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Impact of C-Reactive Protein on In-Stent Restenosis

A Meta-Analysis

We sought to evaluate the impact of C-reactive protein (CRP) levels on in-stent restenosis after percutaneous coronary intervention.

The plasma level of CRP is considered a risk predictor for cardiovascular diseases. However, the relationship between CRP and in-stent restenosis has been a matter of controversy. Meta-analysis reduces variability and better evaluates the correlation.

We performed a systemic search for literature published in March 2008 and earlier, using MEDLINE®, the Cochrane clinical trials database, and EMBASE®. We also scanned relevant reference lists and hand-searched all review articles or abstracts from conference reports on this topic. Of the 245 studies that we initially searched, we chose 9 prospective observational studies (1,062 patients).

Overall, CRP concentration was higher in patients who experienced in-stent restenosis. The weighted mean difference in CRP levels between the patients with in-stent restenosis and those without was 1.67, and the Z-score for overall effect was 2.12 (P=0.03). Our subgroup analysis that compared patients with stable and unstable angina showed a weighted mean difference in the CRP levels of 2.22 between the patients with and without in-stent restenosis, and the Z-score for overall effect was 2.23 (P=0.03) in 5 studies of unstable-angina patients. There was no significance in 4 studies of stable-angina patients.

In spite of significant heterogeneity across the studies, our meta-analysis suggests that preprocedurally elevated levels of CRP are associated with greater in-stent restenosis after stenting and that this impact appears more prominent in unstable-angina patients. ***(Tex Heart Inst J 2010;37(1):49-57)***

Coronary artery diseases remain the major cause of death in the Western world. Inflammation plays an important role in atherosclerotic disorders.[1-3] Modest elevation of plasma inflammatory markers, such as C-reactive protein (CRP), is considered a risk predictor for cardiovascular disease and is thought to reflect inflammation in atherosclerosis.[4,5]

The development of coronary stents has revolutionized the field of interventional cardiology by reducing the incidence of restenosis after balloon angioplasty.[6] Intracoronary stents improve procedural success rates and increase the safety and effectiveness of procedures by decreasing the number of cardiovascular events. However, coronary stenting is still associated with a serious complication—in-stent restenosis (ISR).[7]

Systemic inflammation characterizes the response to vascular injury after percutaneous coronary intervention (PCI).[8-10] Stent implantation, in particular, precipitates arterial intimal cellular proliferation and extracellular matrix synthesis that is mediated largely by inflammatory processes.[11] However, controversy exists regarding the clinical impact of early inflammatory response on ISR after coronary stent implantation. Previous studies have suggested that the magnitude of the systemic inflammation is linked to adverse late clinical outcomes after PCI.[12-14] In contrast, other studies have shown that levels of inflammatory markers after PCI appear similar and that reduction in restenosis after stenting is likely not mediated by the attenuation of systemic markers, such as CRP.[15,16] In view of these conflicting reports, we conducted a sys-

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tematic review of evidence from observational studies, in order to evaluate the association between CRP levels and ISR rates after successful coronary stent implantation in patients with stable angina and unstable angina.

Methods

Meta-analyses of observational studies present particular challenges because of inherent biases and differences in study designs. Consequently, we performed this analysis in accordance with the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) group.[17]

Literature Search. A systemic search for all literature that was published in March 2008 or earlier was performed using MEDLINE®, the Cochrane clinical trials database (2008, issue 1), and EMBASE® (January 1990—March 2008) in order to evaluate the value of CRP in the prediction of ISR after successful coronary stent implantation. Searches combined free-text and MeSH terms relating to "CRP" or "c-reactive protein" or "c reactive protein," "inflammation," and "in-stent restenosis" or "restenosis."

Inclusion Criteria. Studies were considered eligible for this review if they were of a prospective observational design, if they evaluated the potential association between CRP levels before coronary stent implantation and ISR after successful implantation, if they clearly used ISR rates as an outcome index, and if the period of follow-up was 6 months or longer.[18]

We excluded retrospective studies, laboratory studies, review articles, animal studies, and studies that were irrelevant to the current analysis; studies that lacked preprocedural CRP-level data or that did not reflect stent implantation in all patients; studies lacking definite ISR evaluation by quantitative coronary analysis—for example, if clinical outcomes were expressed as major adverse cardiac events (MACEs); or if follow-up periods were shorter than 6 months.

Identification of Studies. We considered studies in any language. We supplemented electronic searches by hand-searching reference lists of relevant articles and reviews and by contacting experts and manufacturers involved with CRP studies. Abstracts and titles of related articles were initially scanned by a reviewer. Potentially relevant articles were then considered by at least 2 independent reviewers. Disagreements were resolved by discussion or upon consensus from a 3rd or 4th reviewer. Two reviewers agreed on the inclusionary or exclusionary status of 90% of the reviewed studies. In addition, a manual search was conducted for all relevant review articles, bibliographies of original papers, and abstracts of the scientific sessions of the American College of Cardiology, the American Heart Association, and the European Society of Cardiology, for the past 20 years.

Quality Determination and Data Extraction. Because quality-scoring varies in meta-analyses of observational studies, we systematically evaluated several key points of study quality in accordance with a previous study.[19] Two reviewers independently appraised each article included in our analysis with use of a checklist from the Dutch Cochrane Centre, which was proposed by MOOSE[17]: clear definition of study population, clear definition of outcomes and outcome assessment, independent assessment of outcome parameters, sufficient duration of follow-up, no selective loss during follow-up, and identification of important confounders and prognostic factors. If studies did not clearly mention one of these points, we concluded that it had not been performed and, consequently, that there was possible underestimation of the reported characteristics.

Two blinded reviewers independently used a standardized data-extraction form to determine eligibility for inclusion and to extract data.[19,20] The extracted data included the lead author's last name, the publication year, and the origin of the studied population; the study design; the characteristics of the studied population (sample size, age, sex, diagnoses, drug therapies, methods of CRP measurement, types of stents, durations of follow-up, and withdrawals and dropouts of patients); endpoint evaluations (definitions of ISR and methods of ISR detection); rates of ISR; and means and SDs of CRP in each group. Disagreements were resolved by consensus from a 3rd or 4th reviewer.

If the study provided medians and interquartile ranges instead of means and SDs, we imputed the means and SDs as described by Hozo and colleagues.[18] We calculated the lower and upper ends of the range by multiplying the difference between the median and ends of the interquartile range by 2 and adding or subtracting the product from the median, respectively, according to previous studies.[18,19]

Statistical Analysis

In order to accommodate differences in the ways in which CRP was measured and reported in various studies, the absolute CRP levels were converted into a common unit by calculating weighted-effect sizes. These sizes were derived by dividing the mean difference of CRP levels in ISR and no-ISR groups of each study by its SD. We used the I2 statistic to measure the extent of inconsistency among the results, and we tested heterogeneity by using the Cochran Q test.[19,20] Because this test has poor power in the event of few studies, we considered both the presence of significant heterogeneity at the 10% level of significance and values of I2 exceeding 56% as an indicator of significant heterogeneity,[21] so that a pooled effect could be calculated with a random-effects model that was used to take into account within-study and between-study variance, or otherwise, with a fixed-effects model. To explore sources of hetero-

geneity, we performed several sensitivity and subgroup analyses. Publication bias was also evaluated by use of a funnel plot. All analyses were conducted with the use of Review Manager, version 4.2 (Revman, The Cochrane Collaboration; Oxford, UK). The data conformed to each test that was used to analyze them.

Results

The search yielded 245 research reports, of which 30 were excluded for having the same title or authors; 167 were excluded because they were laboratory studies, review articles, animal studies, or irrelevant to the current analysis. Of the remaining 48 studies, 15 compared segmental CRP levels (for example, CRP ≤3 mg/L and >3 mg/L), and provided inadequate preprocedural CRP data. Four studies were randomized controlled trials that evaluated drug interventions on ISR after successful coronary stent implantation. Two studies were retrospective. Nine studies compared different groups' CRP levels (for example, bare-metal versus drug-eluting stents, or stable versus unstable angina), and lacked concrete preprocedural CRP data. In 2 studies, not all patients were implanted with a stent. Two studies reported only the difference between preprocedural and postprocedural CRP data and presented no concrete preprocedural CRP data. Four other studies had no data on preprocedural CRP levels. One study provided CRP data and MACE, but no exact information regarding ISR. The foregoing studies were all excluded, and 9 prospective observational cohort studies[22-30] were included in our meta-analysis (Fig. 1). As a result, a total of 1,062 patients were involved in our review: 298 in the ISR group, and 764 in the no-ISR group. All follow-up pe-

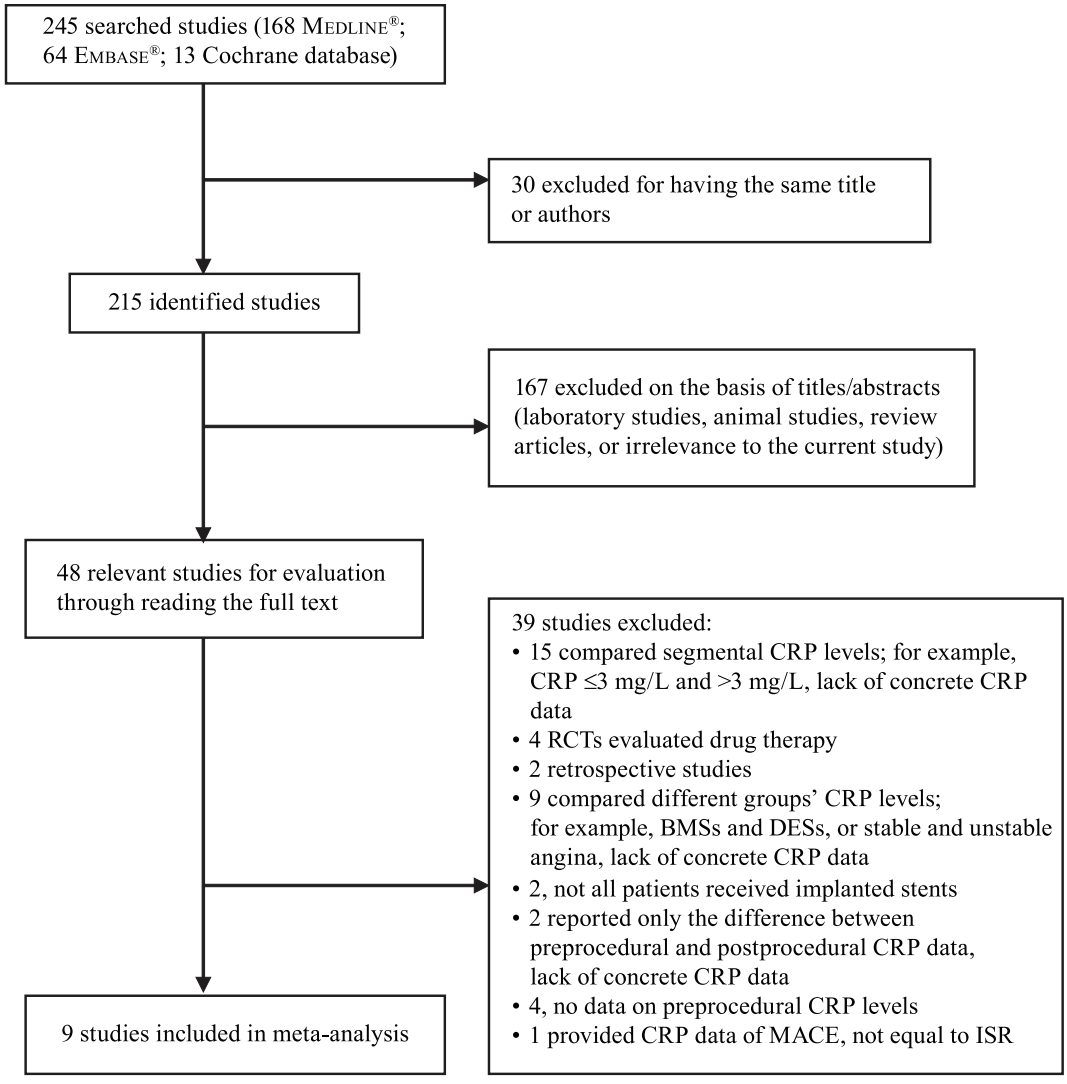

Fig. 1 *Flow diagram of the trial-selection process.*

BMSs = bare-metal stents; CRP = C-reactive protein; DESs = drug-eluting stents; ISR = in-stent restenosis; MACE = major adverse coronary event; RCTs = randomized controlled trials

riods were longer than 6 months. Table I[22-30] shows the qualitative evaluation of the 9 studies; Table II[22-30] presents the characteristics of each study.

Seven studies[22-25,28-30] showed that patients with ISR had higher CRP levels than did patients without ISR, whereas CRP levels did not significantly differ between those groups in 2 other studies.[26,27] Overall, CRP concentration was greater in patients with ISR. The weighted mean difference in the CRP levels between patients with and patients without ISR was 1.67 (95% confidence interval [CI], 0.12–3.21) (Fig. 2), and the Z-score for overall effect was 2.12 (P=0.03).

The heterogeneity test showed significant differences among individual studies (P <0.01; I2=89%). We subsequently performed sensitivity and subgroup analyses in order to identify the origin of this heterogeneity.[19] After the removal of 3 studies that had follow-up periods longer than 6 months, the analysis showed no

TABLE I. Evaluation of the Quality of the 9 Included Studies

Factor	Angioi M, et al.[22]	Gomma AH, et al.[23]	Turker S, et al.[24]	Skowasch D, et al.[25]	Segev A, et al.[26]	Yip HK, et al.[27]	Karaca I, et al.[28]	Naumov VG, et al.[29]	Qi X, et al.[30]
Clear definition of study population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Clear definition of outcomes and outcome assessment?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Independent assessment of outcome parameters?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Sufficient duration of follow-up?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
No selective loss during follow-up?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
Important confounders and prognostic factors identified?	Yes	No	No	Yes	Yes	No	No	Yes	No

TABLE II. Characteristics of the 9 Studies Included in the Meta-Analysis

Authors	Year	Study Population	Male Patients n (%)	Mean Age yr	Type of Stent	Method of CRP Assay	Follow-Up mo	ISR Rate %
Angioi M, et al.[22]	2001	SA and UA	55 (22)	61	BMS	Immunonephelometry test	12	43.6
Gomma AH, et al.[23]	2004	SA and UA	133 (100)	59	BMS	Immunoturbidimetric assay	6	33.8
Turker S, et al.[24]	2006	SA	36 (25)	61	N/A	Enzyme-linked immunosorbent assay	6	27.8
Skowasch D, et al.[25]	2005	UA	219 (173)	63	N/A	Immunonephelometry test	6	28.0
Segev A, et al.[26]	2004	SA	216 (156)	58	N/A	Immunonephelometry test	6	14.8
Yip HK, et al.[27]	2005	UA	168 (123)	61	BMS	Immunonephelometry test	6	29.2
Karaca I, et al.[28]	2005	UA	74 (63)	57	N/A	Immunoturbidimetric assay	6	41.9
Naumov VG, et al.[29]	2005	UA	44 (37)	57	BMS	Solid-phase enzyme immunoassay	9	25.0
Qi X, et al.[30]	2003	SA and UA	119 (108)	64	BMS	Solid-phase enzyme immunoassay	12	29.4

BMS = bare-metal stent; CRP = C-reactive protein; ISR = in-stent restenosis; N/A = not available; SA = stable angina; UA = unstable angina

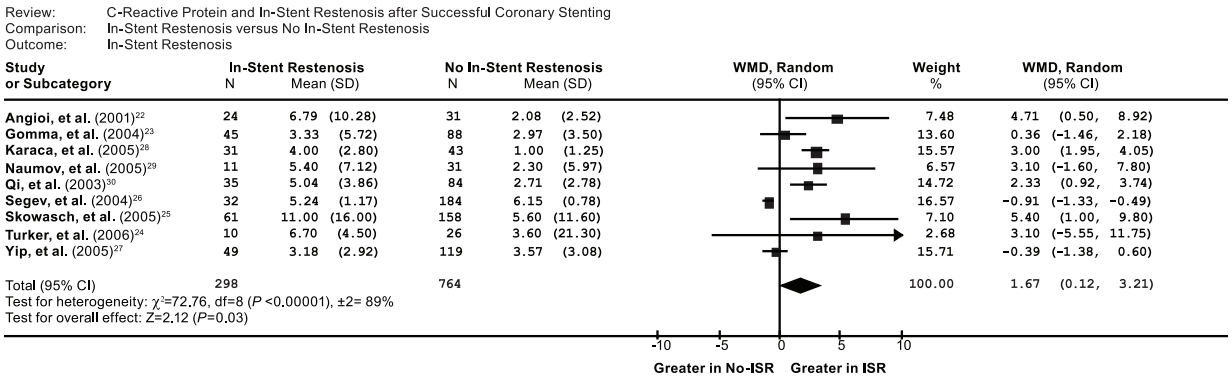

Fig. 2 *Comparison of CRP levels between ISR and no-ISR groups in the 9 included studies.*

CI = confidence interval; ISR = in-stent restenosis; WMD = weighted mean difference

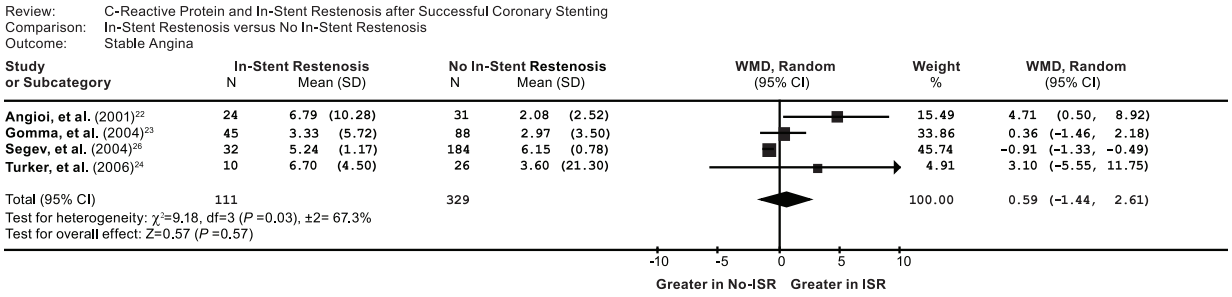

Fig. 3 *Comparison of C-reactive protein levels between ISR and no-ISR groups in the 4 included stable-angina studies.*

CI = confidence interval; ISR = in-stent restenosis; WMD = weighted mean difference

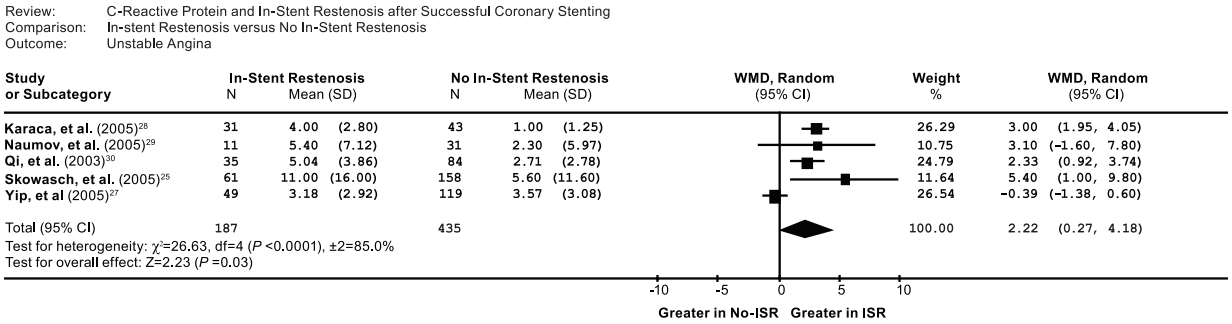

Fig. 4 *Comparison of C-reactive protein levels between ISR and no-ISR groups in the 5 included unstable-angina studies.*

CI = confidence interval; ISR = in-stent restenosis; WMD = weighted mean difference

significant influence on the results, and therefore longer follow-up did not explain the cause of heterogeneity. We also evaluated the influence of 3 CRP assays on the results. In contrast with a previous study,[19] the heterogeneity test showed no significant effects on the results. In addition, after the removal of 3 studies that presented no clear information regarding types of stents, the test showed no significant effects on the results. Therefore, the differences in follow-up period, method of CRP assay, and type of stent were not possible sources of heterogeneity.

We performed a subgroup analysis of studies that were associated with stable angina and unstable angina. In the 5 unstable-angina studies, the weighted mean difference in the CRP levels between the patients with ISR and without ISR was 2.22 (95% CI, 0.27–4.18) (Fig. 3), and the Z-score for overall effect was 2.23 (P=0.03). In contrast, in the 4 stable-angina studies, the weighted mean difference in the CRP levels between the patients with and without ISR was 0.59 (95% CI, –1.44 to 2.61) (Fig. 4), and the Z-score for overall effect was 0.57 (P=0.57), although an increasing trend of CRP

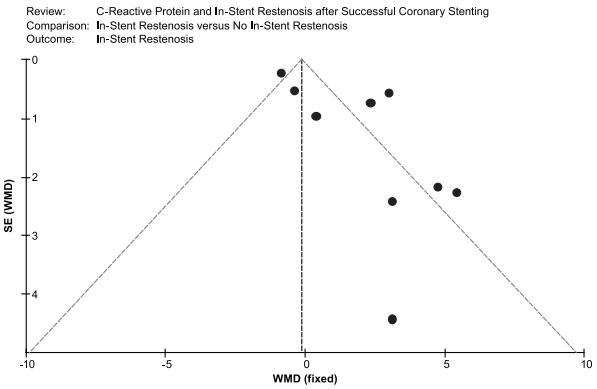

Fig. 5 *Funnel plot of the meta-analysis.*

Comparison: ISR versus no-ISR. Outcome: ISR.

ISR = in-stent restenosis; SE = standard error; WMD = weighted mean difference

was found in the stable-angina patients. The data suggested that the impact of CRP on ISR is more prominent in patients who have unstable angina than in those who have stable angina.

An asymmetric funnel plot shows the possible existence of publication bias (Fig. 5). Because of small sample size, we cannot explain the exact cause of heterogeneity in our meta-analysis.

Discussion

The results of our meta-analysis clearly revealed a strong relationship between preprocedural CRP levels and a subsequently greater risk of ISR after successful coronary stenting in patients with coronary artery disease, although heterogeneity testing showed significant differences among individual studies ($P<0.01$; I2=89%). After the exclusion of 2 studies, the overall impact of CRP elevation on rates of ISR after stenting was much greater in patients with ISR. The weighted mean difference in CRP levels between the patients with and the patients without ISR was 1.67 (95% CI, 0.12–3.21), and the Z-score for overall effect was 2.12 ($P=0.03$) (Fig. 2). Thus, the information provided by our meta-analysis regarding the impact of inflammation on ISR is important because of the clinical significance of ISR after successful coronary stenting and because of the inconsistency of the published results.

Coronary Stent Implantation and Inflammation. Despite intensive studies that have been performed regarding ISR, the factors attributed to ISR have not been fully elucidated, and ISR remains a challenge for the interventional cardiologist.[7,9] Most previous studies have shown that restenosis after coronary stenting is attributable to elastic recoil immediately after balloon deflation, neointimal proliferation triggered by injury to the vascular wall, and late negative remodeling.[31] Research interest is increasing regarding the role of inflammation in the pathophysiology of ISR, and a few data from prospective observational studies have suggested that inflammation contributes to ISR.[32,33] Coronary stenting is a strong inflammatory stimulus, and the acute systemic response to local inflammation that is produced by coronary stenting is a feature of PCI.[34] An experimental study showed that leukocyte recruitment could be detected within 15 minutes after stent deployment, at the level of the coronary segment that had been injured by the stent.[8] In addition, several clinical investigators who focused on early markers or initiators of the inflammatory response after coronary stenting[35,36] found that soluble CD40 ligand exhibited the greatest relative rise during the first 10 minutes after coronary stenting. Moreover, the intensity of such a reaction as measured by high-sensitivity CRP has proved to be correlated with recurrent ischemic events and to be associated with restenosis.[14,37] In patients with stable angina and normal baseline CRP plasma levels, successful stent implantation is followed by a rapid increase of CRP, with peak levels occurring 48 hours after stenting.[10] Finally, local inflammation caused by stent deployment also elicits a systemic inflammatory response that is initially mediated by inflammatory leukins, such as interleukin-1 (IL-1), IL-6, and tumor necrosis factor-α (TNF-α). These molecules cause the liver to produce acute-phase reactants (such as CRP) that rapidly increase in the blood and may directly amplify the inflammatory stimulus.[8]

Inflammation and In-Stent Restenosis. The clinical impact of early inflammatory response on ISR after coronary stent implantation is a matter of controversy. Some data suggest that persistently increased plasma levels of CRP (for longer than 48 hours after coronary stenting) are associated with a higher incidence of cardiovascular events during follow-up.[38] Similarly, Gottsauner-Wolf and colleagues[39] found that increased CRP levels that persisted for longer than 48 hours were associated with a greater incidence of ISR. Kim and associates[13] reported that drug-eluting stent implantation induced a significantly lower increase in plasma CRP levels at 48 and 72 hours after coronary stenting. This early inflammatory response pattern was found to be related to diameter stenosis and late loss at follow-up (6 months after stenting), as evaluated upon quantitative coronary analysis. Over time, patients with higher CRP levels after PCI experienced higher rates of death, up to 5 years after the procedure. Previous data indicated the possibility that an excessive increase in inflammatory mediators after PCI is associated with increased cardiovascular risk because of a short hyperreactivity of coagulation.[40] Yazdani and co-authors[41] studied the effect of PCI on levels of inflammatory markers. They found that IL-6 was significantly elevated after coronary stenting in unstable-angina patients in comparison with stable-angina pa-

tients. However, 1 month after stenting, there were no differences in comparative levels of IL-6 in the patients, which suggested that IL-6 levels correlate with instability of atheromatous plaque and that the decrease of IL-6 levels after stenting signifies plaque re-endothelialization and stabilization. Similarly, Saleh and coworkers[42] showed that coronary stent implantation, but not pathogen burden (including cytomegalovirus, *Chlamydia pneumoniae*, Epstein-Barr virus, *Helicobacter pylori*, and herpes simplex virus), is associated with plasma CRP and IL-6 response to PCI. Some data have shown that events after PCI are associated both with restenosis and with new plaque formation.[43] Therefore, further investigation into the impact of inflammatory response on ISR after PCI appears to be warranted.

Heterogeneity of C-Reactive Protein Across Studies. When between-study variation cannot be explained by chance, exploration of the reasons for heterogeneity rather than deviation of a single summary estimate emerges as the major goal of meta-analysis.[19,44] Our heterogeneity testing showed significant differences among individual studies ($P<0.01$; I2=89%). In our sensitivity and subgroup analyses to find the origin of this heterogeneity, we focused on the potential effect of follow-up periods. The duration of follow-up did not explain the cause of heterogeneity in our results. We subsequently considered and eliminated the method of CRP assay and the type of stent as potential causes of heterogeneity.

According to our subgroup analysis of patients with stable angina and unstable angina, the weighted mean difference in CRP levels between the patients with and without ISR was 2.22 (95% CI, 0.27–4.18), and the Z-score for overall effect was 2.23 ($P=0.03$) in the 5 unstable-angina studies. However, the weighted mean difference in the CRP levels between the patients with and without ISR was 0.59 (95% CI, –1.44 to 2.61), and the Z-score for overall effect was 0.57 ($P=0.57$) in the 4 stable-angina studies. These data are inconsistent with the results of previous studies, which showed that CRP is a predictor of coronary disease severity as well as future cardiovascular events.[4,45] In other words, results of our meta-analysis of the impact of CRP on ISR are similar to those previous observations concerning the impact of CRP on cardiovascular events.

Limitations of the Study

Our meta-analysis may provide novel information regarding the relationship between inflammation and rates of ISR. However, potential limitations include our small sample size. The numbers of studies and patients are rather limited, and the possibility of publication bias cannot be excluded.[19,46] More important, our analysis is founded upon potential observational studies: no randomized studies are covered, which may increase potential bias. Therefore, the results of our analysis should be interpreted cautiously. In addition, converting non-normally distributed statistics (median and range) to normally distributed statistics (mean and SD) may be a cause of bias in our analysis.[19] Finally, although most of the studies attempted to control potential confounders, the degree to which this was accomplished varied among them.[19]

Conclusion

Our meta-analysis shows that elevated preprocedural CRP is correlated with subsequent ISR after stenting in patients who have coronary artery disease. Although there is significant heterogeneity across the enrolled studies, ISR appears to be more prominent in patients who have unstable angina than in patients who have stable angina. The data suggest that inflammatory processes play an important role in the formation of ISR after coronary stent implantation, especially in patients who have unstable coronary disease. The clinical application of CRP levels in predicting ISR after stenting appears promising but warrants confirmation by larger, well-designed prospective and randomized studies.

Acknowledgments

In reporting our methods and results, we relied heavily upon a template that was kindly provided by the authors and publishers of Liu T, Li G, Li L, Korantzopoulos P. Association between C-reactive protein and recurrence of atrial fibrillation after successful electrical cardioversion: a meta-analysis. J Am Coll Cardiol 2007;49(15):1642-8.[19] We used the framework of their excellent Methods and Results sections as a model for the reporting of our own data. We thank Dr. Liu and his co-authors and also the American College of Cardiology (the copyright holder) for their cooperation.

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