Changes of High Sensitivity C-Reactive Protein During Clopidogrel Therapy in Patients Undergoing Percutaneous Coronary Intervention

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1. Background

The crucial role of inflammation in the development and progression of atherosclerosis has been previously described. However, there is insufficient data available to demonstrate the changes in high sensitivity C-reactive protein (hs-CRP) during clopidogrel therapy.

Results: Six hundred-fifty patients including 386 (59.4%) male and 264 (40.6%) female subjects were enrolled in the study. The mean hs-CRP level was 15.36 ± 9.83 mg/L with a median of 14 mg/L (interquartile range 8 to 19.6 mg/L). Female, hypertensive, diabetic, and non-smoking patients had higher reductions in hs-CRP in response to clopidogrel therapy compared to male, non-hypertensive, non-diabetic smoking patients, respectively (all P < 0.005). The changes in the hs-CRP levels were also statistically different in patients with various index events before PCI (P < 0.001). No significant differences were observed in the mean reduction of hs-CRP between the patients without stent implantation and those with bare metal or drug-eluting stents (P = 0.07), respectively.

Conclusions: We found that the use of clopidogrel in patients undergoing PCI had favorable effects on the suppression of hs-CRP. This effect appears to be heightened and more apparent in some group of patients with co-morbidities such as diabetes and hypertension.

Keywords: C-Reactive Protein; Clopidogrel; Coronary Artery Disease; Percutaneous Coronary Intervention
3. Patients and Methods

3.1. Patient Population

The study population included 650 consecutive patients who underwent PCI in the catheterization laboratories of three referral hospitals (Pars General Hospital, Day General Hospital, and the Rajaie Cardiovascular Medical and Research Center) in Tehran, Iran from April 2010 to December 2012. Patients were eligible for enrollment if they had moderate- to high-risk unstable angina (UA/NSTEMI), ST-segment elevation MI (STEMI) with coronary anatomy known to be suitable for PCI (primary PCI), or if they were scheduled to undergo elective PCI without experiencing any type of acute coronary syndromes (with stable angina). Patients with conduction or rhythm abnormalities (bundle branch block, idioventricular rhythm, etc.), early coronary angiography due to recurrent ischemia or failed thrombolysis, treatment with aspirin or thienopyridines, any contraindications to aspirin or clopidogrel, past history of MI or coronary revascularization, presence of clinically assessed heart failure (Killip II/III) or cardiogenic shock, hepatic or renal failure (serum creatinine > 2.5 mg/dL) and thrombocytopenia (< 100,000/mm$^3$), were excluded from the study. Patients with ongoing inflammatory disease or malignant or infective disorders were also excluded. The institutional review board approved the study protocol and patients signed a written informed consent prior to study participation.

3.2. Blood Sampling

Venous blood samples were obtained in the fasting state and before administration of the loading dose of clopidogrel in patients with planned PCI and immediately before PCI and administration of the loading dose of clopidogrel in patients with urgent or emergent PCI. Serum samples were frozen at -70°C until analysis. biochemical and hematological parameters were measured with Olympus AU600 autoanalyzer (Olympus Optical Co., Ltd., Schimatsu-Mishima, Japan) and Bayer Advia 120 Cell CBC Counter Hematologia autoanalyzer (Bayer Advia 120 CBC counter, NJ, USA). High-sensitivity CRP levels were determined by a chemiluminescent immunoassay (Immulite; DPC, Los Angeles, USA) with a limit of quantification of 0.1 mg/L, and an intraassay and interassay coefficient of variation of 2.09% and 5.88%, respectively.

3.3. Clopidogrel Administration

Patients received a 300-mg loading dose of clopidogrel (Plavix®) and aspirin (300 mg PO) either 24 hours before the planned PCI or immediately before the procedure in patients with urgent or emergent PCI, followed by 75-mg daily maintenance dose, for up to 12 weeks (17). At the end of the 12th week, the hs-CRP was reassessed. A decision regarding the continuation of clopidogrel therapy and duration of therapy beyond the study period was prepared for each patient, individually, based on the current treatment guidelines (17). All patients received daily aspirin and statin therapy based on the guideline (17).

3.4. Statistical Analysis

All analyses were conducted using IBM SPSS Statistics 19 for Windows (IBM Inc., Armonk, NY, USA). All data were initially analyzed using the Kolmogorov-Smirnov test to assess for normality. Quantitative variables were presented as means ± standard deviation (SD) for normally distributed variables and as median (interquartile range, IQR) for variables without normal distribution. Categorical data were presented as numbers and percentages. Categorical data were compared with the chi-square test, while quantitative data were compared with Student’s t-test, the Mann-Whitney and Kruskal Wallis tests, as appropriate. All P-values were two-tailed and a P value < 0.05 was considered statistically significant.

4. Results

4.1. Patient Characteristics

Six hundred-fifty patients including 386 (59.4%) male and 264 (40.6%) female subjects were enrolled in the study. The average age was 63.75 ± 8.37 years. Baseline demographic characteristics of patients based on the hs-CRP tertiles, are illustrated in Table 1. The mean hs-CRP level was 15.36 ± 9.83 mg/L, with a median of 14 mg/L (interquartile range 8 to 19.6 mg/L). Tertiles for hs-CRP were < 10, 10 to 17, and > 17 mg/L. No significant differences in age, gender, body mass index (BMI), hypertension, diabetes mellitus, smoking, intake of beta-blocker or ACEI/ARB medications (all P > 0.05) were observed between the patients in the lowest and those in the 2 higher hs-CRP tertiles. However, patients in the lowest hs-CRP tertile were more likely to take statin than patients in the 2 highest hs-CRP tertiles (P < 0.001).

4.2. Association of hs-CRP With the Index Event

Baseline median serum levels of hs-CRP were 6.9 mg/L (IQR, 4.3 - 11 mg/L), 16 mg/L (IQR, 12 - 19.9 mg/L), 19 mg/L (IQR, 14.5 - 23.4 mg/L) and 29.9 mg/L (26 - 41) mg/L in patients with elective, unstable angina, NSTEMI, and STEMI index events, respectively, with statistically significant differences (P < 0.001).

4.3. Association of hs-CRP With the Index Procedure

Patients who underwent multivessel PCI had significantly higher baseline serum levels of hs-CRP compared to patients with single vessel PCI (11.5; IQR, 7 - 16 versus 15.5; IQR, 8.7 - 22 mg/L, P < 0.001).
### Table 1. Baseline Characteristics of Patients According to Tertiles of High-Sensitivity C-Reactive Protein Levels<sup>a,b</sup>

| Variable                     | Tertile I, < 10 mg/L (n = 223) | Tertile II, III, > 10 mg/L (n = 427) | P Values |
|------------------------------|---------------------------------|-------------------------------------|----------|
| **Clinical Characteristics** |                                 |                                     |          |
| Age, y                       | 64.39 ± 8.29                    | 63.22 ± 8.56                       | 0.25     |
| Male gender                  | 140 (63)                        | 246 (57.61)                        | 0.23     |
| Body mass index, kg/m²       | 26.98 (24.01 - 31.18)           | 26.96 (24.7 - 30.14)               | 0.50     |
| Diabetes                     | 55 (25)                         | 124 (29)                           | 0.26     |
| Hypertension                 | 44 (20)                         | III (26)                           | 0.75     |
| Current smoking              | 138 (62)                        | 231 (54)                           | 0.057    |
| Dyslipidemia                 | 107 (48)                        | 143 (33.5)                         | 0.54     |
| **Clinical indication**      |                                 |                                     | < 0.001  |
| Elective                     | 175 (78.5)                      | 71 (16.7)                          |          |
| UA                           | 38 (17)                         | 202 (47.3)                         |          |
| NSTEMI                       | 10 (4.5)                        | III (26)                           |          |
| STEMI                        | 0                               | 43 (10)                            |          |
| **Procedural characteristics**|                               |                                     | < 0.001  |
| One vessel disease           | 94 (42)                         | 119 (28)                           |          |
| Multivessel disease          | 129 (58)                        | 308 (72)                           |          |
| **Medications**              |                                 |                                     |          |
| Beta blockers                | 46 (20)                         | 100 (23.4)                         | 0.41     |
| ACE inhibitors/ARBs          | 43 (19)                         | 55 (13)                            | 0.30     |
| Statins                      | 133 (59.5)                      | 37 (9)                             | < 0.001  |
| Calcium channel blockers     | 4 (1.8)                         | 12 (2.8)                           | 0.65     |

<sup>a</sup> Data are shown as mean ± SD or median (interquartile range) for continuous variables and absolute numbers (percentage) for dichotomous variables.

<sup>b</sup> Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; NSTEMI, non-ST segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST segment elevation myocardial infarction; and UA, unstable angina.

#### 4.4. Changes of hs-CRP After Clopidogrel Treatment

After therapy, median serum level of hs-CRP significantly decreased from 14 mg/L (IQR, 8 - 19.6 mg/L) at baseline to 3.8 mg/L (IQR, 2.1 - 9.0 mg/L) at the 12<sup>th</sup> week (P < 0.001). Female patients had higher reductions in hs-CRP levels in response to clopidogrel therapy compared to male patients (P = 0.006). Moreover, hypertensive patients had higher reductions in hs-CRP levels compared to non-hypertensive patients (P = 0.002). Diabetic patients also had higher reductions in hs-CRP levels after clopidogrel therapy (P = 0.004). Non-smokers had higher reductions in hs-CRP levels compared to patients who smoked (P = 0.001). Patients who had been taking statins before PCI also had lower reductions in hs-CRP levels compared to patients without statin use before PCI (P < 0.001) while patients with and without ACEI/ARB intake had comparable reduction in hs-CRP levels (P = 0.54). The changes in the hs-CRP levels were also statistically different in patients with various index events before PCI (P < 0.001, Figure 1). The percent of changes in hs-CRP levels from baseline to the 12<sup>th</sup> week was -58.5%, -62.34%, -54.86%, and -49.74% in patients with elective, UA, NSTEMI and STEMI index events, respectively (P = 0.57). No significant differences were observed in the mean reduction of hs-CRP levels between patients without stent implantation and those with bare metal or drug-eluting stents (P = 0.07). The summaries of the changes in different subgroups of patients are outlined in Tables 2 - 4 based on clinical traits, medication use, and periprocedural characteristics, respectively. Multivariate regression analysis was performed in order to identify predictors of change in hs-CRP (Table 4).

#### Figure 1. The Changes in the hs-CRP Levels Were Statistically Different in Patients With Various Index Events Before PCI.
**Table 2.** The Effects of Clopidogrel on hs-CRP Levels in Patients With Different Clinical Characteristics

| Clinical Characteristic | Hs-CRP Before Treatment | P Value | Hs-CRP After Treatment | Change | P Value |
|-------------------------|-------------------------|---------|------------------------|--------|---------|
| Gender                  |                         |         |                        |        |         |
| Male                    | 13.00 (8.00 - 18.00)    | 0.013   | 3.60 (2.10 - 7.00)     | -8.00 (-12.00 - 4.90) | 0.006   |
| Female                  | 15.90 (8.90 - 20.50)    |         | 3.40 (2.10 - 9.00)     | -10.00 (-14.00 - 5.40) |         |
| Hypertension            |                         | 0.29    |                        |        |         |
| Yes                     | 14.00 (9.00 - 19.97)    |         | 3.10 (2.09 - 5.80)     | -10.00 (-14.00 - 6.02) | 0.002   |
| No                      | 14.00 (8.00 - 19.00)    |         | 3.60 (2.10 - 8.32)     | -8.25 (-13.00 - 4.67)  |         |
| Diabetes                |                         | 0.59    |                        |        |         |
| Yes                     | 13.65 (8.97 - 19.00)    |         | 2.95 (2.00 - 6.05)     | -9.95 (-13.62 - 6.00)  | 0.004   |
| No                      | 14.00 (8.00 - 19.00)    |         | 3.90 (2.10 - 8.40)     | -8.50 (-13.35 - 4.70)  |         |
| Smoking                 |                         | 0.004   |                        |        |         |
| Yes                     | 13.06 (7.00 - 18.00)    |         | 3.30 (2.10 - 7.00)     | -8.00 (-12.57 - 4.70)  | 0.001   |
| No                      | 15.20 (9.00 - 21.00)    |         | 3.90 (2.10 - 9.00)     | -9.90 (-13.95 - 5.80)  |         |

**Table 3.** The Effects of Clopidogrel on hs-CRP in Patients With Different Medications

| Medication          | Hs-CRP Before Treatment | P Value | Hs-CRP After Treatment | Change | P Value |
|---------------------|-------------------------|---------|------------------------|--------|---------|
| Beta blocker        |                         | 0.94    |                        |        |         |
| Yes                 | 14.00 (8.90 - 17.90)    |         | 3.10 (2.00 - 6.40)     | -9.30 (-13.38 - 5.50) | 0.35    |
| No                  | 14.00 (8.00 - 19.00)    |         | 3.60 (2.10 - 8.30)     | -8.50 (-13.40 - 5.00) |         |
| ACEI/ARB            |                         | 0.57    |                        |        |         |
| Yes                 | 13.00 (8.00 - 19.00)    |         | 3.00 (2.00 - 6.70)     | -8.50 (-12.95 - 5.00) | 0.54    |
| No                  | 14.90 (8.90 - 19.00)    |         | 3.60 (2.10 - 8.80)     | -8.50 (-13.40 - 5.00) |         |
| Calcium channel blocker |                      | < 0.001 |                        |        | < 0.001 |
| Yes                 | 16.00 (14.00 - 19.87)   |         | 4.10 (3.00 - 7.47)     | -11.70 (-14.00 - 8.37) |        |
| No                  | 13.00 (7.00 - 19.00)    |         | 3.10 (2.00 - 8.00)     | -8.00 (-12.97 - 4.61) |        |
| Statins b           |                         | < 0.001 |                        |        | < 0.001 |
| Yes                 | 6.15 (4.08 - 10.30)     |         | 2.10 (1.30 - 3.00)     | -4.05 (-7.20 - 2.19)  | 0.001   |
| No                  | 16.00 (11.00 - 21.00)   |         | 4.15 (2.90 - 9.50)     | -10.20 (-14.00 - 6.90) |         |

*a Abbreviations: ACEI, angiotensin converting enzyme inhibitor; and ARB, angiotensin II receptor blocker.
b Before PCI.

**Table 4.** The Effects of Clopidogrel on hs-CRP in Patients With Different Periprocedural Characteristics

| Periprocedural Characteristics | Hs-CRP Before Treatment | P Value | Hs-CRP After Treatment | Change | P Value |
|--------------------------------|-------------------------|---------|------------------------|--------|---------|
| Clinical indication            |                         | < 0.001 |                        |        | < 0.001 |
| STEMI                          | 7.00 (4.53 - 11.00)     |         | 2.10 (1.50 - 2.90)     | -4.90 (-8.00 - 2.89) |        |
| Elective                       | 16.00 (11.01 - 19.50)   |         | 4.10 (3.00 - 8.15)     | -10.80 (-14.30 - 7.10) |        |
| UA                             | 19.00 (14.00 - 22.00)   |         | 8.40 (4.00 - 12.00)    | -10.50 (-14.00 - 6.00) |        |
| NSTE MI                        | 29.90 (26.00 - 41.00)   |         | 9.00 (8.00 - 14.00)    | -19.60 (-24.00 - 17.00) |        |
| Procedural characteristics     |                         | < 0.001 |                        |        | < 0.001 |
| One vessel                     | 11.00 (7.00 - 16.00)    |         | 3.10 (2.00 - 5.30)     | -7.00 (-10.6 - 4.80)  |        |
| Multivessel                    | 15.50 (9.00 - 21.00)    |         | 3.80 (2.10 - 9.00)     | -10.00 (-14.00 - 5.10) |        |
| Stent implantation             |                         | 0.27    |                        |        | 0.07    |
| No                             | 13.00 (8.95 - 16.00)    |         | 3.90 (2.10 - 8.55)     | -9.80 (-13.95 - 4.87) |        |
| BMS                            | 13.40 (9.00 - 18.00)    |         | 3.20 (2.10 - 6.30)     | -8.00 (-12.90 - 6.00) |        |
| DES                            | 15.00 (8.00 - 19.90)    |         | 3.55 (2.00 - 8.20)     | -10.50 (-14.00 - 6.90) |        |

*a Abbreviations: BMS, bare metal stent; DES, drug-eluting stent; NSTE MI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; and UA, unstable angina.
Table 5. Results of Multiple Linear Regression Analysis for Variables Predicting Change in hs-CRP Levels  

| Predictor | Unstandardized Coefficients | Standardized Coefficients | P Values |
|----------|-----------------------------|---------------------------|---------|
|          | B                           | Standard Error            | Beta    |         |
| Constant | -6.905                      | 1.293                     | 0.718   | < 0.001 |
| Statin   | -4.824                      | 0.175                     | 0.132   | < 0.001 |
| DM       | 1.554                       | 0.306                     |         | < 0.001 |
| CCB      | 2.008                       | 0.392                     | 0.134   | < 0.001 |
| ACEI/ARB | 0.847                       | 0.374                     | 0.058   | 0.024   |
| Smoking  | -0.467                      | 0.222                     | -0.054  | 0.036   |

*a* abbreviations: ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker, and DM, diabetes mellitus.

5. Discussion

The results of the current study should be discussed in three separate sections. First, we tried to find risk factors for a higher baseline hs-CRP level in patients undergoing elective, urgent or emergency PCI. Unsurprisingly, hs-CRP levels varied significantly in patients with various types of acute coronary syndromes. High risk events were associated with higher baseline hs-CRP level. Moreover, patients who underwent multi-vessel PCI had higher hs-CRP levels compared to patients with one-vessel PCI, indicating that more extended coronary artery disease may cause higher levels of hs-CRP.

Second, we assessed changes in the hs-CRP levels in these patients following the administration of clopidogrel for 12 weeks. The main finding was that serum levels of hs-CRP significantly decreased throughout the study period. The anti-inflammatory properties of clopidogrel have been revealed by some of the earlier studies. A reduction in the number of platelet-leukocyte interactions has been reported previously (18, 19). It was also demonstrated that clopidogrel decreased the periprocedural increase in hs-CRP levels in patients undergoing PCI by 65% (20). Quinn and his colleagues also demonstrated that clopidogrel pretreatment reduced platelet inflammatory marker expression in patients undergoing PCI (21). However, the present study is one of the few studies, at least to best of our knowledge, which assessed the long-term anti-inflammatory effects of clopidogrel in patients undergoing PCI.

Third, we performed several subgroup analyses in order to identify patients with higher reductions in hs-CRP from baseline with clopidogrel therapy. The subgroup analysis demonstrated that although the baseline hs-CRP and the magnitude of changes over the study period significantly differed between the patients with various index events, the percentages of changes in the hs-CRP from the baseline values were comparable in all groups, and the decrease in hs-CRP levels was proportional to the baseline values. Although patients with more severe cardiovascular events had higher hs-CRP levels and higher reductions over 3 months, they had the same percentage of reduction in hs-CRP levels as the patients with lower risks for events. This suggests that there are no specific types of cardiovascular events, which benefit more from the clopidogrel therapy, according to its anti-inflammatory effects.

In several studies, statins have been demonstrated to decrease hs-CRP levels and coronary events independently of serum lipid concentrations (4, 11). In our study population, 170 (26%) patients were taking statins before PCI. These patients were more likely to be in the lower tertile of the baseline hs-CRP (78%) compared to the 2 higher hs-CRP tertiles (22%). For the patients that had not previously been on statins, statins were started immediately after PCI, according to the current guidelines (17). We demonstrated that patients who were on statins before PCI had lower reductions in hs-CRP during clopidogrel administration compared to those who started statins after PCI. However, it is possible that the lower reductions in hs-CRP levels in patients taking statins arises from the lower baseline hs-CRP rather than the lower efficacy of clopidogrel in these patients. Aspirin also has anti-inflammatory activities (2). However, since all of the patients received aspirin during the study period, it should not be considered as a confounding factor for the reduction of hs-CRP. Although patients taking ACEIs were more likely to be present in the lower tertile of the baseline hs-CRP, there were no significant differences in the reduction of hs-CRP levels in patients who were taking ACEI during clopidogrel therapy, compared to who were not doing so.

Although both groups had comparable baseline hs-CRP levels, the results of our study demonstrated that diabetic patients had higher decreases in hs-CRP levels compared to non-diabetic patients. This finding may focus the attention on the potentially higher beneficial effects of clopidogrel in diabetic patients and should herald questions in order to clearly define the anti-inflammatory role of clopidogrel in these patients, even in the absence of established coronary heart disease. Moreover, it was demonstrated previously that elevated hs-CRP levels in diabetic patients could predict cardiovascular mortal-
ity independently of traditional risk factors (27). This may provide further rationale for future investigations on the beneficial effects of clopidogrel in diabetic patients, regardless of the concomitant coronary heart disease. Additionally, despite statistically similar baseline hs-CRP values, hypertensive patients also had higher reductions in hs-CRP compared to non-hypertensive patients. We also observed higher reductions in hs-CRP levels in non-smokers compared to smoker patients. Since non-smokers had statistically lower baseline hs-CRP levels as well as similar percentages of change in hs-CRP levels compared to smoker patients, we were unable to definitively determine if smoking alters the anti-inflammatory effects of clopidogrel. Further studies are needed to confirm these results.

Multivariate regression analysis also demonstrated that statins, DM, CCB, ACEI, and smoking were significant independent predictors of the changes in serum hs-CRP levels over the study period. The major limitation of the present study was the lack of a control group. However, since clopidogrel is a class I recommendation for the long-term treatment of patients undergoing PCI, especially in patients with stent implantation, it was impossible to have a control group from an ethical standpoint.

In conclusion, we learned that the use of clopidogrel in patients undergoing PCI had favorable effects on the suppression of hs-CRP levels. This effect appears to be heightened in some group of patients with co-morbidities such as diabetes and hypertension.

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Authors’ Contributions

Shokoufeh Hajsadeghi contributed to the study concept and design, critical revision and approval of the manuscript. Negar Salehi, Ahmad Amin, Majid Maleki, Nima Babaali, Seifollah Abdi, and Maryam Mohsenian contributed to the data collection, critical revision, and approval of the manuscript. Mitra Chitsazan and Mandana Chitsazan also contributed to the study concept and design, data collection, analysis and interpretation, statistics, drafting, critical revision, and approval of the manuscript.

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