

Impact of attenuated plaques on TIMI grade flow and clinical outcomes of coronary artery disease patients: a systematic review and meta analysis

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Background: Plaques with a large necrotic core or lipid pool and thin-cap fibroatheroma manifest as attenuated plaques on intravascular ultrasound (IVUS). Their impact on TIMI grade flow and clinical outcomes remains undefined. We performed a systematic review and meta-analysis to summarize the association between attenuated plaque and distal embolization and clinical outcomes of coronary artery disease (CAD) from pooled data of published eligible cohort studies.

Methods: We searched the literature on TIMI grade flow and clinical outcomes on PubMed, Ovid, EMBASE, the Cochrane Library, CNKI and WanFang databases. Study heterogeneity and publication bias were estimated.

Results: A total of 3,833 patients were enrolled in nine studies. Five studies investigated TIMI grade flow and attenuated plaques. They revealed no difference in TIMI grade flow before percutaneous coronary intervention (PCI) between the attenuated and non-attenuated plaque group (RR =1.25; 95% CI: 0.65 to 2.41; P=0.50). After balloon dilation and stent implantation, the incidence of TIMI 0~2 grade flow in the attenuated plaque group was statistically significant higher than that of the non-attenuated plaque group (RR =4.73; 95% CI: 3.03 to 7.40; P<0.001). Five other studies investigated major cardiovascular events (MACEs) and attenuated plaques and found no difference in MACE rates within three years of follow up.

Conclusions: Our study presents the evidence that plaque with ultrasound signal attenuation would induce slow/no reflow phenomenon and distal embolization during PCI, but this appearance has no impact on MACE rates within three years.

Keywords: Attenuated plaque, intravascular ultrasound (IVUS); meta-analysis; coronary artery disease (CAD); distal embolization; major adverse cardiac events (MACE)

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Introduction

Cardiovascular disease is the first and foremost cause of preventable death globally (1). The National Health and Nutrition Examination Survey (NHANES) estimated that 17,600 000 Americans >20 years of age had coronary artery disease (CAD) in 2003 to 2006 (2). Percutaneous coronary intervention (PCI) and pharmacologic therapies have improved the prognosis of CAD patients (2,3) and utilization of intravascular ultrasound (IVUS) has further contributed to reducing the incidence of stent thrombosis and management of stent underexpansion (4). These improvements led 15% decrease in cardiac deaths of CAD patients from 2000 to 2006 (2). Despite the remarkable progress, the picture still remains grim as 3.6% of US adults suffered from myocardial infarction (MI) from 2003 to 2006 (2).

Plaque rupture and subsequent thrombogenesis induce acute coronary syndrome (ACS) (3,5). Unfortunately, the underlying mechanisms and predictors of plaque rupture are unclear. Pathological studies have shown that the most common cause of MI and cardiac death is thrombotic coronary occlusion after rupture of a lipid-rich atheroma with only a thin fibrous layer of intimal tissue covering the necrotic core, the so-called thickening, thin-cap fibroatheromas (TCFA) (5,6). The PROSPECT study (7) demonstrated that major adverse cardiovascular events (MACEs) are attributed to TCFA with a large plaque burden and/or a small luminal area on gray-scale intravascular ultrasonography (IVUS). On IVUS, attenuated plaques manifest as echo attenuation behind lesion sites in the absence of dense calcification in ACS patients (*Figure 1*). When they are found during coronary intervention, patients are more likely to experience induced coronary microembolism and slow/no reflow phenomenon (8). Several studies have reported that attenuated plaques impact on thrombolysis in myocardial infarction (TIMI) grade flow and portend an adverse prognosis (9-19).

The incidence rate of slow/no reflow (TIMI flow grade 0-2) during PCI was reported to be between 15% and 26% (16,20). Tanaka *et al.* (9) confirmed that coronary microembolization as a result of PCI-induced plaque rupture caused no reflow phenomenon and the entry of the lipid pool into the final microcirculation. According to the modified American Heart Association (AHA) histological classification based on a large series of post-mortem human coronary specimens, IVUS attenuated plaque represents either a fibroatheroma containing a large necrotic core

or pathological intimal thickening with a large lipid pool, which conforms to the morphology of vulnerable plaques that would induce slower TIMI grade flow.

Despite the significant implications of plaque rupture and subsequent thrombogenesis for ACS development, there has been no systemic review of the impact of attenuated plaques on TIMI grade and clinical outcomes of CAD patients. In the present study, we performed a meta-analysis and systematic review of the relationship between attenuated plaques detected by IVUS and the incidence of slow/no reflows during PCI and the clinical outcomes of CAD or ACS patients from pooled data of published eligible cohort studies.

Materials and methods

Sources and search strategy

We searched literature published from January, 2000 to June, 2015 on PubMed, Ovid, EMBASE, the Cochrane Library, CNKI and WanFang databases. The following keywords were used for the search: Attenuated Plaque, Attenuation Plaque, Attenuated, Attenuation, Acute Coronary Syndrome, Angina, Stable Angina, Coronary Disease, Coronary Artery Disease, IVUS, and Intravascular Ultrasound. We further searched the reference lists of all eligible studies, relevant review articles and previous meta-analyses. This meta analysis was carried out in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta Analyses) guidelines (10).

Eligibility criteria

The literature was exclusively limited to cohort studies on CAD patients who received IVUS during PCI. Any of the following efficacy outcomes was required: (I) the incidence of slow/no reflow during PCI of CAD patients with positive or negative attenuated plaques as detected by IVUS; and (II) major adverse cardiac events (MACE), including all-cause death, MI, and TVR. Fully duplicate studies were eliminated using Notexpress software and manual confirmation. Studies that failed to present original data or only provide confounding comparisons were also eliminated. Two investigators (Ruofei Jia and Lianmei Pu) performed the search independently and without language restriction. One investigator (Ruofei Jia) determined whether studies met the inclusion criteria.

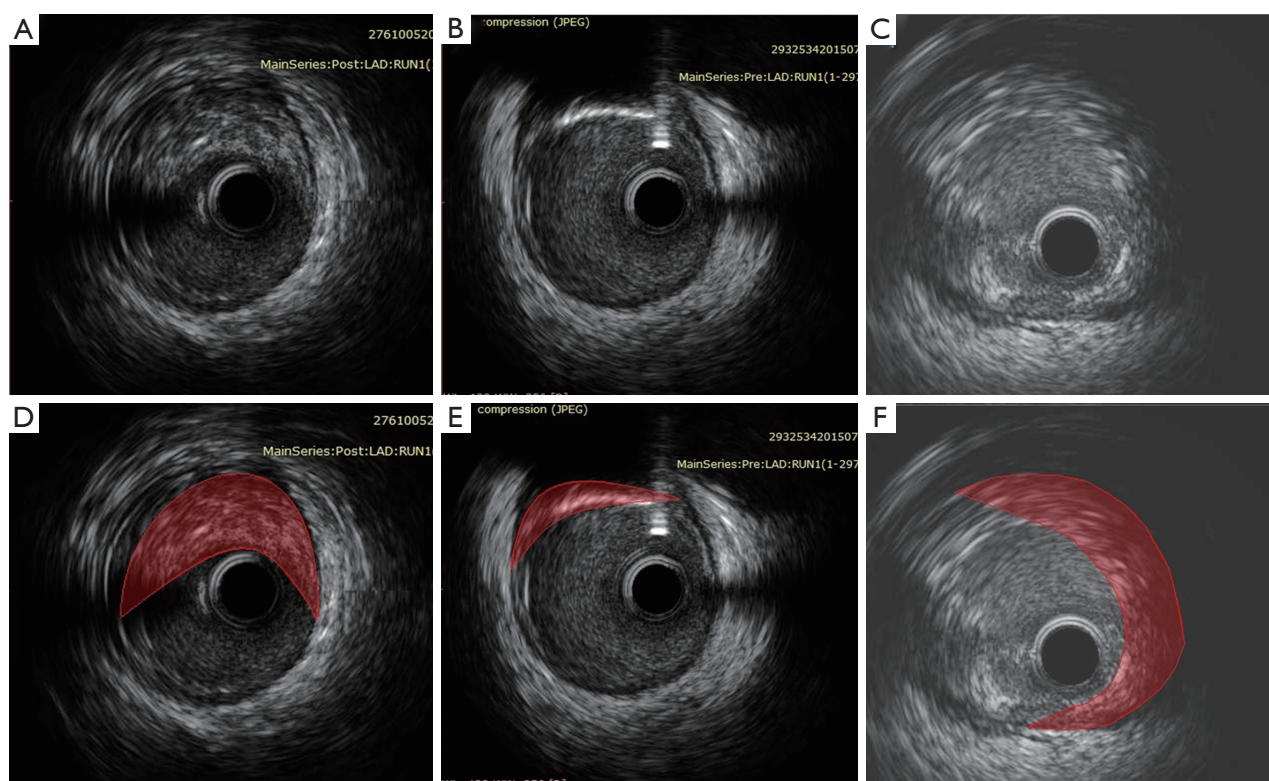


Figure 1 Plaque morphology detected by IVUS. (A,B) Fibrous plaque without signal attenuated; (C,D) calcified plaque with signal attenuated; (E,F) attenuated plaque with signal attenuated.

Study selection

Titles and abstracts obtained from the above databases were independently evaluated by two reviewers (Ruofei Jia and Lianmei Pu) in order to assess the contents of potentially eligible studies. All articles satisfying the criteria were included. Disagreements were discussed by the two reviewers to reach a consensus; if disagreement was still unresolved, a third reviewer (Zening Jin) was consulted. Un-weighted κ statistics was applied to assess agreement between the two reviewers. The quality of studies was evaluated using the cohort Newcastle-Ottawa Scale, which calculates the total scores and assess the bias risk based on the selection, comparability, and outcome items.

Data extraction

Two investigators (Ruofei Jia and Lianmei Pu) independently extracted the data and transferred it into Microsoft Excel 2007 without interposing each other until both of their tasks were completed. Information on participant characteristics such as age and gender, study

design, and primary efficacy outcomes was extracted. After independent data extraction, the two investigators consulted each other to identify disagreement and to reach consensus by discussion. Any disagreement still existing was verified by Zening Jin. Missing data was supplemented by contacting the authors or from the data of previous meta analysis.

Statistical analysis

The original data from the eligible studies was imported from Microsoft Excel 2007 into the Stata system and Winbugs system for subsequent analysis. Traditional meta analysis was done with the aid of Stata software. The primary outcomes measured were relative risk (RR) and 95% confidence interval (95% CI) of developing TIMI in patients who had attenuated plaque. For each study, we calculated their RR and the corresponding 95% CI. The pooled RR with 95% CI was summarized to represent the total effect. To measure the outcome, we used Inverse-Variance random effect model (REM). Heterogeneity between studies, which was analyzed by two techniques:

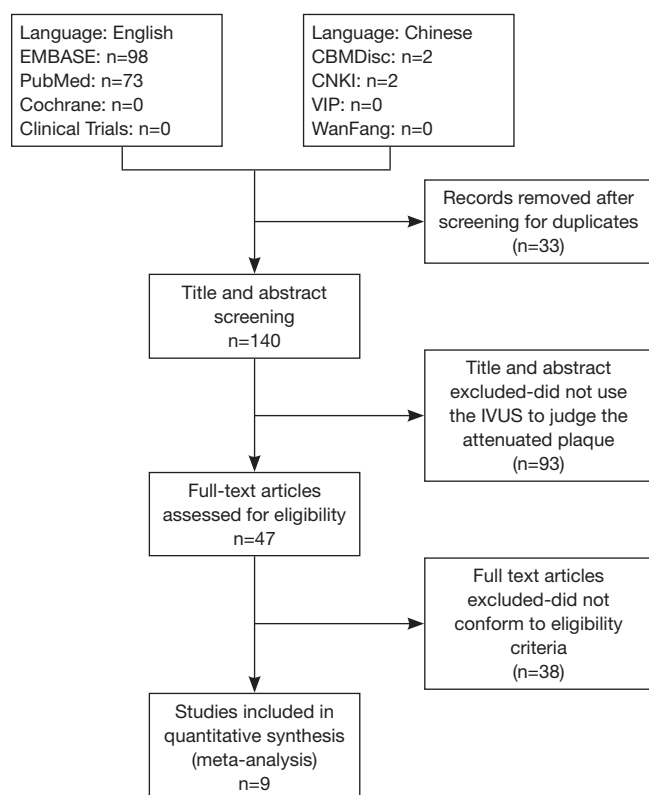


Figure 2 Article selection flowchart. IVUS, intravascular ultrasound.

the Q statistic, which gave a qualitative indicator and was statistically significant for heterogeneity with P value less than 0.1, and the I^2 statistic, which gave a quantitative measurement, with $I^2 < 50\%$ indicating insignificant heterogeneity. Publication bias was addressed using Egger's method, which shows good sensitivity when the number of references is small. Results synthesized from multiple studies and Forest plots were obtained with RevMan ver. 5.3 (The Cochrane Collaboration) and the Egger's test was conducted by Stata ver. 12.0.

Results

Search results

One hundred forty publications were identified for full text assessment with the search strategy (including 73 articles from PubMed, 98 articles from Embase and 2 from CNKI). Ninety-three articles were excluded because the titles and/or abstracts indicated that they were review articles [n=28, case reports (n=9) and others that did not qualify (n=56)]. Further screening by reading through the articles by two

reviews excluded 35 articles that did not use the IVUS to determine attenuated plaques. Three articles were further excluded due to no record of slow/no reflow phenomenon or clinical outcomes (13,15,21). Five observational studies, which described the association between attenuated plaques and incidence of slow/no reflow during PCI (11,14,16,22) and five studies that presented MACEs were included in the final meta analysis (Figure 2) (12,14,18,19,23).

Qualitative study analysis

Table 1 summarizes the main characteristics of the included studies. A total of 3,833 patients (2,028 patients in the attenuated plaque group and 1,805 patients in the non-attenuated plaque group) were enrolled in the nine studies. Five studies described the relationship between attenuated plaques and incidence of slow/no reflow during PCI (11,14,16,17,22). The sample size was 97 to 687 for these studies. Two studies involved unstable and stable angina patients (17,22). Two studies involved ACS patients (13,14) and one study involved all CAD patients (11). Five other studies reported the MACEs (12,14,18,19,23). The sample size was 110 to 2,072 for these studies. Two studies involved ACS patients (14,18), two studies involved CAD patients (12,21) and one study involved patients with ST segment elevation myocardial infarction (STEMI) (23). The attenuated and non-attenuated plaque groups were comparable in age, gender and other demographic and baseline characteristics.

There was excellent agreement between investigators for full text screening ($\kappa=0.93$). The mean total cohort Newcastle-Ottawa Scale score was 7.7 (Table 2). All observational studies had intermediate to low intermediate bias risk according to the Newcastle-Ottawa Scale.

Meta analysis of attenuated plaques and the slow/no reflow phenomenon

In the stage of angiography before PCI was performed, no statistically significant difference was observed between the attenuated and non-attenuated plaque group in the risk of TIMI grade 0–2 flow (RR =1.25; 95% CI: 0.65 to 2.41) (Figure 3) and TIMI 3 (RR =0.89; 95% CI: 0.73 to 1.10) (Figure 4). By contrast, after balloon dilation and stent implantation, the attenuated group showed a more than 4 fold increase in the risk of TIMI grade 0–2 flow compared to the non-attenuated group (RR =4.73; 95% CI: 3.03 to 7.40; $P<0.001$) (Figure 5). Among the

Table 1 Baseline characteristics of studies included in the meta-analysis

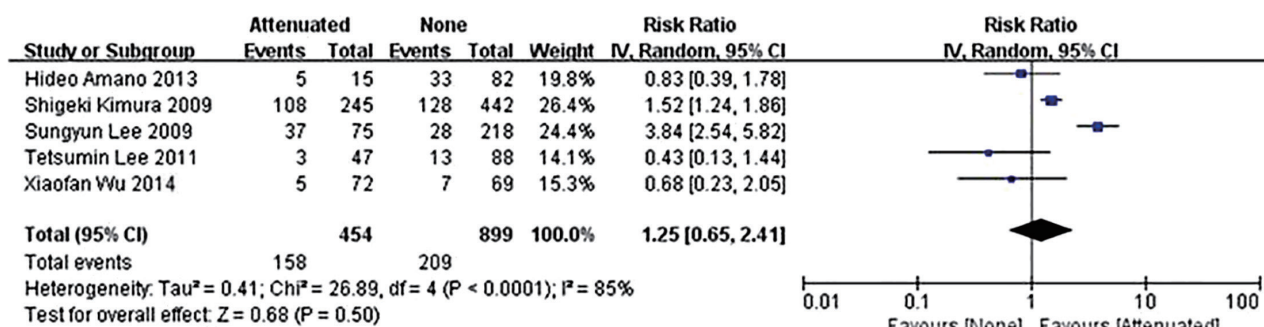
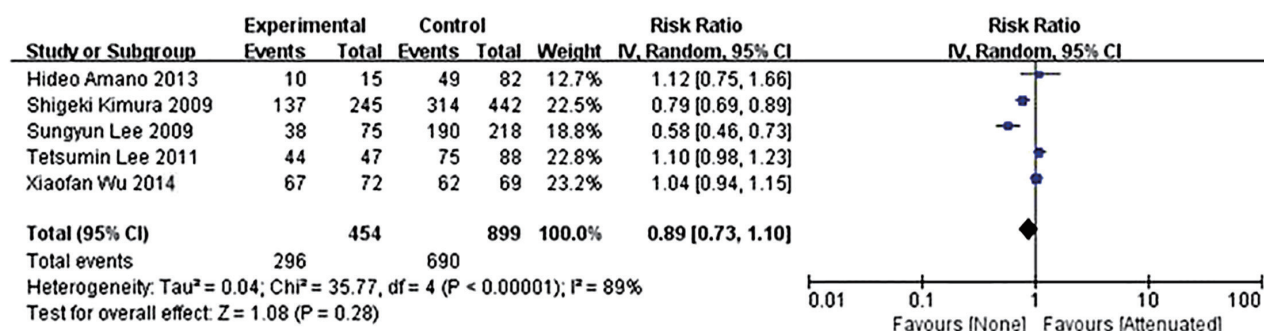
Study	Interval	Location	Sample size*	Design	Clinical scenario	Endpoint	Mean age (years)	Female (%)	Hypertension (%)	Lesion EEM (mm ²)	Lesion plaque burden (%)	Diabetes (%)
Lee T <i>et al.</i> 2011 (17)	12/2008–12/2009	Japan	47/88	Cohort	SAP&UAP	TIMI flow	67/64.6	12.8/22.7	78.7/71.6	18.9/14.2	87.4/82.7	31.9/39.8
Bayturan O <i>et al.</i> 2009 (12)	NR	USA	17/142	Cohort	CAD	MACE	59.8/58.7	5.9/25.4	100/94.4	NR	NR	5.9/11.3
Wu XF <i>et al.</i> 2014 (22)	01/2009–12/2011	China	72/69	Cohort	SAP&UAP	TIMI flow	62.4/59.6	25/29	48.6/43.5	16.3/14.1	79.8/77.3	31.9/27.5
Xu K <i>et al.</i> 2012 (23)	NR	USA	103/36	Cohort	STEMI	MACE	57.6/53	16.5/22.2	54.4/41.7	17.3/16.4	NR	10.7/16.7
Lee SY <i>et al.</i> 2009 (16)	01/2006–03/2007	USA	75/218	Cohort	ACS	TIMI flow	61.9/65.2	25.3/44.5	86.7/79.8	12/11.6	81.8/75.8	28/29.4
Amano H <i>et al.</i> 2013 (11)	07/2005–02/2007	Japan	15/82	Cohort	CAD	TIMI flow	65/64	0/15.9	53/65	17.1/16	NR	53/35
Okura H <i>et al.</i> 2016 (18)	01/2001–12/2012	Japan	73/37	Cohort	ACS	MACE	NR	NR	NR	NR	NR	NR
Kimura S <i>et al.</i> 2009 (20)	06/2004–05/2007	Japan	245/442	Cohort	ACS	TIMI flow & MACE	66/64	22.5/20.1	64.6/65.6	18.9/15.2	88.5/86	36.7/29.6
Qiu F <i>et al.</i> 2014 (19)	NR	USA	1,381/691	Cohort	CAD	MACE	NR	NR	NR	NR	76.7/73.6	NR

*, the attenuated vs. non-attenuated plaque group. ACS, acute coronary syndrome; CAD, coronary artery disease; EEM, external elastic membrane; MACE, major adverse cardiac events; SAP, stable angina pectoris; STEMI, ST segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; UAP, unstable angina pectoris.

Table 2 Newcastle-Ottawa scale of bias risk for the included studies

Author	Selection	Comparability	Outcome	Total
Study				
Lee T. <i>et al.</i> 2011 (17)	4	2	3	9
Bayturan O <i>et al.</i> 2009 (12)	4	2	2	8
Wu XF <i>et al.</i> 2014 (22)	3	2	2	7
Xu K <i>et al.</i> 2012 (23)	4	1	3	8
Lee SY <i>et al.</i> 2009 (16)	4	2	1	7
Amano H <i>et al.</i> 2013 (11)	4	2	2	8
Okura H <i>et al.</i> 2016 (18)	4	1	2	7
Kimura S <i>et al.</i> 2009 (20)	3	2	3	8
Qiu F <i>et al.</i> 2014 (19)	3	2	2	7
Average	3.7	1.8	2.2	7.7

For this scale, each study is judged on eight domains, categorized into three groups: the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure or outcome of interest for cohort studies respectively. Points are awarded such that the highest quality studies are awarded up to nine points.

**Figure 3** TIMI grade 0–2 of the two groups in the stage of angiography.**Figure 4** TIMI grade 3 of the two groups in the stage of angiography.

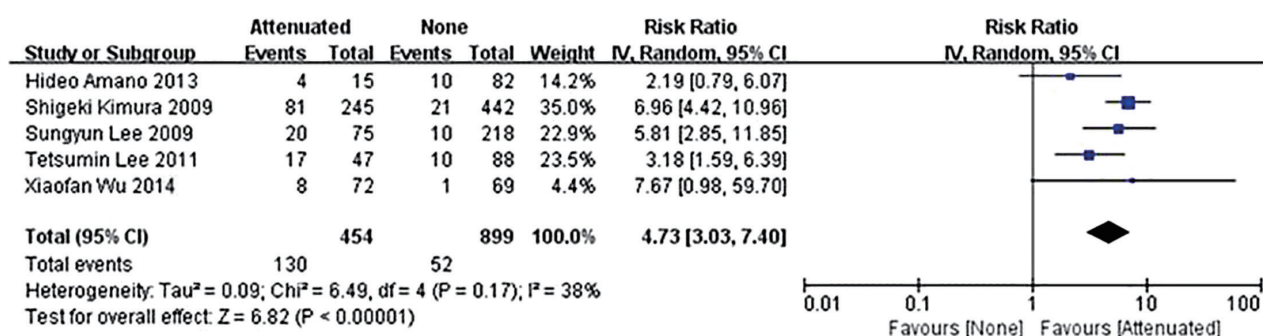


Figure 5 TIMI grade 0-2 of the two groups after balloon dilation and stent implantation.

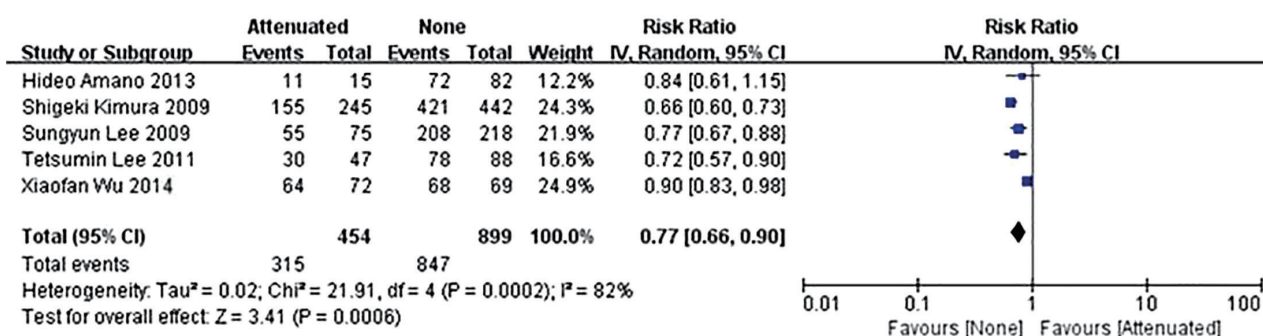


Figure 6 TIMI grade 3 of the two groups after balloon dilation and stent implantation.

attenuated plaque group, 130 of 454 plaques (28.6%) were associated with TIMI 0-2 flow after PCI, while only 52 of 899 non attenuated plaque (5.8%) were associated with TIMI 0-2 flow. On the other hand, the attenuated group exhibited a noticeable reduction in the incidence of TIMI grade 3 compared to the non-attenuated group ($\text{RR} = 0.77$; 95% CI: 0.67 to 0.90; $P = 0.02$) (Figure 6). These findings suggested that the presence of attenuated plaques was associated with increased risk for the slow/no reflow phenomenon after balloon dilation and stent implantation.

Attenuated plaques and clinical outcomes

Five studies analyzed the association between attenuated plaques and clinical outcomes. Xu *et al.* (23) reported that at the 1-year follow-up, only four MACEs occurred in the attenuated plaque group and no significant difference was observed between the two groups ($P = 0.21$). At 3 years, 16 (12%) MACEs occurred in the attenuated plaque group and 9 (17.5%) in the non-attenuated plaque group ($P = 0.38$).

Kimura *et al.* (14) compared ACS patients with attenuated and non-attenuated plaques, 9 (7.6%) MACEs occurred in the attenuated plaque group and 7 (4.4%) in the non-attenuated plaque group ($P = 0.39$). In addition, the two groups exhibited no statistically significant difference in other endpoints such as re-infarction and ischemic target vessel revascularization (TVR). Okura H *et al.* conducted a long-term study (18) with a median follow-up duration of 6.2 years. The authors found no statistically significant difference in the incidence of all cause death, cardiac death, non-cardiac death, congestive heart failure, and ACS between the two groups. The ADAPT-DES IVUS sub-study enrolled 2,072 ACS patients (16) and found no statistically significant difference in the 2-year rates of MACEs ($P = 0.41$) or clinically driven TVR ($P = 0.46$). Bayturan O *et al.* reported (12) that during the 2-year follow-up, one patient in the non-attenuated plaque group developed myocardial infarction (MI) and one patient had stroke, and no patients with attenuated plaques developed MI, death, or stroke. In conclusion, all the studies did not

reveal different MACE rates between the two groups. Xu K *et al.* found that PES implant into attenuated plaques was particularly associated with late acquired stent malapposition (36.8% vs. 15.4% in non-attenuated plaques treated with PES, $P=0.03$) (23).

Publication bias

Due to the limited article number, we chose Egger's test to estimate the publication bias without funnel plot. The results showed TIMI 0~2 grade ($P=0.94$; 95% CI: -15.24 to 14.42) and TIMI 3 grade ($P=0.57$; 95% CI: -12.29 to 8.15) in the stage of angiography, TIMI 0~2 grade ($P=0.51$; 95% CI: -26.36 to 16.39) and TIMI 3 grade ($P=0.79$; 95% CI: -7.99 to 6.62) after the balloon dilation and stent implantation without publication bias.

Discussion

Attenuated plaques are associated with ST-segment elevation MI and no reflow in patients with CAD who undergo PCI (24). However, there has been no systemic review of the impact of attenuated plaques on TIMI grade and clinical outcomes of CAD patients and attenuated plaques are not described in the current IVUS guidelines from the American College of Cardiology or the European Society of Cardiology. We systemically reviewed nine cohort studies that investigated the association between attenuated plaques and incidence of slow/no reflow during PCI (11,14,16,17,22) or the relation between attenuated plaques and MACEs (12,14,16,19,23). We found that the presence of attenuated plaques was associated with more than 4 fold increase in the risk of TIMI grade 0~2 flow after balloon dilation and stent implantation though this was not observed before PCI was performed, suggesting that the presence of attenuated plaques portends an adverse prognosis for CAD patients because of increased post procedural risk of no reflow. To the best of our knowledge, this is the first systemic review and meta analysis of the association of IVUS-detected attenuated plaques and the risk of TIMI grade no reflow, demonstrating that attenuated plaque has a high risk of no-reflow phenomenon after balloon dilation and stent implantation.

Attenuated plaque is common in ACS patients and Shiono Y. *et al.* have recently shown that IVUS-detected attenuated plaque is associated with MRI-derived microvascular obstruction (25), which is known to portend an adverse clinical outcome in acute MI patients (26).

However, our analysis of five studies that investigated the association of attenuated plaques and MACEs (12,14,18,19,23) failed to reveal a significant correlation between IVUS-detected attenuated plaques and MACEs at 1 to 3 years of follow-up. It remains to be seen whether IVUS-detected attenuated plaques is associated with only transient deterioration in coronary flow during PCI (18) or an adverse long term clinical outcome.

The predictor of microvascular obstruction after PCI has not yet been fully elucidated and whether IVUS-detected attenuated plaque may serve as such a predictor still remains debatable. A histopathologic analyses of a small number of specimens showed that echo attenuation has been variously related to microcalcification, hyalinized fibrous tissue, cholesterol crystals, or organized thrombus (8,20,27). Kimura S *et al.* examined 30 atherectomy specimens with attenuated plaques and found advanced atherosclerosis consisting predominantly of cholesterol clefts, macrophage infiltration, and microcalcification (20). Plaque rupture occurs more commonly in patients with attenuated plaques having a larger size of lipid/necrotic core (28-30). Davies MJ *et al.* found that atheroma is at high risk for rupture when more than 40% of the plaque consists of lipid/NC (31). The meta-analysis by Ding S *et al.* revealed that compared with patients with normal flow, significantly higher absolute necrotic core volume and dense calcium were found in ACS patients with distal embolization (32,33). The HORIZONS-AMI Trial showed that the larger the attenuated plaque is, the greater the likelihood of no-reflow is (24). However, Stone GW *et al.* (7) found that, among 51 non-culprit-lesion related recurrent events occurring in the imaged segments, only 26 (51%) occurred at sites with thin-cap fibroatheromas while others were the most common thick-cap fibroatheromas. These findings indicated that predicting clinical outcomes based on ruptured plaque characteristics is still highly debatable and requires more careful studies in the future.

Study limitations

Several limitations of our study should be taken into account. First, though nine studies were included in the current analysis, half of these studies investigated attenuated plaque and TIMI grade flow, and the remaining described MACE rates without data on TIMI grade flow. Only one study provided data on both MACE rate and TIMI grade flow. Therefore, we were unable to obtain the incidence of distal embolization in the studies on MACEs without TIMI grade

flow data. Secondly, there was considerable heterogeneity in TIMI 0~3 grade of angiography and TIMI 3 grade after balloon dilation and stent implantation. Thirdly, because of the limited article number, we chose Egger's test instead of funnel plot to estimate publication bias.

Conclusions

Our study presents the evidence that plaque with ultrasound signal attenuation would induce slow/no reflow phenomenon and distal embolization during PCI, but this appearance has no impact on MACE rates within three years.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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