cle symptoms and plasma creatine phosphokinase is necessary in patients prescribed either statins or fibrates.

Conclusions and Future Prospect of the Guidelines

Non-HDL cholesterol containing both LDL cholesterol and remnant cholesterol, is an excellent predictor of atherosclerotic risk, and should be a treatment target. Non-HDL cholesterol is simple, convenient, and free from dietary variations. These advantages are crucial for nation-wide use of the guidelines and health check activity. This simple measurement could also make it possible to re-evaluate previous clinical studies using this parameter to offer a good chance of estimating the usefulness and importance of this marker in a large meta-analytical scale.

In the current study, we propose that LDL cholesterol is the primary target and non-HDL cholesterol should be the secondary target for elevated TG. Considering that non-HDL and LDL cholesterol are partially redundant, non-HDL could replace LDL as the primary target and as a general marker for both elevated cholesterol and TG. As **Table 1** shows, non-HDL cholesterol could be used as a general and convenient lipid marker for type IIb hyperlipidemia.

This proposal still faces the recent problem of selecting lipid markers for the initial assessment for dyslipidemia. The recent GL focus has been on LDL cholesterol rather than TC, while LDL cholesterol has a problem the lower reliability for direct measurement. In addition, a considerable portion of hypertriglyceridemia is not applicable to this equation. For subjects with hypertriglyceridemia, application of this new GL eventually requires all TC, TG, HDL, and LDL cholesterol measurements to assess both LDL and non-HDL cholesterol. Currently, however, the Japanese medical system covers only three out of four lipid measurements as healthcare services provided by health insurance. Further Japanese clinical studies and careful evaluation of the data, as well as technical improvements of reliable LDL cholesterol measurements, are required to determine the most efficient protocol to select lipid measurements as the initial assessment of dyslipidemia to prevent CVD in Japan. Furthermore, guidelines for HDL cholesterol should also be established, although the relative importance and positioning of non-HDL and HDL is yet to be determined.

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Original Article

Impact of Statin Treatment on the Clinical Fate of Heterozygous Familial Hypercholesterolemia

Mariko Harada-Shiba[1], Takako Sugisawa[2], Hisashi Makino[2], Mitsuru Abe[3], Motoo Tsushima[2], Yasunao Yoshimasa[2], Takahiro Yamashita[2], Yoshihiro Miyamoto[2], Akira Yamamoto[4], Hitonobu Tomoike[5], and Shinji Yokoyama[6]

[1]Department of Bioscience, National Cardiovascular Center Research Institute, Suita, Japan
[2]Division of Atherosclerosis and Diabetes, National Cardiovascular Center, Suita, Japan
[3]Division of Cardiology, National Cardiovascular Center, Suita, Japan
[4]Emeritus Scientist, National Cardiovascular Center Research Institute, Suita, Japan
[5]Hospital, National Cardiovascular Center, Suita, Japan
[6]Department of Biochemistry, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Aim: **Familial hypercholesterolemia (FH) patients are at particular risk for premature coronary artery disease (CAD) caused by high levels of low density lipoprotein (LDL). Administration of statins enabled us to reduce LDL-C levels in heterozygous FH patients. To evaluate the impact of statins on the clinical fate of heterozygous FH, a retrospective study was performed.**
Methods: **We analyzed the clinical influence of statins on age at the first clinical onset of CAD in 329 consecutive FH patients referred to the lipid clinic of the National Cardiovascular Center. Among 329 heterozygous FH patients, the onset of CAD was identified in 101.**
Results: **The age at onset of CAD was 58.8 ± 12.5 years in the 25 patients on statins at onset, significantly higher than that in the 76 patients not on statins (47.6 ± 10.5 years) ($p<0.001$). The average age at CAD onset was significantly higher after widespread use of statins (54.2 ± 13.2 years in 48 patients; Group 1) compared to before October 1989 when statins were approved in Japan (46.9 ± 9.6 years in 53 patients; Group 2, $p=0.002$). A significant difference was seen between Groups 1 and 2 in the variables, including sex, prevalence of smoking habit, LDL-C, and the use of statins, aspirin and probucol. After adjusting for these variables, only statin use was independently associated with the difference in age at CAD onset by multivariable analysis.**
Conclusion: **Statins have improved the clinical course of patients with heterozygous FH.**

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Key words; Familial hypercholesterolemia, Statin, Coronary artery disease, LDL cholesterol

Introduction

Familial hypercholesterolemia (FH) is a heritable disease of high prevalence with an autosomal-dominant mode of transmission and is linked to mutations in the low-density lipoprotein (LDL) receptor or its related gene. It is characterized by phenotypes of the elevation of plasma LDL, cutaneous and tendenous xanthomas, arcus corneae, and coronary artery disease (CAD) due to premature atherosclerosis[1]. The earliest clinical sign of heterozygous FH is an elevation of plasma LDL cholesterol (LDL-C), noted as early as at birth[2]. All other clinical manifestations seem due to an increase of LDL-C in plasma. CAD is the most serious clinical manifestation and determines the prognosis of FH. According to a previous report, Japanese FH heterozygotes generally develop the first CAD event in their 40s or later for men and 50s or later for

Address for correspondence: Mariko Harada-Shiba, Department of Bioscience, National Cardiovascular Center Research Institute, 5-7-1 Fujishirodai, Suita, Osaka 565-8565 Japan.
E-mail: mshiba@ri.ncvc.go.jp
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women[3].

To reduce plasma LDL-C in FH heterozygotes, bile acid-sequestering resins have been used since the 1970s to upregulate the LDL receptor, but their effect is limited to a 10 to 20% decline because of the concomitant induction of hepatic cholesterol synthesis[4]. Statins, competitive inhibitors of a rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl (HMG) CoA reductase, were introduced onto the market in the late 1980s. Pravastatin, the first approved statin in Japan, became commercially available at the beginning of October 1989 and simvastatin one year later[5]. Synthetic analogues became available in the late 1990s, including several "strong" statins, which lower the level of LDL-C by more than 40%[6]. Many large-scale clinical trials of statins worldwide, including Japan, showed that they reduced the risk of cardiac events or stroke in hypercholesterolemic populations[7-10]. Effective reduction of LDL-C by statins was also shown in FH heterozygotes[11, 12]; however, their clinical benefits in FH patients have not been clearly demonstrated with fixed clinical endpoints. This is partly because of the extremely high risk for CAD in FH patients, thus making controlled clinical trials of sufficient size to yield significant outcomes unethical.

Aim

Substantial numbers of FH patients have been referred to and regularly treated at the lipid clinic of the National Cardiovascular Center (NCVC) since it was founded in 1977. We therefore retrospectively analyzed the clinical records of these patients to assess the impact of the introduction of statins on the clinical prognosis of FH heterozygous patients, using patient age at the development of CAD. This parameter is specific and solid for each patient and the analysis is less influenced or biased by other factors. In addition, Mabuchi and colleagues used the same parameter in their study of Japanese FH reported before statin availability[13].

Methods

Subjects

Of the patients referred to the lipid clinic at NCVC from 1977 to 2007, 329 consecutive patients (139 men, 190 women) were diagnosed as FH heterozygotes using the criteria previously described[14]. Most of the FH patients analyzed in the present paper were referred to our lipid clinic by their general practitioner because of hypercholesterolemia. The medical records of patients were examined according to the analysis protocol approved by our institutional ethics committee (ID#M20-25-2). Of the 329 FH patients, 101 were identified as having CAD, specifically, coronary artery stenosis (more than 75%) on angiography, including 53 patients who had CAD at the first clinic visit. The other 228 patients did not have clinical or angiographic evidence of CAD. For each patient, the age at onset of CAD was determined by the first sign, ascertained by a standardized questionnaire, which included fixed clinical endpoints of CAD, administered by attending physicians at the clinic. The compliance with statins was evaluated from the medical records.

Clinical Risk Factors

Body mass index (BMI) was calculated as weight (kg) divided by height (m) squared (kg/m^2). Hypertension was defined as the use of antihypertensive drugs or a blood pressure level higher than 140 mmHg systolic or 90 mmHg diastolic or both at the first clinic visit (the criteria for hypertension of the Japanese Society of Hypertension Guidelines)[15]. Diabetes mellitus was defined according to the 2002 Guideline for the Treatment of Diabetes Mellitus of the Japan Diabetes Society[16]. A family history of CAD was identified by the standardized questionnaire. Smoking was identified from patients' self-reporting. Achilles tendon thickness was measured as previously described[17].

Analysis of Serum Lipids

Fasting plasma lipid concentration was measured before any lipid-lowering treatment. Total cholesterol (TC), triglycerides (TG), and HDL cholesterol (HDL-C) levels were measured enzymatically using an automated system in the clinical laboratory of the NCVC. LDL-C level was calculated by the Friedewald formula when the TG level was less than 400 mg/dL; three patients with TG level more than 400 mg/dL were omitted from this particular analysis. TG values were expressed as the median, (range), and logarithmically transformed before analysis.

Statistical Analysis

Statistical analysis was performed using the SPSS 15.0 (SPSS Inc., Chicago, IL) program. Parametric values are expressed as the mean ± standard deviation (SD). The statistical significance of differences in continuous variables was evaluated by Student's t test for unpaired data or ANOVA. The Pearson's χ^2 test was used to assess differences in the distribution of categorical traits.

Table 1. Clinical characteristics of heterozygous FH patients with or without coronary artery disease (CAD) at first visit to our center.

	Total subjects	CAD (+)	CAD (−)	*p value*
n	329	101	228	
Age (years)	43.8±16.0	48.9±10.2	41.6±17.6	<0.001
Sex				
Men	139 (42.2%)	66 (65.3%)	73 (32.0%)	<0.001
BMI (kg/m^2)	22.0±3.2	23.0±2.7	22.6±3.3	<0.001
Total cholesterol (mg/dL)	319±70	333±85	313±61	0.039
Triglyceride (mg/dL)	(114) 80-176	(147) 96-193	(109) 76-162	0.263
HDL cholesterol (mg/dL)	50±17	42±14	54±17	<0.001
LDL cholesterol (mg/dL)	241±72	259±84	232±65	<0.001
Hypertension (*n*, %)	54 (16.4%)	33 (32.7%)	21 (9.2%)	<0.001
Diabetes Mellitus (*n*, %)	13 (4%)	8 (7.9%)	5 (2.2%)	0.014
Family history of CAD (*n*, %)	121 (36.8%)	46 (45.5%)	75 (32.9%)	0.028
Smoking habits (*n*, %)	127 (38.6%)	72 (71.3%)	55 (24.1%)	<0.001
Achilles tendon thickness (mm)	13.5±5.4	16.2±5.7	12.1±4.6	<0.001
CAD present at first visit (*n*, %)	53 (16.1)	53 (52.5)	0 (0)	<0.001
Statin treatment at first clinic visit	39 (11.9)	18 (17.8)	21 (9.2)	0.541

Values are shown as the mean ± SD except for triglyceride. For triglyceride, the median (range) is shown.
BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; CAD, coronary artery disease

Results

Patient Background

The baseline clinical characteristics of the 329 heterozygous FH patients analyzed in this study are shown in **Table 1**. Their plasma lipid and lipoprotein profiles are similar to patients in previous reports of Japanese FH[3, 18]. Patients with CAD were older, had higher levels of BMI, TC, and LDL-C, lower HDL-C, and a higher incidence of diabetes mellitus, hypertension, a family history of CAD, and smoking habit, compared to patients without CAD.

Onset of CAD

In the 101 patients with CAD, age by decade at the first onset of CAD is illustrated in **Fig. 1**. The average age was 45.8±10.6 years in men and 59.0±9.5 years in women, and this is consistent with a previous report of Japanese FH patients[13]. Analysis of CAD onset in relation to the presence (+) or absence (−) of statin treatment showed that in the 66 FH men with CAD, 13 did and 53 did not have statin treatment, and in the 35 FH women with CAD, 12 did and 23 did not have statin treatment. The age distribution at the first onset of CAD in statin (+) or statin (−) patients is shown in **Fig. 2**. The peak was at an older age in statin (+) men and women (Panels A and B, respectively) compared to statin (−). The lipid profile at the time of first onset of CAD in statin (+) and statin (−)

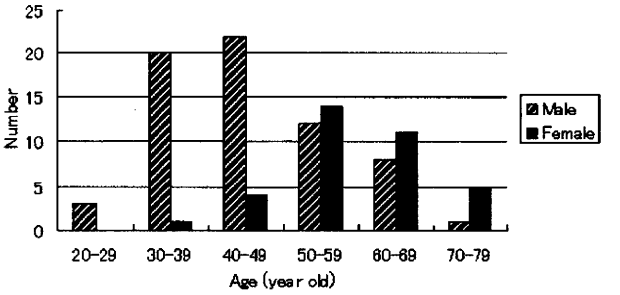

Fig. 1. Distribution of age when CAD was first identified in 101 men and women with heterozygous familial hypercholesterolemia (FH) and coronary artery disease (CAD), for the study period of 1969 to June 2007

patients is shown in **Table 2**. Statin (+) patients were older when CAD was identified and had lower TC and LDL-C levels than statin (−) patients.

To identify the factors that may influence the age at which CAD developed in statin (+) and statin (−) patients, we analyzed covariates (ANCOVA; **Table 3**), which included sex, smoking, BMI, hypertension, diabetes mellitus, family history of CAD, thickness of Achilles tendon, LDL-C levels, and the use of aspirin, probucol, and cholestyramine. We found that statin (+) patients were older when CAD developed, about 10 years older for each variable compared to statin (−) patients, which may be due to the use of statins and

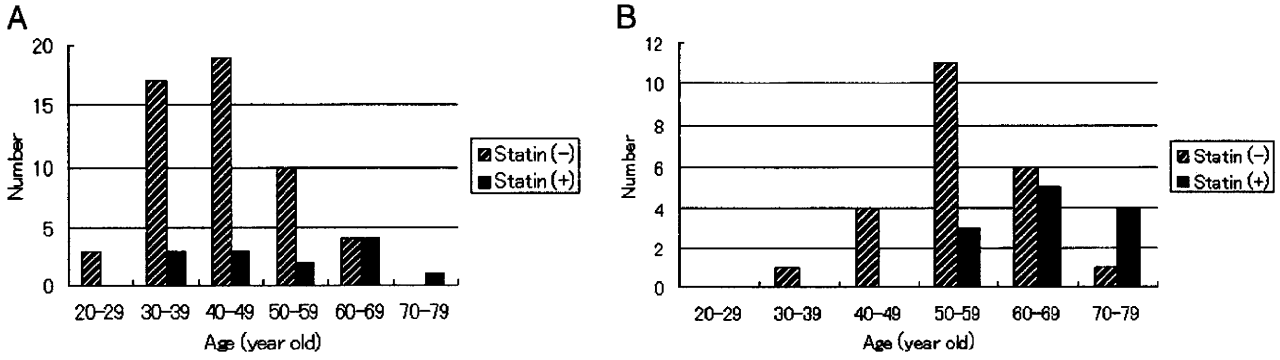

Fig. 2. Distribution of age when CAD was first identified in men (Panel A) and women (Panel B) with CAD taking a statin (+) or not (−)

Table 2. Age, lipid and lipoprotein profiles of FH at the onset of CAD in relation to statin use.

	Statin (+)	Statin (−)	*p value*
n	25	76	
Age of onset of CAD	57.8 ± 12.5	47.6 ± 10.5	<0.001
Lipid and lipoprotein profile at the event			
Total cholesterol (mg/dL)	242 ± 55	315 ± 108	<0.001
Triglycerides (mg/dL)	(127) 93-171	(115) 91-153	0.922
HDL cholesterol (mg/dL)	40 ± 12	38 ± 13	0.569
LDL cholesterol	167 ± 35	250 ± 108	<0.001

Values are shown as the mean ± SD except for triglyceride. For triglyceride, the median (range) is shown.

Table 3. Onset age of CAD adjusted by each variable.

Variables	Age (95% CI) in Statin (+)	Age (95% CI) in Statin (−)	*p value*
Overall	57.8 (55.3-60.3)	47.6 (46.4-48.8)	<0.001
Smoking habit	58.2 (54.1-62.3)	47.3 (44.8-49.7)	<0.001
Sex	57.2 (53.3-61.0)	48.1 (45.9-50.3)	<0.001
BMI	58.9(54.4-63.3)	47.5 (45.0-50.1)	<0.001
Hypertension	59.4 (54.8-64.4)	47.4 (44.8-49.9)	<0.001
Diabetes mellitus	58.7 (54.3-63.1)	47.7 (45.2-50.3)	<0.001
Family history of CAD	58.8 (54.4-63.2)	47.1 (44.6-49.7)	<0.001
Achilles tendon thickness	58.7 (54.3-63.2)	46.7 (44.0-49.4)	<0.001
LDL cholesterol	58.4 (53.9-63.0)	47.6 (45.0-50.3)	<0.001
Aspirin	57.2 (52.9-61.5)	48.2 (45.7-50.7)	0.001
Probucol	56.0 (51.0-61.0)	48.6 (46.0-51.3)	0.017
Cholestyramine	58.2 (53.0-63.3)	47.9 (45.2-50.6)	0.001

the reduction of LDL-C.

To determine the impact of statin treatment on the age at which CAD developed, we analyzed the same data for the pre- and post-statin eras. Pravastatin was the first statin approved in Japan. Patients were divided into two groups: Group 1 developed CAD before the end of September 1989 (n=53) and Group 2 developed CAD from October 1989 (to June 2007; n=48). Of the 66 men with CAD, 39 were in Group 1 and 27 in Group 2, and of the 35 women with CAD, 14 were in Group 1 and 21 in Group 2. The men and women whose CAD developed after the beginning of October 1989 were older than those who developed CAD before that date (**Fig. 3A, B**). At the

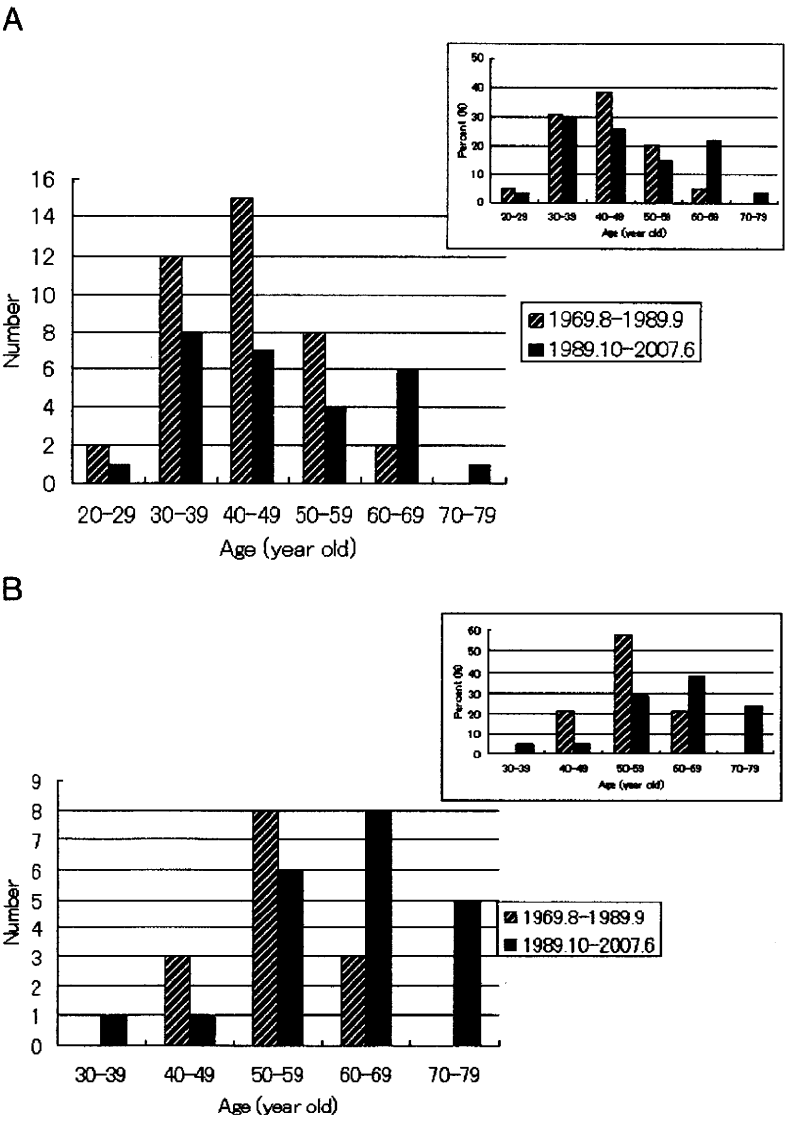

Fig. 3. Distribution of age at CAD onset in men (Panel A) and women (Panel B) who developed CAD before the end of September 1989 from October 1989

Each inset figure shows the percent of distribution, respectively.

first clinic visit, no clinical differences were seen in these patients in average age, BMI, plasma lipid and lipoprotein profile, Achilles tendon thickness and the incidence of hypertension, diabetes mellitus, and family history of CAD (**Table 4**); however, significantly more of the patients who developed CAD before the end of September 1989 were smokers. Assessment of clinical parameters obtained at the time CAD was identified shows that patients who developed CAD after the beginning of October 1989 were older (**Table 5**), reflecting the influence of statins on the onset age of CAD (**Fig. 3A, B**), and that TC and LDL-C levels were lower, reflecting that more of these patients were receiving lipid-lowering treatment than patients who developed CAD before this date.

Analysis of Factors that Affect Age at the First Onset of CAD

Age at the development of CAD in Groups 1 and 2 was analyzed using analysis of covariance (AN-

Table 4. Clinical characteristics (at first visit) of FH Patients depending on the onset date of CAD

	Group 1 1969–Sept. 1989	Group 2 Oct. 1989–June 2007	*p value*
n	53	48	
Age	48.4 ± 9.1	49.5 ± 11.4	0.584
Sex			
Male	39 (73%)	27 (56%)	0.068
BMI (kg/m^2)	22.6 ± 2.8	23.5 ± 2.6	0.288
Total cholesterol (mg/dL)	343 ± 84	321 ± 85	0.195
Triglycerides (mg/dL)	(114) 103–193	(148) 82–208	0.785
HDL cholesterol (mg/dL)	40 ± 15	44 ± 13	0.127
LDL cholesterol (mg/dL)	268 ± 80	250 ± 87	0.279
Hypertension (*n*, %)	21 (39.6%)	12 (25.0%)	0.118
Diabetes Mellitus (*n*, %)	2 (4%)	4 (8.3%)	0.535
Family history of CAD (*n*, %)	23 (43.4%)	25 (52.1%)	0.317
Smoking habits (*n*, %)	41 (83.7%)	31 (64.6%)	0.036
Achilles tendon thickness (mm)	16.0 ± 5.3	16.5 ± 6.1	0.710

Values are shown as the mean ± SD except for triglyceride. For triglyceride, the median (range) is shown.

Table 5. Age, lipid and lipoprotein profiles and medication of FH at the onset of CAD.

	Group 1 1969–Sept. 1989	Group 2 Oct. 1989–June 2007	*p value*
n	53	48	
Age of onset of CAD	46.9 ± 9.6	54.2 ± 13.2	0.002
Lipid and lipoprotein profile at the event			
Total cholesterol (mg/dL)	323 ± 100	267 ± 95	0.011
Triglycerides (mg/dL)	(119) 96–162	(121) 79–152	0.427
HDL cholesterol (mg/dL)	36 ± 13	41 ± 12	0.088
LDL cholesterol	257±100	199 ± 95	0.011
Medication, *n* (%)			
Statin	1 (2.0)	24 (50.0)	< 0.0001
Probucol	6 (11.8)	17 (35.4)	0.005
Cholestyramine	3 (5.7)	11 (22.9)	0.015
Aspirin	1 (2.0)	7 (14.6)	0.021
No medication	44 (83.0)	22 (45.8)	< 0.001

Values are shown as Mean ± SD except for triglyceride. For triglyceride, median (range) is shown.

Table 6. Onset age of CAD adjusted by each variable.

Variables	Age (95% CI) in Group 1	Age (95% CI) in Group 2	*p value*
Overall	46.9 (44.2–50.0)	54.2 (50.3–58.0)	0.002
Smoking habits	46.9 (43.7–50.0)	53.4 (50.2–56.5	0.005
Sex	47.9 (45.2–50.7)	53.1 (50.2–55.9)	0.013
LDL cholesterol	48.2 (44.2–52.3)	54.5 (50.8–58.2)	0.029
Statin	49.1 (45.8–48.3)	51.8 (48.3–55.4)	0.325
Aspirin	47.9 (44.8–51.0)	53.2 (50.0–56.4)	0.021
Probucol	48.1 (45.0–51.2)	53.0 (49.8–56.2)	0.034
Cholestyramine	47.6 (44.4–50.8)	53.6 (50.2–56.9)	0.013

COVA; **Table 6**). Significant differences between groups were seen for sex, prevalence of smoking, LDL-C, and the use of statins, aspirin and probucol. After adjusting for these variables, statin use was independently associated with age at the onset of CAD.

Discussion

The mortality rate for CAD is 11 times higher in heterozygous FH patients than in the general population; thus, prevention of CAD is the key therapeutic goal for these patients[14]. Treatment to reduce high levels of LDL-C in FH patients was limited before statins became available, and a clinically meaningful decrease in LDL-C levels was difficult to obtain. Pravastatin was first introduced onto the Japanese market at the beginning of October 1989 and thereafter, LDL-C reductions of 20% to 30%, even in FH heterozygous patients, became possible[19]. Recently, the risk of myocardial infarction in heterozygous FH was reported to be reduced by 76%, similar to the general population of the Netherlands[20]. In the present paper, we assessed the impact of statin use on the clinical prognosis of Japanese FH patients visiting our lipid clinic by retrospectively analyzing their clinical records. The use of statins delayed the first CAD event by about 7 years in FH patients whose first event occurred after the introduction of statins, compared to FH patients whose first event occurred prior to the introduction of statins.

In this study, 101 of 329 (30.6%) consecutive heterozygotes of FH had clinical evidence of CAD. The profile of CAD patients is similar to previous reports, that is, more men than women[3, 21, 22], and higher BMI, higher TC and LDL-C levels, lower HDL-C levels, and a higher incidence of hypertension, diabetes mellitus, family history of CAD, and smoking[3, 13, 23, 24].

The time span of our study allowed us to assess the impact on the development of CAD of the introduction of statins onto the Japanese market at the beginning of October 1989. Comparing clinical parameters at the first clinic visit in the patients whose CAD developed before the end of September 1989 with after that date, revealed that only smoking was different, perhaps reflecting the social trend against smoking (**Table 4**). In contrast, interesting differences between these groups were seen in relation to when they developed CAD. Patients who developed CAD prior to the introduction of statins were younger on average (46.9 years old) and had higher levels of TC and LDL-C (323 and 257 mg/dL, respectively). Two other prominent differences were the improved lipid-lowering drug regimens, including statins, cholestyramine, probucol, and aspirin, and a decline in the number of smokers. Notably, statin use was independently and significantly associated with age at CAD onset in the 101 FH patients on covariate analysis of factors known to affect the age of developing CAD. Besides these factors, many other factors should be considered for the potential influence on the onset age of CAD, such as the widespread recognition of FH and the regimen for the treatment of other risk factors, such as hypertension and diabetes mellitus. Nevertheless, we should conclude from this analysis that the use of statins is a major factor contributing to the improvement of the clinical prognosis of FH patients in Japan.

More recently, "strong" statins have become available, making it possible to reduce LDL-C levels to much lower levels compared to conventional statins in FH patients[25-27]. The possible impact of these stronger statins on delaying the development of CAD in FH patients will be of interest.

One diagnostic criterion for heterozygous FH in the existing guidelines is a family history of premature CAD[28-30]. However, our results suggest that this criterion may need to be reconsidered because of the proven ability of statin treatment to delay the development of CAD to an age similar to that in persons who do not have heterozygous FH.

We showed in this retrospective analysis that the development of CAD was delayed by about 7 years in FH patients whose CAD developed after the introduction of statins in Japan compared to those whose CAD developed before the current statin era.

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NEURO

Yoshiyuki Watanabe
Kensuke Uotani
Tetsuro Nakazawa
Masahiro Higashi
Naoaki Yamada
Yoshiro Hori
Suzu Kanzaki
Tetsuya Fukuda
Toshihide Itoh
Hiroaki Naito

Dual-energy direct bone removal CT angiography for evaluation of intracranial aneurysm or stenosis: comparison with conventional digital subtraction angiography

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Y. Watanabe · K. Uotani ·
T. Nakazawa · M. Higashi ·
N. Yamada · Y. Hori · S. Kanzaki ·
T. Fukuda · H. Naito
Department of Radiology,
National Cardiovascular Center,
Osaka, Japan

Y. Watanabe (✉)
Department of Radiology,
St. Luke's International Hospital,
9-1 Akashicho, Chuo-ku,
Tokyo, 104-8565, Japan
e-mail: yowatana@luke.or.jp
Tel.: +81-6-68335012
Fax: +81-6-68727486

T. Itoh
Siemens Asahi Medical Technologies,
Tokyo, Japan

Abstract Dual energy CT can be applied to bone elimination for cerebral CT angiography (CTA). The aim of this study was to compare the results of dual energy direct bone removal CTA (DE-BR-CTA). To those of DSA. Twelve patients with intracranial aneurysms and/or ICA stenosis were performed on a dual-source CT in dual energy mode. A post-processing software selectively remove bone structures using the two energy data sets. 3D-images with and without bone removal were reviewed and compared to DSA. Dual energy bone removal was successful in all patients. For 10 patients, bone removal was good and CTA MIP images could be used for vessel evaluation. For 2 patients, bone removal was moderate with some bone remnants but this did not disturb the 3D visualization. Three aneurysms adjacent to the skull base were only partially visible in conventional CTA but were fully visible in DE-BR-CTA. In 5 patients with ICA stenosis, DE-BR-CTA revealed the stenotic lesions on the MIP images. The correlation between DSA and DE-BR-CTA was good (r2=0.822), but DE-BR-CTA lead to an overestimation of stenosis. DE-BR-CTA is able to eliminate bone structure using only a single CT data acquisition and is useful to evaluate intracranial aneurysms and stenosis.

Keyword Cerebral CTA · Dual-energy CT · Dual-source CT · Bone elimination · Brain

Introduction

Cerebral computed tomography angiography (CTA) has become a powerful, noninvasive diagnostic tool for evaluating cerebrovascular disease [1–3]. However, single-source CTA still has drawbacks compared to digital subtraction angiography (DSA), in particular for the evaluation of arteries with calcified plaque or vessels located next to the skull bone, as these vasculatures cannot be unambiguously distinguished from surrounding bony or calcified structures. This problem can be solved by applying subtracting CTA to a noncontrast and a contrast CT data set to eliminate bones [4–8]. Dual-source, dual-energy CT has the potential to distinguish iodine from bone or calcifications using the attenuation difference between the two energies [9].

Here, we evaluated the performance of dual-energy direct bone removal CTA (DE-BR-CTA) for diagnosing

brain aneurysms, internal carotid artery (ICA) stenosis, or both. We also compared the DE-BR-CTA findings with those of DSA.

Materials and methods

Subjects

This study was performed after obtaining approval of the local institutional review board. Written informed consent was obtained from all patients. We prospectively selected 12 patients (7 male, 5 female; 36–78 years, mean 64 years) who underwent both DE-BR-CTA and DSA within 30 days of each other. Nine patients were suspected of intracranial unruptured aneurysms with MR angiography. Five patients were suspected of ICA stenosis. Of these five, three patients had a stroke and in two patients the asymptomatic stenosis was found during the evaluation for aneurysm.

CTA protocol

CTA was performed using a dual-source CT system (SOMATOM Definition, Siemens, Germany). CT parameters in the dual-energy mode were 140 and 80 kV tube voltage, 80 and 360 effective mAs, respectively, 0.5-s rotation time, 64×0.6-mm collimation with z-flying focal spot, and a pitch of 0.6. The 140 and 80 kV images (dual-energy images) were reconstructed separately in sections that were 0.75 mm wide at 0.5 mm increments using a D30 kernel for a field of view of 180 mm. Contrast material (350 mg I/ml) was injected for 20 s via the antecubital vein, followed by a 25 ml saline flush. Injection rate and dose depended on the patient's weight: 3.0 ml/s, 60 cc for patients weighing less than 60 kg; 3.5 ml/s, 70 cc for patients weighing less than 70 kg; and 4 ml/s, 80 cc for those over 70 kg. The delay time of the CT data acquisition after the injection was determined using a bolus tracking software at the basilar artery or ICA.

DSA was performed using a biplane DSA unit with rotational 3D DSA (INTEGRIS BV3000, Philips Healthcare, Best, Netherland).

Image processing and analysis

The dual-energy images were transferred to a workstation (Multi Modality Workplace; Siemens Medical Solutions, Germany), and the prototype of a commercial software (Syngo 2008G) was used to create a DE-BR-CTA from which the bone voxels had been removed ("head bone removal" application). The combined images of both energy data were reconstructed and used for diagnostic reading (conventional CTA).

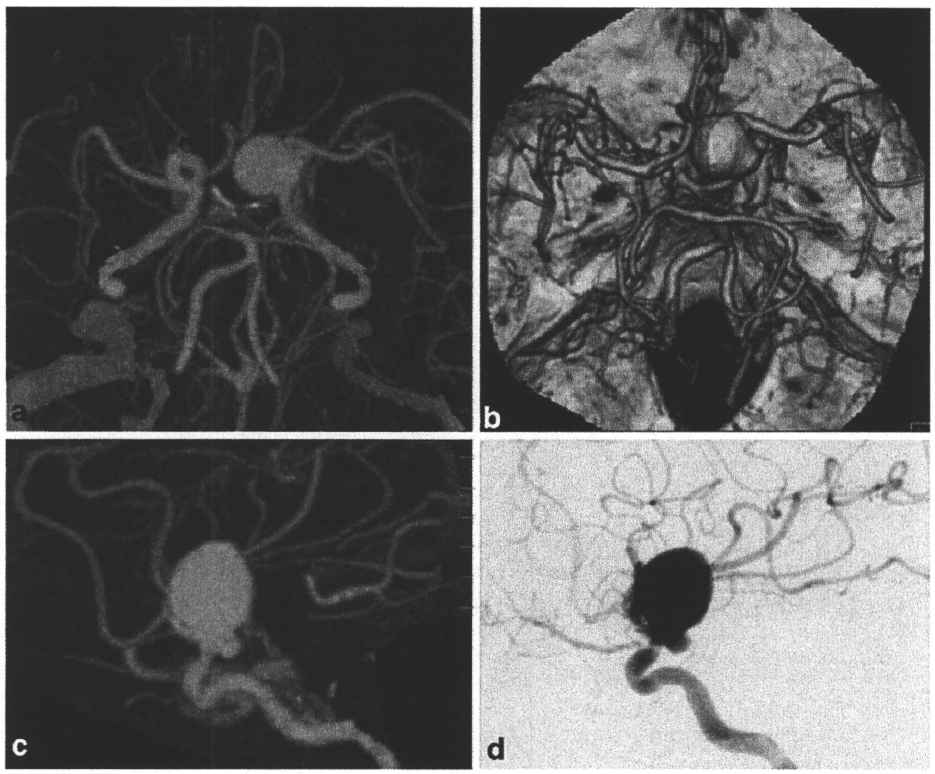

Fig. 1 Right ICA large aneurysm of a 75-year-old female patient. MIP images of DE-BR-CTA (**a**, **c**) delineate the general shape and configuration of aneurysm as well as DSA (**d**). VR image of conventional CTA (**b**) did not show the caudal side of aneurysm with bone

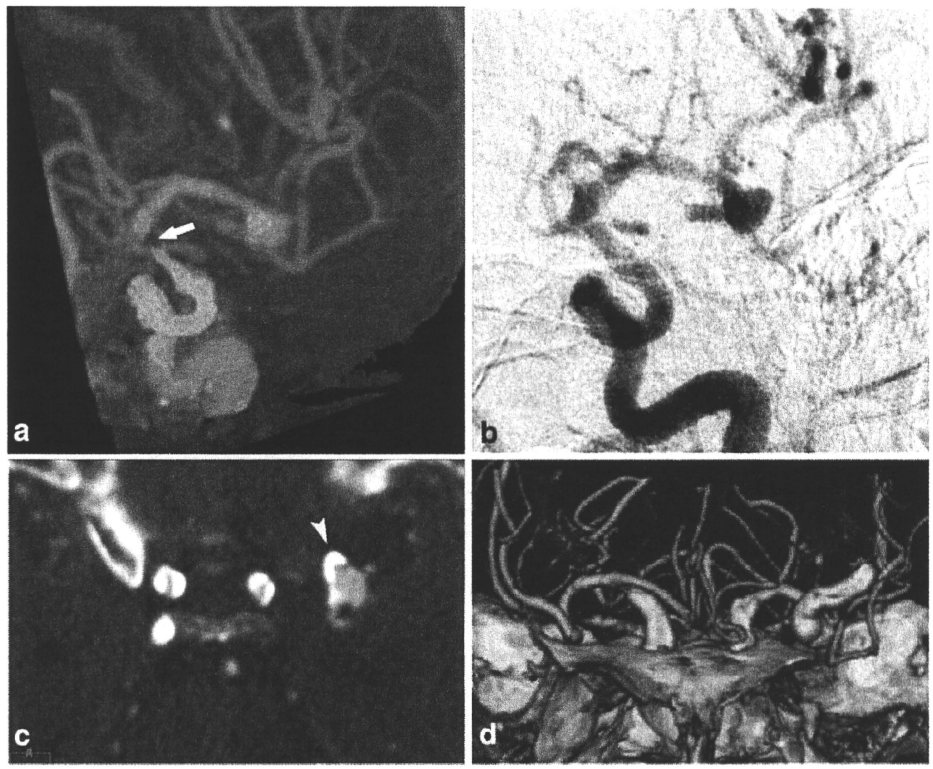

Fig. 2 Left MCA calcified aneurysm and bilateral ICA stenosis with hard plaque in a 77-year-old female patient. MIP image of DE-BR-CTA (**a**) removed the calcifications of ICA and aneurysm and revealed the same aneurysm shape as with DSA (**b**). However, the DE-BR-CTA (**a**) shows a short defect at the severe stenotic site at ICA terminal (*arrow*). CTA source images (**c**) show dense calcifications around the whole circumference of the ICA and anterior wall of the left MCA aneurysm (*arrowheads*). VR image of conventional CTA (**d**) showed the dense calcification at bilateral ICA and aneurysms, but failed to reveal details

Two neuroradiologists blinded to all clinical information independently reviewed the DE-BR-CTA in maximum-intensity projection (MIP) and the conventional CTA in volume-rendering (VR) technique on a 3D workstation. Disagreements regarding final conclusions were resolved by consensus.

The quality of the dual-energy bone removal was rated according to a four-point scale. "Excellent" was defined as clearly visible vasculature and no bone remnants, "good" as discernable vasculature and containing only tiny bone remnants, "moderate" as containing larger bone remnants that did not however disturb the vessel visualization, and

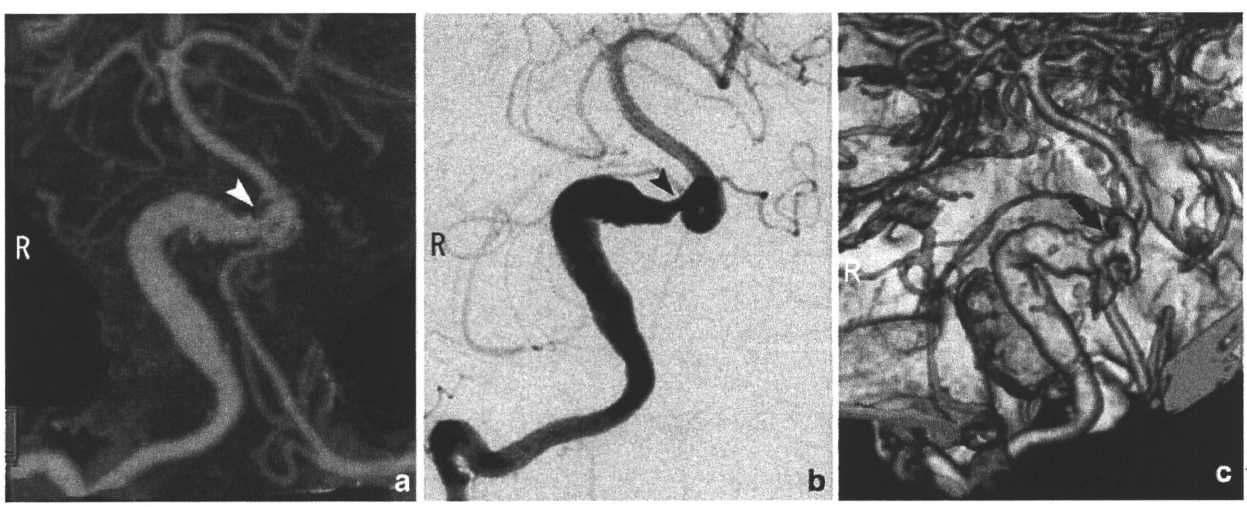

Fig. 3 Right vertebral artery fusiform aneurysm with calcification in a 55-year-old male patient. MIP image of DE-BR-CTA (**a**) removed the calcification of aneurysm and revealed the distal-end stenosis (*arrowhead*) of the aneurysm as with DSA (**b**). VR image of conventional CTA (**c**) showed the calcification (*arrow*), but the stenosis is hard to see

"poor" as including large bone remnants or artifacts covering parts of the vessels.

Further, the visibility of the ophthalmic artery in DE-BR-CTA was rated according to a four-point scale. "Excellent" was defined as the ophthalmic artery being visible from the origin to the intra-orbital portion, "good" as one artery being visible and the other with only the origin or other short segments being detected, "poor" as the long segment of the ophthalmic artery being detected, and "not visible" as the ophthalmic artery not being discernable at all.

For the evaluation of aneurysm, conventional CTA and DE-BR-CTA were compared for the detection and delineation of aneurysms and compared to the DSA results.

For the evaluation of ICA stenosis, the DE-BR-CTA and DSA were compared and the degree of stenosis was calculated using the Warfarin-Aspirin Symptomatic Intracranial Disease Study method [10], which is the ratio of the diameter of the maximum stenotic site to the diameter of the proximal normal ICA.

Kappa statistics were used to assess interobserver reliability. Kappa values above 0 were considered to indicate positive agreement: less than 0.4, positive but poor agreement; 0.41–0.75, good agreement; and more than 0.75, excellent agreement.

Results

Dual-energy bone removal was successful in all patients and the post-processing of DE-BR-CTA took an average of 53 s, excluding data transfer and saving time. The quality of dual-energy bone removal was rated "excellent" for two of the patients, "good" for eight patients, and "moderate" for two patients.

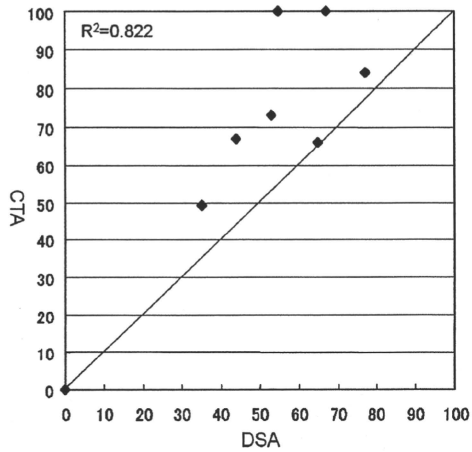

Fig. 5 Scatterplots illustrate percentages of carotid artery stenosis at DE-BR-CTA versus DSA. Good correlation was noted between the two methods (R^2=0.822), but the stenosis diagnosed by CTA was higher than that by DSA for most cases

Of the 24 ophthalmic arteries, the visibility of 7 was rated "excellent," 14 were rated "good," 1 was rated "poor," and 2 arteries were rated "not visible." The two ophthalmic arteries that were not visible in DE-BR-CTA were found by DSA to be occluded. Interobserver reliability between two readers was good for quality of bone removal (k=0.60) and visibility of ophthalmic arteries (k=0.65).

Aneurysms were located in the vertebral artery (two patients), basilar artery (one patient), ICA (two patients),

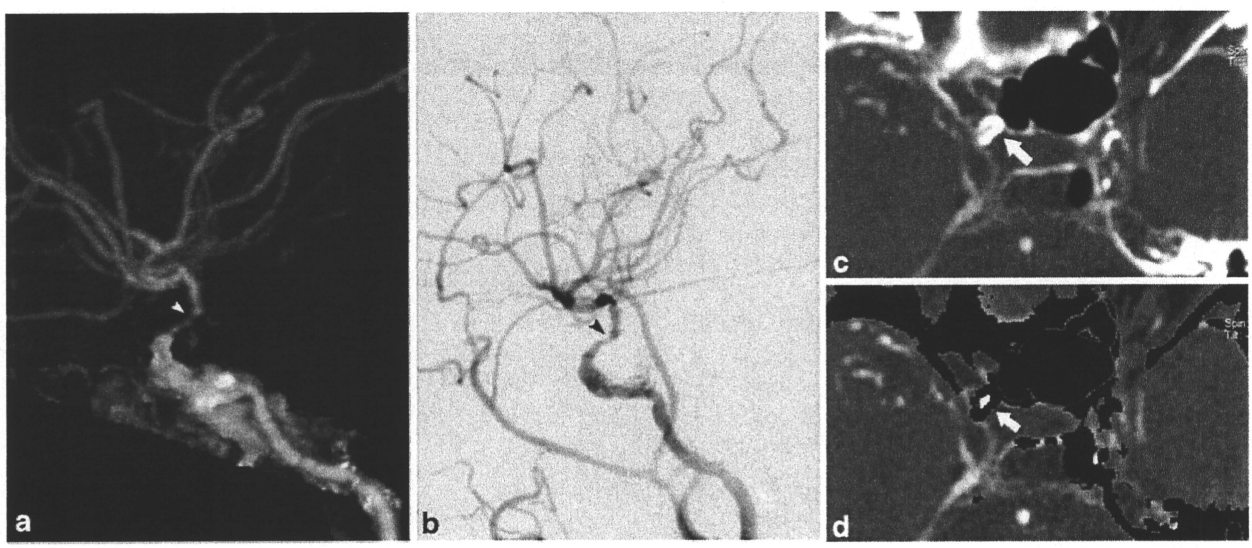

Fig. 4 Right ICA severe stenosis of a 67-year-old female patient. C2 portion of ICA had severe stenosis (*arrowhead*) demonstrated by DE-BR-CTA (**a**) and DSA (**b**). The ophthalmic artery is not visualized by DE-BR-CTA or by DSA. CTA source images (**c**) show dense calcifications around the whole circumference of the right ICA, and these calcifications were removed after DE bone-removal post-processing (**d**)

middle cerebral artery (MCA; three patients) and anterior communicating artery (ACOM; one patient).

Three aneurysms (two ICA and one MCA) adjacent to the skull base were only partially visible in conventional CTA but were fully visible in DE-BR-CTA (Fig. 1). For three aneurysms with calcifications [two MCA and one vertebral artery (VA)], the calcifications were removed by the head bone removal applications, and the intraluminal shape of the aneurysms was visualized precisely with results confirmed by DSA (Figs. 2, 3).

In five patients with ICA stenosis by calcification at the intercavernous or paraclinoid portion, the eight stenotic lesions were not visible in conventional CTA. However, after bone removal post-processing with dual energy, all stenotic lesions became clearly visible on the MIP images (Figs. 2, 4). The agreement of percent stenosis for the two methods is represented in the scatterplots shown in Fig. 5. The correlation between DSA and CTA was good (R^2= 0.822), and the majority of discordant points were above the line of correlation, indicating an overestimation of stenosis found on DE-BR-CTA compared to DSA.

Discussion

Our study shows that bone removal brain CTA using dual-energy data was useful to evaluate aneurysms and ICA stenosis with a short calculating time, and the results with DE-BR-CTA were comparable to those with DSA.

Dual-energy CT was developed during the late 1970s for tissue characterization using single-source, single-slice CT [11, 12] and mainly applied for bone densitometries [13, 14]. However, the limitation of CT hardware and software technology hampered expansion to further clinical applications [15].

Dual-source CT with dual-energy mode can acquire two different energy data into a single acquisition. Dual-energy CT imaging makes it possible to differentiate between certain materials, since X-ray absorption is material specific and dependent on the energy of the X-rays. Dual-energy CT for tissue characterization was reported for urinary stone differentiation [16–18], visualization of the knee ligament [19], and differentiation of iodine from bone and calcification [9].

Multi-slice CTA has a high sensitivity and specificity for the detection of intracranial aneurysm [1, 20].

Subtraction methods for bone removal in cerebral CTA have been reported for the evaluation of skull base aneurysm or extracranial ICA, such as simple subtraction from enhanced data to noncontrast data [4, 21]. More recently, selective bone removal or "matched mask bone elimination" have been widely used for bone-subtraction CTA where the bone mask image as well as the 3D registration to the enhanced CT acquisition were determined by a low-dose unenhanced CT acquisition [6–8].

In our study, DE-BR-CTA removed the bone structures very well, and the three aneurysms adjacent to the skull base were fully visible from all directions, in contrast to the partial view in conventional CTA.

Calcification of the aneurysmal wall makes surgical clipping difficult, so this information was important for deciding treatment strategies [22]. Conventional CTA images revealed calcifications but neither VR nor MIP images allowed a precise evaluation of the intraluminal aneurysmal shape. By comparison, the geometry of intraluminal aneurysms was clearly visible on DSA, yet calcifications could not be displayed. We found that calcifications of three aneurysms were removed by dual-energy bone removal, therefore the wall and luminal information of the aneurysms could be analyzed with both DE-BR-CTA and conventional CTA.

The advantage of the dual-energy bone removal method compared to CT digital subtraction methods is that it avoids the additional preliminary unenhanced CT acquisition. Single data acquisition reduces the radiation dose to the patient and also shows no misregistration artifacts. Subtraction methods use position adjustment, but if a patient moves between the two consecutive acquisitions, it becomes difficult to achieve a perfect match between the two images.

For the evaluation of intracranial stenosis and occlusion, DSA has been considered the reference standard [10]. The correlation between degree of intracranial stenosis based on CTA and DSA was excellent [23], and CTA has a higher sensitivity and positive predictive value than MRA [24]. Evaluation of ICA stenosis at the petrosal portion of carotid siphon or in cases of calcified plaque has not been reported previously, because CTA did not allow 3D visualization of ICA with these conditions. In contrast, DE-BR-CTA removed bone and calcifications and was able to measure the degree of stenosis.

As described above, we quantitatively evaluated ICA stenosis on MIP image. The correlation coefficient between DE-BR-CTA and DSA results was good, but stenosis tends to be overestimated in DE-BR-CTA compared to DSA. In our study, two severe stenotic arteries were misclassified as occluded (100% stenosis) with DE-BR-CTA. The main reason for this overestimation is blooming effects from calcifications. The poor enhancement of an artery with severe stenosis compared to a nonstenotic artery also makes it difficult to draw a clear demarcation between calcification and iodine. This problem might be resolved by optimization of demarcation parameters and reconstruction kernel.

Conclusion

Dual-energy bone removal using dual-source CT is able to eliminate bone and calcification from CTA images using only a single contrast-enhanced scan. DE-BR-CTA is a useful tool to evaluate intracranial aneurysms and stenosis.

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Angiographic documentation of aortoiliac occlusion in Leriche's syndrome

Masateru Takigawa MD[1], Koichi Akutsu MD[1], Satoshi Kasai MD[1], Yuiichi Tamori MD[1], Tsuyoshi Yoshimuta MD[1], Masahiro Higashi MD[2], Satoshi Takeshita MD FACC[2]

A 65-year-old man with familial hypercholesterolemia presented with intermittent claudication. Computed tomography (CT) angiography documented severe stenosis of the right common iliac artery and complete occlusion of the left common iliac artery (Figure 1). Although catheter intervention was recommended, the patient chose a conservative medical therapy.

Eight months later, the patient came back for worsening claudication and development of erectile dysfunction. Follow-up CT angiography revealed complete occlusion of the infrarenal abdominal aorta and bilateral common iliac arteries (Figure 2).

Leriche's syndrome (1,2) is an aortoiliac occlusive disease in men, with associated signs and symptoms of thigh, hip or buttock claudication, atrophy of the leg muscles, impotence and a reduced femoral pulse. The main cause of this syndrome is an atherosclerotic obstruction of aortoiliac arteries. It typically begins at the distal aorta or common iliac artery origins, and slowly progresses proximally and distally over time. This progression is quite variable, but it may ultimately extend to the level of the renal arteries or result in total aortic occlusion. Serial CT angiographies performed in the present patient demonstrated that the process of aortic occlusion in this syndrome was indeed the result of a retrograde propagation of a thrombotic occlusion initiating in the bilateral iliac lesions.

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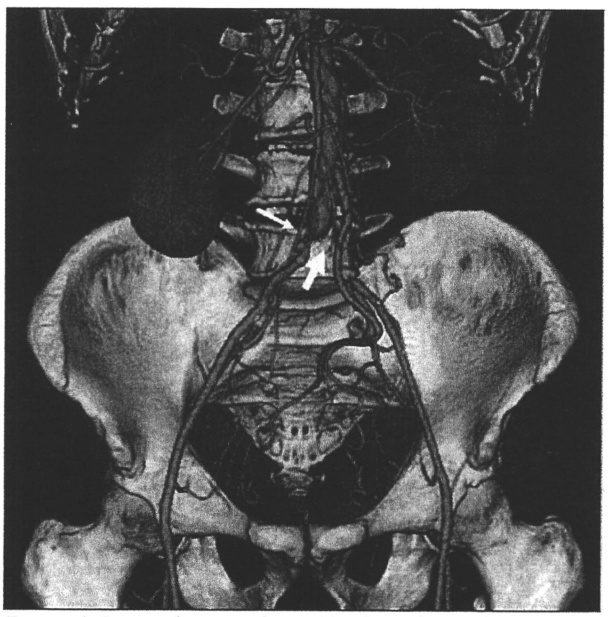

Figure 1) *Computed tomography angiography at the initial presentation, showing severely stenosed right common iliac artery (small arrow) and completely obstructed left common iliac artery (large arrow)*

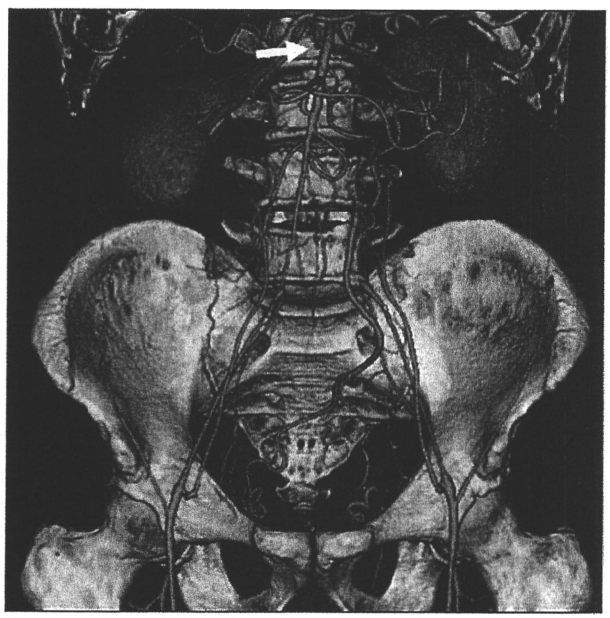

Figure 2) *Computed tomography angiography at follow-up, showing completely obstructed infrarenal aorta (arrow) and bilateral common iliac arteries*

[1]*Department of Medicine (Cardiology);* [2]*Department of Radiology, National Cardiovascular Center, Osaka, Japan*
Correspondence and reprints: Dr Satoshi Takeshita, Department of Medicine (Cardiology), National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita, Osaka 565-8565, Japan. Telephone 81-6-6833-5012 ext 8668, fax 81-6-6872-7486, e-mail stake@muse.ocn.ne.jp
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Long-Term Outcome After Percutaneous Peripheral Intervention vs Medical Treatment for Patients With Superficial Femoral Artery Occlusive Disease

Chizuko Kamiya, MD; Shingo Sakamoto, MD; Yuiichi Tamori, MD; Tsuyoshi Yoshimuta, MD; Masahiro Higashi, MD*; Ryoichi Tanaka, MD*; Koichi Akutsu, MD; Satoshi Takeshita, MD

Background Percutaneous peripheral intervention (PPI) for superficial femoral artery (SFA) stenosis is associated with a high restenosis rate. Whether PPI improves the long-term outcome of patients with SFA occlusive disease remains to be determined.

Methods and Results A review was done of 107 patients with SFA occlusive disease. Fifty-five patients received PPI for SFA (ie, PPI group) and 52 patients received conservative medical therapy (ie, control group). Clinical records were searched for adverse events (eg, death, limb amputation, re-hospitalization, new onset of coronary artery disease and cerebrovascular disease) for an average of 30.6±17.7 months. At follow-up, only 5 patients (9.1%) in the PPI group experienced improved limb symptoms compared with baseline, and 6 patients (10.9%) showed ischemic skin ulcer or gangrene. In addition, 2 of these 6 patients were unsuccessful PPI cases complicated with distal embolization and perforation. In the control group, 3 patients (5.8%) presented with improved limb symptoms, and an equal number of patients had worsening of symptoms. Although 2 patients showed ischemic skin ulcers at follow-up, both patients had these lesions at baseline. Adverse events were observed more frequently in the PPI group than the control group (69.1% vs 46.2%, $p<0.05$). This was mainly due to a higher frequency of re-hospitalization in the PPI group than in controls (52.7% vs 15.4%, $p<0.001$).

Conclusions The current study demonstrates that PPI for patients with SFA occlusive disease does not provide superior long-term benefits compared with conservative medical therapy, and that medical therapy will continue to remain the primary treatment strategy for this group of patients. (*Circ J* 2008; **72:** 734–739)

Key Words: Angioplasty; Claudication; Peripheral vascular disease; Restenosis

Patients with lower extremity peripheral artery disease (PAD) experience substantial functional disability due to claudication, rest pain, and the loss of tissue integrity in the distal limbs![1–4] Exercise rehabilitation, drug therapy, and percutaneous or surgical revascularization are the current therapeutic options for these patients?[2,5]

The outcome of percutaneous peripheral intervention (PPI) depends on the anatomic location of the target lesions. For example, PPI for suprainguinal lesions provides a low morbidity and excellent long-term vessel patency[6] whereas PPI for infrainguinal lesions is associated with a high restenosis rate. In fact, for superficial femoral arteries (SFA), restenosis occurs in up to 60% of cases at 1 year after PPI?[7–9] Therefore, PPI for infrainguinal lesions has been confined to unusual circumstances, such as when patients are high risk for surgical treatment![10]

In recent years, with continuing advances in imaging techniques, angioplasty equipment, and endovascular expertise, patients with SFA occlusive disease have undergone a shift in management to include PPI as a primary treatment strategy?[9,11–14] Yet, there are no data to support the assumption that PPI for SFA results in lasting benefit in these patients.

Accordingly, in the current study, we retrospectively reviewed the long-term outcome of patients with SFA occlusive disease. The results indicate that for these patients, PPI does not provide superior long-term benefit compared with conservative medical therapy, suggesting that medical therapy still remains a viable primary treatment strategy for this group of patients. To our knowledge, this is the first report that directly compares the long-term outcome of PPI with medical therapy for patients with SFA occlusive disease.

Methods

Study Participants

The patient population consisted of 641 patients who were admitted consecutively to the National Cardiovascular Center in Japan for the treatment of PAD between January 2000 and December 2004. All patients received angiographic assessment by magnetic resonance imaging, computed tomography, or digital subtraction angiography. Of the 641 patients, 107 were identified to have SFA stenosis as a culprit lesion, and were included in the study (Fig 1). Of these 107 patients, 55 patients then underwent PPI (ie, PPI group) for SFA, and the remaining 52 patients received medical therapy and were used as controls (ie, control group). All 107 patients were primary cases, and those who had previ-

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*Departments of Medicine, *Radiology, National Cardiovascular Center, Suita, Japan*

Mailing address: Satoshi Takeshita, MD, Department of Medicine (Cardiology), National Cardiovascular Center, 5-7-1 Fujishiro-dai, Suita 565-8565, Japan. E-mail: stake@muse.ocn.ne.jp

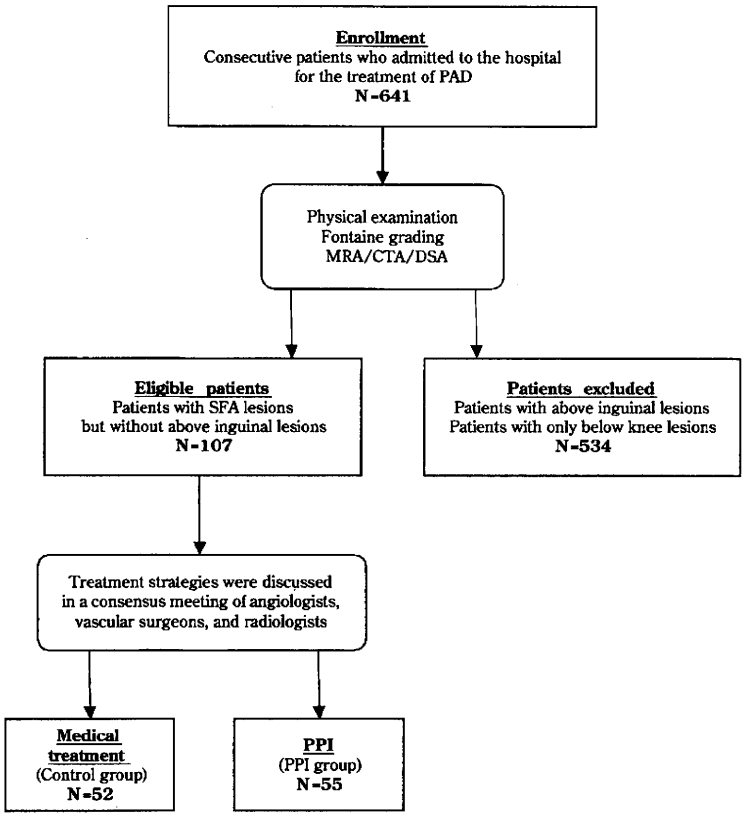

Fig 1. Flowcharts of patients. PAD, peripheral artery disease; MRA, magnetic resonance angiography; CTA, computed tomographic angiography; DSA, digital subtraction angiography; SFA, superficial femoral artery; PPI, percutaneous peripheral intervention.

ously undergone PPI or bypass surgery were excluded.

PPI Procedure

Indications for PPI were made by several cardiologists, surgeons and interventional radiologists at our hospital after considering patients' clinical status. Briefly, angiography was reviewed and SFA lesions were categorized under the modified TransAtlantic Inter-Society Consensus (TASC) system (Table 1). PPI was considered when a patient had Fontaine grade II symptoms with the lesion morphologies of TASC types A and B, or when a patient had Fontaine grade III or IV symptoms (ie, critical limb ischemia). PPI was also considered regardless of the lesion morphologies if a patient did not tolerate claudication symptoms under optimal drug therapy.

All PPI procedures were performed under systemic administration of heparin. Conventional balloon angioplasty was carried out as a primary strategy. Stent implantation was not routinely performed, but was considered when the lesions showed either flow-limiting dissections, a stenosis diameter of >30%, or acute closure. Procedural success was defined as having a stenosis diameter of <30%, pressure gradients of the lesion of <10 mmHg, or improvement in ankle–brachial pressure index (ABI) of >0.10. When there were no contraindications, patients undergoing PPI were prescribed aspirin as well as at least one other antiplatelet or anticoagulant agent. If worsening or recurrence of limb symptoms was observed during the follow-up period, patients received ultrasound and/or angiographic assessment to ascertain restenosis of the dilated lesions.

Long-Term Outcome

Clinical records of 107 patients were retrospectively reviewed to determine whether long-term outcome differed between patients undergoing PPI and those receiving conservative medical therapy. Specifically, for each patient, baseline demographic information, limb symptom (Fontaine grade), ABI, comorbidities, atherosclerotic risk factors, and oral medications were identified. When SFA showed diffuse or multiple lesions, the lesion showing the most severe degree of TASC category was assigned as the lesion category for that patient. These baseline clinical variables were statistically analyzed and correlated with long-term adverse events, which included death, limb amputation, re-hospitalization due to worsening of limb symptoms, new onset of coronary artery disease, and new onset of cerebrovascular disease. The information relating to long-term outcome was obtained by means of patients attending an outpatient clinic.

Table 1 Modified TASC Morphologic Stratification of Femoropopliteal Lesions

*Type A**	*Single stenosis <3 cm in length*
Type B	*Single stenosis or occlusion 3–5 cm long* *Multiple stenoses or occlusions each <3 cm*
Type C	*Single stenosis or occlusion >5 cm* *Multiple stenoses or occlusions each 3–5 cm long*
Type D	*Complete superficial artery occlusion* *Complete popliteal or proximal trifurcation occlusion*

**Type A does not apply for superficial femoral artery lesions according to the original TASC morphologic stratification.*
TASC, TransAtlantic Inter-Society Consensus.

Definitions

Resting ABI was calculated as the quotient of absolute

Table 2 Patient Characteristics

	Control (n=52)	PPI (n=55)	p value
Age (years)	71.8±7.5	70.6±6.6	NS
Male	41 (78.8%)	51 (92.7%)	NS
Fontaine grade	2.15±0.33	2.07±0.18	NS
I	1 (1.9%)	1 (1.8%)	
II	46 (88.5%)	51 (92.7%)	
III	1 (1.9%)	1 (1.8%)	
IV	4 (7.7%)	2 (3.6%)	
Major risk factors and comorbidities			
Current smoker	44 (84.6%)	53 (96.4%)	NS
Hypertension	45 (86.5%)	52 (94.5%)	NS
Dyslipidemia	29 (55.8%)	38 (69.1%)	NS
Diabetes mellitus	34 (65.4%)	39 (70.9%)	NS
Chronic renal impairment	3 (5.8%)	7 (12.7%)	NS
Hemodialysis	1 (1.9%)	4 (7.3%)	NS
History of CAD	26 (50.0%)	28 (50.9%)	NS
History of CVD	2 (3.8%)	5 (9.1%)	NS
TASC lesion characteristics (types A and B)	18 (34.6%)	42 (76.4%)	<0.001
ABI on admission	0.61±0.17	0.61±0.15	NS
ABI on discharge	0.61±0.17	0.81±0.20	<0.001
Mean number of antiplatelets and anticoagulants on discharge	1.87±0.81	2.27±0.78	<0.05
Aspirin	31 (59.6%)	46 (83.6%)	NS
Cilostazol	18 (34.6%)	28 (50.9%)	NS
Ticlopidine	4 (7.7%)	21 (38.2%)	<0.001
Beraprost	24 (46.2%)	18 (32.7%)	NS
Sarpogrelate	8 (15.4%)	12 (21.8%)	NS
Limaprost	8 (15.4%)	7 (12.7%)	NS
Warfarin	4 (7.7%)	6 (10.9%)	NS

PPI, percutaneous peripheral intervention; NS, not significant; CAD, coronary artery disease; CVD, cerebrovascular disease; ABI, ankle–brachial pressure index. Other abbreviation see in Table 1.

ankle pressure and brachial pressure. Each patient's ABI was measured upon admission and at follow-up. In patients receiving PPI, ABI was also measured after PPI. Hypertension was defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg, or as taking antihypertensive medications. Dyslipidemia was defined as having a fasting cholesterol of ≥220 mg/dl, low-density lipoprotein of ≥140 mg/dl, high-density lipoprotein of <40 mg/dl, triglycerides of ≥150 mg/dl, or currently taking lipid-lowering medications. Diabetes mellitus was defined as a fasting plasma glucose of ≥126 mg/dl, hemoglobinA_{1c} of ≥6.5%, or currently taking antidiabetic medications. Coronary artery disease was defined as a history of angina pectoris, myocardial infarction, or prior coronary revascularization. Cerebrovascular disease included a history of stroke, transient ischemic attack, or carotid artery revascularization. Chronic renal impairment was defined as a serum creatinine level of ≥2.0 mg/dl, or being on hemodialysis.

Statistical Analysis

Data were expressed as the mean value±standard deviation. Statistical significance was evaluated using paired and unpaired Student's t-test for comparisons between 2 means, and chi-square test for categorical data. Event-free survival was estimated using the Kaplan–Meier survival method with log-rank statistics. Statistical significance was defined as a p-value of <0.05.

Results

Patient Population

Of the 107 patients with SFA occlusive disease, 55 patients received PPI (ie, PPI group) and 52 underwent conservative medical therapy (ie, control group). Indications for PPI in these 55 patients included critical limb ischemia in 3 patients, and intermittent claudication in 51. Another patient was asymptomatic under pharmacologic therapy; however, PPI was performed based on the patient's request.

Age, gender, follow-up period, Fontaine grade, atherosclerotic risk factors, comorbidities, and ABI on admission were not statistically different between the groups. With regard to lesion characteristics, patients receiving PPI showed less severe types of lesions (ie, TASC types A and B lesions rather than types C and D lesions) compared with those receiving conservative medical therapy (p<0.01) (Table 2).

Short-Term Outcomes of PPI

PPI was successfully performed in 50 of 55 patients (90.9%). Forty patients were treated by balloon angioplasty alone, and 10 received stent implantation, including 7 Palmatz stents, 4 Easy Wall stents, and 1 Smart stent. Indications for stent implantation were residual stenosis of >30% in 5 patients and flow limiting dissection in 5. Procedural failure was observed in 5 patients, of whom 3 patients were on chronic hemodialysis. The reasons for the failure were unsuccessful wire crossing in 4 patients, and wire perforation in 1 patient. Lesion characteristics of the failed cases were TASC type B lesion in 2 patients, type C in 2, and type D in 1. Four of the 5 patients had chronic total occlusions of SFA.

Upon discharge, a significantly greater number of antiplatelet and anticoagulant agents were prescribed in the PPI group than in the control group (2.27±0.78 vs 1.87±0.81, p<0.05). This was mainly due to the higher number of patients taking ticlopidine in the PPI group compared with the control group (38.2% vs 7.7%, p<0.001). ABI in the PPI group significantly improved from 0.61±0.15 to 0.81±0.20