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REVIEW

Autoimmune Diseases May Increase Adverse Cardiovascular Events After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis

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Background Outcomes of patients with autoimmune diseases after percutaneous coronary intervention (PCI), as compared to those without autoimmune disease, remain unclear.

Methods We searched Medline, EMBASE, and the Cochrane Library from their inception to 1 April 2017. All studies comparing the following outcomes of patients with and without autoimmune diseases after PCI were included: long-term mortality, major adverse cardiovascular events (MACE), repeat revascularisation, myocardial ischaemia or myocardial infarction (MI), restenosis, and in-hospital mortality. The Newcastle-Ottawa Quality Assessment Scale (NOS) and the quality assessment form of the Agency for Healthcare Research and Quality (USA) (AHRQ) were used for assessing the risk of bias, and the certainty of evidence was rated by the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).

Results A total of 11 studies were included in our analysis. Compared with patients without autoimmune diseases, those with autoimmune diseases carried an increased risk of MACEs (relative risk (RR): 2.24, 95% confidence interval (CI): 1.20–4.16; heterogeneity: $p = 0.128$, $I^2 = 56.9\%$), repeat revascularisation (RR: 1.66, 95% CI 95%: 1.01–2.72; heterogeneity: $p = 0.057$, $I^2 = 65.1\%$), ischaemia or MI (RR: 2.80, 95% CI: 1.38–5.65; heterogeneity: $p = 0.871$, $I^2 = 0.0\%$), and restenosis (RR: 2.06, 95% CI: 1.39–3.07; heterogeneity: $p = 0.665$, $I^2 = 0.0\%$) during the one-year follow-up after PCI, and carried an increased risk of MACEs (RR: 1.10, 95% CI: 1.04–1.17) and death (RR: 1.38, 95% CI: 1.25–1.51) during the 11-year follow-up after PCI.

Conclusions Evidence of very low quality showed that during the one-year follow-up period, patients with autoimmune diseases after PCI were more likely to experience MACEs, repeat revascularisation, myocardial ischaemia or MI, and restenosis. During the 11-year follow-up period, patients with autoimmune diseases after PCI were more likely to die. It is therefore important to watch for restenosis, repeat ischaemia or MI and other adverse events more carefully in patients with autoimmune diseases after PCI.

Keywords Autoimmune disease • Percutaneous coronary intervention • Outcome • Systematic review

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Background

Cardiovascular events such as myocardial infarction (MI), revascularisation, and death frequently occurred in patients with autoimmune diseases such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and antiphospholipid antibody syndrome (APS), etc [1–9]. Most tellingly, patients with RA have an equivalent risk of MI as patients with diabetes mellitus [10]. Therefore, patients with autoimmune diseases are likely to present for revascularisation, such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting, more frequently than the overall population. However, how well these patients do following PCI and how their autoimmune disease status influences them is still unclear. Subgroup analysis in two large cross-sectional studies of patients diagnosed with MI showed that those with RA who underwent PCI exhibited better in-hospital mortality than those without RA after adjusting for confounders [11,12]. Another cohort study found that RA and SLE were independent predictors of in-hospital mortality and such patients were more likely to succumb to death, ischaemic events, and MACE after PCI than those without RA during an 11-year follow-up [13]. One study revealed that patients with APS had higher rates of target vessel revascularisation after PCI than those without APS, and that rates of MI or mortality did not differ between the two groups during a one-year follow-up [14]. In a well-matched cohort study, patients with significant coronary heart disease undergoing PCI had similar outcomes irrespective of RA [15]. Another study with a one-year follow-up demonstrated that patients with SLE had higher rates of MI and re-PCI than those without SLE after adjusting for critical confounders [16]. Based on these contradictory findings, we may want to know whether vascular disease in autoimmune disease patients is in fact more aggressive, or if these patients need more careful follow-up for adverse events. We performed a systematic review and meta-analysis of controlled studies comparing the outcomes of patients with and without autoimmune diseases after PCI, in an effort to answer these questions.

Methods

This review was performed in accordance with the registered protocol at the PROSPERO International Prospective Register of Systematic Reviews (CRD 42017072230).

Eligibility Criteria

Types of Studies

Our analysis included only controlled observational studies comparing the outcomes of patients with and without autoimmune disease after PCI.

Types of Participants

The present study included adults aged ≥18 years, who underwent PCI for the management of coronary heart disease, including stable coronary heart disease, asymptomatic coronary heart diseases, unstable angina pectoris, acute coronary syndrome, and acute MI. The types of PCI included percutaneous coronary angioplasty (PTCA), bare-metal stent (BMS), and drug-eluting stent (DES).

Types of Exposures

The outcomes of the following two groups of participants were compared:

1. Participants who had been diagnosed with an autoimmune diseases at the time of the PCI.
2. Participants with no diagnosis of autoimmune disease at the time of the PCI.

Types of Outcome Measures

Primary Outcomes

1. Long-term mortality (defined as all-cause mortality during follow-up of greater than one year).
2. MACE (defined as a composite of MI, repeat revascularisation, and all-cause death).
3. Repeat revascularisation (as defined by the authors of the study).
4. Myocardial ischaemia or MI (as defined by the authors of the study).
5. Restenosis (as defined by the authors of the study).

Secondary Outcomes

In-hospital mortality.

Data Sources and Search Strategy

We searched Medline, EMBASE, and the Cochrane Library, from their inception until 1 April 2017. Then, we performed a manual search of the references of the included studies. The keywords used were ''autoimmune disease'' and ''percutaneous coronary intervention''. The search results were combined with the Boolean operator ''and''. No restrictions were applied on languages or other factors.

Study Selection

Two reviewers independently reviewed the titles and abstracts of all of the retrieved results for potentially eligible studies. If either reviewer determined that a study was potentially relevant, the full text of the specific study was accessed and reviewed in order to determine its eligibility.

Data Extraction

A data collection form was utilised for obtaining the required information, which was piloted on a minimum of one study. Two reviewers independently extracted the required data from all of the eligible studies and cross-checked the data. Details of the process were entered into the PRISMA flow chart. The extracted data included

funding, eligibility criteria, demographic characteristics, number of participants, type of autoimmune diseases, indication for PCI, type of PCI, outcomes, the period from initiation to outcome event, rates of outcome events, and proportions of patients lost to follow-up.

Quality Assessment

Two reviewers assessed the risk of bias of the included cohort studies using the Newcastle-Ottawa Quality Assessment Scale (NOS), in three domains, including selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertainment of exposure, and demonstration that the outcome of interest was not present at the start of study), comparability (comparability of cohorts on the basis of the design or analysis), and outcome (assessment of outcome, if the follow-up period was long enough for outcomes to occur, and adequacy of the follow-up of cohorts) [17,18]. In addition, two reviewers assessed the risk of bias of the included studies using the quality assessment form of the Agency for Healthcare Research and Quality (USA) (AHRQ) [19].

The reviewers also used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) [20] methodology in order to rate the certainty of the evidence for each outcome as high, moderate, low, and very low. The detailed GRADE guidelines were employed to assess the overall risk of bias [21], imprecision [22], inconsistency [23], indirectness [24], and publication bias [25], after which, an evidence profile was summarised. The reviewers reached a consensus through discussion to overcome discrepancies with respect to eligibility, data extraction, assessment of the risk of bias, and certainty of evidence.

Data Synthesis and Statistical Analysis

Descriptive statistics were reported as proportions for categorical variables and means (plus standard deviations) for continuous variables. Outcomes included long-term mortality, MACE, repeat revascularisation, myocardial ischaemia or MI, restenosis, and in-hospital mortality, which were assessed by pooled relative risk (RR) among the cohort studies or pooled odds ratio (OR) among the cross-sectional studies. The corresponding 95% confidence intervals (CIs) were calculated by the random-effects model ($I^2 > 50\%$) or fixed-effects model ($I^2 < 50\%$).

Statistical heterogeneity was assessed using the I^2 statistic (0–40%, might not be important; 30–60%, moderate heterogeneity may be present, 50–90%, substantial heterogeneity may be present, and 75–100%, considerable heterogeneity may be present) and p-value (a two-tailed $p < 0.05$ was considered to be statistically significant). Sensitivity analysis was conducted to assess the potential impact of bias when $I^2 > 60\%$. Subgroup analysis was performed according to the length of the follow-up period.

All statistical analyses were performed using Revman (Review Manager [Computer program] version 5.3. Copenhagen: The Nordic Cochrane Centre, the Cochrane Collaboration, 2014) and Stata (version 12.0. StataCorp LP, College Station, TX, USA.)

Results

Studies Identification

The current search retrieved 730 abstracts, of which, 21 were eligible for full-text review, and 10 were subsequently excluded. Thus, 11 studies were included [11–16,26–30] (Figure 1).

Study and Patient Characteristics

A total of 824,745 participants, of whom, 6,801 were diagnosed with autoimmune diseases, were included in the current study. Tables 1 and 2 summarise the characteristics of the 11 included studies. Among these, two cross-sectional studies presented data from a PCI subgroup, three were retrospective cohort studies, and six were prospective cohort studies. Indications for PCI included stable coronary heart disease, asymptomatic coronary heart disease, acute coronary syndrome, and MI. The types of PCI included PTCA, BMS, and DES. Autoimmune diseases included RA, SLE, APS, positive anticardiolipin antibodies, and positive antiphospholipid antibodies. The period of long-term follow-up varied from one to 11 years. The study by Lai et al. [13] was analysed as a subgroup due to its significantly prolonged duration of follow-up compared to the other studies. The study by Sintek et al. [30] was treated similarly, and the number of lesions, rather than the number of participants, was analysed in this study. One study [14] presented 3-year follow-up data; however, only data from the 1-year follow-up was used, as 42% of the participants were lost by 3 years.

Assessment of Risk of Bias of Included Studies

The risk of bias originated primarily from the comparability of cohorts on the basis of design or analysis (Figures 2 and 3).

Outcomes Assessment

The confidence in the estimates of the effect was assessed with GRADE (Table 3).

MACE

During the one-year follow-up period, of the 47 patients with autoimmune disease and 3,737 patients without autoimmune disease, 17 and 756 experienced MACEs, respectively. Patients with autoimmune disease showed an increased risk of MACEs (RR: 2.24, 95% CI: 1.20–4.16; heterogeneity: $p = 0.128$, $I^2 = 56.9\%$) (Figure 4) [14,16]. The overall rating of confidence in the estimates was very low, owing to the risk of bias and inconsistency.

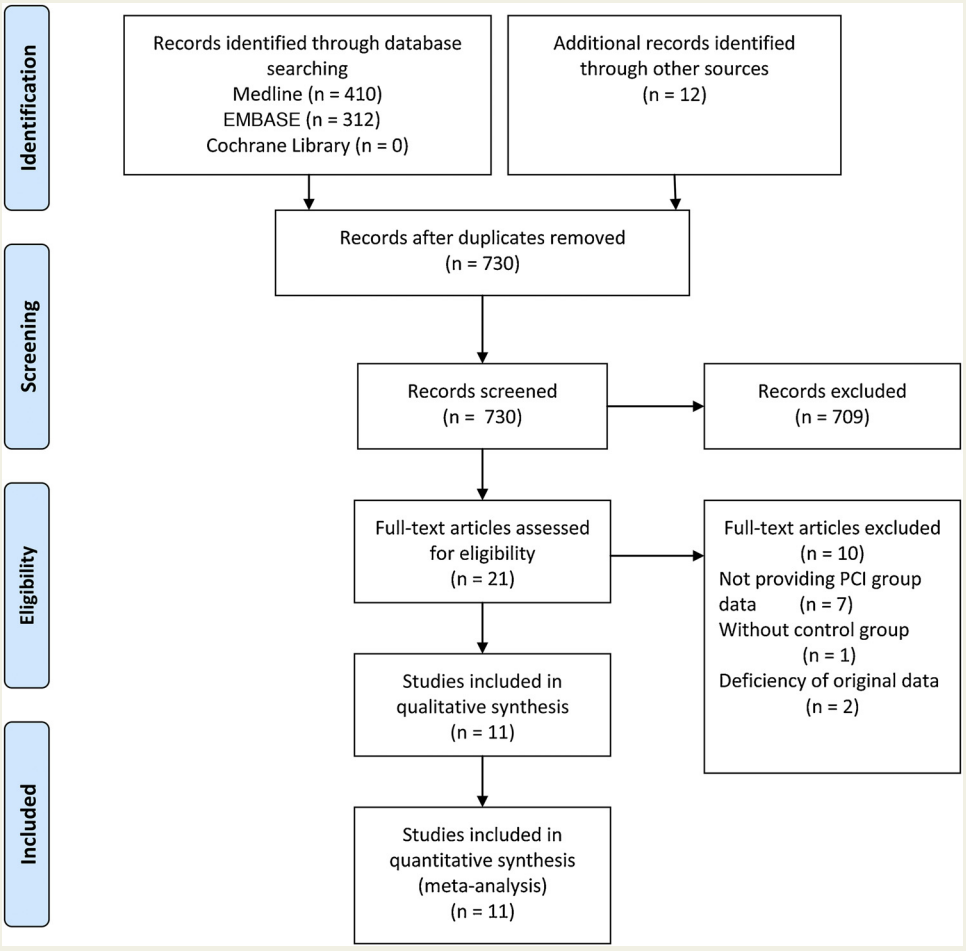

Figure 1 Study flow chart.

During the 11-year follow-up period, of the 736 patients with autoimmune disease and 170,762 patients without autoimmune disease, 456 and 95,824 experienced MACEs, respectively. Patients with autoimmune disease showed an increased risk of MACEs (RR: 1.10, 95% CI: 1.04–1.17) (Figure 4) [13]. The overall rating of confidence in the estimates was very low, owing to the risk of bias.

During the 1 and 11 years follow-up, of the 783 patients with autoimmune disease and 174,499 patients without autoimmune disease, 473 and 96,580 experienced MACEs, respectively. Patients with autoimmune disease did not show an increased risk of MACEs (RR: 1.69, 95% CI: 0.93–3.05; heterogeneity: $p = 0.002$, $I^2 = 84.2\%$) (Figure 4) [13,14,16]. The overall rating of confidence in the estimates was very low, owing to the risk of bias.

Long-Term Mortality

During the 1-year follow-up, of the 77 patients with autoimmune disease and 3,787 patients without autoimmune disease, 5 and 191 patients died, respectively. Patients with autoimmune disease did not show an increased risk of death (RR: 1.20, 95% CI: 0.47–3.07; heterogeneity: $p = 0.665$, $I^2 = 0.0\%$) (Figure 5) [14,16,27]. The overall rating of confidence in the estimates was very low, owing to the risk of bias and imprecision.

During the 11-year follow-up, of the 736 patients with autoimmune disease and 170,762 patients without autoimmune disease, 270 and 45,489 died, respectively. Patients with autoimmune disease showed an increased risk of death (RR: 1.38, 95% CI: 1.25–1.51) (Figure 5) [13]. The overall rating of confidence in the estimates was very low, owing to the risk of bias.

During the 1 and 11 years follow-up, of the 813 patients with autoimmune disease and 174,549 patients without autoimmune disease, 275 and 45,680 patients died, respectively. Patients with autoimmune disease showed an increased risk of death (RR: 1.38, 95% CI: 1.25–1.51; heterogeneity: $p = 0.852$, $I^2 = 0.0\%$) (Figure 5) [13,14,16,27]. The overall rating of confidence in the estimates was very low, owing to the risk of bias and imprecision.

Repeat Revascularisation

During the one-year follow-up period, of the 287 patients with autoimmune disease and 4,937 patients without autoimmune disease, 68 and 777 experienced repeat revascularisation, respectively. Patients with autoimmune disease

Table 1 Summary of general characteristics of included studies for meta-analysis.

Study ID	Study type	Sampling Strategy	Autoimmune disease (exposure)	Indication for PCI	Type of PCI	Number of participants (patients/control)	Measured outcomes	Follow-up (mean, years)	Lost to follow-up (%)	Study location
Sintek, 2016	Retrospective cohort	cluster sampling	RA	ACS, Positive Stress Test	BMS, DES	143/541	TLR, TVR	5	0	USA
Desai, 2010	Retrospective cohort	cluster sampling	RA	ACS, SAP Asymptomatic	PTCA, BMS, DES	43/43	In-hospital mortality	3.8	22	USA
Lai, 2016	Retrospective cohort	cluster sampling	RA, SLE	ACS, others	PTCA, Stent	525/211/170,762[a]	In-hospital mortality, ischaemia, Repeat ReVas, long-term mortality, MACE	11	N/A	Taiwan
Maksimowicz-McKinnon, 2008	Prospective cohort	cluster sampling	SLE	Asymptomatic, SAP, ACS, others	PTCA, BMS, DES	28/3357	MI, Repeat ReVas, Long-term mortality, MACE	1	0/4.5	USA
Francis, 2010[b]	Controlled cross-sectional	cluster sampling	RA	MI	PCI	1562/157,869	In-hospital mortality	In-hospital	0	USA
Varghese, 2010[b]	Controlled cross-sectional	cluster sampling	RA	N/A	PTCA, Stent	3974/483,615	In-hospital mortality	In-hospital	0	USA
Perl, 2012	Prospective cohort	cluster sampling	APS	ACS, SAP	DES, other	19/380	TVR, long-term mortality, MACE	1[c]	10.3	Israel
Gürlek, 2005	Prospective cohort	N/A	ACL+	ACS	Stent	30/50	In-hospital mortality, restenosis, MI, long-term mortality	1	0[d]	Turkey
Kang, 2012	Prospective cohort	cluster sampling	RA	MI, others	Non-stenting PCI	240/1200	In-hospital mortality, Repeat ReVas	1	N/A	Taiwan
Ludia, 1998	Prospective cohort	N/A	APL+	ACS, SAP	PTCA	15/45	Restenosis	1.25	10	Italy
Eber, 1992	Prospective cohort	N/A	ACL+	CHD[e]	PTCA	11/54	Restenosis	1.2	0	Austria

Abbreviations: PCI, percutaneous coronary intervention; PTCA, percutaneous coronary angioplasty; CHD, coronary heart disease; ACS, acute coronary syndrome; SAP, stable angina pectoris; TLR, target lesion revascularisation; TVR, target vessel revascularisation; MI, myocardial infarction; Repeat ReVas, repeat revascularisation; MACE, major adverse cardiovascular events; APS, antiphospholipid syndrome; ACL+ positive, anticardiolipin antibodies; APL+ positive, antiphospholipid antibodies; NA, not available; MI, myocardial infarction; RA, rheumatoid arthritis; BMS, bare metal stent; DES, drug eluting stent; SLE, systemic lupus erythematosus.

[a]Data were presented as RA/SLE/control.

[b]subgroup data.

[c]data of 1-year follow-up was used because of high rate of loss to follow-up after 1 year.

[d]7 patients without data of coronary angiography.

[e]> = 75% stenosis.

Table 2 Baseline characteristics of included studies for meta-analysis.

Study ID	Indication for PCI				Types of PCI			Clinical confounders				
	STEMI P/C	NSTEMI P/C	UAP P/C	Others P/C	PTCA P/C	BMS P/C	DES P/C	Age(years ± SD) P/C	Female P/C	HTN P/C	DM P/C	Smokers P/C
Sintek, 2016	11/9	26/25	37/34	24/29	0/0	40/40	60/60	64 ± 12/64 ± 11.5	61/54	85/87	33/38	54/52
Desai, 2010	74/67[a]			26/33	N/A	N/A	35/44	N/A	N/A	N/A[b]	N/A[b]	N/A[b]
Lai, 2016	45.9/47.6[a]			54.1/52.4	51.3/42.4[c]	48.7/57.6[c,d]		68.0 ± 10.0/55.7 ± 12.6/65.3± 12.1[c,e]	59.0/28.1[c]	69.0/65.9	32.5/38.7[c]	N/A
Maksimowicz-McKinnon, 2008	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	N/A[b]	55.0/63.5[c]	89.3/35.7[c]	N/A[b]	N/A[b]	N/A[b]
Francis, 2010	100/100[f]		0/0	0/0	100/100[g]			N/A	N/A	N/A	N/A	N/A
Varghese, 2010	N/A	N/A	N/A	N/A	N/A	N/A	N/A	66.8 ± 10.9/64.4 ± 12.3[c]	56.7/33.9[c]	66.1/63.4[c]	N/A	N/A
Perl, 2012	52.6/52.6[a]			47.4/47.4	63.2/58.7[h]	36.8/41.3		60.2 ± 11.8/60.1 ± 9.0	42.1/42.9	84.2/78.9	31.6/32.9	36.8/48.9
Gürlek, 2005	100/100[a]			0/0	0/0	100/100[d]		61 ± 10/58 ± 11	N/A[b]	43/48	13/32	57/46
Kang, 2012	32.1/35.9[f]			67.9/64.1	100/100	0/0	0/0	N/A	45.0/45.0	75.0/64.4	40.8/40.3	N/A
Ludia, 1998	0/0	0/0	40/46	60/54	100/100	0/0	0/0	66/61	N/A	40/35	26/6[c]	13/11
Eber, 1992	100/100[i]				100/100	0/0	0/0	N/A	N/A	N/A	N/A	N/A

Abbreviations: P/C, corresponding proportion in patients/control; PCI, percutaneous coronary intervention; HTN, hypertension; PTCA, percutaneous coronary angioplasty; BMS, bare metal stent; DES, drug eluting stent; SD, standard deviation; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; STEMI, ST elevation myocardial infarction; NSTEMI, non-ST elevation myocardial infarction; UAP, unstable angina pectoris; N/A, not available; DM, diabetes mellitus.

[a]acute coronary syndrome.

[b]no exact data, only description of no significant difference between patients and the control in article.

[c]$P < 0.01$.

[d]BMS and DES together.

[e]data were presented as RA/SLE/control for this study.

[f]STEMI and NSTEMI together.

[g]PTCA, BMS and DES together.

[h]PTCA and BMS together.

[i]coronary heart disease with > = 75% stenosis.

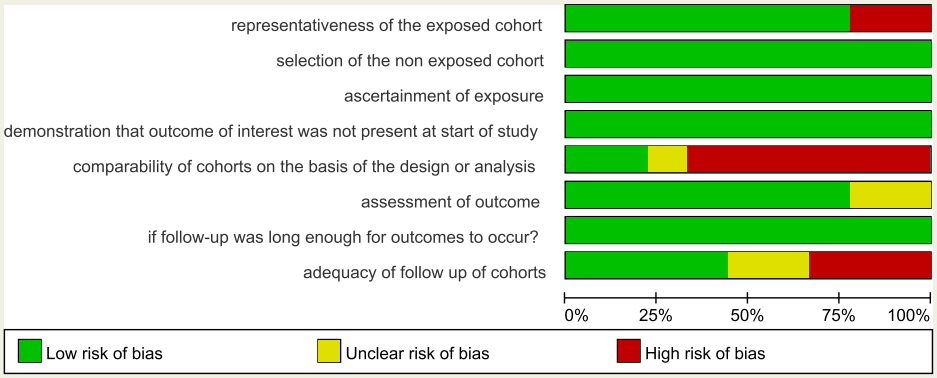

Figure 2 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

showed an increased risk of repeat revascularisation (RR: 1.66, 95% CI 95%: 1.01–2.72; heterogeneity: $p = 0.057$, $I^2 = 65.1\%$) (Figure 6) [14,16,28]. Sensitivity analysis revealed stability and low sensitivity. The overall rating of confidence in the estimates was very low, owing to the risk of bias and inconsistency.

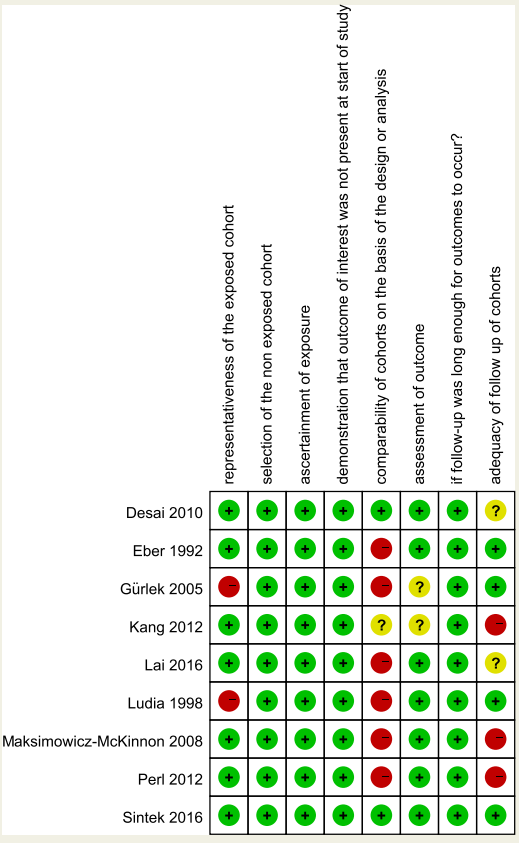

Figure 3 Risk of bias summary: review of authors' judgements about each risk of bias item for each included study.
+, low risk of bias; -, high risk of bias; ?, risk of bias underminable.

During the 5-year follow-up period, of the 228 lesions in patients with autoimmune disease and 667 lesions in patients without autoimmune disease, 89 and 213 experienced repeat revascularisations, respectively. Patients with autoimmune disease did not show an increased risk of repeat revascularisation (RR: 1.22, 95% CI: 1.00–1.49) (Figure 6) [30]. The overall rating of confidence in the estimates was very low, owing to the imprecision.

During the 11-year follow-up, of the 736 patients with autoimmune disease and 170,762 patients without autoimmune disease, 252 and 61,872 experienced repeat revascularisations, respectively. Patients with autoimmune disease did not show an increased risk of repeat revascularisation (RR: 0.94, 95% CI: 0.85–1.04) (Figure 6) [13]. The overall rating of confidence in the estimates was very low, owing to the risk of bias.

During the 1 and 11 years follow-up, of the 1,023 patients with autoimmune disease and 175,699 patients without autoimmune disease, 320 and 62,649 experienced repeat revascularisations, respectively. Patients with autoimmune disease did not show an increased risk of repeat revascularisation (RR: 1.33, 95% CI: 0.94–1.90; heterogeneity: $p = 0.002$, $I^2 = 79.2\%$) (Figure 6) [13,14,16,28]. The overall rating of confidence in the estimates was very low, owing to the risk of bias and inconsistency.

Ischaemia or MI

During the one-year follow-up period, of the 58 patients with autoimmune disease and 3,407 patients without autoimmune disease, 12 and 166 experienced ischaemia or MI, respectively. Patients with autoimmune disease showed an increased risk of ischaemia or MI (RR: 2.80, 95% CI: 1.38–5.65; heterogeneity: $p = 0.871$, $I^2 = 0.0\%$) (Figure 7) [16,27]. The overall rating of confidence in the estimates was very low, owing to the risk of bias.

During the 11-year follow-up, of the 736 patients with autoimmune disease and 170,762 patients without autoimmune disease, 219 and 49,586 experienced ischaemia or MI, respectively. Patients with autoimmune disease did not show an increased risk of ischaemia or MI (RR: 1.02, 95% CI: 0.92–

Table 3 GRADE assessment of confidence in estimates of effect.

Outcomes	Period of follow-up (mean, years)	Partcipants (studies) n(n)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Quality	Risk ratio (95% CI)
Restenosis	1	205(3)	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	not detected	very low	2.06 (1.39 - 3.07)
Ischaemia or MI	1	3,465(2)	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	not detected	very low	2.80 (1.38 - 5.65)
Ischaemia or MI	11	171,498(1)	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	not detected	very low	1.02 (0.92 - 1.15)
Ischaemia or MI	1-11	174,963(3)	serious[a]	serious[b]	no serious indirectness	no serious imprecision	not detected	very low	1.80 (0.79 - 4.09)
Repeat ReVas	1	5,224(3)	serious[a,c]	serious[b]	no serious indirectness	no serious imprecision	not detected	very low	1.66 (1.01 - 2.72)
Repeat ReVas	5	895(1)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[d]	not detected	very low	1.22 (1.00 - 1.49)
Repeat ReVas	11	171,498(1)	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	not detected	very low	0.94 (0.85 - 1.04)
Repeat ReVas	1-11	176,722(4)	serious[a,c]	serious[b]	no serious indirectness	no serious imprecision	not detected	very low	1.33 (0.94 - 1.90)
Long-term mortality	1	3,864(3)	serious[a]	no serious inconsistency	no serious indirectness	serious[d]	not detected	very low	1.20 (0.47 - 3.07)
Long-term mortality	11	171,498(1)	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	not detected	very low	1.38 (1.25 - 1.51)
Long-term mortality	1-11	175,362(4)	serious[a]	no serious inconsistency	no serious indirectness	serious[d]	not detected	very low	1.38 (1.25 - 1.51)
MACE	1	3,784(2)	serious[a,c]	serious[b]	no serious indirectness	no serious imprecision	not detected	very low	2.24 (1.20 - 4.16)
MACE	11	171,498(1)	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	not detected	very low	1.10 (1.04 - 1.17)
MACE	1-11	175,282(3)	serious[a]	no serious inconsistency	no serious indirectness	no serious imprecision	not detected	very low	1.69 (0.93 - 3.05)

Abbreviations: MI, myocardial infarction; Repeat ReVas, repeat revascularisation; MACE, major adverse cardiac events; CI, confidence interval.

[a]Failure to match for prognostic factors and/or adjustment in statistical analysis.

[b]Heterogeneity: I-squared $> 50\%$, $P < 0.05$.

[c]Incomplete follow-up.

[d]The 95% CI for effects suggests potential for benefit and harm.

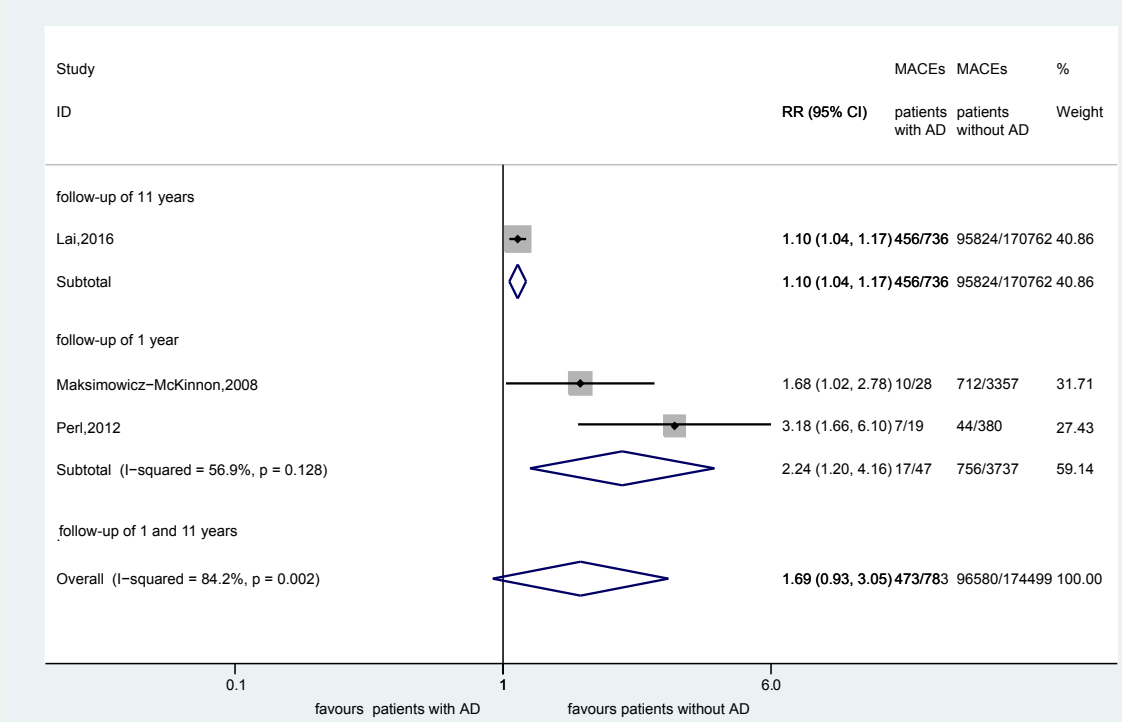

Figure 4 Forest plots of relative risk for major adverse cardiovascular events.
Abbreviations: RR, relative risk; AD, autoimmune disease.

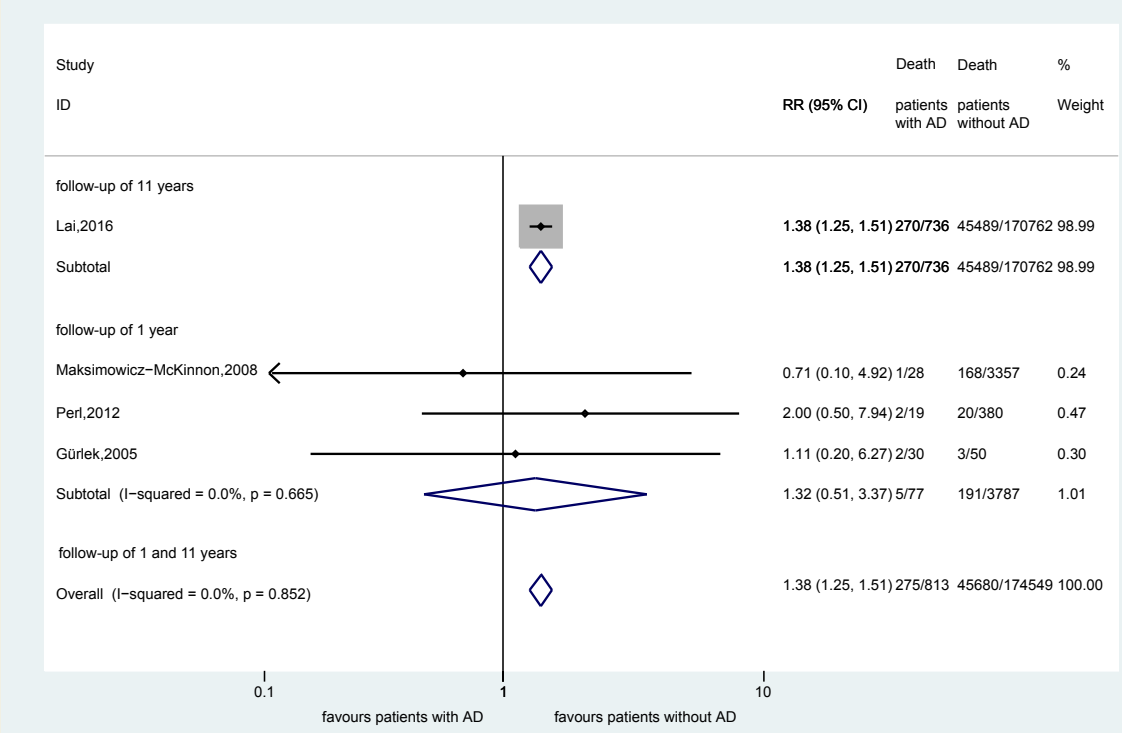

Figure 5 Forest plots of relative risk for long-term mortality.
Abbreviations: RR, relative risk; AD, autoimmune disease.

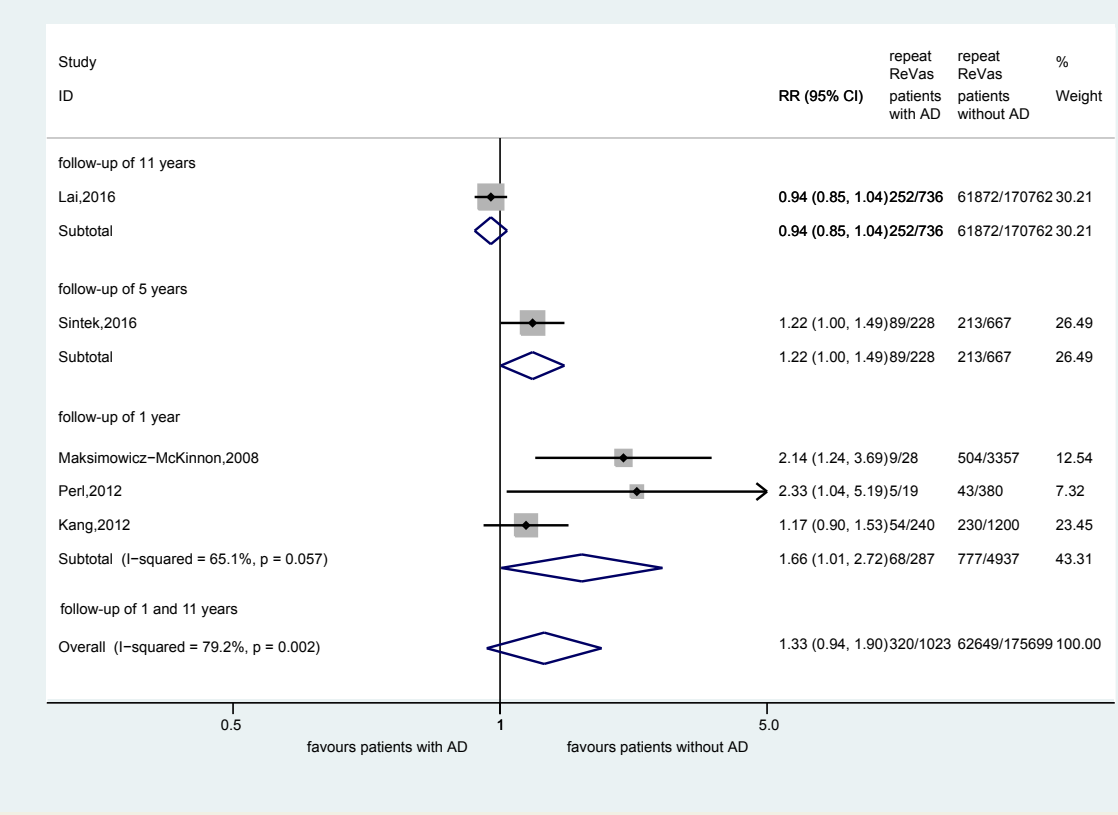

Figure 6 Forest plots of relative risk for repeat revascularisation.
The result of 5-year follow-up was presented as ''repeat ReVas/lesion''. The overall RR did not include the result of 5-year follow-up because the above reason.
Abbreviations: RR, relative risk; repeat ReVas, repeat revascularisation; AD, autoimmune disease.

1.15) (Figure 7) [13]. The overall rating of confidence in the estimates was very low owing to the risk of bias.

During the 1 and 11 years follow-up, of the 794 patients with autoimmune disease and 174,169 patients without autoimmune disease, 231 and 49,752 experienced ischaemia or MI, respectively. Patients with autoimmune disease did not show an increased risk of ischaemia or MI (RR: 1.80, 95% CI: 0.70–4.09; heterogeneity: $p = 0.016$, $I^2 = 76.0\%$) (Figure 7) [13,16,27]. The overall rating of confidence in the estimates was very low owing to the risk of bias and inconsistency.

Restenosis

Of the 56 patients with autoimmune disease and 149 patients without autoimmune disease, 23 and 38 experienced restenosis after PCI during follow-up, respectively. Patients with autoimmune disease showed an increased risk of restenosis (RR: 2.06, 95% CI: 1.39–3.07; heterogeneity: $p = 0.665$, $I^2 = 0.0\%$) (Figure 8) [26,27,29]. The overall rating of confidence in the estimates was very low, owing to the risk of bias.

In-Hospital Mortality

A total of four cohort studies and two cross-sectional studies reported in-hospital mortality data. Among these four cohort studies, comprising 1,049 patients with autoimmune disease and 172,055 patients without autoimmune disease, 50 and 3,482 died in the hospital, respectively. Patients with autoimmune disease did not show an increased risk of in-hospital death (RR: 1.62, 95% CI: 0.73–3.57; heterogeneity: $p = 0.026$, $I^2 = 67.5\%$) (Figure 9) [13,15,27,28]. The overall rating of confidence in the estimates was very low, owing to the imprecision.

Among the two cross-sectional studies, comprising 5,536 patients with autoimmune disease and 641,484 patients without autoimmune disease, only ORs were reported with respect to in-hospital mortality and thus the pooled OR was calculated. Patients with autoimmune disease showed a reduced risk of in-hospital death (OR: 0.75, 95% CI: 0.58–0.96; heterogeneity: $p = 0.678$, $I^2 = 0.0\%$) (Figure 10) [11,12]. However, the participants of both cross-sectional studies were selected from the same group of patients; one study enrolled patients diagnosed with MI, while the other enrolled those who underwent PCI. Thus, a potential risk of bias cannot be avoided.

As only a small number of studies were included for each outcome, we did not assess the risk of publication bias.

Discussion

The pooled analysis of 11 observational studies encompassed 824,745 participants, of whom, 6,801 were diagnosed with autoimmune diseases. We found that, during the one-year

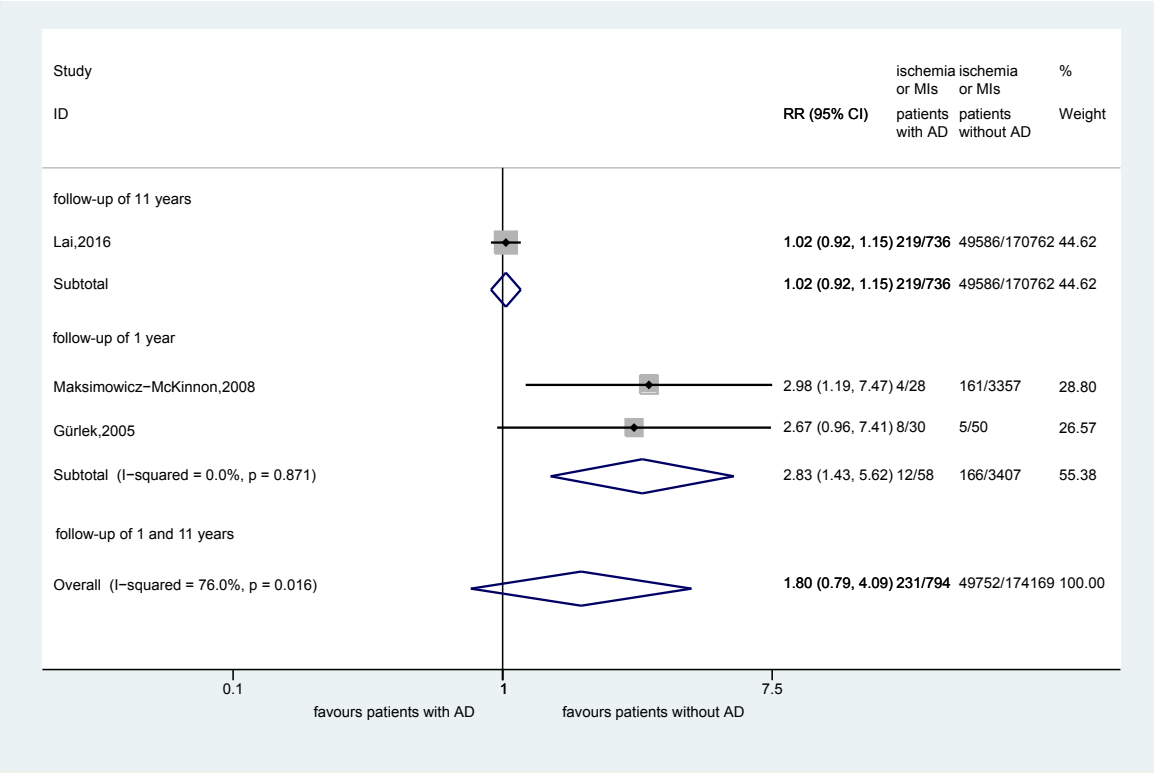

Figure 7 Forest plots of relative risk for ischaemia or myocardial infarction.
Abbreviations: RR, relative risk; MI, myocardial infarction; AD, autoimmune disease.

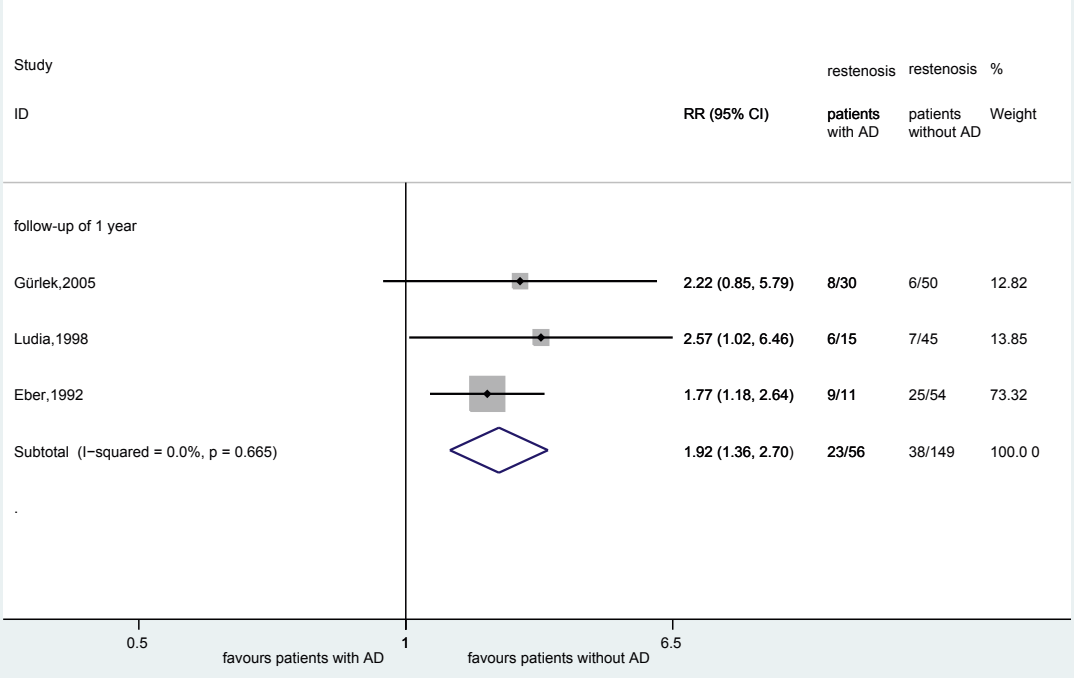

Figure 8 Forest plot of relative risk for restenosis.
Abbreviations: RR, relative risk; AD, autoimmune disease.

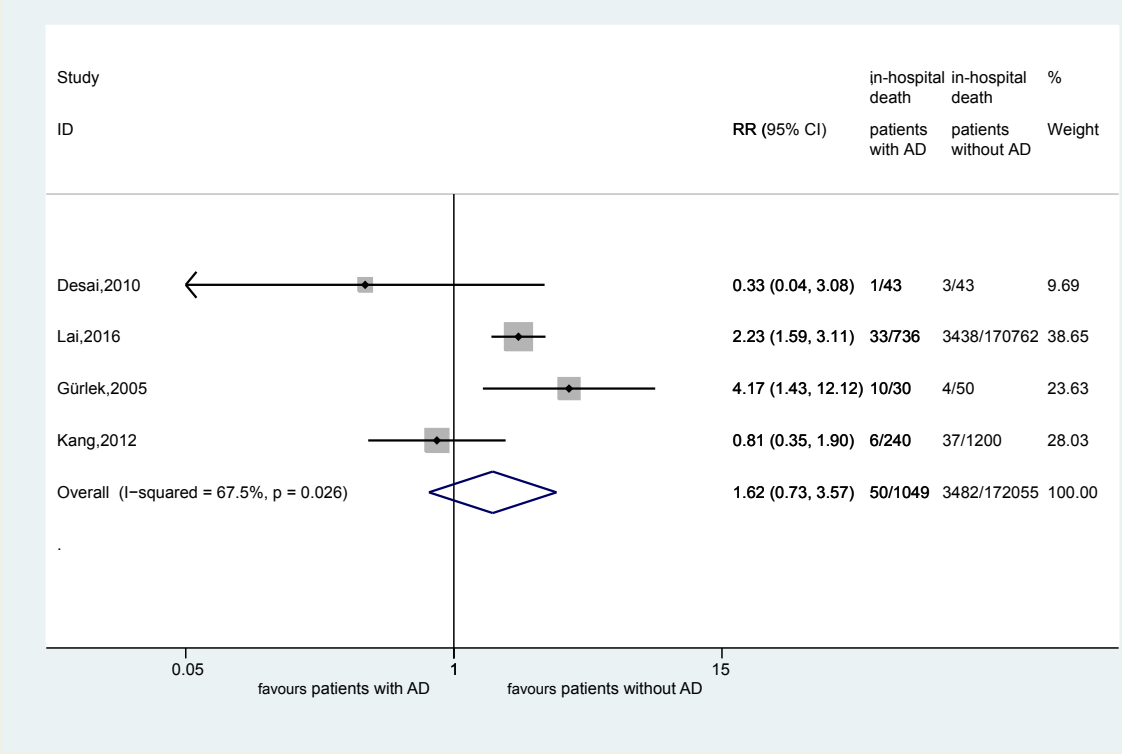

Figure 9 Forest plot of relative risk for in-hospital mortality. Abbreviations: RR, relative risk; AD, autoimmune disease.

follow-up period, the rates of MACE, repeat revascularisation, ischaemia or MI, and restenosis after PCI were higher in patients with autoimmune disease, while the rate of mortality did not differ between the groups. During the 11-year follow-up, the rates of mortality and MACE after PCI were higher in patients with autoimmune disease, while the rates of ischaemia or MI and repeat revascularisation did not differ between the groups.

Patients with autoimmune disease are predisposed to accelerated atherosclerosis and adverse cardiovascular events. The pathophysiological mechanisms underlying this phenomenon may be attributed to chronic inflammation, which exists in almost all autoimmune diseases and has been regarded as a major pathogenic factor. Response to chronic systemic inflammation, indicated by C-reactive protein level and erythrocyte sedimentation rate, has been found to be positively associated with cardiovascular events and mortality in RA patients [31]. A high level of the anticardiolipin antibody has also been found to be correlated with an increased rate of restenosis after PCI [26]. Patients with positive anticardiolipin levels showed a high rate of restenosis after PCI, even in the absence of potential autoimmune disease [27]. Patients with SLE exhibited a higher prevalence of anticardiolipin antibodies, relative to other patients [32]. Because inflammation occurs extensively and plays a significant role in adverse cardiovascular events after PCI, in patients with autoimmune disease, we attempted to pool all of the available studies addressing any autoimmune disease in order to obtain the present results.

Restenosis is a major factor triggering a series of adverse cardiovascular events, such as ischaemia or MI and repeat revascularisation, and often occurs within the first year after PCI, including PTCA, BMS, or DES [33–37]. The chronic inflammation occurring in patients with autoimmune disease might serve as a critical factor in the genesis of restenosis, as demonstrated previously [26,27]. Thus, in the current study, patients with autoimmune disease experience higher rates of restenosis during the one-year follow-up period. Similarly, patients with autoimmune disease experienced more myocardial ischaemia, MI, and repeat revascularisations during the one-year follow-up, as an increase in these outcomes in these patients can be attributed in part to the high rate of restenosis. That the rates of myocardial ischaemia, MI, and repeat revascularisation did not differ between the groups during the five-year or 11-year follow-up might be explained in part by a similar rate of restenosis over time between the groups.

In the current study, mortality within the first year after PCI did not differ between the patients with and without autoimmune diseases, while during the 11-year follow-up, patients with autoimmune disease suffered more mortality. In the study by Lai et al. [13], >171,000 participants, including 736 patients diagnosed with RA or SLE, were followed for approximately 10 years. The Kaplan–Meier survival curves displayed a distinct difference in mortality between patients

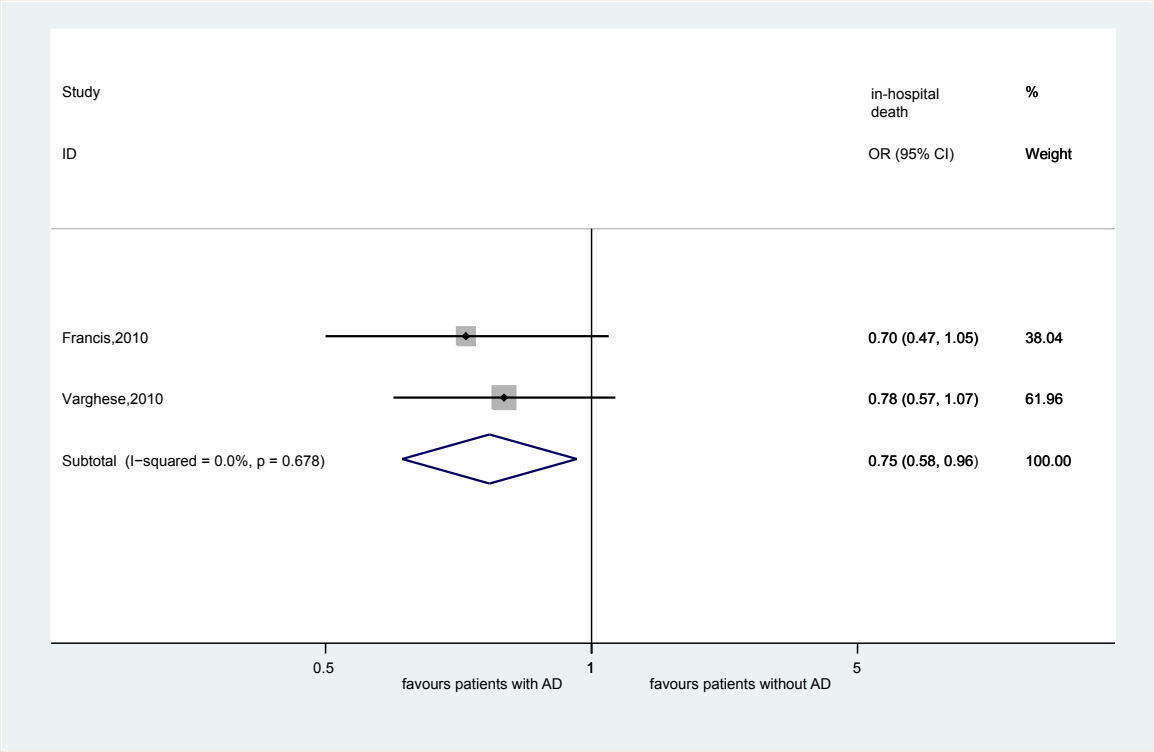

Figure 10 Forest plot of odds ratio for in-hospital mortality. Abbreviations: OR, odds ratio; AD, autoimmune disease.

with and without autoimmune disease over this period. Several potential factors might be responsible for increasing mortality in patients with autoimmune disease in the later years after PCI, thereby necessitating further studies.

The current systematic review is not the only study that has compared outcomes after PCI in patients with and without autoimmune disease. A study by Bundhun et al. analysed seven studies, including patients with SLE and/or APS, with a follow-up period of greater than one year [38]. The study found that rates of mortality, MI, repeat revascularisation, and MACE were higher in the patients with autoimmune disease (OR: 2.02, 95% CI: 1.63–2.49, $p < 0.00001$; OR: 1.59, 95% CI: 1.23–2.05, $p = 0.0004$; OR: 2.59, 95% CI: 1.26–5.31, $p = 0.001$; OR: 2.40, 95% CI: 1.42–4.03, $p = 0.001$, respectively) during follow-up periods of greater than 1 year but less than 3 years. The mortality did not differ between the groups during follow-up of greater than 3 years. Although their results were similar to the current study, our study has several advantages that should be considered. By including additional categories of autoimmune disease, the real conditions of the various autoimmune diseases were displayed comprehensively, based on the present evidence. First, we obtained data for restenosis from the eligible studies, which was a crucial outcome after PCI. Subsequently, the outcomes for 1-year, 5-year, and 11-year follow-up periods provided a comprehensive view of the issue. Moreover, we found that the mortality rate in patients with autoimmune disease increased and, in fact, was higher than that of the control group when the follow-up period was prolonged from 1 to 11 years, as compared to the previous study. This outcome was a reasonable one, as chronic inflammation in patients with autoimmune disease may be increasingly detrimental with the passage of time.

Nevertheless, the current study has several advantages as compared to other reviews. First, according to reasonable inference, we included and analysed the maximum number of studies on autoimmune disease, with a novel theory. Second, we assessed the quality of evidence using the GRADE approach. Third, we registered the protocol for the systematic review on the PROSPERO International Prospective Register of Systematic Reviews (CRD42017072230), which substantiates the originality of the present systematic review.

The current review also has some limitations. The small number of eligible studies could result in a potential bias, and the conclusions are also subject to bias as they are drawn from observational studies.

Conclusions

According to the pooled analysis of 11 observational studies encompassing 824,745 participants, the rates of repeat revascularisation, ischaemia or MI, and restenosis, of patients with autoimmune disease after PCI were higher during the one-year follow-up period, and the rates of MACE and mortality

were higher during the 11-year follow-up than those of the control group. It is therefore important to watch for restenosis, repeat ischaemia or MI, and other adverse events more carefully in patients with autoimmune diseases after PCI.

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Authors' Contributions

Conception and design: Hongwei Li, Guodong Ma, Aidong Shen.

Analysis and interpretation of the data: Hui Chen, Hongwei Li, Guodong Ma, Aidong Shen, Yutong Fei.

Drafting of the article: Guodong Ma, Aidong Shen, Yutong Fei.

Critical revision of the intellectual content: Hui Chen, Hongwei Li, Aidong Shen.

Final approval of the article: Hui Chen, Hongwei Li, Huiqiang Zhao, Guodong Ma, Aidong Shen, Yutong Fei.

Collection and assembly of data: Hui Chen, Huiqiang Zhao, Guodong Ma.

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Disclosure

The authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.07.012.

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