angiographic no-reflow phenomenon.²⁷ In our analysis, we noted patients with the no-reflow phenomenon had a smaller percentage of fibrous component in culprit plaques. Our study is in line with previously published data.¹¹

The present meta-analysis has several features that distinguish it from a similar meta-analysis.^{28,29} First, to limit bias in the selection of included studies, we used only patients with no-reflow or slowreflow phenomenon. Second, compared with meta-analysis by Jang and associates,²⁸ we included two additional observational studies.^{22,23} Third, compared with meta-analysis based on 10 studies by Ding and colleagues,²⁹ 14 studies were included in our pooled analysis. In our meta-analysis, we also analyzed IVUS measurement parameters such as EEM-CSA, lumen CSA, plaque area, plaque burden, and remodeling index, except for the absolute volume and percentage of four different plaque compositions.

Study Limitations

There are limitations to the present study. First, 14 studies included in our meta-analysis were observational studies. The potential effects of selection bias and confounding must be considered when interpreting their results. Second, some heterogeneity was observed among the included studies, which was due primarily to the design of the included trials (most were not randomized controlled trials), IVUS measurements were not usually reported uniformly in the individual studies, and the patient characteristics. Third, not all studies included in our review reported complete IVUS data concerning the no-reflow phenomenon.

Conclusions

Our pooled analysis showed that high absolute volume of fibrofatty plaque, EEM-CSA, plaque area, coronary artery remodeling index, and decreased percentage of fibrous plaque in culprit lesions are linked with the patients with no-reflow after PCI.

The authors declare no real or apparent conflicts of interest. This work was supported by China Postdoctoral Science Foundation Research Funds (Grant No: 2013M540468), The Natural Science Foundation of Jiangsu Province (Grant No: BK20141137), and Jiangsu Planned Projects for Postdoctoral Research Funds (Grant No: 1302169C). We also thank Mr. Jurgen M.R. Ligthart (senior technician, Department of Interventional Cardiology, Thoraxcenter, Erasmus University Medical Center, The Netherlands) for providing the IVUS image.

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MAIN POINTS

- The "no-reflow" phenomenon refers to the inability to reperfuse myocardial tissue despite the reopening of the infarct-related artery. No-reflow often happens in acute myocardial infarction patients during primary percutaneous coronary intervention (PCI), which has a strong negative impact on clinical outcome, negating the potential benefit of primary PCI. No-reflow is associated with a higher rate of mortality and early postinfarction complications.
- Meta-analysis based on currently available published observational studies demonstrates that, among
 intravascular ultrasound (IVUS) measurement parameters, absolute volume of fibrofatty plaque, external
 elastic membrane cross-sectional area, plaque area, and coronary artery remodeling index in culprit lesions are
 significantly greater in patients with no-reflow after PCI compared with patients with normal reflow; however, the
 percentage of the fibrous plaque was significantly smaller in the patients with no-reflow.
- Coronary plaque composition of culprit/target lesions based on IVUS analysis is closely related to the development of impaired myocardial perfusion following primary angioplasty, which suggests the importance of evaluation of plaque volume and composition by IVUS prior to mechanical therapy.