

# Significance of Inflammatory Markers in Diabetic Patients with Stable Coronary Artery Disease

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**Background/Aims:** Patients with diabetes are prone to coronary artery disease (CAD); however, the majority of diabetic patients show normal coronary arteries. We examined differences in the clinical aspects of diabetic patients with insignificant and with significant stenosis of the coronary artery.

**Methods:** A total of 418 consecutive diabetic patients with stable angina who had undergone coronary angiography from January 2004 to March 2007 were included in this study. Patients were subdivided into control and CAD groups and then clinical characteristics and CAD-associated factors were evaluated.

**Results:** A total of 92 (22%) patients were assigned to the control group and 326 (78%) patients were assigned to the CAD group. Using univariate regression analysis, we found that patients with CAD were significantly older (control vs. CAD; 59±21 vs. 64.7±33.7, years,  $p<0.001$ ), had a longer duration of diabetes (8.2±21.8 vs. 10.2±29.8, years,  $p=0.027$ ), higher titers of high sensitivity C-reactive protein (hsCRP; 0.3±6.79 vs. 0.9±12.6, mg/dL,  $p=0.015$ ), and increased hemoglobin A1c (HbA1c) levels (7.1±3.8 vs. 7.5±4.8, %,  $p=0.007$ ) compared to control patients. Multivariate regression analysis showed that only differences in age, hsCRP, and HbA1c were statistically significant. When patients were subdivided into groups based on hsCRP levels (208 patients in the low group [49.8%], 210 patients in the high group [50.2%]), we found that patients with higher hsCRP levels showed more frequent multivessel disease.

**Conclusions:** In diabetic patients, age, hsCRP, and HbA1c were associated with stable CAD. Among these factors, hsCRP levels were significantly correlated with multivessel involvement in diabetic CAD. Therefore, high hsCRP levels may be a strong predictor for atherosclerotic progression of the coronary arteries in diabetic patients, suggesting that regular screening tests should be performed. (*Korean J Intern Med* 2009;24:212-219)

**Keywords:** C-reactive protein; Diabetes mellitus; Coronary artery disease, stable

## INTRODUCTION

The incidence and prevalence of diabetes mellitus (DM) is rapidly increasing worldwide, due almost exclusively to increases in non-insulin-dependent (type 2) DM. Type 2 DM represents more than 90% of all cases of diabetes [1,2]. Cardiovascular complications are the leading cause of morbidity among patients with diabetes, and ischemic heart disease is the most common cause of death [3,4].

The excess risk for cardiovascular disease (CVD) is two- to eight-fold higher in patients with diabetes compared to non-diabetic individuals of similar age, sex, and ethnicity [5-7]. Furthermore, among patients with coronary artery disease (CAD), diabetes is associated with an increased risk of developing acute coronary syndrome and an increased risk of death after an acute myocardial infarction [8,9]. The pathophysiological mechanism of type 2 DM is insulin resistance, a proinflammatory and

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**Table 1. Comparison of clinical characteristics and association factors between control and CAD groups**

	Control (n=92)	CAD (n=326)	p value
Age, years	59±21	64.7±33.7	<0.001
Sex			0.119
Male	40 (43.5)	184 (56.4)	
Female	52 (56.5)	142 (43.6)	
BMI, kg/m <sup>2</sup>	25.4±9.1	24.5±11.2	0.102
DM duration, years	8.2±21.8	10.2±29.8	0.027
Type of DM treatment			0.072
Diet only	4 (4.3)	14 (4.3)	
OHA	88 (95.7)	274 (84.1)	
Insulin	0 (0)	20 (6.1)	
OHA+Insulin	0 (0)	18 (5.5)	
Hypertension	58 (63)	206 (63.2)	0.985
Smoking history	36 (39.1)	134 (41.1)	0.810
FBS, mg/dL	144.3±85.7	161.5±459.5	0.099
HbA1c, %	7.1±3.8	7.5±4.8	0.015
LVH	32 (34.8)	90 (27.6)	0.346
LVEF			0.056
≥50%	90 (97.8)	286 (87.7)	
<50%	2 (2.2)	40 (12.3)	
Proteinuria	16 (17.4)	76 (23.3)	0.392
hsCRP, mg/dL	0.3±6.79	0.9±12.6	0.007
Lipoprotein, mg/dL	25.8±108.4	25.7±148.9	0.061
Total-C, mg/dL	184.9±86.1	184.1±205.9	0.076
TG, mg/dL	197.2±369.8	179.4±991.6	0.730
LDL-C, mg/dL	104.0±139.4	112.8±108.2	0.094
HDL-C, mg/dL	44.4±72.6	39.2±25.8	0.356

Values are number (percentage) or mean±SD.

CAD, coronary artery disease; BMI, body mass index; DM, diabetes mellitus; OHA, oral hypoglycemic agent; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; hsCRP, high sensitivity C-reactive protein; Total-C, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

hypercoagulable state that predisposes patients to develop CVD. Type 2 DM is associated with risk factors for atherosclerosis including dyslipidemia, hypertension, inflammation, and altered hemostasis [10].

To date, studies have documented that diabetic CVD is increasing; however, questions regarding the temporal relationship between diabetes and CVD, the metabolic and cellular etiologic mechanisms underlying diabetic CVD, and the most effective strategies for predicting and reducing CVD risk in patients with diabetes remain unanswered. Although the risk of CAD is high in diabetic patients, most show normal coronary arteries. Here we compared the clinical aspects of patients with insignificant

stenosis of the coronary artery to those of patients with diabetes and CAD. Furthermore, we examined the association between CAD severity and high sensitivity C-reactive protein (hsCRP) levels.

## METHODS

### Patients and definitions

We retrospectively analyzed the clinical records and catheterization reports of type 2 diabetic patients with chest pain who underwent coronary angiography at Kangnam St. Mary's Hospital Seoul, Korea from January

**Table 2. Comparisons of clinical characteristics and association factors between control and CAD groups based on multivariate regression analyses**

	Control (n=92)	CAD (n=326)	OR (95%CI)	p value
Age, years	59±21	64.7±33.7	1.079	<0.001 (1.034-1.132)
HbA1c, %	7.1±3.8	7.5±4.8	1.386	0.010 (1.022-2.115)
hsCRP, mg/dL	0.3±6.79	0.9±12.6	1.797	0.006 (1.682-1.912)
DM duration, years	8.2±21.8	10.2±29.8	1.047	0.167 (1.016-1.105)

Values are number (percentage) or mean±SD.

CAD, coronary artery disease; OR, odds ratio; HbA1c, hemoglobin A1c; hsCRP, high sensitivity C-reactive protein; DM, diabetes mellitus.

2004 to March 2007. In total, there were 541 consecutive study subjects. The decision to perform coronary angiography was based on symptoms consistent with the diagnosis, an abnormal electrocardiogram (ECG), positive findings in standard exercise tests, or abnormal findings in radionuclear studies. We subsequently excluded 123 patients who had one or more of the following characteristics: platelet count <100,000/mm<sup>3</sup>; serum creatinine levels >2.5 mg/dL; cardiogenic shock; acute myocardial infarction within 48 hour; unstable CAD; variant angina; history of coronary artery bypass graft surgery; prior revascularization; malignancy; autoimmune disease; or recent infectious disease.

Patients were further subdivided into a control (insignificant CAD of <50% stenosis) and CAD group (significant coronary arterial stenosis ≥50%). Baseline clinical characteristics and CAD-associated factors among these groups were investigated. The association between the severity of CAD and hsCRP levels was also examined. In a second analysis, the 418 patients were divided into low and high hsCRP groups based on median hsCRP levels (0.24 mg/dL). The physical examination included measurements of height and weight, which were recorded based on standardized methods, and body mass index, which was calculated as weight (kg)/height (m<sup>2</sup>). Patients were also divided into two groups based on smoking behavior (*i.e.*, smokers and non-smokers). Patients who had stopped smoking for 10 years or less were classified as smokers. The diagnosis of DM was based on fasting plasma glucose levels of ≥126 mg/dL (7.0 mmol/L) or 2-h postprandial plasma glucose levels of ≥200 mg/dL (11.1 mmol/L). The type of diabetic treatment administered

was characterized, and patients were subdivided into four groups based on treatment: diet only, oral hypoglycemic agent, insulin, and combination therapy with oral hypoglycemic agents and insulin. A diagnosis of hypertension was based on the Seventh Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, or current use of antihypertensive drugs. Serum levels of lipoprotein, total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) were measured via enzymatic methods using an automatic analyzer. Serum levels of hsCRP were measured by immunonephelometry.

Left ventricular hypertrophy was considered present when the left ventricular mass index at initial echocardiographic M-mode measurement was greater than 134 g/m<sup>2</sup> in men and greater than 110 g/m<sup>2</sup> in women (based on American Society of Echocardiography recommendations). Left ventricular ejection fraction (LVEF) was determined by echocardiogram (Simpson's method) and patients were divided into two groups (>50% and <50%). Proteinuria levels greater than 500 mg/day were defined as overt proteinuria. Both right and left coronary arteries were studied in at least two oblique projections (right anterior oblique 30° and left anterior oblique 60°). The CAD group was defined as those patients who had at least one coronary artery lesion that occupied at least 50% of the luminal diameter, as indicated by coronary angiography. Patients with coronary artery lesions occupying less than 50% of the luminal diameter were assigned to the control group.

Clinical factors associated with CAD were analyzed,

**Table 3. Comparison of clinical characteristics, association factor, and CAD severity between the low and high hsCRP groups**

	All patients (n=418)	Low hsCRP group (n=208)	High hsCRP group (n=210)	<i>p</i> value*
Age, years	63.50±9.4	62.2±9.1	64.8±9.6	0.005
Male	224 (53.6)	108 (51.9)	116 (55.2)	0.498
BMI, kg/m <sup>2</sup>	24.7±3.1	24.6±2.7	24.9±3.5	0.338
DM duration, years	9.81±7.5	8.9±6.3	10.7±8.4	0.012
DM treatment				0.467
Diet only	18 (4.2)	8 (3.8)	10 (4.8)	
OHA	348 (83.3)	174 (83.7)	174 (82.9)	
Insulin	30 (7.2)	12 (5.8)	18 (8.6)	
OHA + Insulin	22 (5.3)	14 (6.7)	8 (3.8)	
Hypertension	264 (63.2)	130 (62.5)	134 (63.8)	0.782
Smoking history	170 (40.7)	82 (39.4)	88 (41.9)	0.607
FBS, mg/dL	157.7±62.3	150.0±50.9	165.3±71.2	0.012
HbA1c, %	7.5±1.2	7.3±1.3	7.6±1.2	0.034
LVH	122 (29.2)	52 (25)	70 (33.3)	0.061
LVEF				<0.001
≥50%	376 (90)	200 (96.2)	176 (83.8)	
<50%	42 (10)	8 (3.8)	34 (16.2)	
Proteinuria	92 (22)	34 (16.3)	58 (27.6)	0.005
Lipoprotein, mg/dL	25.7±22.8	23.4±19.8	27.9±25.3	0.044
Total-c, mg/dL	184.2±42.8	181.8±44.7	186.7±40.9	0.246
TG, mg/dL	183.3±136.3	190.9±137.9	175.7±134.4	0.254
LDL-C, mg/dL	110.8±34.9	104.2±35.0	117.3±33.6	<0.001
HDL-C, mg/dL	40.4±11.6	42.9±14.0	37.9±8.0	<0.001
Severity of CAD				<0.001
Normal	90 (21.5)	70 (33.7)	20 (9.5)	
1 Vessel disease	114 (27.3)	50 (24.0)	64 (30.5)	
2 Vessel disease	118 (28.2)	56 (26.9)	62 (29.5)	
3 Vessel disease	96 (23)	32 (15.4)	64 (30.5)	

Values are number (percentage) or mean±SD.

CAD, coronary artery disease; hsCRP, high sensitivity C-reactive protein; BMI, body mass index; DM, diabetes mellitus; OHA, oral hypoglycemic agent; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; LVH, left ventricular hypertrophy; LVEF, left ventricular ejection fraction; Total-C, total cholesterol; TG, triglyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

\*statistical *p* value between the low hsCRP group and the high group.

and patients were divided into two groups based on median hsCRP levels (low and high). CAD-associated factors and the severity of stable diabetic CAD were compared between low and high hsCRP groups.

### Statistical analysis

Statistical analyses were performed using the SPSS statistical package, version 12.0 (SPSS Inc., Chicago, IL, USA). Unless otherwise noted, all tests were two-tailed

and a *p* value less than 0.05 was considered significant. Potential associations between clinical and biologic parameters were tested by univariate and multivariate regression analyses using a Student's *t*-test or chi-square test. All data are presented as means and standard deviations.

**Table 4. Multivariate logistic regression analysis between the low hsCRP group and the high group**

Severity of CAD	OR	95% CI	p value*
Normal			<0.001
1 vessel disease	4.480	2.411-8.324	<0.001
2 vessel disease	3.875	2.096-7.163	<0.001
3 vessel disease	7.000	3.642-13.455	<0.001

hsCRP, high sensitivity C-reactive protein; CAD, coronary artery disease; OR, odds ratio; CI, confidence interval.

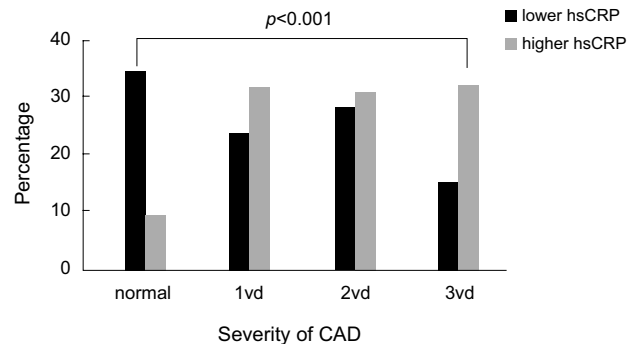
\*statistical p value between the low hsCRP group and the high group.

## RESULTS

In total, 418 diabetic patients were enrolled in the study. Based on angiography, 92 (22%) cases were assigned to the control group and 326 (78%) cases were assigned to the CAD group. Sample population characteristics with respect to investigated risk parameters are presented in Table 1. No relevant differences in baseline characteristics (except age), medical history, or diabetic medication use were significantly different between the control and CAD groups. Based on univariate regression analysis, patients with CAD were significantly older (control vs. CAD;  $59 \pm 21$  vs.  $64.7 \pm 33.7$ , years,  $p < 0.001$ ) and had a longer duration of diabetes (control vs. CAD;  $8.2 \pm 21.8$  vs.  $10.2 \pm 29.8$ , years,  $p = 0.027$ ), higher hsCRP titers (control vs. CAD;  $0.3 \pm 6.79$  vs.  $0.9 \pm 12.6$ , mg/dL,  $p = 0.015$ ), and higher hemoglobin A1c (HbA1c) levels (control vs. CAD;  $7.1 \pm 3.8$  vs.  $7.5 \pm 4.8\%$ ,  $p = 0.007$ ) compared to control patients. However, multivariate regression analysis showed that age, hsCRP, and HbA1c were statistically different between the two groups (Table 2). The duration of diabetes in the CAD group tended to be longer; however, this difference was not significantly different. No relevant differences were observed in the degree of left ventricular hypertrophy, left ventricular ejection fraction, fasting plasma glucose, proteinuria, or lipid profiles between the groups.

We calculated odds ratios (OR) for factors associated with CAD in diabetic patients between the control and CAD groups. The OR for CAD and age was 1.079 (95% confidence interval [CI], 1.034-1.132); for HbA1c was 1.386 (95% CI, 1.022-2.115); and for hsCRP was 1.797 (95% CI, 1.682-1.912; Table 2).

Among the 418 diabetic patients, 208 (49.8%) had low hsCRP levels and 210 (50.2%) had high hsCRP levels based on median titer values (0.24 mg/dL). Patients in the high hsCRP group were significantly older than patients in the low hsCRP group (low hsCRP vs. high hsCRP;  $62.2 \pm 9.1$  vs.  $64.8 \pm 9.6$  years,  $p < 0.001$ ). In addition, fasting blood sugar (low hsCRP vs. high hsCRP;  $150.0 \pm$



**Figure 1.** Comparison of CAD severity between the high hsCRP group and the low hsCRP group. hsCRP, highly sensitive C-reactive protein; vd, vessel disease; CAD, coronary artery disease.

$50.9$  vs.  $165.3 \pm 71.2$  mg/dL,  $p = 0.012$ ) and HbA1c (low hsCRP vs. high hsCRP;  $7.3 \pm 1.3$  vs.  $7.6 \pm 1.2\%$ ,  $p = 0.034$ ) were higher; the duration of diabetes (low hsCRP vs. high hsCRP;  $18.0$  vs.  $27.3$  years,  $p = 0.012$ ) was longer; LDL-c levels (low hsCRP vs. high hsCRP;  $104.2 \pm 35.0$  vs.  $117.3 \pm 33.6$  mg/dL,  $p = 0.022$ ), lipoprotein levels (low hsCRP vs. high hsCRP;  $23.4 \pm 19.8$  vs.  $27.9 \pm 25.3$  mg/dL,  $p = 0.044$ ), and the amount of patients with  $<50\%$  LVEF (low hsCRP vs. high hsCRP;  $3.8$  vs.  $16.2\%$ ,  $p < 0.001$ ) were higher; and HDL-c levels (low hsCRP vs. high hsCRP;  $42.9 \pm 14.0$  vs.  $37.9 \pm 8.0$  mg/dL,  $p < 0.001$ ) were lower. Finally, both proteinuria (low hsCRP vs. high hsCRP;  $16.3$  vs.  $27.6\%$ ,  $p = 0.005$ ) and multivessel disease (low hsCRP vs. high hsCRP; normal:  $33.7$  vs.  $9.5$ ; 1 vessel disease:  $24.0$  vs.  $30.5\%$ , 2 vessel disease:  $26.9$  vs.  $29.5$ , 3 vessel disease:  $15.4$  vs.  $30.5\%$ , respectively,  $p < 0.001$ ) was more frequent (Table 3, Fig. 1). Multivariate logistic regression analysis showed that the severity of CAD between the low hsCRP group and the high group (normal vs. 1 vessel disease, OR=4.480,  $p < 0.001$ ; normal vs. 2 vessel disease, OR=3.875,  $p < 0.001$ ; normal vs. 3 vessel disease, OR=7.000,  $p < 0.001$ ) was significantly different (Table 4).

## DISCUSSION

The prevalence, incidence, and mortality of all forms of CVD were strikingly higher for people with diabetes than those without diabetes [5-7]. According to the World Health Organization, the prevalence of CVD in diabetic patients ranges from 26 to 36% [11]. Our study also shows a lower prevalence of significant CAD (22%) in diabetic patients with stable CAD.

Measurement of hsCRP, an inflammatory biomarker that independently predicts future vascular events, improves global classification of risk, regardless of LDL-c levels [12-16]. In the Bezafibrate Infarction Prevention (BIP) study [17], high CRP levels was a strong predictor for subsequent ischemic stroke among patients with pre-existing atherosclerotic disease; a greater than two-fold increased risk was observed between the top versus bottom tertiles. In the Inflammation and Carotid Artery-Risk for Atherosclerosis study (ICARAS) [18], elevated hsCRP levels indicated the systemic nature of progressive atherosclerotic disease and suggested that patients with enhanced inflammation are generally at high risk for progression of atherosclerotic disease and may exhibit multiple vulnerable lesions.

We presumed that, although the risk for CVD is high in diabetics, patients often have insignificant coronary artery stenosis. Therefore, we compared the clinical aspects of insignificant stenosis in coronary artery patients to those of diabetic patients with significant CAD. We found that diabetic patients with stable CAD are significantly older and have higher hsCRP titers and HbA<sub>1c</sub> levels compared to control patients. One of the most important findings of this report is that high hsCRP levels strongly predict an increased risk for atherosclerotic progression among groups of patients with diabetic stable CAD. Specifically, a 1.797-fold increased risk was observed between the CAD and control group after adjusting for potential confounding variables. A meta-analysis of studies with long-term follow-up data showed that the risk for stroke in healthy individuals in the highest quartile of CRP concentrations was nearly 1.7-fold higher than that of those in the lowest quartile [19]. In a nested case-controlled study among patients who had experienced a cerebrovascular event (the Perindopril Protection Against Recurrent Stroke Study, or PROGRESS [20]), the OR for a recurrent event associated with the top versus bottom tertile was 1.39 for CRP.

We also examined the association between CAD severity and hsCRP titers in patients with low and high hsCRP

levels based on median level values. In patients with stable diabetic CAD, multivessel disease was significantly correlated with increased hsCRP levels (OR of three-vessel disease=7.0 compared to normal vessel disease). A strong prediction of risk was estimated in our study, as characterized by the presence of atherosclerotic CAD. These strong associations are likely applicable to diabetic populations at high risk for CAD in pre-existing atherosclerotic disease.

Several pharmacological agents that are proven to reduce vascular risk also reduce hsCRP levels. Among these, all statins lower hsCRP, with more potent statins having greater effects. On average, median hsCRP levels decline 15-25% after 6 weeks of therapy [21-23].

Current guidelines recommend screening for CAD in diabetic patients with a high cardiovascular risk. The American Diabetes Association (ADA) recommends cardiac testing for diabetic patients with the following characteristics: typical or atypical cardiac symptoms; resting ECGs suggestive of ischemia or infarction; peripheral or carotid occlusive arterial disease; a sedentary lifestyle; over 35 years old; plan to begin a vigorous exercise program; or show traditional and diabetes-specific risk factors (lipid profile, blood pressure, smoking, or with family history of premature CAD, micro/macroalbuminuria) [24]. Another guideline edited by the Société Française de Cardiologie/ Association de Langue Française pour l'Etude du Diabète et des Maladies métaboliques (SFC/ALFEDIAM) makes similar recommendations [25]. These guidelines do not emphasize the evaluation of inflammatory markers such as hsCRP; however, based on our results, hsCRP is a good surrogate marker for CAD. A prospective follow-up study in diabetes showed that high CRP levels were associated with an increased risk of major coronary events [26]. Therefore, we recommend that prevention should also focus on patients with high CRP.

We are aware of several limitations to our study. It was conducted at a single center and was not a randomized. Therefore, it is necessary to validate these data with multicenter-randomized studies. We considered hsCRP levels a predictor of atherosclerotic progression; however, we could not show long-term effects of hsCRP levels on atherosclerotic progression and thus we should continue to conduct follow-up on all patients involved in this study. In January 2003, the American Heart Association and the Centers for Disease Control released the following new recommendations for CRP levels as a predictor of CVD: low risk, <0.1 mg/dL; average risk, 0.1-0.3 mg/dL;

and high risk, >0.3 mg/dL. In the Justification for the Use of Statins in Primary prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study [21,27], high hsCRP levels were 0.2 mg/dL or higher. The cut-off point of hsCRP levels is not clear; therefore, we divided patients into two groups based on the median value measured. Our median hsCRP level was 0.24 mg/dL, which was greater than the cut-off point for the JUPITER study. This discrepancy is thought to be mainly due to the characteristics of our study group, namely, diabetic stable CAD (we did not include all types of CAD in this study). Patients with acute myocardial infarction and unstable CAD were excluded from the study because CAD in the acute phase shows increased expression of inflammatory markers. The only inflammatory marker studied was hsCRP, and thus further evaluations of other inflammatory markers are warranted.

In conclusion, age and levels of HbA<sub>1c</sub> and hsCRP of diabetic patients were associated with stable CAD, and may be used as surrogate markers of CAD in diabetes. High hsCRP levels were uniquely correlated with multi-vessel disease in diabetic CAD. Therefore, high hsCRP levels in patients with stable diabetic CAD may represent a strong predictive factor for an increased risk of atherosclerotic progression in the coronary arteries. We suggest that diabetic patients with high hsCRP levels require regular screening tests for CAD (using noninvasive methods or invasive coronary angiography) when there are no other reasons for elevated hsCRP levels other than atherosclerotic disease. Future studies will examine the utility of these findings as a guide to monitor the progression of atherosclerotic disease and its subsequent treatment.

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