Atherosclerosis 284 (2019) 194–201

Contents lists available at ScienceDirect

Atherosclerosis

journal homepage: www.elsevier.com/locate/atherosclerosis

Review article

Coronary atheroma regression and adverse cardiac events: A systematic review and meta-regression analysis

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HIGHLIGHTS

- Meta-regression analysis of trials using intravascular ultrasound to assess regression induced by lipid medications was performed.
- A 1% decrease in percent atheroma volume was associated with approximately a 20% reduction in the odds of incurring a major cardiovascular event.
- Percent atheroma volume changes represent a surrogate measure of cardiovascular events.

ARTICLE INFO

Keywords:
Atherosclerosis
Plaque regression
Major adverse cardiac events
Intravascular ultrasound
Anti-atherosclerotic therapy

ABSTRACT

Background and aims: The relationship between plaque regression induced by dyslipidemia therapies and occurrence of major adverse cardiovascular events (MACE) is controversial. We performed a systematic review and meta-regression of dyslipidemia therapy studies reporting MACE and intravascular ultrasound (IVUS) measures of change in coronary atheroma.

Methods: Prospective studies of dyslipidemia therapies reporting percent atheroma volume (PAV) measured by IVUS and reporting death, myocardial infarction, stroke, unstable angina or transient ischemic attack (MACE) were included. The association between mean change in PAV and MACE was examined using meta-regression via mixed-effects binomial logistic regression models, unadjusted and adjusted for mean age, baseline PAV, baseline low density lipoprotein-cholesterol and study duration.

Results: The study included 17 prospective studies published between 2001 and 2018 totaling 6333 patients. Study duration varied from 11 to 104 weeks. Mean change in PAV, across the study arms, ranged from −5.6% to 3.1%. MACE ranged from 0 to 72 events per study arm: 13 study arms (38%) reported no events, 8 (24%) reported 1–2 events and 13 (38%) reported 3 or more events. Meta-regression demonstrated a decline in the odds of MACE associated with reduction in mean PAV: unadjusted odds ratio (OR): 0.78, 95% Confidence Interval (CI): [0.63, 0.96], $p = 0.018$; adjusted OR: 0.82, 95% CI: [0.70, 0.95], $p = 0.011$, per 1% decrease in mean PAV.

Conclusions: A 1% reduction in mean PAV as induced by dyslipidemia therapies was associated with a 20% reduction in the odds of MACE.

1. Introduction

There is a generally accepted relationship between a reduction of low density lipoprotein-cholesterol (LDL-C) and major adverse cardiovascular events (MACE) as well as regression of atherosclerosis using LDL-C lowering medications [1]. But the relationship between changes in measures of atherosclerosis and reduction in major adverse cardiovascular events (MACE), built upon the concept of surrogacy, remains controversial [2]. Detailed measurements afforded by intravascular ultrasound (IVUS) have eclipsed prior, angiographic studies of coronary atherosclerosis progression/regression but to date, there have been few analyses attempting to relate change in percent atheroma volume (PAV) using IVUS to MACE and none include more current studies [3–5]. Our goal was to provide an updated systematic review and meta-regression analysis of IVUS trials of lipid lowering agents that also reported MACE.

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https://doi.org/10.1016/j.atherosclerosis.2019.03.005
Received 11 January 2019; Received in revised form 6 March 2019; Accepted 7 March 2019
Available online 11 March 2019

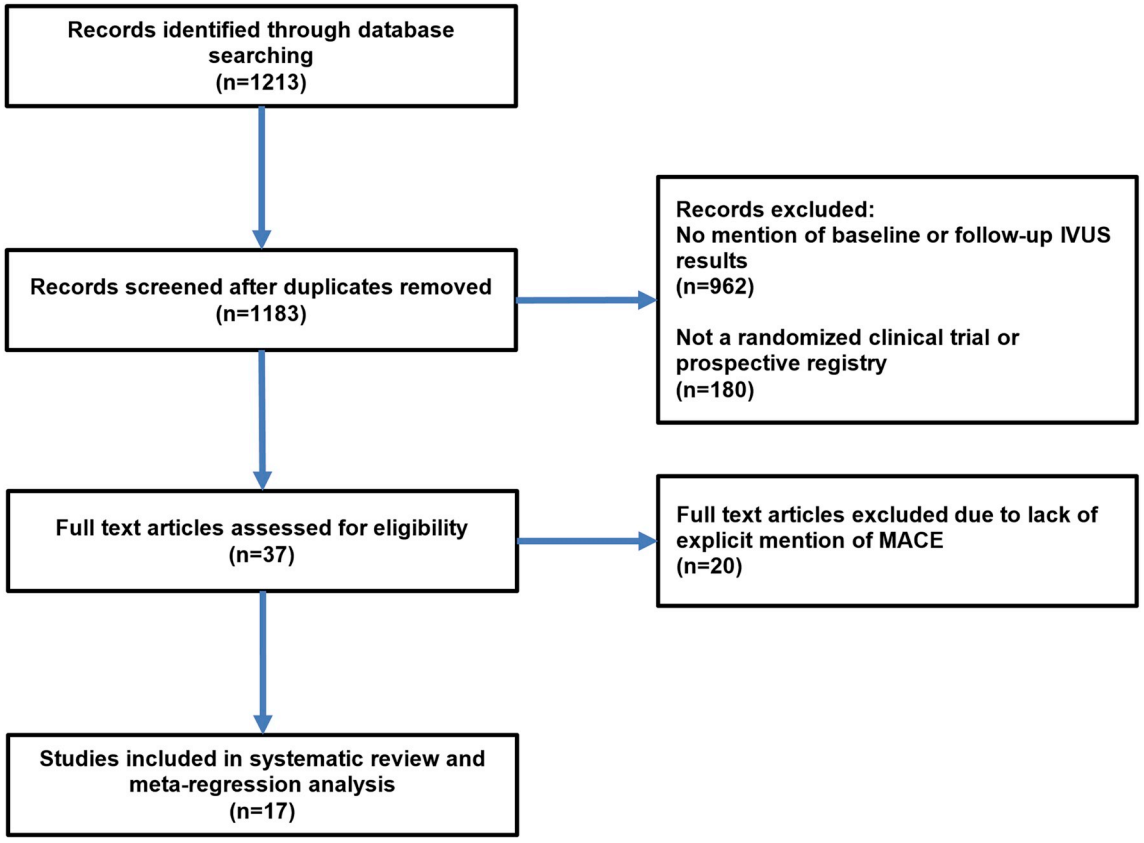

Fig. 1. Consort diagram.
The flow diagram depicts the flow of information through the different phases of the systematic review. It maps out the number of records identified, included and excluded, and the reasons for exclusions. PAV = percent atheroma volume, MACE = major adverse cardiac events.

2. Materials and methods

2.1. Study identification

We systematically searched PubMed, Web of Science, and EMBASE for prospective studies of dyslipidemia therapies published up to 2018 reporting coronary plaque progression/regression measured by IVUS and also reporting MACE. The search strategy is detailed in Fig. 1. Search terms are provided in Supplementary Materials. We limited our search to articles published in English and to studies conducted in adults over the age of 18 years. Reference lists of all retrieved original papers were hand-searched to identify further relevant studies. Finally, we searched for multiple publications of retrieved articles to obtain the most complete and up-to-date study results. Thus the main pre-specified study inclusion criteria were: 1) randomized and non-randomized prospective cohort studies utilizing IVUS, 2) patients.

With acute coronary syndrome (ACS) or stable coronary artery disease, 3) study of one or more lipid-lowering drugs, 4) reported change in PAV or plaque volume (PV) at baseline and follow-up; 5) explicit reporting of presence or absence of any component of MACE (myocardial infarction [MI], stroke, transient ischemic attack [TIA], unstable angina [UA] or all-cause mortality) in each study. To emphasize, studies not mentioning events were excluded but those explicitly reporting presence or absence of any of these events were retained.

2.2. Study selection and data extraction

We used standardized data extraction protocols, resolution of differences by consensus, initially by 3 independent reviewers and then through secondary review and verification by a member of the statistical team. We extracted information on study design, first author's name, year of publication, number of participants in the study, the number with IVUS follow-up, duration of follow-up, proportion of males, and mean and standard deviation (SD), where applicable, of the following variables for each study arm: age, LDL-C at baseline and follow-up, baseline and follow-up PAV, or change in PAV. The reviewers also extracted data on the specified components of MACE (Table 1 and Supplementary Table 1).

2.3. Data preparation

Among studies directly reporting change in PAV, PAV was calculated consistently using the formula Σ (EEM_{area} - $Lumen_{area}$)/ $\Sigma EEM_{area} \times 100$, where EEMarea is the cross-sectional area the external elastic membrane and Lumenarea is the cross-sectional area of the lumen. Among the six studies that did not report mean PAV, but reported mean PV and mean EEM_{area}, we approximated mean PAV as mean PV/mean EEM_{area}. Mean change in PAV was then obtained.

As mean PAV at follow-up minus mean PAV at baseline. MACE was reported as the total number of events. If a component of MACE was not reported in a study that explicitly commented on other components of MACE, that component was assumed to be zero. The ratio of the MACE count over the total number of patients in each study arm was calculated.

2.4. Meta-regression analysis of mean change in PAV and MACE

None of the studies reported the patient-level association between change in PAV and MACE. Therefore, average patient-level association could not be addressed. Instead, based on the aggregated data, we undertook a meta-regression analysis to assess the association between

Table 1
Baseline characteristics and treatment.

First Author, year (Ref. #)	Treatment	Sample size, n	Follow-up, weeks	Mean age, yrs (SD)	Men, %	Baseline LDL (mg/dL)	Follow-up LDL (mg/dL)	Baseline PAV	Mean change in PAV (SD)	MACE, n[a]
Schartl, 2001 [6] [b]	Atorvastatin	65	52	60.7 (8.9)	85	155	86	44.5	0.14 (5.1)	2
	Usual care	66		59.8 (7.2)	85	166	140	41.9	0.37 (4.9)	5
Nissen, 2004 [7]	Pravastatin 40 mg daily	327	18	56.6 (9.2)	56	150.2	110.4	39.5	1.9 (4.9)	9
	Atorvastatin 80 mg daily	327		55.8 (9.8)	55	150.2	78.9	38.4	0.6 (5.1)	6
Okazaki, 2004 [8] [b]	Atorvastatin 20 mg daily	35	24	61.3 (10.1)	86	124.6	70	42.6	−4.66 (6.9)	0
	Usual care	35		62.5 (11.2)	86	123.9	119.4	42.6	3.07 (6.2)	1
Nissen, 2006 [9]	Rosuvastatin 40 mg daily	507	24	58.5 (10)	48	130.4	60.8	39.6	−0.98 (3.2)	17
	Control	158								
Nissen, 2007 [10]	Atorvastatin	597	104	57 (9.2)	71	84.3	87.2	37.1	0.19 (2.8)	64
	Atorvastatin + Torcetrapib	591		56.9 (9.1)	71	83.1	70.1	37	0.12 (3)	72
Nasu, 2009 [11] [b]	Fluvastatin 60 mg daily	40	12	63 (10)	80	144.9	98.1	54.1	−2.05 (2.9)	0
	Control	39		62 (12)	82	122.3	121	48.7	0.98 (5.1)	1
Hiro, 2009 [12] [b]	Pitavastatin 4 mg daily	147	32–52	62.5 (11.5)	70	130.9	81.1	49.7	−5.01 (4.9)	0
	Atorvastatin 20 mg daily	149		62.4 (10.6)	69	133.8	84.1	50.8	−5.48 (4.7)	3
Takayama, 2009 [13] [b]	Rosuvastatin	126	76	62.6 (7.7)	76	140.2	82.9	47.8	−2.89 (4.4)	0
	Control					130.9	89.7			
Nicholls, 2011 [14]	Atorvastatin 80 mg daily	689	104	57.9 (8.5)	56	119.9	70.2	36	−0.99 (3.7)	28
	Rosuvastatin 40 mg daily	691		57.4 (8.6)	55	120	62.6	36.7	−1.22 (3.7)	32
Nozue, 2012 [15]	Pitavastatin 4 mg daily	77	32	66 (9)	68	126	74	55.2	−0.2 (3.4)	2
	Pravastatin 20 mg daily	77		67 (11)	61	137	95	53.9	0.2 (4.8)	0
Lee, 2012 [16]	Atorvastatin 10 mg daily	19	24	65.1 (9.99)	74	122.4	68.5	49.9	0.38 (4.1)	1
	Atorvastatin 40 mg daily	20		63.7 (9.8)	90	112.4	52.1	51.6	−1.5 (3.9)	0
Masuda, 2015 [17]	Rosuvastatin 5 mg daily	24	24	70.2 (7.6)	67	123	75.1	46.4	−0.6 (5.5)	0
	Rosuvastatin 5 mg + ezetimibe 10 mg daily	26		64 (7.9)	73	131.8	57.3	52.5	−5.6 (5.5)	0
Tsujita, 2015 [18]	Atorvastatin + ezetimibe 10 mg daily	122	36–52	66 (10)	64	109.8	63.2	51.3	−1.4 (4.7)	2
	Atorvastatin	124		67 (10)	65	108.3	73.3	50.9	−0.3 (5.1)	1
Takayama, 2016 [19] [b]	Rosuvastatin 20 mg daily	25	48	65.1 (10.1)	52	130.3	61.7	47.9	−0.24 (5.9)	0
	Rosuvastatin 2.5 mg daily	25		63.8 (8.5)	64	130.9	89.7	45.4	0.02 (5.5)	1
Matsushita, 2016 [20]	Atorvastatin 20 mg daily	26	40	62.4 (8.7)	92	135	72	50.2	−3.6 (5.1)	0
	Pitavastatin 4 mg daily	26		62.8 (11.4)	85	140	78	44.1	−2.9 (5.2)	0
	Pravastatin 10 mg daily	25		63.8 (8.6)	72	152	107	46	1.5 (9.9)	0
	Fluvastatin 30 mg daily	25		62.4 (12.2)	72	139	103	44.7	0.4 (5.8)	0
Nicholls, 2016 [21]	Evolocumab 420 mg subcutaneously every month	484	78	59.8 (9.6)	72	92.6	36.6	37.2	−0.95 (3.9)	18
	Placebo	484		59.8 (8.8)	72	92.4	93	36.4	0.05 (3.8)	25
Nicholls, 2018 [22]	Weekly intravenous infusions of CER-001 + statin	147	11	60.6 (9.5)	77	86	79	37.3	−0.09 (6.9)	3
	Placebo + statin	146		59.1 (9.4)	83	81	74	38.4	−0.41 (8.1)	5

PAV = percent atheroma volume.
[a] MACE = myocardial infarction (MI), stroke, transient ischemic attack (TIA), unstable angina (UA) and death; see Supplementary Table 1 for individual events.
[b] Change in PAV estimated from published data.

the reported mean change in PAV and proportion with MACE at the study arm level.

When the number of events is zero (relevant to 13 of the 34 study arms), the widely used DerSimonian-Laird method [23] requires a continuity constant to be added to the event count in order to calculate the log odds estimate and its variance. However, with a high proportion of zero counts in the data, adding a constant might substantially bias the heterogeneity indicator and the estimates [24]. Therefore, we adopted a mixed-effects logistic regression model [25,26] that directly specified the binomial distribution of the MACE counts, and accounted for the heterogeneity between studies and between treatment arms within the same study. This approach has been shown to be superior to the traditional DerSimonian-Laird method in the presence of many zero counts [27].

We initially created an unadjusted three-level mixed-effects logistic regression model with two independent variance components, τ_1 at study level and τ_2 at treatment arm level nested. Within the study, and a fixed effect of mean change of PAV. As τ_2 was estimated as zero in our preliminary analysis, a reduced two-level model was utilized. The proportion of variance explained by PAV (R^2) was estimated using a coefficient of determination based on the total variance of the random effects from the models with and without mean change of PAV [28]. The results are reported as odds ratios or the change in odds per 1% decrease in mean PAV.

The influence of clinically important covariates (baseline PAV, mean age, proportion of males, study duration, LDL-C at baseline, change in LDL-C, on-treatment LDL-C) on the association between MACE and mean change in PAV was examined by adjusting for each of the covariates separately. Based on these analyses, all the covariates associated with MACE with a p-value < 0.1 were then selected to be included in a final multivariable model.

2.5. Evaluation of study heterogeneity of MACE

A dataset including only active lipid therapy study arms was created to assess heterogeneity of MACE with the active therapy study arms collapsed within the studies. Although the Cochran Q test and I^2 statistics are widely used in traditional meta-analysis to report heterogeneity, we determined that because of excessive zero counts, it would not be appropriate for our data structure. Instead we used a X^2 statistic, which is based on an analysis of variance for binary data [27], to test the equality of event rate across studies, and an intra-class correlation coefficient, ρ, to measure the proportion of variation contributed by study.

2.6. Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of the association between change in PAV and proportion of patients with MACE. The restricted cubic spline was used to explore the non-linear relationship between change in PAV and MACE and nonlinearity was evaluated using the likelihood ratio test. The influence of each study on the findings was evaluated by refitting the unadjusted model with one study removed at a time. The influence of study design was evaluated by refitting the same model first with the three non-randomized trials excluded and then with the four studies of ACS patients excluded.

All the analyses were conducted using RStudio (1.0.136) [29]. The mixed-effects logistic regression model was implemented using the glmer function in the lme4 package [30], where both fixed effects and variance components were estimated via maximum likelihood using the Laplace approximation. A two-sided p-value < 0.05 was considered statistically significant.

3. Results

3.1. Characteristics of included studies

A total of 17 studies with 34 study arms published between 2001 and 2018 were included (Table 1). Three studies were non-randomized trials [9,11,13] and four studies only included patients with ACS [8,12,20,22]. Among the 17 studies, three were placebo-controlled, and the rest were all lipid therapy studies with a wide range of types and doses administered (Table 1).

The number of patients included in the studies ranged from 39 to 1380, with a total of 6333. Among these patients, 5775 were allocated to lipid intervention groups. Mean patient age ranged from 55.8 to 70.2 years. Thirteen studies either stated in the paper that a core laboratory was used to review the findings or we received confirmation via email that a core laboratory was used. Mean baseline PAV ranged from 36.0% to 55.2%, with higher baseline PAV reported in studies with older patients. The percentage of males ranged from 48.3 to 92.3%. Study duration varied from 11 to 104 weeks with a median of 40 weeks; 4 studies had more than 1-year follow-up mean change in PAV ranged from −5.6% to 3.1%. MACE counts varied from 0 to 72, with 13 of 34 (38%) study arms reporting no events, 8 (24%) with 1–2 events and 13 (38%) reporting 3 or more events. A higher number of events were typically reported in studies with larger sample sizes and longer follow-up times, as expected. The proportion of patients with MACE ranged between 0 and 12.2%.

3.2. Meta-regression analysis of mean change in PAV and MACE

The ORs (95% CIs) for MACE per 1% reduction in mean PAV from different models are reported in Table 2. In the unadjusted model, a strong association was observed between mean change in PAV and MACE, with change in PAV accounting for an estimated 38% of the variation in MACE (R^2 = 38%). Per 1% reduction in mean PAV, the odds of experiencing a MACE outcome decreased 22%, CI: 4%, 37%, p = 0.018).

To further elucidate this relationship, we included change in PAV and one other factor at a time (Table 2). The resulting, adjusted OR's ranged between 0.75 and 0.86.

To determine the most parsimonious multivariable adjustment for the impact of Change in PAV, we identified in univariate analyses that baseline PAV, baseline LDL-C, study duration, and mean age were each associated with MACE, using the conservative p-value < 0.1; whereas follow-up LDL-C, change in LDL-C and sex did not meet p < 0.1. Thus,

Table 2
Unadjusted and adjusted odds ratios (95% CIs) and p-values for MACE per 1% reduction in mean PAV under a two-level binomial logistic mixed-effects model.

Model	Odds ratio per 1% reduction in mean PAV (95% CI)	*p*-value
Unadjusted change in PAV	0.78 (0.63, 0.96)	0.018
Adjusted for single covariate:		
Change in PAV + Baseline PAV	0.86 (0.71, 1.05)	0.131
Change in PAV + Baseline LDL-C	0.78 (0.64, 0.95)	0.014
Change in PAV + Follow up LDL-C	0.76 (0.60, 0.97)	0.029
Change in PAV + Change in LDL-C	0.81 (0.64, 1.03)	0.088
Change in PAV + Study duration	0.75 (0.63, 0.89)	< 0.001
Change in PAV + Age	0.82 (0.67, 1.00)	0.05
Change in PAV + Sex	0.78 (0.63, 0.96)	0.018
Multivariable adjusted[a]	0.82 (0.70, 0.95)	0.011

[a] In the multivariable analysis, only covariates independently associated with MACE (p-value < 0.1) after accounting for the effect of change in PAV were included and consisted of baseline PAV, baseline LDL-C, study duration and age.

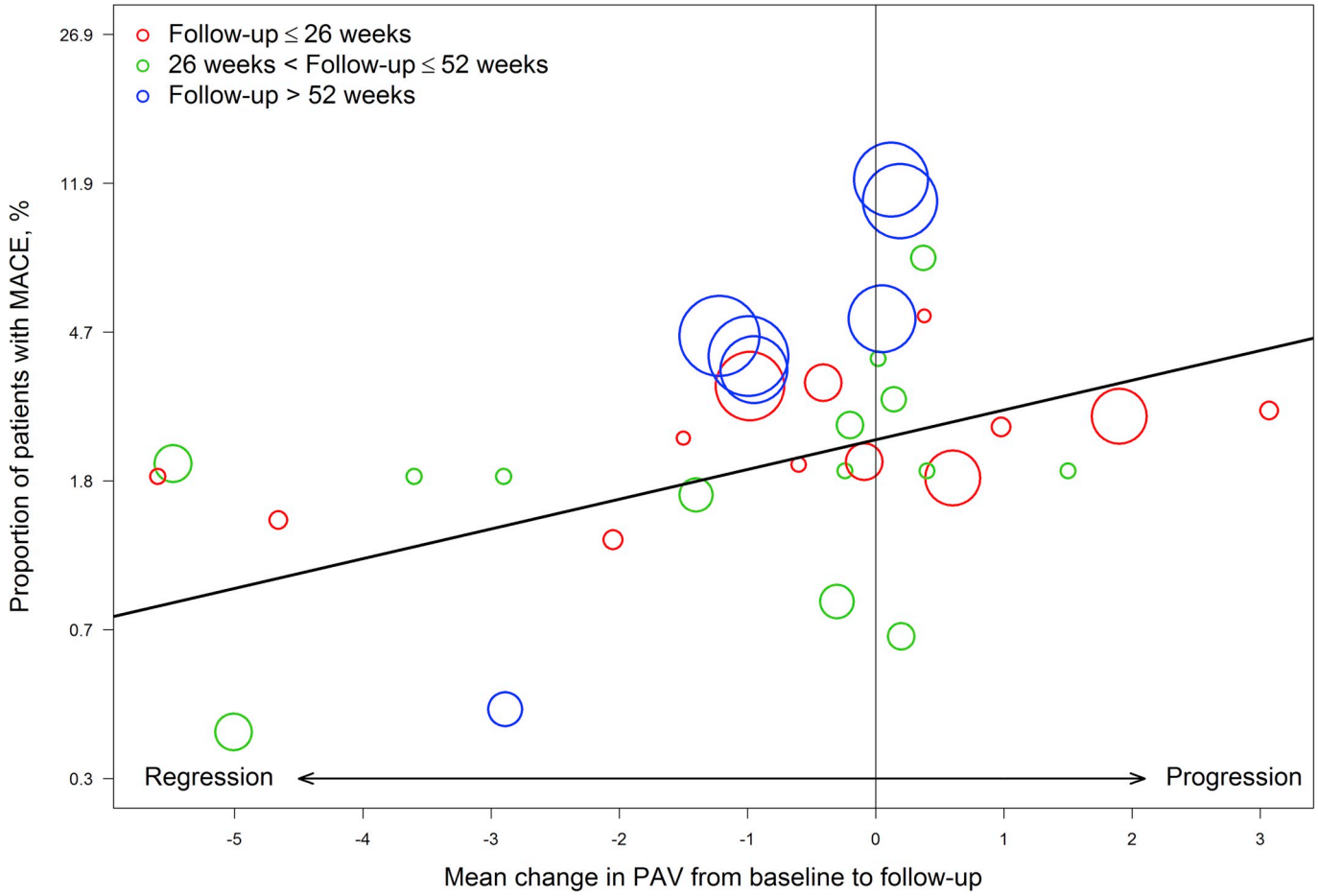

Fig. 2. Association between mean change in PAV and MACE.
Each circle represents a single study arm. The size of the circle is proportional to the sample size of that study arm and the color represents the study duration. The MACE proportion was converted to log odds and a constant 0.5 was added to zero counts to allow the conversion of log odds. The regression line is based on the adjusted mixed-effects logistic regression model (see Results). Abbreviations as in Fig. 1.

with multivariable adjustment for baseline PAV, baseline LDL-C, study duration, and mean age, the association between PAV and MACE was slightly attenuated, demonstrating an 18% reduction in the odds of MACE per 1% reduction in mean PAV (95% CI: 5%, 30%), $p = 0.011$ (Table 2).

Fig. 2 shows the observed mean change in PAV and the corresponding observed proportion of patients with MACE by study arm. The regression line is based on the adjusted model and the slope reflects the estimated association between mean change in PAV and MACE with baseline PAV fixed at mean baseline PAV of 45%, age fixed at mean age of 62 years, baseline LDL fixed at mean baseline LDL of 124 mg/dL.

3.3. Evaluation of study heterogeneity in MACE

The observed $X^2 = 173.8$ ($d.f. = 16$, p-value < 0.001) indicates significant heterogeneity across studies. However, the estimated intra-class correlation $\rho = 3.2\%$ implies that the contribution of inter-study variability to the overall variability was not large (Fig. 3).

3.4. Sensitivity analysis

The model using the restricted cubic spline did not show a significant nonlinear relationship between mean change in PAV and MACE ($p = 0.422$). Fig. 4 illustrates the robustness of the association between the mean change in PAV and MACE outcome after removal of one study at a time. Effect of mean change in PAV on MACE was found to be consistent irrespective of the removal of any study. Furthermore, the association was unaffected by excluding the three non-randomized studies and the four studies of ACS patients.

4. Discussion

To our knowledge, this is the most current and comprehensive systematic review and meta-regression of lipid treatment trials to evaluate the association between plaque regression assessed by IVUS and MACE. With this comprehensive analysis representing data in over 6000 patients, and using extremely rigorous statistical methods, we demonstrate a direct and significant association between a surrogate measure (change in PAV) and MACE. The results indicate every 1% decline in mean PAV is associated with approximately a 20% decline in the odds of MACE (22% in an unadjusted model and 18% based on a fully adjusted model). The results provide strong validation for change in PAV as a surrogate marker of MACE and a strong rationale for use of such approaches in early phases of development of lipid modifying drugs.

It is important to emphasize that these conclusions remained consistent in both unadjusted and adjusted models and also with our extensive sensitivity analyses excluding one study at a time, including the largest trial [21]. It is also important to emphasize that the overall strength of the association between change in PAV and MACE was attenuated somewhat by adjustment for baseline PAV, age, baseline LDL-C level and study duration. These effects suggest strongly that the benefits of therapy, as reflected by change in PAV, are affected or mediated by duration of therapy, particularly in cohorts with higher

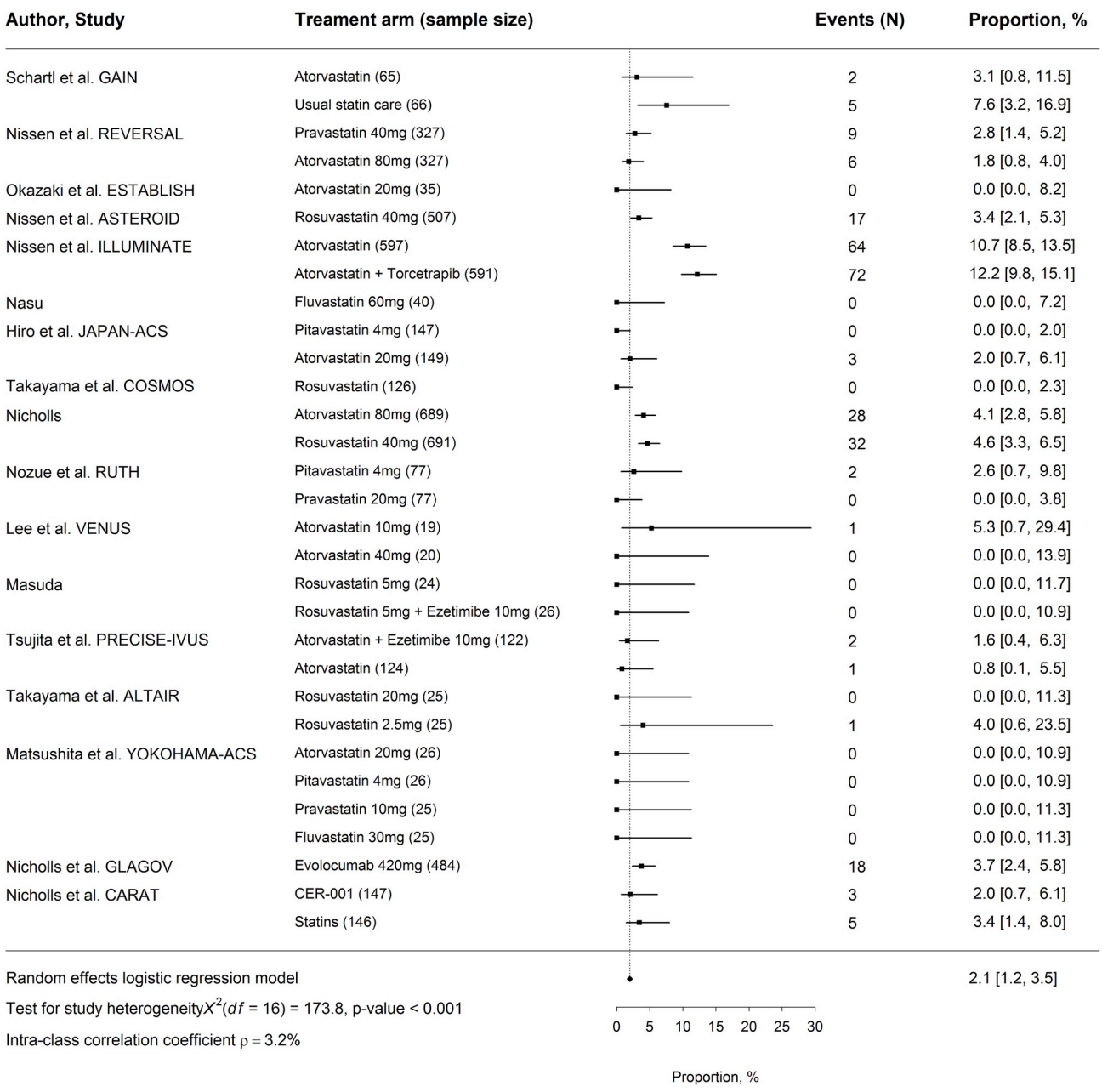

Fig. 3. Evaluation of heterogeneity of observed MACE.
This forest plot includes only study arms with active lipid-lowering therapy as identified by author and acronym. MACE is presented for each study arm as total counts and as the proportion of patients with MACE. For zero MACE counts, the lower confidence limit was set as zero, and the upper confidence limit was calculated as $(1–0.05^{(1/n)})$, where n is the sample size in the study arm. For nonzero MACE counts, the confidence interval was obtained from the log odds and then converted back to proportions.

baseline LDL-C and with more advanced age or PAV, all of which might reasonably be associated with a plaque substrate most amenable to the benefits of lipid lowering.

There are some limitations in this analysis. The observed association between change in PAV and MACE events does not necessarily infer a causal relation on a patient level. To assess the causal relation between PAV change and MACE outcome would require temporal ordering of PAV change and MACE events in individuals as would be the case in studies trying to detect specific, culprit lesions. The studies included in this review provided event counts but did not provide information on the timing of the events other than the fact that repeat IVUS imaging identified the end of the follow-up period. As a result, the changes in PAV reported in these studies may have occurred not only prior to but possibly after the MACE outcome, if it is a non-fatal event. Therefore, the estimated association should not be interpreted simplistically and is not intended to imply causality. Our estimate of the proportion of patients with MACE may not be precise for two reasons. First, because the number of patients with a MACE event was obtained by summing the number of individual MACE events, a patient who experienced two events would be double counted. Conversely, the proportion of patients with MACE may be underestimated, because not all components of MACE were reported in every study. We reason, however, that such causes of slight over or underrepresentation of events are expected to be rare given the low event rates overall. Additionally, there were only a few studies that reported stroke and unstable angina, and only one study reported transient ischemic attacks. Because of the significance of these types of events and the expectations that they would be few in number, it is.

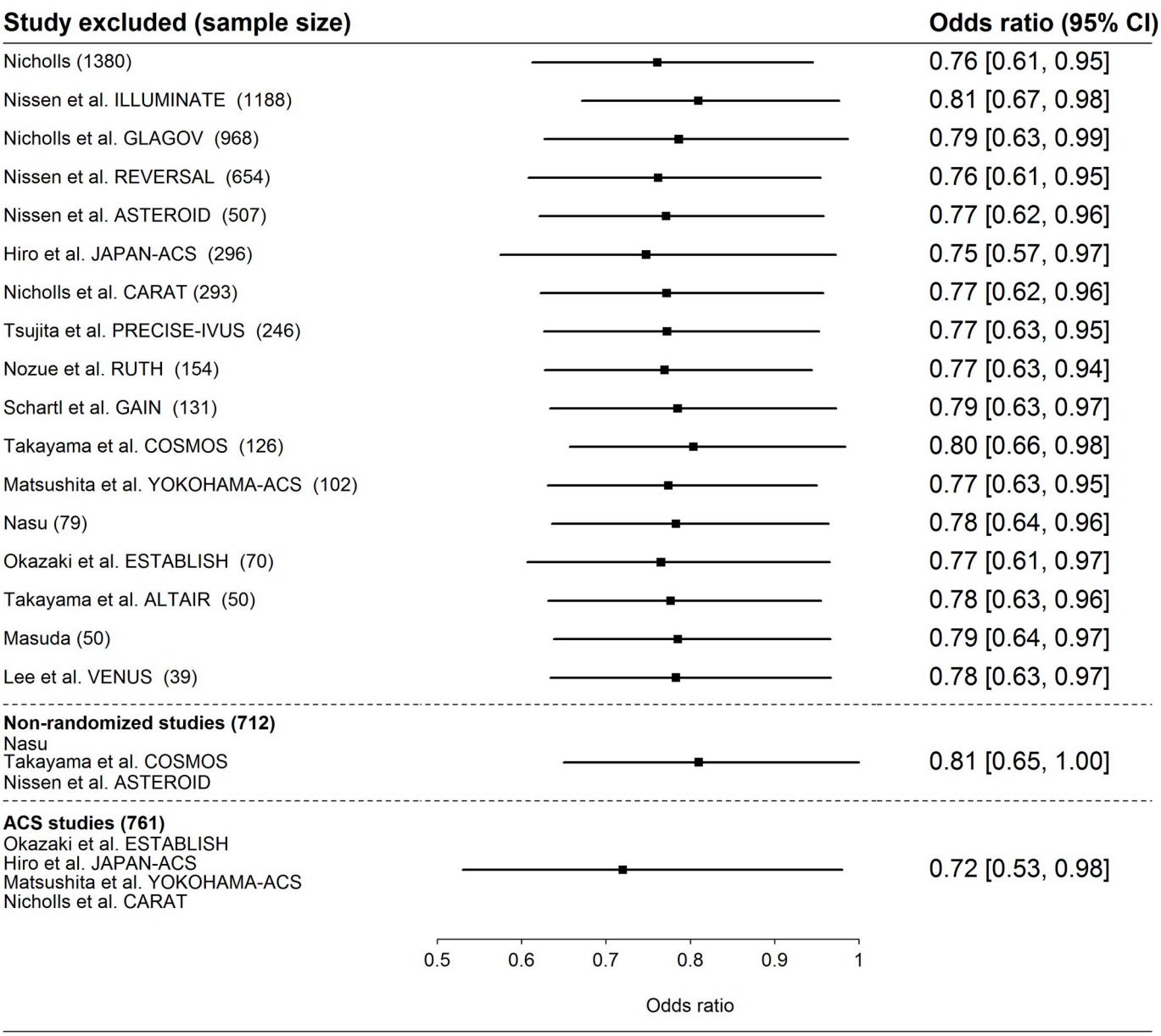

Fig. 4. Sensitivity analysis.
The odds ratio (OR) and 95% confidence intervals CI for MACE per 1% reduction in mean PAV is demonstrated after exclusion of one trial at a time (indicated by author and acronym and sample size); after excluding non-randomized studies; and after excluding studies performed in patients with acute coronary syndromes (ACS). The Odds ratios ranged between 0.72 and 0.81.

Not unreasonable to assume that studies explicitly commenting on MACE would have identified such events during follow-up, making our assumption that they were absent when not reported a reasonable one. Patient-level follow-up time was not provided in any publications; therefore, the proportion of patients with MACE may have been underestimated, because we could not account for early withdrawal or loss to follow-up. Not everyone who contributed to the MACE count was evaluated by IVUS, and thus the validity of our findings relies on the assumption that the event rate in patients with and without PAV measurement was similar. Finally, although our results support the validity of PAV as a surrogate marker for MACE, this finding should in no way detract from the absolute requirement to evaluate lipid therapies in studies that are long enough to ensure safety and powered adequately to demonstrate clinical benefits. In this context, IVUS studies may best serve the purpose of helping provide mechanistic insights and an integrated measure of vascular benefit in smaller cohorts during shorter time periods while larger and longer, definitive trials of safety and risk reduction proceed.

It has been demonstrated that each 1-mmol/L (38.7-mg/dL) reduction in LDL-C level is associated with a relative risk (RR) of 0.77 (ie, a 23% risk reduction) for major vascular events [31]. This relationship considers change in LDL-C as a surrogate of the outcomes that can be expected during therapy using safe medications, mainly but not solely statins. The current systematic review and meta-regression demonstrated that, at the study arm level, a reduction in mean PAV of 1% is associated with approximately a 20% reduction in the odds of MACE, specifically a 22% (95% CI: 4.0%, 37%, $p = 0.018$), unadjusted reduction and an 18% [95% CI: 5%, 30%, p- 0.011) reduction after adjusting for baseline PAV, age, study duration and baseline LDL). The demonstration of an association between the change in PAV and MACE supports use of this parameter as a surrogate end-point in lipid therapy trials.

Conflicts of interest

Mancini: Advisory Board Activity: Amgen, Sanofi, Esperion; Grants from Amgen, Sanofi, Astra Zeneca, Merck. The other authors have nothing to disclose.

Author contributions

Bhindi: Literature review and selection of papers, initial draft, critical review of revisions. Guan, Zhao, Humphries: All statistics, critical review of selected papers, critical review of manuscript, creation and critical review of figures and statistical tables. Mancini: Genesis of idea, literature review and selection, critical review of all and final revisions.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.atherosclerosis.2019.03.005.

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