EDITOR'S CHOICE

Early C-reactive protein in the prediction of long-term outcomes after acute coronary syndromes: a meta-analysis of longitudinal studies

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ABSTRACT

Objective To assess the overall effects by a meta-analysis.

Data sources Electronic searches on PubMed and Ovid Medline from their start to October 2009 were carried out.

Objective Cohort studies and secondary analysis of randomised controlled trials reporting the relative risk (RR) of recurrent cardiovascular events or death associated with C-reactive protein (CRP) obtained within 72 h from acute coronary syndromes (ACS) onset.

Data extraction Two epidemiologists independently abstracted information on study design, study and participant characteristics, level of CRP, outcomes, control for potential confounding factors and risk estimates using a standardised form.

Results A general variance-based method was used to pool the estimates of risk. Thirteen studies containing 1364 new cases identified from 9787 patients during the follow-up periods reported the risk estimates by CRP categories. Compared with the bottom CRP category (≤3 mg/l), the pooled RRs and their 95% CIs were 1.40 (1.18 to 1.67) for the middle (3.1∼10 mg/l) category and 2.18 (1.77 to 2.68) for the top (>10 mg/l) category of CRP values with a random-effects model, respectively. Another four and three studies reported the risk by unit of CRP or logarithmically transformed CRP. The pooled RRs (95% CI) were 1.49 (1.06 to 2.08) per 5 mg/l and 1.26 (0.95 to 1.69) per natural logarithm of CRP (mg/l), respectively.

Conclusions Greater early blood CRP moderately increases long-term risk of recurrent cardiovascular events or death, and may be a valuable prognostic predictor in patients after ACS.

Atherosclerosis is an inflammatory disease.[1] Inflammation has a pivotal role in plaque destabilisation, which results in acute coronary artery syndrome.[2] There is intense interest in the relationship between inflammation and cardiovascular diseases, especially acute cardiovascular events. Of all the inflammatory markers for cardiovascular diseases, C-reactive protein (CRP) is considered to be one of the most important markers and has been extensively studied in recent years. A meta-analysis of prospective studies of general populations reported that a higher CRP level was related to a 58% increase in the incidence of cardiovascular diseases,[3] which indicated that CRP was a moderately valuable marker in predicting the development of cardiovascular diseases.

The use of CRP for prognosis is believed to be of value. Centers for Disease Control and Prevention (CDC) of America and the American Heart Association (AHA)[4] recommended that CRP should be measured in patients with acute coronary syndromes (ACS) as an independent marker of prognosis. A large number of studies have examined the prognostic value of CRP in patients with acute cardiovascular events at baseline.[5–24] Although most of them found a dose-dependent positive association between CRP and late adverse outcomes, the strength of the association varied with each study owing to different settings, populations and outcomes, etc. There is an increasing need to synthesise all the evidence. This meta-analysis aims to quantify the pooled long-term risk of adverse outcomes in patients with ACS using CRP obtained within 72 h from the onset of symptoms.

METHODS

Search strategy and selection criteria

We conducted a computer search through PubMed and Ovid Medline (from their start to October 2009) for follow-up studies and randomised controlled trials (RCTs), with the languages limited to English and the subjects limited to adults. We used the terms related to cardiovascular diseases (sudden death, coronary, myocardial, stunning, infarction, ischaemia, cardiovascular, angina, cerebrovascular, stroke, cerebral haemorrhage), CRP (C-reactive protein, CRP, acute phase protein), follow-up studies (cohort, longitudinal, follow-up, prospective, retrospective) and randomised controlled trial (Random*, allocate*, blind*, assign*, interven*, trial*, controlled, RCT) in our core search. We also screened the related articles of each included study generated by PubMed and checked the references of all the included studies.

We included studies if they met all the following criteria: (*a*) all patients had ACS at baseline; (*b*) blood samples for CRP determination were obtained within 72 h from the onset of symptoms or on admission to hospital; (*c*) outcomes were death, heart failure and other non-fatal cardiovascular events such as re-infarction, postinfarction angina, recurrent ischaemia and need for revascularisation with either angioplasty or bypass surgery; (*d*) a follow-up duration of at least 1 month; (*e*) risk estimates with 95% confidence intervals were reported by at least three CRP categories, or unit of CRP or logarithmically transformed CRP. We excluded studies if they were not related to CRP and the outcomes of ACS. Case–control studies and cross-sectional studies were also excluded owing to the uncertainty of time relationship. Details are given in the online supplementary file. When articles were from the same author at the same setting with varied sample size and different follow-up duration, the article with larger sample size and longer follow-up duration was used in this meta-analysis.

Data extraction and quality assessment

Two epidemiologists (LH and YC) independently assessed the eligible studies, collected information and assessed the quality. We extracted information on the authors' names, year of publication, country of origin, study design, subject characteristics, sample size, inclusion and exclusion criteria, duration of follow-up, treatments, time at which blood samples were obtained, method of CRP determination, outcome measurements and their risk estimates, and adjusted covariates. We also tried to contact the authors to request the unpublished relevant information for the included articles. We assessed the quality of each study according to the rating scheme developed by Hayden *et al*.[25] Thirty questions about six domains of potential bias were evaluated, including study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and adjustment, and analysis. Studies meeting four or more of the six criteria were considered to be high quality, otherwise they were classed as low quality. Discrepancies between the two reviewers were resolved by re-examination of the original articles by a third investigator and discussion between the authors.

Meta-analysis and statistical analysis

We conducted separate meta-analyses for the eligible studies reporting the risk estimates by CRP categories, unit CRP or natural logarithm of CRP. For the first type of studies, we converted categories of CRP concentration to three standardised categories according to the statement by the American CDC and AHA[4]: the bottom group (the referent, ≤3.0 mg/l), the middle group (3.1–10.0 mg/l) and the top group (>10.0 mg/l). The category-specific risk estimates of each study were assigned to the standardised categories according to the mid-point for closed categories and the median or the corresponding median previously defined—20% lower than the lowest cut-off point and 20% higher than the highest cut-off point for the open categories. One of the included studies reported the risk estimates by CRP quintiles.[9] For this study, quartile 1 (lowest) was assigned to the referent group, quartiles 2 and 3 were assigned to the middle group and quartile 4 was assigned to the top group, respectively. We pooled the risk estimates and their 95% CIs if more than one group in a single study fell into the same standardised category. The pooled estimates were then used for the overall effect analysis. For the studies reporting the risk estimates by unit CRP (mg/l) or natural logarithm of CRP (mg/l), we pooled the standardised risk estimates (RR per 5 mg/l of CRP, or RR per 1 unit of natural logarithm of CRP (mg/l)). One eligible study was excluded owing to its unreasonably high CRP-associated RR (51.54 per 5 mg/l CRP).[26]

We assessed the statistical heterogeneity between studies by Q statistic. Inconsistency was quantified with the I^2 statistic. A value of $p<0.10$ for Q tests or $I^2 \geq 50\%$ indicated significant heterogeneity between studies. We estimated the pooled risks and 95% CIs by the general variance-based method using a random-effects model.[27] When no 95% CIs were presented, they were calculated using numbers of cases and total subjects or person-time. The 95% CIs were used to assess the variance and the relative weight of each study. Adjusted risk estimates, when available, were preferred. We used only the results with the longest follow-up period when multiple results were reported by different durations of follow-up. The combined multiple end points of adverse outcomes were considered to be the primary end points. We analysed the dose–response relationship using the method proposed by Greenland and coworkers.[28 29] Study-specific slopes (linear trends) were computed from the natural log of the RRs across different exposure levels correlated with their corresponding CRP contents. Original dose groups were used in the dose–response relationship analysis.

We performed a sensitivity analysis for the main effect by excluding all the studies one by one. Subgroup analyses were performed to assess the source of heterogeneity by different end points (heart failure, cardiac death and all-cause death), time of collection of blood samples from the onset of symptoms (≤24 h or not), duration of follow-up (>1 y or not), study settings (Europe or not), mean age (≥65 years or not), confounder adjustments (adjusted or not), quality of the study (high quality or not) and the original study design (cohort study or trial).

Publication bias was assessed by the combination of a funnel plot, Egger's linear regression[30 31] and fail-safe number. Publication bias was absent for $p>0.1$ in Egger's linear regression test and higher fail-safe number meant better reliability of the meta-analysis. A trim-and-fill method was used to adjust for publication bias in the overall effect estimation.[32]

STATA (version 10.0, Stata Corp) was used for the above analyses. The meta-analysis was conducted adhering to the MOOSE guidelines.[33]

RESULTS

Study characteristics

Twenty studies with 17 422 patients with ACS were included in the analysis (figure 1). Table 1 summarises the characteristics of

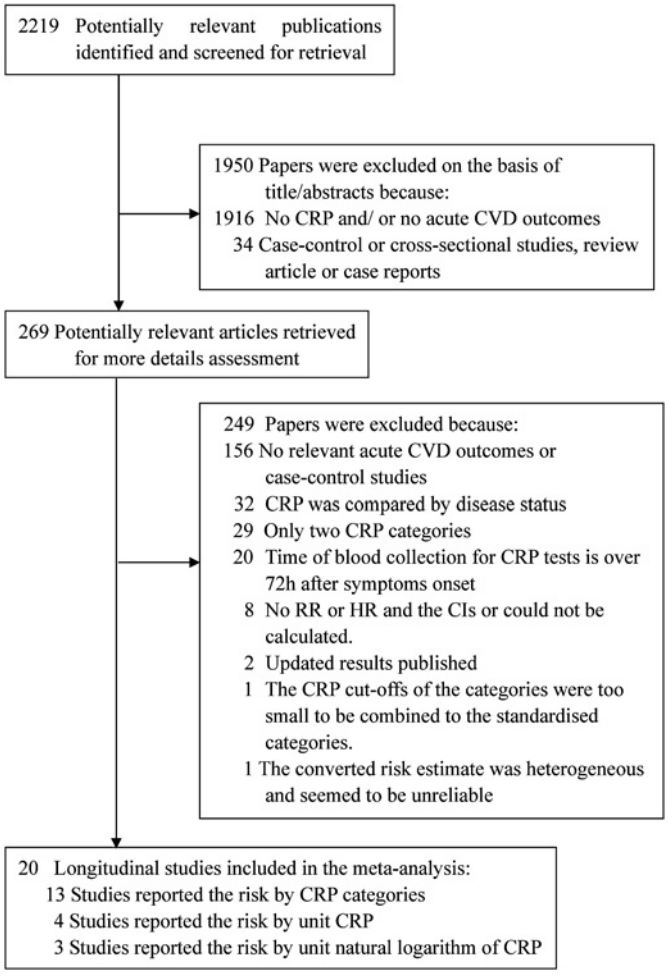

Figure 1 Flow diagram of search strategy and study selection. CRP, C-reactive protein; CVD, cardiovascular disease.

Table 1 Characteristics of studies included in the meta-analysis

Source§	Original design	Country	Study size (n)		Mean age (years)	Male (%)	Mean follow-up (months)	Diseases at baseline	Outcomes	CRP sample collection	Adjustments	Quality problems*
			Participants	Cases								
Apple 2007[5]	Cohort	America	457	36	57	57	4	ACS	Death, F_CVD NF_CVD	3.1h†	Age, sex, DM, renal disease	3[a, b, e]
Bursi 2007[6]	Cohort	America	329	75	69	52	12	AMI	HF, death	6.1h†	Age, sex, comorbidity, peak cTnT, ECG, KC, MI, recurrent ischaemic events	2[a, f]
Foussas 2007[7]	Cohort	Greece	786	93	60.7	78.8	1	STEMI	Failed thrombolysis, F_CHD	3.5h‡	Age, DM, anterior MI, Killip class, BP, HR, failed thrombolysis, cTnI	2[b, c]
Foussas 2008[8],[B]	Cohort	Greece	934	340	65.5	71.4	60	STEMI, NSTE-ACS	Death	4.3 h for STEMI, 8.7h for NSTE-ACS‡	Age, sex, HBP, smoke, DM, angina, MI, angioplasty, CABG, HF, history of CVD or PAD, anterior STEMI, Killip class, time from index pain to treatment, cTnI, tHcy	1[c]
Hartford 2007[9]	Cohort	Sweden	757	166	65	73	75	ACS	Death	<24 h after a dmission	—	3[c, e, f]
Jernberg 2004[10]	Cohort	Sweden	726	161	70.4	33.2	40	NSTE-ACS	Death, MI	5.7 h†	Age, DM, HBP, MI, HF, ECG, cTnT, NT-proBNP, cystatin C	2[b, c]
Kavsak 2007[11]	Cohort	Canada	446	—	64	59	96	ACS	Death, readmission for AMI or HF	3 h†	Age, sex, cTnI	6[a, b, c, d, e, f]
Kilcullen 2007[12],[A]	Cohort	United Kindom	1448	296	72.5	61	12	ACS	Death	12–24 h†	Age, HF, MI, HR, BP, ECG, Cr, inpatient PCI, H-FABP, cTnI	3[c, e, f]
Kim 2006[13],[A]	Cohort	Korea	215	24	65	65.1	8	ACS	Death, NF_CVD HF	Admission	Age, sex, NT-proBNP, cTnI, HBP, DM, smoke, HC, LVEF, diagnosis	2[c, d]
Lindahl 2000[14]	RCT‖	Sweden	917	124	70	65.3	37	Unstable CHD	Death	24 h†	Age, sex, BMI, smoke, HBP, previous AMI, history of HF, DM, stable angina, stroke, number of drugs taking at admission, ECG, the index diagnosis, cTnT, fibrinogen level	1[c]
Nikfardjam 2000[15]	Cohort	Austria	729	118	61	75	36	AMI	F_CVD	Admission	Age, smoke, treatment, time from onset to admission, Cr kinase, DM, HC, HBP	3[c, d, e]
Oldgren 2003[16]	RCT‖	Sweden	320	22	66.5	—	1	UA, AMI	Death, MI	<24 h†	—	6[a, b, c, d, e, f]
Ray 2007[17],[B]	RCT‖	America	2200	567	62.2	69.0	6	NSTE-ACS	Death, NF_MI	41 h†	Age, sex, DM, smoke, HBP, MI, ECG, NSTEMI, prior revascularisation, medication, treatment	2[a, c]
Sanchis 2004[18],[A]	Cohort	Spain	665	45	66	74	6	AMI	Death	48 h after admission	Age, Killip class, HP, smoke, DM, previous ischaemic heart disease, ejection fraction	4[a, b, c, d]
Scirica 2007[19]	RCT‖	America	1992	185	61.1	12.8	10	ACS	Death, NF_CVD	40 h†	Age, sex, BMI, DM, HC, MI, PAD, smoke, KC, treatment	4[a, c, d, f]
Soeki 2002[20],[A]	Cohort	Japan	92	10	66	77.2	50	MI	Death, NF_CVD	Admission	—	5[a, c, d, e, f]
Suleiman 2006[21]	Cohort	Israel	1044	194	61	72.3	23	AMI	Death, HF	12–24 h†	Age, sex, Cr, HF, HBP, DM, smoke, MI, KC, HR, treatment, LVEF	0
Toss 1997[22]	RCT‖	Sweden	965	138	70	65	5	Unstable CHD, MI	Death, MI	<72 h†	—	3[c, e, f]
Wollert 2007[23],[B]	RCT‖	Germany	2081	143	66	63.2	12	NSTE-ACS	Death	<24 h†	Age, sex, delay time, smoke, HBP, HC, DM, angina, MI, ECG revascularisation, HF	3[a, d, f]

Continued

Table 1 Continued

Source§	Original design	Country	Study size (n)		Mean age (years)	Male (%)	Mean follow-up (months)	Diseases at baseline	Outcomes	CRP sample collection	Adjustments	Quality problems*
			Participants	Cases								
Zairis 2002[24]	Cohort	Greece	319	52	60	73.7	22	STEMI	F_CHD	4.4 h‡	Age, sex, DM, time from onset to treatment, STEMI, complete ST resolution, TIMI, LVEF	2[b, d]

*The number of quality problems according to the six criteria, including sampling, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and analysis.[25] [a]No clear inclusion or exclusion criteria, or the settings of sampling were not described adequately; [b]no adequate collection or reporting of the information of participants who dropped out of the study; [c]no clear description or no blind operation of CRP measurement; [d]no clear definition of the outcome of interest or the outcome measurements were not valid and reliable; [e]no clear definition of the confounders or no (not all) important confounders were adjusted for; [f]insufficient data presentation or no appropriate strategy for model building.
†The median time from onset of symptoms to collection of blood samples.
‡The mean time from onset of symptoms to administration of drugs. Blood samples for CRP measurements were obtained on admission and before the administration of any drugs.
§Three kinds of studies were included in this meta-analysis: [A]studies investigating the prognostic value of CRP by unit CRP; [B]by a unit change of natural logarithmically transformed CRP, and otherwise, by CRP categories.
‖Articles were secondary-analyses of randomised controlled trials.
ACS, acute coronary syndrome; AMI, acute myocardial infarction; BMI, body mass index; BP, blood pressure; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CK-MB, creatine phosphokinase isoenzyme MB; Cr, creatinine; CRP, C-reactive protein; cTnI, cardiac troponin I; cTnT, cardiac troponin T; CVD, cardiovascular disease; DM, diabetes mellitus; ECG, electrocardiogram; F_MI, F_CHD and F_CVD, fatal MI, CHD and CVD; HBP, high blood pressure; HC, hypercholesterolaemia; HF, heart failure; H-FABP, heart fatty acid-binding protein; HR, heart rate; KC, Killip class; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NF_CHD, NF_CVD and NF_MI, non-fatal CHD, CVD and MI; NSTE-ACS, non–ST Elevation ACS; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; RCT, randomised controlled trial; STEMI, ST-segment elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction; tHcy, total homocysteine; UA, unstable angina.

the included studies. Of these 20 studies, 14[5–13 15 18 20 21 24] were cohort studies, and six[14 16 17 19 22 23] were secondary-analyses of randomised controlled trials. All blood samples were obtained within 72 h from the onset of symptoms or on admission to hospital. The mean age of participants at baseline ranged from 57 to 72.5 years. Mean duration of follow-up varied between 1 and 96 months. Twelve[7–10 12 14–16 18 22–24] studies were from Europe, five[5 6 11 17 19] were from America and three[13 20 21] were from Asia.

Data synthesis

Of the 13 studies reporting the risk estimates by CRP categories, nine[5–7 9–11 15 21 24] were cohort studies and 4[14 16 19 22] were secondary analyses of RCTs. A total of 1364 new cases of adverse outcomes identified from 9787 patients with ACS were included in pooling the overall effects. The p values for between-study heterogeneity were 0.80 and 0.02, and coefficients of inconsistency (I^2) were 0% and 51.9% for the middle and top CRP category, respectively. As compared with the referent group (CRP ≤3 mg/l), the pooled RRs (95% CIs) of long-term adverse outcomes were 1.40 (1.18 to 1.67) (p<0.001) for the middle CRP category (3.1–10.0 mg/l) and 2.18 (1.77 to 2.68) (p<0.001) for the top CRP category (>10.0 mg/l) with the random-effects model, respectively (figure 2). Twelve studies were included in the dose–response meta-analysis of blood CRP levels and the outcomes. One study[15] was excluded because the dose–response model could not be established when included. The estimated summary RR (95% CIs) for an increase of 5 mg/l CRP was 1.23 (1.19 to 1.28) (figure 3).Another four[12 13 18 20] and three[8 17 23] studies reported the risk estimates by each unit of CRP or logarithmically transformed CRP and the pooled RRs (95% CIs) were 1.49 (1.06 to 2.08) per 5 mg/l CRP and 1.26 (0.95 to 1.69) per unit increase of natural logarithmic CRP (mg/l), respectively (figure 4).

Sensitivity and subgroup analyses

We conducted sensitivity and subgroup analyses for the pooled risks by CRP groups. The pooled RRs (95% CIs) ranged between 1.37 (1.14 to 1.63) and 1.45 (1.21 to 1.74) for the middle CRP category and between 2.06 (1.68 to 2.83) and 2.30 (1.88 to 2.80) for the top category when omitting all the studies one by one in sensitivity analyses. The p values for heterogeneity were both 1.00 for the two categories, which indicated that there were no statistically significant differences when any one of the included studies was excluded. We explored the prognostic value of CRP for different end points and the findings were not significantly different (table 2). The pooled risk estimate in European studies was significantly lower than that in non-European studies (RR=1.83 vs 2.81) in the top CRP group (p=0.01). The pooled estimate adjusted for potential confounding factors was smaller than that without adjustment from the same seven studies (RR=2.31 vs 3.53) (p=0.05). No significant heterogeneities were observed in subgroups stratified by time of blood collection, follow-up duration, age, study quality and original study design (p for group heterogeneity, 0.21–0.99) (table 2).

Publication bias and data quality

No significant publication bias was observed by reviewing the classic funnel plot and by using Egger-weighted regression method for either the middle group (p=0.35) or the top group (p=0.26) (figure 5). The publication bias adjusted estimates were 1.33 (1.12 to 1.56) for the middle group and 2.06 (1.68 to 2.52) for the top group. The corresponding fail-safe numbers for the middle and top CRP groups were 36 and 318, respectively.

The quality of the included studies was assessed by a qualitative method (table 1). Up to 11 studies (55%) met the criteria for sampling and more than half of the articles reported the necessary information about follow-up (65%) and outcome measurement (55%). Seven (35%) studies collected data of confounding factors sufficiently, six (30%) had reported reliable measurements of CRP and 12 (60%) analysed the data with an appropriate approach.

DISCUSSION

Our meta-analysis has quantitatively assessed the relation between early blood CRP after ACS and risk of adverse outcomes in 20 longitudinal studies comprising 2789 cases from 17 422 patients. In our study, we found that patients with higher CRP levels of 3.1–10.0 and >10.0 (mg/l) after ACS were associated with 1.40-fold and 2.18-fold higher risks of adverse outcomes as compared with the referent (CRP ≤3.0 mg/l). This finding was consistent with the recommendation (class IIa, evidence B) by the American CDC and AHA.[4]

The publication bias diagnostics and sensitivity analysis confirmed the reliability and stability of this meta-analysis. Significant between-study heterogeneity was observed in the

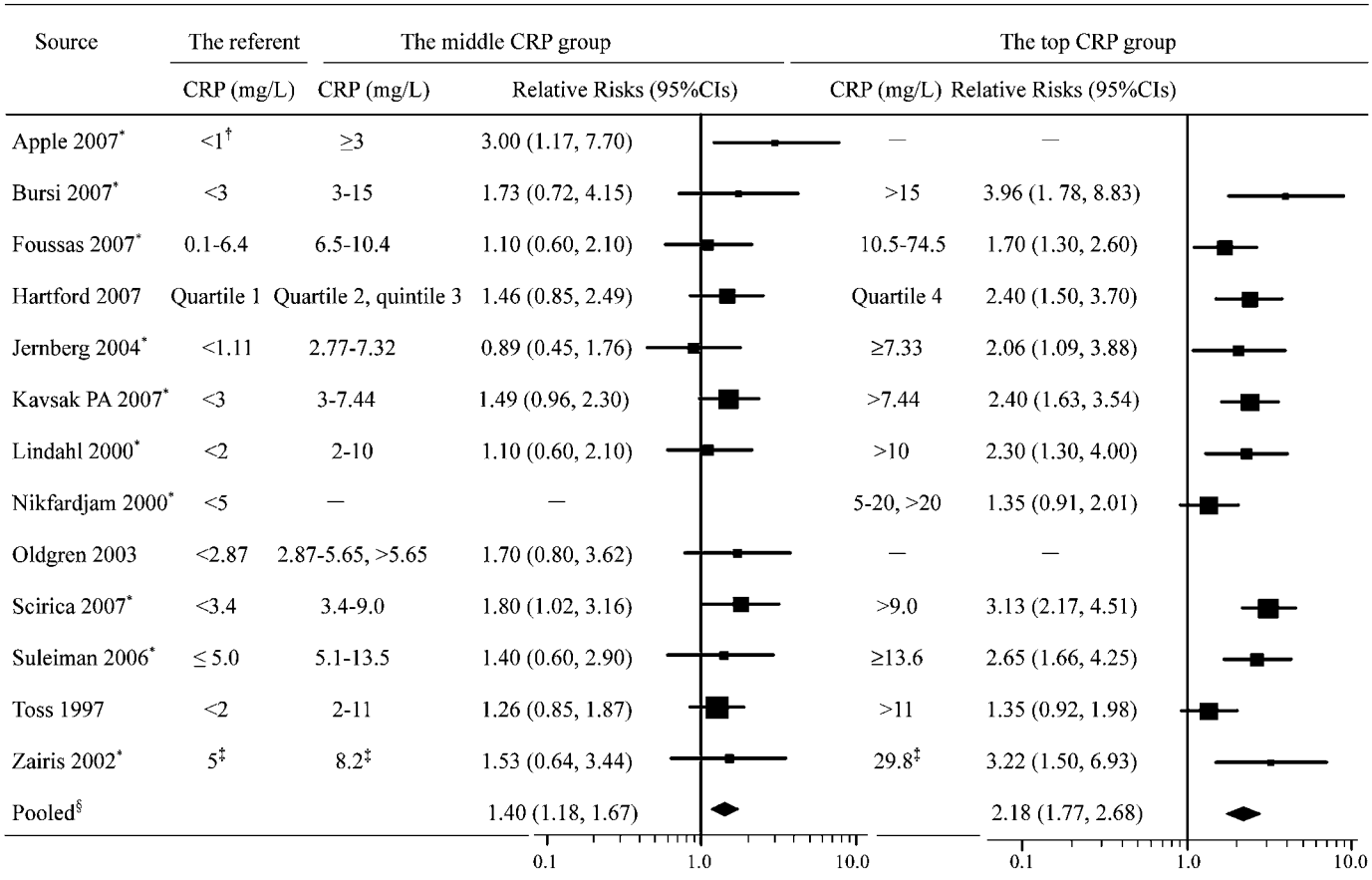

Figure 2 RR estimates from longitudinal studies of acute coronary syndromes. Error bars indicate 95% CIs. CRP, C-reactive protein. *The RRs were adjusted for potential confounding factors in original studies. †The middle category (1.0-2.9 mg/l) of this study was omitted because this small cut-off point was not able to be combined with the standardised category. ‡The median value of the tertile. §Random-effects model was used. The middle CRP group: p for heterogeneity=0.80, I^2=0%; The top CRP group: p for heterogeneity=0.02, I^2=51.9%.

top CRP group (p=0.02). Subgroup analyses were used to explore potential heterogeneity sources. We found that the pooled risk was significantly higher in non-Europe region than those in Europe (p for group heterogeneity=0.01), which might be related to heredity, host susceptibility, environmental factors[34] or random error since only three studies were conducted in non-European regions. Seven articles[6 10 14 15 21 24 35] reported both non-adjusted and adjusted risks. Non-adjusted risk tended to be overestimated (adjusted vs non adjusted, p=0.05). There was no significant group heterogeneity stratified by age, duration of follow-up, outcome, time of CRP sample collection, study quality and original study design. As there was no standard tool for quality assessment for cohort studies, we used a qualitative checklist, which was introduced to assess the quality of prognosis studies in systematic reviews, to evaluate the study quality of the included studies.[25] The pooled CRP-associated risks were not significantly affected by the study quality.

Our findings suggest that early CRP is a valuable predictor for adverse outcomes in patients with ACS. However, whether CRP is the best and most cost-effective measurement is still a matter of debate. White blood cell count, a much simpler and less expensive measurement, is an independent prognostic predictor

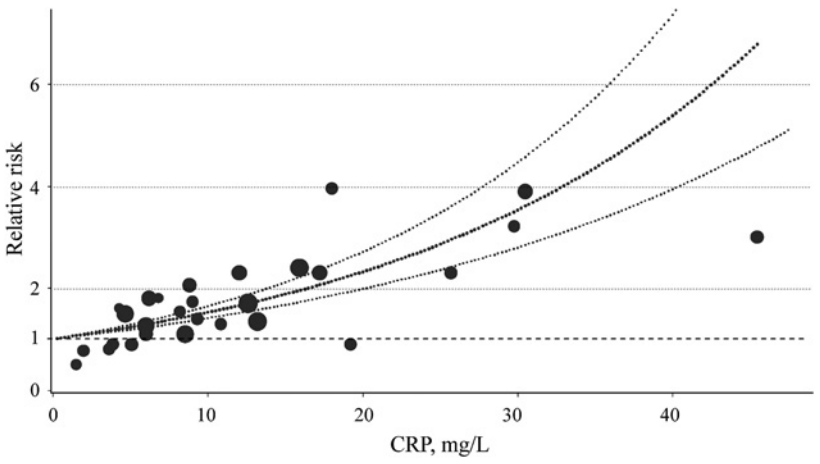

Figure 3 Dose–response relationships between early C-reactive protein and risk of major adverse cardiovascular events. The dots represent the RRs corresponding to C-reactive protein concentration in each individual study. The area of the dots is inversely proportional to the logarithm of the RR variance. The three curves are the RR estimates and their 95% CIs according to the dose–response model of 'ln(RR)= 0.2105 (SE, 0.0199)×C-reactive protein (in 5 mg/l), p<0.001'. CRP, C-reactive protein.

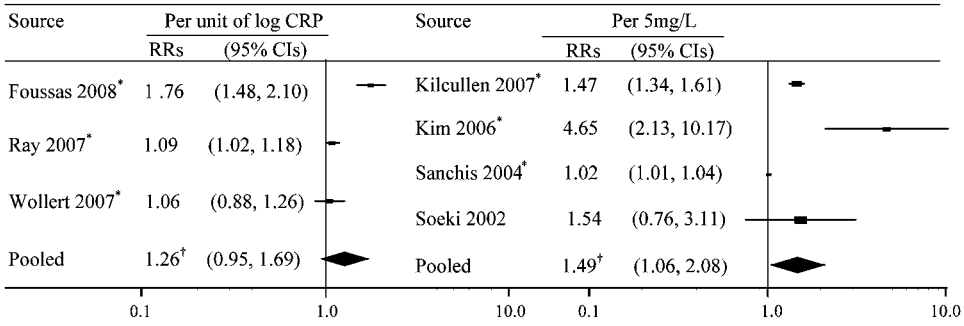

Figure 4 Forest plot for C-reactive protein analysed as a continuous variable. Error bars indicate 95% CIs. CRP, C-reactive protein. *The RRs were adjusted for potential confounding factors. †p for heterogeneity <0.001, I^2>90%.

of 12-month mortality after acute myocardial infarction (HR=1.48, 95% CI 1.08 to 2.04 per 1000 cells/μl).[36] Berton *et al*[37] reported that the RR (95% CI) of 1-year mortality in men with a heart rate of ≥80 (vs <80) beats/min on the first day of hospitalisation for acute myocardial infarction is 3.1 (1.4 to 7.0). Moreover, admission electrocardiogram, a widely available measurement, was also considered to be a good predictor of adverse outcomes of ACS.[38–40] These studies suggested that many simple clinical measurements were good predictors of prognosis of ACS. But, it was uncertain which clinical measurement was the most valuable or most cost-effective in clinical use since no study had compared their independent prognostic value under the same conditions. Further studies are needed to compare the prognostic values of common clinical markers or joint multiple markers in the same study.

There are several possible explanations for the prognostic value of CRP in patients with ACS. It has been shown that CRP is related to the dysfunction of endothelial cells and the progression of atherosclerosis. Pasceri *et al*[41] found that CRP induced a significant increment of adhesion molecule expression in human endothelial cells, indicating the direct proinflammatory effect of CRP. Second, CRP has a role in the progression of

Table 2 Pooled RRs for adverse cardiovascular outcomes by subgroups of study variable

	C-reactive protein groups				
	≤3.0 mg/l	3.1 ~ 10.0 mg/l		>10.0 mg/l	
Subgroups	**Referent**	**N**	**RR (95% CI)**	**N**	**RR (95% CI)**
Overall	1.00	12[5–7 9–11 14 16 19 21 22 24]	1.40 (1.18 to 1.67)	11[6 7 9–11 14 15 19 21 22 24]	2.18 (1.77 to 2.68)
Outcome					
Heart failure	1.00	3[6 11 21]	1.72 (1.17 to 2.55)	3[6 11 21]	2.89 (2.07 to 4.02)
Cardiac death	1.00	3[7 14 24]	1.19 (0.80 to 1.77)	3[7 14 24]	2.10 (1.50 to 2.92)
All-cause death	1.00	9[5–7 9 11 14 19 21 24]	1.49 (1.21 to 1.84)	8[5–7 9 11 14 21 24]	2.50 (2.12 to 2.96)
p for heterogeneity			0.42		0.41
Time for blood samples obtained from the onset of symptoms					
≤24 h	1.00	9[5–7 10 11 14 16 21 24]	1.39 (1.11 to 1.74)	7[6 7 10 11 14 21 24]	2.34 (1.92 to 2.85)
>24 h or on admission	1.00	3[9 19 22]	1.43 (1.08 to 1.88)	4[9 15 19 22]	1.92 (1.26 to 2.95)
p for heterogeneity			0.86		0.42
Follow-up year					
>1 year	1.00	6[9–11 14 21 24]	1.32 (1.04 to 1.69)	7[9–11 14 15 21 24]	2.18 (1.77 to 2.69)
≤1 year	1.00	6[5–7 16 19 22]	1.49 (1.16 to 1.91)	4[6 7 19 22]	2.19 (1.36 to 3.52)
p for heterogeneity			0.51		0.99
Region					
Europe	1.00	7[7 9 10 14 16 22 24]	1.26 (1.01 to 1.57)	7[7 9 10 14 15 22 24]	1.83 (1.46 to 2.29)
Non-Europe	1.00	5[5 6 11 19 21]	1.67 (1.26 to 2.21)	4[6 11 19 21]	2.81 (2.25 to 3.52)
p for heterogeneity			0.12		0.01
Confounder adjustments*					
Unadjusted	1.00	6[6 10 11 14 21 24]	1.54 (1.19 to 1.99)	7[6 10 11 14 15 21 24]	3.53 (2.54 to 4.91)
Adjusted	1.00	6[6 10 11 14 21 24]	1.36 (1.05 to 1.76)	7[6 10 11 14 15 21 24]	2.31 (1.78 to 3.00)
p for heterogeneity			0.52		0.05
Mean age					
<65 y	1.00	6[5 7 11 19 21 24]	1.55 (1.20 to 2.00)	6[7 11 15 19 21 24]	2.23 (1.68 to 2.98)
≥65 y	1.00	7[6 9–11 14 16 22]	1.33 (1.08 to 1.64)	6[6 9–11 14 22]	2.15 (1.65 to 2.80)
p for heterogeneity			0.37		0.85
Study quality†					
High	1.00	6[6 7 10 14 21 24]	1.21 (0.90 to 1.62)	6[6 7 10 14 21 24]	2.31 (1.84 to 2.91)
Low	1.00	6[5 9 11 16 19 22]	1.52 (1.23 to 1.89)	5[9 11 15 19 22]	2.01 (1.43 to 2.83)
p for heterogeneity			0.21		0.51
Original study design					
Cohort	1.00	8[5–77 9–11 21 24]	1.42 (1.13 to 1.78)	8[6 7 9–11 15 21 24]	2.18 (1.74 to 2.72)
Trial	1.00	4[14 16 19 22]	1.39 (1.06 to 1.82)	3[14 19 22]	2.13 (1.24 to 3.67)
p for heterogeneity			0.91		0.94

*The results were from the articles that provided both crude and adjusted RRs (95% CIs).
†High quality was defined as articles that met four or more of the six quality criteria. Low quality was defined as articles that met three or fewer of the six quality criteria.
N, number of the study.

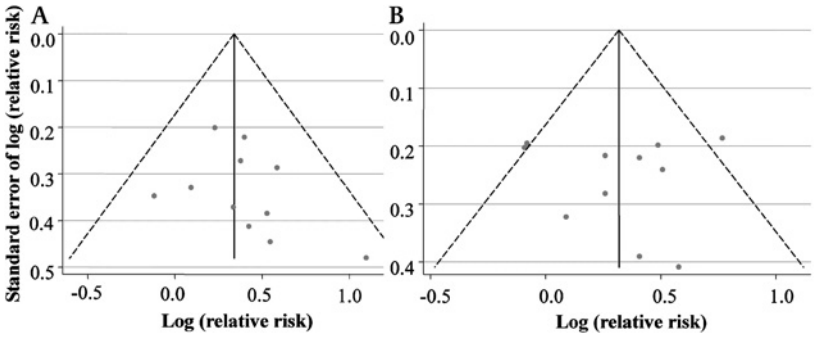

Figure 5 Funnel plots for publication bias in overall effect estimation in the middle C-reactive protein group (A) and the top C-reactive protein group (B). Publication bias was not statistically significant for either the middle (p=0.35) or the top (p=0.26) C-reactive protein group by Egger weighted regression method.

atherosclerosis by decreasing the production of nitric oxide and prostacyclin produced by endothelial cells.[42 43] Moreover, CRP can amplify the immune response through complement activation,[44 45] which has the effect of expanding the infarct size.[46] An animal study showed directly harmful effects on ischaemic myocardium. A significantly enlarged infarct size was found when human CRP was injected into rats after ligation of the coronary artery.[47] In addition, elevated CRP might independently affect the coagulation system and increase mortality.[48] When an ACS occurs, serum CRP concentration apparently increases and reaches a peak at 72 h.[49 50] CRP obtained within 72 h from the onset of symptoms is a reflection of the acute response of tissue injury. A higher level of CRP was related to more sever damage caused by the cardiovascular events and further damage caused by CRP itself.[51] The early phase of the inflammatory response was also related to the ventricular function and remodelling,[52] ischaemia and reperfusion injury,[46] which can cause long-term events.

The strength of this meta-analysis is that we included a large number of patients in the overall analysis, which increases the power of testing and makes the results more reliable. Second, we only included longitudinal studies, which are better than case–control studies as there is less bias and a clearer time relationship. Third, 17 of these 20 eligible studies used the high-sensitivity method to determine the concentration of CRP precisely and this reduces the bias of misclassification. Furthermore, 16/20 studies included provided confounder-adjusted risks and their 95% CIs, which may eliminate the effect of confounders. We limited the studies to those in which CRP samples were obtained within 72 h since the onset of symptoms, so that misclassification bias due to CRP sample collection would be reduced. Finally, the results of both the funnel plot and the Egger-weighted regression method showed no significant publication bias.

LIMITATIONS

This study has several limitations. First, the meta-analysis included a limited number of eligible studies, which made it more difficult to detect the heterogeneity between studies. Next, varied end points were used in the included studies. However, we observed similar CRP-associated risks for the major end points, including heart failure, cardiac death and all-cause deaths. Third, seven articles reported the risks of CRP-associated end points by unit CRP or logarithmically transformed CRP. The results of these studies could not be pooled with those obtained by CRP categories. Fourth, some studies included in the overall effect did not adjust or fully adjust for some important confounders, such as measures of cardiac damage, treatments, diabetes, etc. Fifth, the cut-off point of each CRP quintile was not described in Hartford *et al*,[9] which might increase the risk of misclassification. Finally, only articles published in English were included.

CONCLUSIONS

This meta-analysis found a moderately dose-dependent positive association between early blood CRP value and long-term risk of adverse outcomes in patients with ACS. Our findings suggest that early CRP is a valuable prognostic marker for patients with ACS.

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