Atherosclerosis 207 (2009) 272–276

Contents lists available at ScienceDirect

Atherosclerosis

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

Prognostic value of plasma high-sensitivity C-reactive protein levels in Japanese patients with stable coronary artery disease: The Japan NCVC-Collaborative Inflammation Cohort (JNIC) Study

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ARTICLE INFO

Article history:
Received 5 February 2009
Received in revised form 3 April 2009
Accepted 8 April 2009
Available online 17 April 2009

Keywords:
Coronary artery disease
C-reactive protein
Cardiovascular events

ABSTRACT

High-sensitivity C-reactive protein (hsCRP) levels can predict cardiovascular events among apparently healthy individuals and patients with coronary artery disease (CAD). However, hsCRP levels vary among ethnic populations. We previously reported hsCRP levels in Japanese to be much lower than in Western populations. We investigated the prognostic value of hsCRP levels in Japanese patients with stable CAD. The hsCRP levels were measured in 373 Japanese patients who underwent elective coronary angiography and thereafter decided to receive only medical treatment. Patients were followed up for 2.9 ± 1.5 years for major cardiovascular events (death, myocardial infarction, unstable angina, stroke, aortic disease, peripheral arterial disease, or heart failure). The median hsCRP level was 0.70 mg/l. During the follow-up, cardiovascular events occurred in 53 (14%) of the 373 patients. Compared with 320 patients without events, 53 with events had higher hsCRP levels (median 1.06 vs. 0.67 mg/l, $P < 0.05$). To clarify the association between hsCRP levels and cardiovascular events, the 373 study patients were divided into tertiles according to hsCRP levels: lower (<0.4 mg/l), middle (0.4–1.2 mg/l), and higher (>1.2 mg/l). The Kaplan–Meier analysis demonstrated a significant difference in the event-free survival rate between higher vs. middle or lower tertiles ($P < 0.05$). In multivariate Cox regression analysis, the hsCRP level of >1.0 mg/l was an independent predictor for cardiovascular events (hazard ratio, 2.0; 95%CI, 1.1–3.4; $P < 0.05$). Thus, in Japanese patients with stable CAD who received only medical treatment, higher hsCRP levels, even >1.0 mg/l, were found to be associated with a significantly increased risk for further cardiovascular events.

1. Introduction

Inflammation has been recognized to play an important role in the development of atherosclerotic disease, such as coronary artery disease (CAD) [1,2]. High-sensitivity C-reactive protein (hsCRP) levels, which are one of the biomarkers of systemic inflammation, have been reported to predict cardiovascular events among apparently

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doi:10.1016/j.atherosclerosis.2009.04.015

healthy individuals [3–5] and patients with CAD [6–8]. However, hsCRP levels vary remarkably among different ethnic populations [9,10]. We [11] and others [12,13] reported serum hsCRP levels in Japanese populations to be much lower in comparison to those in Western populations. We also showed plasma hsCRP levels in Japanese patients with stable CAD to be very low [14]. However, the cut-off point of hsCRP levels for high-risk of cardiovascular events in Japanese patients with stable CAD has not been elucidated yet. Recently, the Hisayama Study [15] demonstrated that hsCRP levels were associated with future coronary events in a general population of Japanese, as reported in Western populations. They also showed the hsCRP cut-off point for high-risk of CAD in the Japanese population to be >1.0 mg/l, which is much lower than that for Western populations. The present study therefore investigated the prognostic value of plasma hsCRP levels and the hsCRP cut-off point for high-risk of cardiovascular events in Japanese patients with stable CAD.

2. Methods

2.1. Study patients

We investigated hsCRP levels in 373 consecutive Japanese patients (mean age, 64 ± 9 years; male, 79%) who underwent elective coronary angiography for suspected or known CAD and thereafter decided to receive only medical treatment at the National Defense Medical College Hospital, National Cardiovascular Center, and Kumamoto Medical Center in Japan. Any patients who decided to receive either percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) following angiography were excluded from our study. In addition, any patients with acute coronary syndrome within 3 months, those with a history of PCI within 6 months, those with a history of CABG, those with cardiomyopathies or valvular heart disease, or those with any inflammatory disease or malignancy were excluded. Our study was approved by the institutional ethics committees of the three hospitals. After written informed consent was obtained from all the study patients, blood samples were taken in a fasting state on the morning of the day when coronary angiography was performed. Serum lipid levels were measured by standard laboratory methods. Plasma hsCRP levels were measured using a BNII nephelometer (Dade Behring, Tokyo, Japan). The measurement of hsCRP in the three hospitals was standardized, as we previously reported [16]. The inter-assay and intra-assay coefficients of variation (CV) values were 1.3% and 1.4%, respectively [11]. Of the 373 patients, 211 (57%) had hypertension (blood pressures of ≥140/90 mmHg or on drugs), and 177 (47%) had hyperlipidemia (a total cholesterol level of >220 mg/dl or on drugs), of whom 162 (43%) were taking statins. Diabetes mellitus (a fasting plasma glucose level of ≥126 mg/dl or on insulin or hypoglycemic drugs) was present in 71 (19%) patients, and 139 (37%) were smokers.

2.2. Clinical follow-up for cardiovascular events

On coronary angiograms, CAD was defined as at least one coronary artery having >50% luminal diameter stenosis, and the severity of CAD was represented as the number of >50% stenotic vessels. Of the 373 patients, 269 (72%) were found to have CAD and selected medical treatment over either PCI or CABG after the discussions with the physicians in charge of them. All the study patients were followed up for 2.9 ± 1.5 years for major cardiovascular events (death from all causes, myocardial infarction, need for revascularization procedures for unstable angina, hospitalization for stroke, peripheral arterial disease (PAD) or aortic diseases, or hospitalization for heart failure). This clinical outcome was evaluated by reviewing their medical records and supplemented by a telephone interview with the patients and their family.

2.3. Statistical analysis

Any differences between the two groups were evaluated by the unpaired *t*-test for parametric variables, by the Mann–Whitney *U*-test for nonparametric variables, and by the chi-square test for categorical variables. The correlation between hsCRP levels and the number of stenotic coronary vessels was evaluated by Spearman's rank correlation test. The event-free survival rate in patients with lower, middle and higher tertiles of hsCRP levels was analyzed using the Kaplan–Meier method and was compared by the log-rank test. A multivariate Cox proportional hazards regression analysis was used to identify independent predictors for cardiovascular events. The receiver operating characteristics (ROC) curve analysis was performed to determine the optimal cut-off point of hsCRP levels for cardiovascular events. All the statistical analyses were performed with the SPSS for Windows 11.0.1 software package (SPSS Japan Inc., Tokyo, Japan). A two-sided *P* value of <0.05 was considered to be statistically significant. The results are presented as the mean value ±SD, except for hsCRP levels that are presented as the median value.

3. Results

Table 1 shows the baseline characteristics of the 373 study patients. Of the 373 patients, 269 (72%) were found to have CAD (>50% stenosis) on coronary angiograms, of whom 124 had 1-vessel disease, 95 had 2-vessel disease, and 59 had 3-vessel disease. The median hsCRP level in the 373 study patients was 0.70 mg/l, and the median hsCRP levels in 269 patients with CAD and 104 without CAD were 0.70 and 0.73 mg/l, respectively. The hsCRP levels did not significantly correlate with the number of >50% stenotic coronary vessels (*P* = NS). Moreover, 162 (43%) patients were taking statins, and 83 (22%) had a history of myocardial infarction.

During the follow-up of 2.9 ± 1.5 years, major cardiovascular events occurred in 53 (14%) of the 373 study patients (6 death, 3 myocardial infarction, 29 unstable angina, 11 stroke, 2 PAD/aortic disease, and 2 heart failure). Compared with 320 patients without events, 53 with cardiovascular events were older (68 ± 7 vs. 63 ± 9 years) and had higher rates of hypertension (72% vs. 54%) and CAD (92% vs. 69%) ($P < 0.05$) (Table 1). The number of >50% stenotic coronary vessels was greater in patients with events than in those without events (1.69 ± 0.89 vs. 1.17 ± 1.01, $P < 0.001$). Notably, patients with events had higher hsCRP levels than those without events (median 1.06 vs. 0.67 mg/l, $P < 0.05$).

To clarify the association between hsCRP levels and cardiovascular events, the 373 study patients were divided into tertiles according to hsCRP levels: lower (<0.4 mg/l), middle (0.4-1.2 mg/l), and higher (>1.2 mg/l) tertiles. The Kaplan–Meier analysis demonstrated a significant difference in the event-free survival rate for patients in the higher tertile compared with those in the middle or lower tertiles ($P < 0.05$), but no significant difference was observed in event-free survival rate between the middle and lower tertiles (*P* = NS) (Fig. 1). In a multivariate Cox proportional hazards analysis, compared with those in the lower tertile, patients in the middle tertile had an adjusted hazard ratio (HR) of 0.9 (95%CI, 0.4–2.1, *P* = NS), and patients in the higher tertile had an adjusted HR of 2.3 (95%CI, 1.3–4.0, $P < 0.01$). To determine the optimal cut-off point of hsCRP levels, the ROC curve analysis was performed. As shown in Fig. 2, the optimal cut-off point of hsCRP was found to be around 0.95 mg/l. Because the Centers for Disease Control and Prevention and the American Heart Association categorized patients by the hsCRP cut-off points of <1.0, 1.0–3.0, and >3.0 mg/l into low-, moderate-, and

Table 1
Clinical characteristics of patients with and without cardiovascular events.

	All (n = 373)	Events (+) (n = 53)	Events (−) vs. (+)	Events (−) (n = 320)
Age (years)	64 ± 9	68 ± 7	<0.001	63 ± 9
Gender (male)	294 (79%)	42 (79%)	NS	252 (79%)
Hypertension	211 (57%)	38(72%)	<0.05	173 (54%)
Systolic blood pressure (mmHg)	132 ± 18	140 ± 18	<0.01	131 ± 18
Hyperlipidemia	177 (47%)	27 (51%)	NS	150 (47%)
Total cholesterol (mg/dl)	200 ± 33	203 ± 33	NS	199 ± 34
HDL-cholesterol (mg/dl)	51 ± 15	50 ± 14	NS	51 ± 15
Statin use	162 (43%)	25 (47%)	NS	137 (43%)
Diabetes mellitus	71 (19%)	14 (26%)	NS	57 (26%)
HbA1c (%)	5.6 ± 1.0	6.0 ± 1.3	<0.01	5.6 ± 0.9
Obesity	139 (37%)	23 (43%)	NS	116 (36%)
Smoking	251 (67%)	38 (72%)	NS	213 (67%)
CAD	269 (72%)	49 (92%)	<0.001	220 (69%)
1-vessel disease	124 (33%)	17 (32%)		107 (33%)
2-vessel disease	95 (25%)	22 (42%)		73 (23%)
3-vessel disease	50 (13%)	10(19%)		40 (13%)
The number of >50% stenotic coronary vessels	1.24 ± 1.01	1.69 ± 0.89	<0.001	1.17 ± 1.01
History of myocardial infarction	83 (22%)	13 (25%)	NS	70 (22%)
HsCRP (mg/l)	0.70	1.06	<0.05	0.67

Data are presented as the mean value ±SD or the number (%) of patients, except for the hsCRP levels that are presented as the median value. Obesity was defined as a body mass index of >25.0.

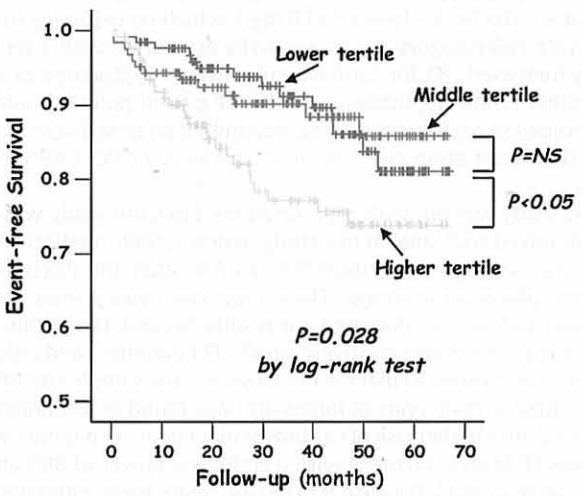

Fig. 1. Event-free survival from major cardiovascular events. The Kaplan–Meier analysis demonstrated a lower event-free survival rate in patients in the higher hsCRP tertile (>1.2 mg/l) than those in the middle (0.4–1.2 mg/l) and lower (<0.4 mg/l) tertiles (P < 0.05), but no significant difference was observed in event-free survival rate between the middle and lower tertiles (P = NS).

high-risk categories [32], we decided to use >1.0 mg/l as the hsCRP cut-off point. In a multivariate Cox proportional hazards analysis, an hsCRP level of >1.0 mg/l as well as age and the number of stenotic coronary vessels were found to be independent predictors for cardiovascular events (Table 2). The HR for cardiovascular events was 2.0 (95%CI, 1.1–3.4) for the hsCRP level of >1.0 mg/l (P < 0.05).

4. Discussion

The present study investigated the prognostic value of hsCRP levels in 373 Japanese patients who underwent elective coronary angiography. As a result, in Japanese patients with stable CAD who had only medical treatment, higher hsCRP levels, even >1.0 mg/l, were found to be associated with a significantly increased risk for further cardiovascular events.

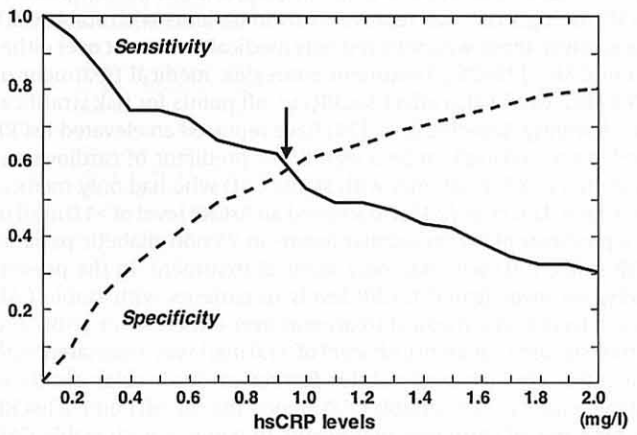

Fig. 2. Receiver operating characteristics (ROC) curves of cut-off points for hsCRP levels. The ROC curves indicated that the optimal cut-off point of hsCRP for major cardiovascular events was around 0.95 mg/l.

Many studies have reported hsCRP levels to predict cardiovascular events among patients with CAD [6–8,17–28] as well as apparently healthy individuals [3–5]. However, as shown in Table 3, most of studies reporting the prognostic values of hsCRP in patients with CAD included a mixture of patients with unstable angina and those with stable angina [6–8,17–22]. Since patients with unstable angina are known to have higher hsCRP levels than those with sta-

Table 2
Factors associated with major cardiovascular events (Multivariate Cox proportional hazards analysis in the 373 study patients).

Variables	Hazard ratio (95%CI)	P value
hsCRP level >1.0 mg/l	2.0 (1.1–3.4)	<0.05
Number of stenotic coronary vessels	1.5 (1.1–2.0)	<0.01
Age (10-year increase)	1.9 (1.3–2.7)	<0.01

The dependent variable was major cardiovascular events. This analysis included age, gender, hypertension, hyperlipidemia, diabetes, smoking, body mass index, the number of >50% stenotic coronary vessels, statin, antiplatelet drugs, ARB/ACEI, and hsCRP >1.0 mg/l.

Table 3
Reported hsCRP levels for high-risk of cardiovascular events in patients with CAD.

Study	Reference numbers	Study patients	Treatment strategy	Endpoints	hsCRP
Unstable or stable angina					
Liuzzo et al.	[6]	31 Patients with UAP	Medically or PCI	Death or MI	>3.0 mg/l
Haverkate et al.	[7]	2121 Patients with UAP or SAP	Medically, PCI, or CABG	Death or MI	>3.6 mg/l
Zebrack et al.	[8]	2554 Patients with UAP or SAP	Medically, PCI, or CABG	Death or MI	>10.0 mg/l
Khor et al.	[17]	2254 Patients with UAP or SAP	Medically, PCI, or CABG	Death or MI	>12.0 mg/l
Horne et al.	[18]	985 Patients with UAP, AMI, or SAP	Medically, PCI, or CABG	Death	>12.0 mg/l
Buffon et al.	[19]	121 Patients with UAP or SAP	PCI (POBA)	Cardiovascular events*	>8.0 mg/l
de Winter et al.	[20]	1458 Patients with UAP or SAP	PCI (POBA or stenting)	Death or MI	>7.0 mg/l
Walter et al.	[21]	276 Patients with UAP, AMI, or SAP	PCI (stenting)	Cardiovascular events*	>5.0 mg/l
Zairis et al.	[22]	483 Patients with UAP, AMI, or SAP	PCI (stenting)	Death, MI, or UAP	>6.8 mg/l
Stable CAD					
Leu et al.	[23]	75 Non-DM patients with stable CAD	Medically	Cardiovascular events**	>1.0 mg/l
Sabatine et al.	[24]	3771 Patients with stable CAD	Medically	Death, MI, or stroke	>1.0 mg/l
Speidl et al.	[25]	124 Patients with stable CAD (<50 years)	Medically or PCI	Cardiovascular events***	>1.6 mg/l
Ikonomidis et al.	[26]	100 Patients with stable CAD	Medically, PCI, or CABG	Death, MI, or UAP	>2.5 mg/l
de Winter et al.	[27]	501 Patients with stable CAD	PCI (POBA or stenting)	Death, MI, or UAP	>3.0 mg/l
Dibra et al.	[28]	1152 Patients with stable CAD	PCI (stenting)	Death or MI	>5.0 mg/l

The hsCRP level indicates the cut-off point for high-risk of cardiovascular events. UAP, SAP, AMI, and POBA indicate unstable angina, stable angina, acute myocardial infarction, and balloon angioplasty.

* Cardiovascular events: death, MI, or coronary revascularization.

** Cardiovascular events: death, MI, coronary revascularization, UAP, stroke, or peripheral artery disease.

*** Cardiovascular events: death, MI, coronary revascularization, or UAP.

ble angina [6,29], the reported cut-off points of hsCRP for high-risk of cardiovascular events seem to be high in a mixture of patients with unstable and stable angina. In contrast, the cut-off point of hsCRP for high-risk was relatively low in patients with stable CAD, especially in those who selected only medical treatment over either PCI or CABG [23–28]. Treatment strategies, medical treatment or PCI/CABG, would also affect hsCRP cut-off points for risk stratification. Recently, Sabatine et al. [24] have reported an elevated hsCRP level, even >1.0 mg/l, to be a significant predictor of cardiovascular events in 3771 patients with stable CAD who had only medical treatment. Leu et al. [23] also showed an hsCRP level of >1.0 mg/l to be a predictor of cardiovascular events in 75 non-diabetic patients with stable CAD who had only medical treatment. In the present study, we investigated hsCRP levels in patients with stable CAD who selected only medical treatment over either PCI or CABG and demonstrated that an hsCRP level of >1.0 mg/l was associated with a significantly increased risk for further cardiovascular events in Japanese patients with stable CAD. Hence, the cut-off point of hsCRP for high-risk of cardiovascular events in patients with stable CAD who had only medical treatment would be >1.0 mg/l in Japanese as well as in other ethnic populations.

It is well known that hsCRP levels vary remarkably among different ethnic populations [9,10]. A twin study demonstrated hsCRP levels to have a moderate degree of heritability [30], and some CRP gene polymorphisms were reported to influence hsCRP levels [31]. These suggest that some genetic factors may contribute to ethnic differences in hsCRP levels. The hsCRP levels in Japanese populations have been reported to be much lower than those in Western populations [11–13]. In the present study, the median hsCRP level in Japanese patients with stable CAD was 0.70 mg/l, which was much lower than those in other ethnic patients with stable CAD in the studies of Sabatine et al. [24] and Leu et al. [23] (1.71 and 1.02 mg/l). The hsCRP levels in Japanese patients with CAD seem to be lower than those in other ethnic patients with CAD. Therefore, the cut-off point of hsCRP for high risk in patients with stable CAD should be much lower in Japanese than in other ethnic patients. However, in patients with stable CAD who selected only medical treatment over either PCI or CABG, the hsCRP level of >1.0 mg/l was found to be a significant predictor of further cardiovascular events in the present study as well as in both studies of Sabatine et al. [24] and Leu et al. [23]. The Centers for Disease Control and Prevention and the American Heart Association categorized patients by the hsCRP cut-off points of <1.0, 1.0–3.0, and >3.0 mg/l into low-, moderate-, and high-risk categories, respectively [32]. Therefore, in patients with stable CAD who received only medical treatment, the hsCRP level of >1.0 mg/l, which corresponds to the moderate-risk category, was found to be associated with a significantly increased risk for cardiovascular events in Japanese as well as in other ethnic populations. The hsCRP cut-off points should be determined in each patient group depending on unstable or stable CAD, treatment strategies (medical treatment or PCI/CABG), and ethnics.

Our study was not without limitations. First, our study was not a randomized trial, and, in our study patients, their medical treatment was selected over either PCI or CABG after the discussions with the physician in charge. These may have caused some selection bias and have confounded our results. Second, the number of our study patients was relatively small (373 patients), and only 53 patients had cardiovascular events. However, the sample size of our study (1082 person-years of follow-up) was found to be enough to detect a 2-fold higher risk of cardiovascular events in patients with high hsCRP level (>1.0 mg/l) with a statistical power of 80% and a alpha value of 0.05, because 935 person-years were estimated as the adequate size with the event rate of 0.049 per person-year in the present study. Finally, our study had only patients with stable CAD who received only medical treatment. Our study excluded any patient who received PCI or CABG following angiography. Therefore, our results cannot be applicable to patients who received PCI or CABG. To determine the prognostic value of pre-procedural hsCRP levels in Japanese patients with stable CAD undergoing PCI, another study is needed.

In conclusion, the present study showed that hsCRP levels in Japanese patients with stable CAD were low in comparison to those in Western populations. However, in patients with stable CAD who received only medical treatment, higher hsCRP levels, even >1.0 mg/l, were found to be associated with a significantly increased risk for further cardiovascular events in Japanese patients, as reported in other ethnic patients.

Acknowledgements

The JNIC study was supported by a Research Grant for Cardiovascular Diseases (14-6) from the Ministry of Health, Labor and Welfare (Principal investigator, Dr. Motoo Tsushima).

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