

# Impact of Atherosclerosis Detection by Carotid Ultrasound on Physician Behavior and Risk-Factor Management in Asymptomatic Hypertensive Subjects

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## ABSTRACT

**Background:** There are limited data regarding the impact of atherosclerosis detection by carotid ultrasound (CUS) on physician prevention efforts and risk-factor management for cardiovascular disease.

**Hypothesis:** Atherosclerosis detection by CUS in asymptomatic hypertensive patients would lead to physician prevention efforts, including target low-density lipoprotein cholesterol (LDL-C) level and prescription. Also, it may improve risk-factor management.

**Methods:** A total of 347 asymptomatic hypertensive subjects (age  $61 \pm 8$  years, 189 men) were prospectively recruited from 22 hospitals. Prior to CUS, physicians were surveyed regarding target LDL-C level. After CUS, patients were classified into positive CUS ( $n = 182$ ) and negative CUS ( $n = 165$ ) groups based on CUS results. Physicians were resurveyed to assess whether the initial target LDL-C goals were changed. At 6 months, cardiovascular risk-factor modification status was reassessed.

**Results:** The proportion of lowered target LDL-C levels was significantly larger in the positive CUS group than in the negative CUS group (52% vs 23%,  $P < 0.001$ ). These results were observed even in subjects who had low and moderate risk according to National Cholesterol Education Program–Adult Treatment Panel III guidelines. Lipid-lowering agents were similarly added or switched to another class in both groups (7% in the positive CUS group vs 11% in the negative CUS group,  $P = 0.153$ ). LDL-C was significantly decreased in the positive CUS group ( $\Delta = -24 \pm 38$  mg/dL,  $P < 0.001$ ), whereas it was not significantly decreased in the negative CUS group ( $\Delta = -6 \pm 31$  mg/dL,  $P = 0.105$ ).

**Conclusions:** Atherosclerosis detection by CUS lowered physicians' target LDL-C level and improved cardiovascular risk management in terms of LDL-C reduction.

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## Introduction

Atherosclerosis detection by carotid ultrasound (CUS) is widely used because of its lack of radiation exposure, relatively low cost, and ability to detect early-stage atherosclerosis. Also, the association between carotid intima-media thickness (cIMT) and cardiovascular disease (CVD) is well established.<sup>1,2</sup> However, there are limited data regarding the impact of atherosclerosis detection by CUS on physician and patient prevention efforts. Some studies suggested that screening for atherosclerosis and knowing the results altered the physician treatment plan.<sup>3–5</sup> In addition, it might help motivate patients to modify their health behaviors, such as adherence to medications and lifestyle changes, and increase their perception of cardiovascular risk.<sup>6–8</sup> In contrast to these studies, others assessing the impact of atherosclerosis screening reported that it was not associated with patient lifestyle modifications.<sup>3,9</sup> Furthermore, the role of screening for atherosclerosis in the clinical setting is still controversial, and it is debated whether imaging should be considered only in certain groups of subjects or extended to healthy adults, leading to controversial guidelines.<sup>10–12</sup>

However, recent studies have shown some limitations with risk stratification according to traditional methods. When we previously assessed the cardiovascular risk factors solely according to the Third Report of the National Cholesterol Education Program–Adult Treatment Panel III (NCEP-ATP III) guidelines, two-thirds of acute myocardial infarction patients were not qualifying for drug therapy.<sup>13</sup> Also, other studies showed that nearly 40% of asymptomatic subjects with low risk according to the Framingham Risk Score (FRS) had abnormal CUS findings, and they were associated with increased risk for cardiovascular events.<sup>14</sup> Similarly, cIMT and plaque assessment revised the traditional FRS in asymptomatic patients without CVD.<sup>15</sup>

Thus, this prospective multicenter observational study was designed to examine the hypothesis that atherosclerosis detection by CUS in asymptomatic hypertensive patients would lead to physician prevention efforts including target low-density lipoprotein cholesterol (LDL-C) level and prescription. Also, we examined whether atherosclerosis detection by CUS leads to improved risk-factor management.

## Methods

### Subjects

Study participants consisted of 347 subjects who were recruited from 22 hospitals in Korea between January 2010 and May 2011. Included were men age 45 to 75 years and women age 55 to 75 years with hypertension (systolic blood pressure [SBP]  $\geq 140$  mm Hg or taking antihypertensive medication). Patients with previously documented coronary artery disease (CAD), cerebrovascular disease, peripheral arterial disease, or heart failure with symptoms were excluded. The study protocols were approved by the institutional review board at each participating institution, and written informed consent was obtained from all patients before recruitment.

## Study Protocol

Potential patients were screened for the study during routine office visits and underwent routine procedures such as history-taking, physical examination, and laboratory tests. Ten-year risk for CAD was calculated by the FRS and NCEP-ATP III risk category.<sup>16,17</sup> After routine procedures, we surveyed physicians regarding target LDL-C for their patients. In addition, medications that patients were taking, including antihypertensive, lipid-lowering, and antiplatelet agents, were recorded on the case report form.

After the survey was completed, CUS examination was performed to measure cIMT and to identify carotid plaques. Based on CUS findings, patients were classified into either a positive CUS group or a negative CUS group. After the CUS examination, physicians were resurveyed as to whether they changed target LDL-C goals according to classified groups. After that, patients were informed of the test results and their physician's recommendations. Patients were educated that there was a strong association between carotid artery disease and CVD and that their risks for heart attack, stroke, and death were increased if they had plaque or increased cIMT.

A total of 326 patients were then prospectively followed up over 6 months (21 patients were lost to follow-up). At 6 months after the initial visit, risk-factor management was re-evaluated, including body mass index (BMI), waist circumference, SBP, diastolic blood pressure (DBP), and lipid profile.

### Carotid Ultrasound Examination

The CUS examination was performed at each participating hospital according to the protocol recommended by the American Society of Echocardiography and the Society of Vascular Medicine.<sup>18</sup> The examination included a thorough scan of the extracranial carotid arteries for the presence of carotid plaque, defined as focal wall thickening that was 50% greater than that of the surrounding vessel wall and cIMT  $> 1.5$  mm. In the absence of identified plaque, cIMT measurements were made in the distal 1 cm of the far wall of the common carotid artery using the semiautomated border-detection program. A mean value for cIMT was calculated on the basis of 3 separate measures of IMT on R wave-gated still frames from each of 3 scan planes.<sup>18</sup> In our study, patients who had carotid plaque or cIMT  $> 0.9$  mm were classified into the positive CUS group, as recommended by the European Society of Hypertension and the European Society of Cardiology.<sup>19</sup>

### Statistical Analysis

Continuous variables are presented as mean  $\pm$  SD and categorical data are presented as frequencies and group percentages. Patient characteristics were compared between the positive CUS group and negative CUS group using the  $\chi^2$  test for categorical variables and the Student *t* test for continuous variables. The paired *t* test was used to assess changes in risk-factor management before and 6 months after CUS measurements. These changes were compared between the positive CUS group and negative CUS group using the Student *t* test.

All analyses were conducted using SAS version 9.2 (SAS Institute Inc., Cary, NC). A *P* value of <0.05 was considered statistically significant.

## Results

### Baseline Characteristics

Baseline characteristics according to CUS findings are summarized in Table 1. Patients with positive CUS were older and had longer duration of hypertension. Sex, BMI, underlying disease, and blood pressure (BP) were similar. All laboratory findings except triglycerides were similar between the 2 groups. Sixty-nine percent of the patients were receiving antihypertensive agents and 39% were receiving lipid-lowering agents. More patients in the positive CUS group were taking antiplatelet agents compared with those in the negative CUS group (40% vs 29%, *P* = 0.030). The proportion of low risk for coronary heart disease by FRS (FRS <10%) was significantly higher in the negative CUS group compared with the positive CUS group (66% vs 47%, *P* = 0.005).

### Physicians' Changes in Target Low-Density Lipoprotein Cholesterol and Prescription After CUS Examination

After confirmation of CUS examination results, physicians lowered the target LDL-C level in 92 patients (52%) in the positive CUS group (Table 2). The most frequent change was from <130 mg/dL to <100 mg/dL. However, physicians lowered the target LDL-C level only in 39 patients (23%) in the negative CUS group (Table 2). Thus, the proportion of lowered target LDL-C level was significantly larger in the positive CUS group compared with the negative CUS group (*P* < 0.001; Figure 1). Of note, these findings even persisted in the low-risk and moderate-risk patients according to the NCEP-ATP III guidelines (Figure 2).

When we evaluated whether the initial target LDL-C were settled higher or lower than the recommended target level by the NCEP-ATP III guidelines, 52% of the subjects were initially targeted the same as the recommended goals. However, 28% of subjects were initially targeted higher than the guidelines and 20% were targeted lower than the guidelines. In the initially appropriately targeted group, 55% in the positive CUS group lowered the target LDL-C after CUS test, although only 37% in the negative CUS group lowered the target LDL-C (*P* = 0.018). This finding was consistent in the initially targeted higher group (85% vs 19%, *P* < 0.001) and the initially targeted lower group (21% vs 6%, *P* = 0.054).

Regarding the changes in prescription, lipid-lowering agents were added or switched to another class in 12 (7%) patients in the positive CUS group and in 18 (11%) patients in the negative CUS group, and there were no significant differences between the 2 groups (*P* = 0.153).

### Risk-Factor Management at 6 Months After Carotid Ultrasound Examination

Changes in risk-factor management are summarized in Table 3. Body mass index was decreased at 6 months only in the negative CUS group ( $\Delta$  =  $-0.1 \pm 0.4$  kg/m<sup>2</sup>, *P* = 0.006). Waist circumference was not changed at 6 months

Table 1. Baseline Characteristics According to Results of CUS Examination

	Positive CUS, n = 182	Negative CUS, n = 165	<i>P</i> Value
Age, y	62 ± 7	60 ± 8	<0.001
Male sex	103 (56.6)	86 (52.1)	0.404
Hypertension duration, y	5.3 ± 6.0	4.0 ± 4.3	0.024
BMI, kg/m <sup>2</sup>	25.7 ± 2.9	25.1 ± 3.0	0.053
Waist circumference, cm	87.3 ± 9.2	86.7 ± 9.8	0.630
Family history of premature CAD	32 (17.6)	17 (10.4)	0.055
DM	28 (15.4)	17 (10.3)	0.159
Dyslipidemia	139 (76.4)	120 (72.7)	0.436
Smoking			0.438
Current smoker	28 (15.4)	34 (20.6)	
Past smoker	50 (27.5)	41 (24.9)	
Nonsmoker	104 (57.1)	90 (54.5)	
SBP, mm Hg	136 ± 18	134 ± 13	0.376
DBP, mm Hg	83 ± 12	83 ± 10	0.627
TG, mg/dL	138 ± 71	156 ± 96	0.040
LDL-C, mg/dL	115 ± 35	110 ± 32	0.198
HDL-C, mg/dL	51 ± 12	52 ± 19	0.402
TC, mg/dL	189 ± 37	186 ± 37	0.555
FBG, mg/dL	108 ± 31	107 ± 26	0.824
HbA <sub>1c</sub> , %	6.3 ± 1.2	6.1 ± 1.0	0.206
Cr, mg/dL	0.9 ± 0.2	0.9 ± 0.2	0.677
Medications			
Antihypertensive agents	120 (65.9)	119 (72.1)	0.214
Lipid-lowering agents	72 (39.6)	62 (37.6)	0.705
Antiplatelet agents	72 (39.6)	47 (28.5)	0.030
FRS			0.005
FRS <10%	73 (46.5)	84 (65.6)	
FRS 10%–20%	71 (45.2)	33 (26.4)	
FRS >20%	13 (8.3)	8 (6.4)	

Abbreviations: BMI, body mass index; CAD, coronary artery disease; cIMT, carotid intima-media thickness; Cr, creatinine; CUS, carotid ultrasound; DBP, diastolic blood pressure; DM, diabetes mellitus; FBG, fasting blood glucose; FRS, Framingham Risk Score; HbA<sub>1c</sub>, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Data are presented as means ± SD or as n (%). Subjects with carotid plaque or cIMT >0.9 mm were classified in the positive CUS group as recommended by the European Society of Cardiology.<sup>19</sup>

Table 2. Changes in Target LDL-C After CUS Examination

Initial target LDL-C, mg/dL	Target LDL-C After CUS Examination, mg/dL							
	Positive CUS, n = 182				Negative CUS, n = 165			
<160	<130	<100	<70	<160	<130	<100	<70	
<160	13 (7.1) <sup>a</sup>	15 (8.2) <sup>b</sup>	16 (8.8) <sup>b</sup>	0 <sup>b</sup>	24 (14.5) <sup>a</sup>	3 (1.8) <sup>b</sup>	0 <sup>b</sup>	
<130	1 (0.5) <sup>c</sup>	45 (24.7) <sup>a</sup>	55 (30.2) <sup>b</sup>	2 (1.1) <sup>b</sup>	3 (1.8) <sup>c</sup>	52 (31.5) <sup>a</sup>	32 (19.4) <sup>b</sup>	1 (0.6) <sup>b</sup>
<100	0 <sup>c</sup>	0 <sup>c</sup>	25 (13.7) <sup>a</sup>	6 (3.3) <sup>b</sup>	0 <sup>c</sup>	1 (0.6) <sup>c</sup>	36 (21.8) <sup>a</sup>	3 (1.8) <sup>b</sup>
<70	0 <sup>c</sup>	1 (0.5) <sup>c</sup>	0 <sup>c</sup>	3 (1.6) <sup>a</sup>	0 <sup>c</sup>	0 <sup>c</sup>	0 <sup>c</sup>	10 (6.1) <sup>a</sup>

Abbreviations: CUS, carotid ultrasound; LDL-C, low-density lipoprotein cholesterol.  
 Data are presented as frequencies (% within group).  
<sup>a</sup>Subjects whose target LDL-C remained unchanged after CUS examination. <sup>b</sup>Subjects whose target LDL-C decreased after CUS examination. <sup>c</sup>Subjects whose target LDL-C increased after CUS examination.

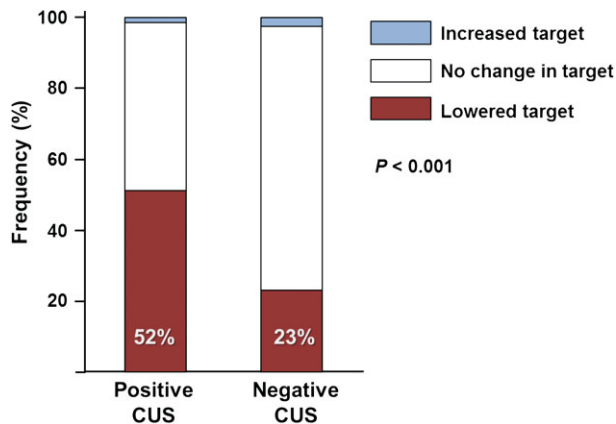


Figure 1. Changes in target LDL-C after CUS examination. After confirmation of CUS examination results, the proportion of lowered target LDL-C level was significantly larger in the positive CUS group compared with the negative CUS group (52% vs 23%,  $P < 0.001$ ). Abbreviations: CUS, carotid ultrasound; LDL-C, low-density lipoprotein cholesterol.

in either group. However, SBP and DBP were significantly decreased regardless of the results of CUS examination, and the degree of change in BP was similar between the 2 groups ( $P = 0.914$  for SBP,  $P = 0.736$  for DBP). Low-density lipoprotein cholesterol was significantly decreased in the positive CUS group ( $\Delta = -24 \pm 38$  mg/dL,  $P < 0.001$ ), whereas it was not significantly decreased in the negative CUS group ( $\Delta = -6 \pm 31$  mg/dL,  $P = 0.105$ ), indicating significantly different changes between the 2 groups ( $P = 0.003$ ). Similarly, total cholesterol was decreased only in the positive CUS group ( $\Delta = -23 \pm 46$  mg/dL,  $P < 0.001$ ), but high-density lipoprotein cholesterol was not changed at the 6-month follow-up in either group.

## Discussion

The principal findings of the present study are that (1) physicians lowered LDL-C target levels if atherosclerosis was detected by CUS, and these findings were persistent even in the low-risk and moderate-risk patients according to NCEP-ATP III guidelines; and (2) cardiovascular risk management in terms of LDL-C reduction improved if atherosclerosis was detected by CUS.

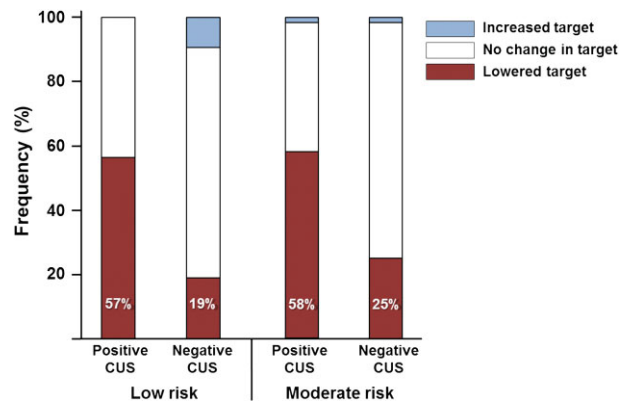


Figure 2. Changes in target LDL-C after CUS examination stratified by risk according to NCEP-ATP III guidelines. The proportion of lowered target LDL-C level was significantly larger in the positive CUS group compared with the negative CUS group, both in the low-risk and moderate-risk patients, according to NCEP-ATP III guidelines. Abbreviations: CUS, carotid ultrasound; LDL-C, low-density lipoprotein cholesterol; NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Program III.

Assessment of subclinical atherosclerosis by CUS is a safe, inexpensive, feasible, and accurate method for detecting early signs of atherosclerosis. Also, the association between cIMT and CVD is well established. A single measurement of cIMT and plaque assessment improves predictions of risk of CVD.<sup>1,2</sup> However, whether atherosclerosis detection by CUS can improve physician behavioral change as well as patient compliance with CVD preventive therapies remains unclear. Previous studies reported that abnormal results of CUS examination were associated with greater initiation of aspirin and lipid-lowering medications.<sup>3,4</sup> Similar to reports with regard to CUS, abnormal coronary calcium scores also resulted in increased use of aspirin and lipid-lowering agents.<sup>5,6,20</sup> However, in the present study, a positive finding of CUS was not associated with the changes in physicians' prescribing patterns. This discrepancy can be attributed to our study subjects. Even though they had hypertension, they were healthy and asymptomatic and had relatively lower LDL-C compared with those enrolled in the previous studies. Physicians did not change or add medications after CUS



Table 3. Changes in Risk-Factor Management at 6 Months After CUS Examination

	Positive CUS			Negative CUS			
	Baseline	Change ( $\Delta$ )	<i>P</i> Value <sup>a</sup>	Baseline	Change ( $\Delta$ )	<i>P</i> Value <sup>a</sup>	<i>P</i> Value <sup>b</sup>
BMI, kg/m <sup>2</sup>	25.7 $\pm$ 2.9	-0.0 $\pm$ 1.0	0.685	25.1 $\pm$ 3.0	-0.1 $\pm$ 0.4	0.006	0.384
Waist circumference, cm	87.3 $\pm$ 9.2	0.4 $\pm$ 5.2	0.361	86.7 $\pm$ 9.8	-0.3 $\pm$ 5.0	0.525	0.870
SBP, mm Hg	136 $\pm$ 18	-6 $\pm$ 19	<0.001	134 $\pm$ 13	-6 $\pm$ 15	<0.001	0.914
DBP, mm Hg	83 $\pm$ 12	-5 $\pm$ 12	<0.001	83 $\pm$ 10	-4 $\pm$ 11	<0.001	0.736
LDL-C, mg/dL	115 $\pm$ 35	-24 $\pm$ 38	<0.001	110 $\pm$ 32	-6 $\pm$ 31	0.105	0.003
HDL-C, mg/dL	51 $\pm$ 12	1 $\pm$ 7	0.416	52 $\pm$ 19	2 $\pm$ 10	0.166	0.493
TC, mg/dL	189 $\pm$ 37	-23 $\pm$ 46	<0.001	186 $\pm$ 37	-2 $\pm$ 37	0.583	0.001

Abbreviations: BMI, body mass index; CUS, carotid ultrasound; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol.  
<sup>a</sup>Denotes *P* values for comparison between baseline and 6-month follow-up. <sup>b</sup>Denotes *P* values for comparison of changes between the positive CUS and negative CUS groups.

examination, but they lowered target LDL-C after CUS examination if patients had abnormal findings according to CUS. Furthermore, it is noteworthy that these findings were observed even in the patients with low and moderate risk according to NCEP-ATP III guidelines. Based on our findings, CUS examination could provide possibilities of further risk stratification and physician change in improving CVD risk-factor management.

It is also interesting that physicians reacted so inconsistently to the positive CUS findings. Because we did not survey the reasons why the physicians did not lower their therapeutic target even after the confirmation of the positive CUS findings specifically, it can be partially attributed to the compliance with the guidelines. Recent guidelines recommended that if patients had documented CVD by noninvasive testing, they should be classified into the very-high-risk category for CVD, with a recommended target LDL-C of <70 mg/dL.<sup>21</sup>

Our study has strength in that it included longitudinal outcome measures such as 6-month risk-factor management. Although several studies demonstrating the utility of screening with noninvasive testing were performed, studies including longitudinal outcomes were limited, and they had relatively short follow-up periods. As regards patient risk-factor management and patient behavior change after noninvasive cardiovascular imaging, there are conflicting results. Some studies reported that there was limited evidence that noninvasive cardiovascular imaging altered primary prevention efforts.<sup>9,22–24</sup> In contrast to these reports, in the Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) trial, compared with no scanning, randomization to coronary artery calcium scanning was associated with superior CAD risk-factor control.<sup>25</sup> Also, determination of coronary artery calcium scores by electron-beam computed tomography or CAD by coronary computed tomography angiography improved behavioral modification.<sup>20,26</sup> In the present study, pronounced improvement risk-factor management in terms of LDL-C reduction in the CUS positive group was observed. Although we did not measure patient effort in CVD risk-factor management,

physicians' behavioral changes combined with patients' behavioral changes might contribute to improvement of risk-factor management.

Several limitations of the present study need consideration. First, physicians' behavior could have been affected simply because they were being observed. Thus, changes in target LDL-C level by physicians could have been overestimated. Second, we did not appropriately evaluate patient effort in CVD risk-factor management, which could be an important contribution to reduction of LDL-C at 6 months.

## Conclusion

Atherosclerosis detection by CUS was associated with lowering physicians' target LDL-C level and improved cardiovascular risk-factor management regarding reduction of LDL-C.

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