

Cultural Barriers in the Treatment of Dyslipidemia: A Survey of Japanese Physician Attitudes

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Aims: To gain a more accurate understanding of the current real-world management of dyslipidemia in Japan, an online survey was conducted in a variety of physicians from five medical fields.

Methods: A web-based survey with online questionnaire was designed, and members of an on-line information service for physicians were invited to participate. The survey enrolled 500 physicians, 100 in each of five categories: cardiology; diabetes, metabolism and endocrinology; neurology/neurosurgery/stroke medicine; general internal medicine (hospitals ≥ 20 beds), and general internal medicine (self-employed practitioners at clinics or small hospitals ≤ 19 beds).

Results: Regardless of their specialties, most physicians recognized high low density lipoprotein cholesterol level as an important risk for atherosclerotic cardiovascular disease. Physicians with expertise in cardiology, diabetes, metabolism and endocrinology were most in favor of drug-based cholesterol lowering. Specialists in neurology/neurosurgery/stroke medicine and in general internal medicine were more concerned about statin safety and aggressive lipid-lowering therapy than those in cardiology and diabetes, metabolism and endocrinology, and tended to treat fewer patients with familial hypercholesterolemia (FH). Especially, those in general internal medicine (self-employed practitioners at clinics or small hospitals ≤ 19 beds) made less use of techniques for diagnosing FH.

Conclusions: Awareness of target values for lipid management and of adverse reactions to drug therapy appears to vary somewhat depending on the participant's medical specialty. We also found that FH is probably underdiagnosed in Japan today. Further educations on proper diagnosis and management of dyslipidemia are required for physicians who are not specialized in cardiovascular health.

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Key words: Physician attitudes, Dyslipidemia, Treatment, Diagnosis, Japan

Introduction

Evidence increasingly supports the correlation between reduction of low density lipoprotein cholesterol (LDL-C) level and inhibition of cardiovascular (CV) events, and an international consensus is growing to support the "lower is better" model of LDL-C

management¹⁻³). Japanese physicians are increasingly aware of cholesterol-related issues in cardiovascular health, and guidelines from the Japan Atherosclerosis Society (JAS) continue to recommend specific target values for LDL-C management⁴). However, some studies reveal that the attainment rate of LDL-C target remains elusive, especially in subjects under care for sec-

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Table 1. Participants' characteristics

	Physician specialty [F1]					
	Total <i>n</i> = 500	Cardiology <i>n</i> = 100	Diabetes, metabolism and endocrinology <i>n</i> = 100	Neurology/ Neurosurgery/ Stroke <i>n</i> = 100*	General internal medicine (bed ≥ 20) <i>n</i> = 100	General internal medicine (bed ≤ 19) <i>n</i> = 100
Type of practice [F2]						
University hospital	61 (12.2)	14 (14.0)	22 (22.0)	16 (16.0)	9 (9.0)	0 (0.0)
National hospital	76 (15.2)	23 (23.0)	15 (15.0)	25 (25.0)	13 (13.0)	0 (0.0)
Private Hospital	217 (43.4)	51 (51.0)	39 (39.0)	49 (49.0)	78 (78.0)	0 (0.0)
Doctors' office/Medical office/Clinic	146 (29.2)	12 (12.0)	24 (24.0)	10 (10.0)	0 (0.0)	100 (100.0)
Number of beds [F3]						
0	132 (26.4)	10 (10.0)	20 (20.0)	8 (8.0)	0 (0.0)	94 (94.0)
1 to 19	14 (2.8)	2 (2.0)	4 (4.0)	2 (2.0)	0 (0.0)	6 (6.0)
20 to 49	8 (1.6)	1 (1.0)	0 (0.0)	0 (0.0)	7 (7.0)	0 (0.0)
50 to 99	35 (7.0)	3 (3.0)	5 (5.0)	7 (7.0)	20 (20.0)	0 (0.0)
100 to 199	75 (15.0)	18 (18.0)	8 (8.0)	10 (10.0)	39 (39.0)	0 (0.0)
200 to 299	44 (8.8)	12 (12.0)	10 (10.0)	11 (11.0)	11 (11.0)	0 (0.0)
300 to 499	83 (16.6)	29 (29.0)	18 (18.0)	24 (24.0)	12 (12.0)	0 (0.0)
≥ 500	109 (21.8)	25 (25.0)	35 (35.0)	38 (38.0)	11 (11.0)	0 (0.0)
Sex [F4]						
Male	451 (90.2)	95 (95.0)	83 (83.0)	96 (96.0)	87 (87.0)	90 (90.0)
Female	49 (9.8)	5 (5.0)	17 (17.0)	4 (4.0)	13 (13.0)	10 (10.0)
Age [F5]						
20s	3 (0.6)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)	1 (1.0)
30s	92 (18.4)	21 (21.0)	40 (40.0)	10 (10.0)	14 (14.0)	7 (7.0)
40s	153 (30.6)	35 (35.0)	25 (25.0)	42 (42.0)	34 (34.0)	17 (17.0)
50s	198 (39.6)	31 (31.0)	26 (26.0)	40 (40.0)	41 (41.0)	60 (60.0)
60s	53 (10.6)	12 (12.0)	9 (9.0)	8 (8.0)	10 (10.0)	14 (14.0)
≥ 70	1 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.0)
Number of years in clinical practice [F6]						
(years, mean±SD)	21.3 ± 8.2	20.1 ± 8.6	17.6 ± 9.0	22.5 ± 7.2	21.2 ± 7.4	25.0 ± 7.1
Type of facility where you received residency training [F7]						
University hospital in Japan	347 (69.4)	62 (62.0)	61 (61.0)	77 (77.0)	70 (70.0)	77 (77.0)
Other facility in Japan	151 (30.2)	38 (38.0)	37 (37.0)	23 (23.0)	30 (30.0)	23 (23.0)
University hospital abroad	2 (0.4)	0 (0.0)	2 (2.0)**	0 (0.0)	0 (0.0)	0 (0.0)
Affiliated academic organizations [F9]						
Japan Atherosclerosis Society	36 (7.2)	14 (14.0)	11 (11.0)	6 (6.0)	3 (3.0)	2 (2.0)
The Japanese Society of Internal Medicine	387 (77.4)	90 (90.0)	91 (91.0)	52 (52.0)	86 (86.0)	68 (68.0)
The Japan Endocrine Society	69 (13.8)	3 (3.0)	60 (60.0)	0 (0.0)	5 (5.0)	1 (1.0)
The Japanese Circulation Society	111 (22.2)	92 (92.0)	3 (3.0)	0 (0.0)	10 (10.0)	6 (6.0)
The Japanese of Society of Hypertension	34 (6.8)	17 (17.0)	5 (5.0)	0 (0.0)	7 (7.0)	5 (5.0)
The Japan Diabetes Society	129 (25.8)	9 (9.0)	90 (90.0)	3 (3.0)	17 (17.0)	10 (10.0)
Japanese Society of Nephrology	23 (4.6)	4 (4.0)	8 (8.0)	0 (0.0)	4 (4.0)	7 (7.0)
The Japan Stroke Society	72 (14.4)	1 (1.0)	0 (0.0)	67 (67.0)	3 (3.0)	1 (1.0)
The Japan Society of Adult Diseases	8 (1.6)	0 (0.0)	5 (5.0)	0 (0.0)	2 (2.0)	1 (1.0)
None of the above applicable	54 (10.8)	2 (2.0)	1 (1.0)	10 (10.0)	12 (12.0)	29 (29.0)

(Cont. Table 1)

	Physician specialty [F1]					
	Total <i>n</i> = 500	Cardiology <i>n</i> = 100	Diabetes, metabolism and endocrinology <i>n</i> = 100	Neurology/ Neurosurgery/ Stroke <i>n</i> = 100 *	General internal medicine (bed ≥ 20) <i>n</i> = 100	General internal medicine (bed ≤ 19) <i>n</i> = 100
Specialist qualifications [F10]						
Arteriosclerosis	15 (3.0)	5 (5.0)	5 (5.0)	1 (1.0)	3 (3.0)	1 (1.0)
Endocrinology and metabolism	37 (7.4)	1 (1.0)	31 (31.0)	0 (0.0)	4 (4.0)	1 (1.0)
Cardiovascular disease	98 (19.6)	82 (82.0)	2 (2.0)	0 (0.0)	9 (9.0)	5 (5.0)
Diabetes	88 (17.6)	3 (3.0)	71 (71.0)	3 (3.0)	6 (6.0)	5 (5.0)
Nephrology	11 (2.2)	3 (3.0)	2 (2.0)	0 (0.0)	3 (3.0)	3 (3.0)
Stroke	60 (12.0)	0 (0.0)	0 (0.0)	56 (56.0)	3 (3.0)	1 (1.0)
Cerebral endovascular treatment	7 (1.4)	0 (0.0)	0 (0.0)	7 (7.0)	0 (0.0)	0 (0.0)
Cardiovascular surgery	1 (0.2)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiovascular intervention	26 (5.2)	24 (24.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (1.0)
Plasma exchange therapy	1 (0.2)	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
Certified educator of the Japan Society of Adult Diseases	3 (0.6)	0 (0.0)	1 (1.0)	0 (0.0)	2 (2.0)	0 (0.0)
None of the above obtained	244 (48.8)	16 (16.0)	19 (19.0)	41 (41.0)	78 (78.0)	90 (90.0)

Data are presented as number of subjects (%) except for the number of years in clinical practice.

[] indicated question numbers on participants' background.

*Neurology, *n* = 55; Neurosurgery, *n* = 45; Stroke, *n* = 0

**Overseas training experience [F8]

ondary prevention of CV events in Japan⁵⁻⁷. This situation in Japan may be due to several issues. One may be the suspicion that drug-induced very low LDL-C levels can increase the risk of hemorrhagic stroke. Several epidemiological studies have shown an association between extremely low levels of serum LDL-C and an increase in cerebral hemorrhage^{8, 9}. Another reason may be the insufficient evaluation of CV risk status in patients with hypercholesterolemia. JAS has recently launched guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases (ASCVD)¹⁰ in order to assess comprehensive CV risk. JAS has set the diagnostic level for hyper-LDL-cholesterolemia at 140 mg/dL.

The Japanese Society of Internal Medicine and affiliated organizations have published the Comprehensive Risk Management Chart for the Prevention of Cerebro-Cardiovascular Diseases¹¹, which focuses on the prevention and risk management of ASCVD by general practitioners at the clinical level, just like the JAS guidelines. However, we do not know whether these general practitioners are aware of the chart, or are using it effectively in their daily medical practice.

We realized that, to promote effective lipid management in Japan, we must first understand the current status of physician awareness and attitudes for lipid-lowering therapy. After that, we may be able to

develop measures to help physicians treat patients more easily and effectively. The International Atherosclerosis Society (IAS) is also interested in the situation in Japan, so JAS and IAS conducted a joint web-based survey for Japanese physicians. Our objective was to identify cultural barriers to the appropriate management for ASCVD focusing the treatment of dyslipidemia in Japan. This survey was designed to analyze physicians' attitudes toward lipid-lowering therapy in each area of clinical expertise.

Aim

Our aim was to gain a more accurate understanding of the current real-world management of dyslipidemia by a variety of physicians with expertise in cardiology, diabetes, metabolism and endocrinology, neurology/neurosurgery/stroke medicine, general internal medicine (hospitals with ≥ 20 beds), and general internal medicine (self-employed practitioners at clinics or small hospitals with ≤ 19 beds).

Methods

Study Design

We designed this study as a web-based survey, using an online questionnaire. The project was coordi-

Table 2. Number of examined patients with dyslipidemia, history of ischemic stroke, or coronary heart disease

(A) Patients with dyslipidemia						
	Total <i>n</i> = 500	Physician specialty				
		Cardiology <i>n</i> = 100	Diabetes, metabolism and endocrinology <i>n</i> = 100	Neurology/ Neurosurgery/ Stroke <i>n</i> = 100*	General internal medicine (bed ≥ 20) <i>n</i> = 100	General internal medicine (bed ≤ 19) <i>n</i> = 100
Examined	124.4 ± 97.5	118.4 ± 92.2	168.6 ± 107.4	80.1 ± 57.1	114.8 ± 96.7	140.2 ± 104.4
Receiving drug treatment for dyslipidemia	104.0 ± 84.2	106.3 ± 89.6	138.6 ± 99.3	68.7 ± 53.8	90.8 ± 64.5	115.7 ± 89.3
(B) Patients with a history of ischemic stroke						
	Total <i>n</i> = 500	Physician specialty				
		Cardiology <i>n</i> = 100	Diabetes, metabolism and endocrinology <i>n</i> = 100	Neurology/ Neurosurgery/ Stroke <i>n</i> = 100*	General internal medicine (bed ≥ 20) <i>n</i> = 100	General internal medicine (bed ≤ 19) <i>n</i> = 100
Examined	35.9 ± 47.1	23.8 ± 32.4	28.0 ± 20.6	76.9 ± 80.4	28.2 ± 25.1	22.5 ± 22.0
Receiving drug treatment for dyslipidemia	27.2 ± 27.3	20.4 ± 29.1	24.1 ± 17.1	49.1 ± 35.3	22.2 ± 18.2	20.5 ± 20.9
(C) Patients with (or with a history of) coronary heart disease						
	Total <i>n</i> = 500	Physician specialty				
		Cardiology <i>n</i> = 100	Diabetes, metabolism and endocrinology <i>n</i> = 100	Neurology/ Neurosurgery/ Stroke <i>n</i> = 100*	General internal medicine (bed ≥ 20) <i>n</i> = 100	General internal medicine (bed ≤ 19) <i>n</i> = 100
Examined	31.0 ± 41.0	68.9 ± 68.6	30.3 ± 24.5	14.9 ± 19.0	20.6 ± 22.9	20.3 ± 18.7
Receiving drug treatment for dyslipidemia	27.9 ± 38.1	62.3 ± 64.2	27.4 ± 22.6	13.0 ± 18.4	18.0 ± 20.5	18.8 ± 18.3

Data presented as mean ± SD.

*Neurology, *n* = 55; Neurosurgery, *n* = 45; Stroke, *n* = 0

nated by the JAS in collaboration with the IAS.

Study Participants

Medical doctors who met the following conditions were included in the survey:

Group 1) Physicians with expertise in cardiology who had examined at least 50 patients with dyslipidemia in the previous month.

Group 2) Physicians with expertise in diabetes, metabolism, and endocrinology who had examined at least 50 patients with dyslipidemia in the previous month.

Group 3) Physicians with expertise in neurology/neurosurgery/stroke medicine who had examined at least 50 patients with dyslipidemia in the previous month and at least 20 patients with a history of ischemic stroke in the previous month.

Group 4) Physicians with expertise in general internal medicine who had examined at least 50 patients

with dyslipidemia in the previous month at a hospital with at least 20 beds.

Group 5) Physicians with expertise in general internal medicine who had examined at least 50 patients with dyslipidemia in the previous month at self-employed practitioners at clinics or small hospitals with ≤ 19 beds.

The definition of dyslipidemia was left to the individual physician. In Japan, dyslipidemia is generally defined under the JAS guidelines; a borderline hyper-LDL cholesterolemia (LDL-C ≥ 120 mg/dL) or hyper-LDL cholesterolemia (LDL-C ≥ 140 mg/dL), hypo-HDL cholesterolemia (HDL-C < 40 mg/dL), or hypertriglyceridemia (triglyceride ≥ 150 mg/dL) in a fasting state.

Planning the Survey

IAS and JAS organized a committee to develop and implement a survey on the current management

Q2. Do you consider elevated LDL cholesterol to be an important contributor to coronary artery disease and ischemic stroke in Japan?

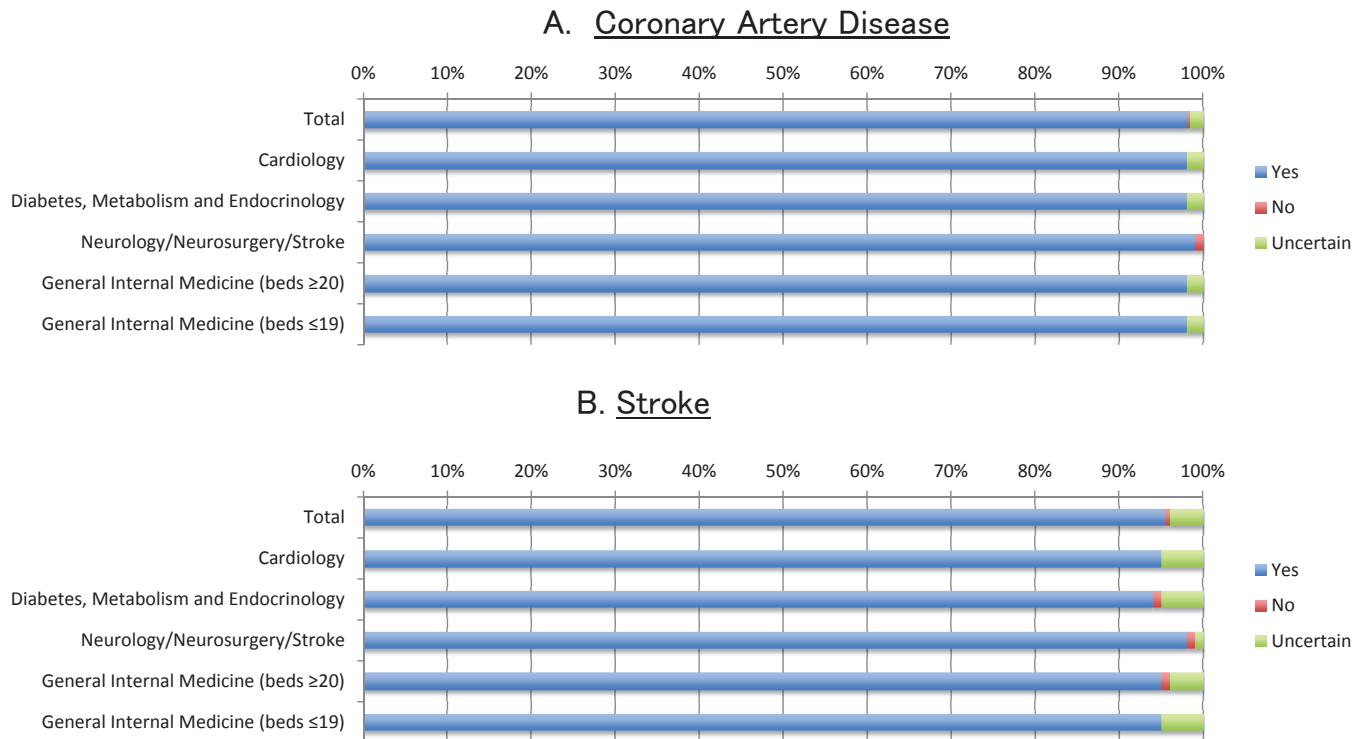


Fig. 1. Attitudes on the impact of LDL-C on CAD and ischemic stroke

This figure summarizes participant responses to whether LDL-C has an impact on CAD (A) and ischemic stroke (B). LDL-C, low density lipoprotein cholesterol; CAD, coronary artery disease

of ASCVD, with focus on the treatment of dyslipidemia in Japan. The survey contained 20 items (in 12 questions, Q1 through Q12) and an additional 10 items regarding participant characteristics (F1 through F10). The questions addressed the number of patients under treatment for dyslipidemia (Q1), the individual physician's thoughts on the correlation between ASCVD and LDL-C (Q2), side effects of statins (Q3), percentage of statin intolerance (Q4), target level (Q5) and safety limit of LDL-C lowering (Q6), effect of LDL-C lowering on ASCVD risk (Q7), the individual physician's use of non-HDL-C (Q8) and the Risk Management Chart (Q9) in clinical practice, the diagnosis (Q10) and treatment of patients with familial hypercholesterolemia (FH) (Q11), and impressions regarding Japanese patients (Q12).

Implementing the Survey

The survey was conducted by CareNet, Inc., an online Japanese-language medical information service for physicians. All candidates were registered members

of CareNet, Inc. and received an email from CareNet, Inc., introducing the study and inviting them to participate. Physicians from five medical categories (groups 1, 2, 3, 4 and 5) were invited to participate in a web-based survey by answering questions. Those who were interested in the topic chose to participate of their own free will. Participants in each category were the first 100 responders, with preference given to earliest completion date (500 participants in total). Participants were required to log in to access the survey but were not asked to provide their names when responding to the questions. Each participant could submit only one survey; his or her access to the survey was blocked after submission was completed.

Survey responses were handled in a series of steps. Participants responded first to the screening question (Q1), then to the main questions (Q2 through Q12), and last to the questions on participant background (F1 through F10). Only the invited CareNet members who satisfied the conditions of the screening question could answer these questions. If the participant entered

Q3. In relation to statin use, do you have concerns related to any of the following? (multiple answers)

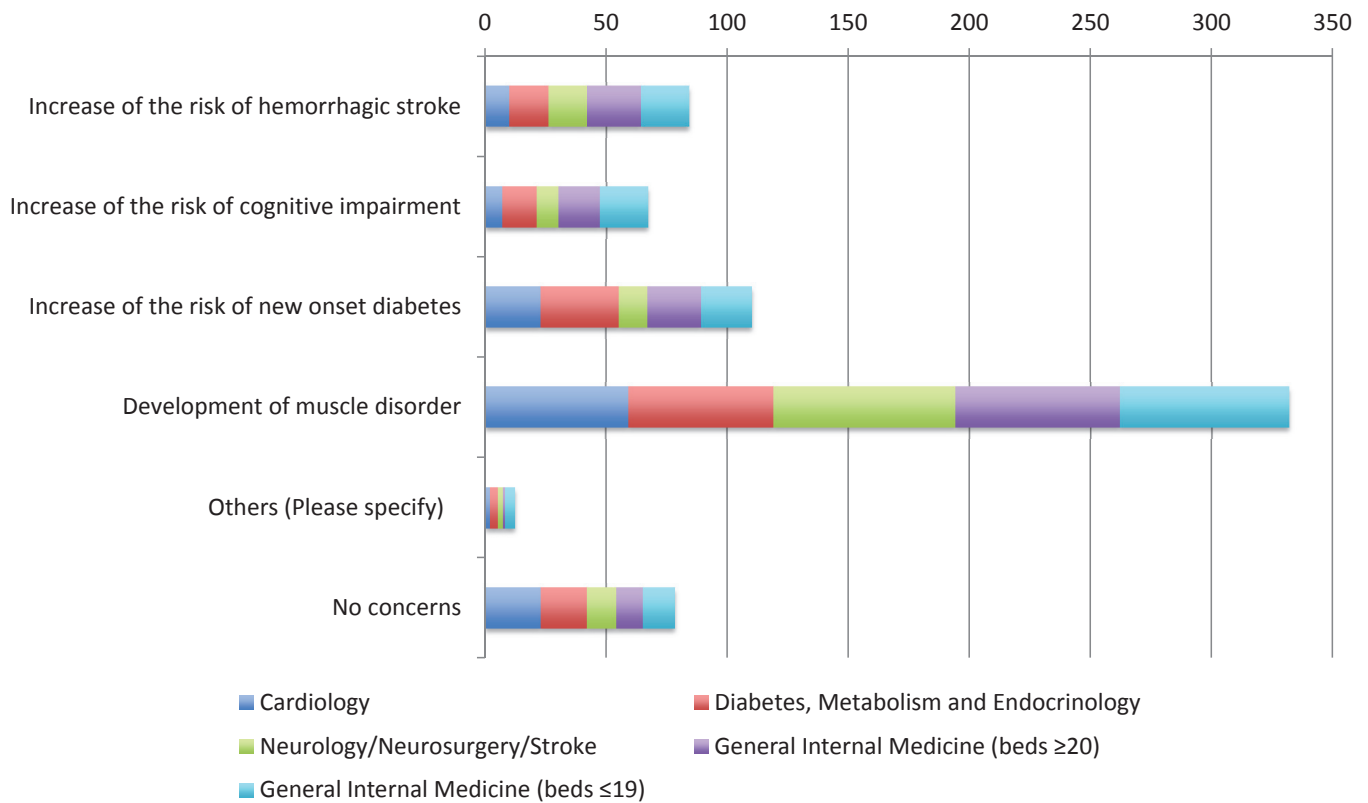


Fig. 2. Concerns about statin therapy

Attitudes on statin-related risks were queried, and the number of participants who reported being concerned about each category of risk were graphed. Participants were subdivided as shown, by area of clinical expertise.

contradictory numbers in the reply, an error message appeared and he or she could not proceed to the next question (Q1). If the answer violated the selection criteria or if contradictory responses were selected, an error message appeared and the participant was unable to proceed to the next question (Q3, 6, 12). Q10 was visible only to those participants who met specific criteria. For participants who did not meet those criteria, the survey skipped Q10. After the answers were completed through F10 of attribute registration, the survey questionnaire was closed for that participant.

Data from the survey was aggregated by CareNet Inc. After the grand total was obtained, cross-totals were calculated for the five categories. Results were to be used by the authors for descriptive analysis. Findings from participants' characteristics (years in clinical practice) and from Q1 and Q5 (LDL-C level) were presented as mean $\pm$ SD, and findings for the other questions were presented as the percentage of partici-

pants. No statistical analysis was planned.

Results

The survey was conducted January 19–27, 2017. CareNet, Inc. sent emails to a total of 25,194 candidates, introducing the study and inviting them to participate.

Participants' Characteristics

Participants' characteristics are summarized in [Table 1](#). Number of participants were as follows: Group 1 ($n=100$), Group 2 ($n=100$), Group 3 (neurology, $n=55$, neurosurgery, $n=45$, stroke medicine, none), Group 4 ($n=100$) and Group 5 ($n=100$).

In total, 90.2% of participants were male (9.8% female). Overall, most participants were in their 40s (30.6%) and 50s (39.6%). Two-thirds of participants worked in hospitals (university hospital, national hos-

Q4. What percentages of your patients who try statin therapy are unable to continue because of adverse effects (muscle symptoms, etc.)?

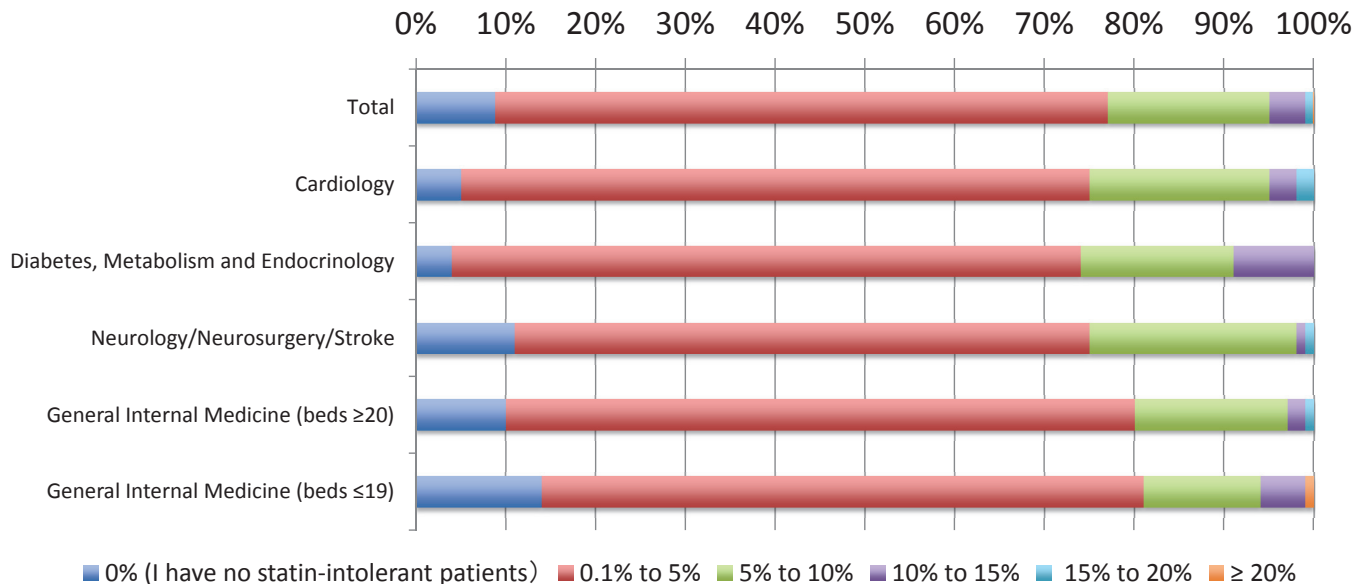


Fig. 3. Percentages of adverse effects of statins reported by participants

Participants reported the percentages of adverse effects leading to discontinuation of statin therapy.

pital organization, public or private hospitals) and the rest worked in doctor's offices, medical offices, or clinics. Participants had been practicing medicine for a mean of 21.3 ± 8.2 years. Most of the participants had undergone training in Japan, at a university hospital or a designated training hospital for postgraduate clinical training other than a university hospital. The clinical specialties of the participants were reflected by the academic societies with which they were affiliated. Specialist qualifications also reflected participants' areas of expertise. However, half of participants (48.8%) were not affiliated with any of the 11 academic societies listed on the survey form (Table 1).

Survey Results

Question 1 (Screening): During the previous month, how many patients did you examine for dyslipidemia, and how many of those patients received drug treatment for dyslipidemia?

On average, participants examined 124 patients with dyslipidemia and prescribed drug treatment for 104 of them (Table 2A). For patients with a history of ischemic stroke, on average 36 were examined for dyslipidemia and 27 of them received drug treatment for that condition; for patients with coronary artery disease (CAD) or a history of CAD, those numbers were 31 and 28, respectively.

Question 2: Do you consider elevated LDL cholesterol to be an important contributor to coronary disease and ischemic stroke in Japan?

For CAD, 98.2% (491 of 500) of all participants answered "yes," indicating that they believe that elevated LDL-C does have an impact on it (Fig. 1A). For stroke, 95.4% (477 of 500) of all participants answered "Yes," indicating that they also believe that elevated LDL-C does have an impact on stroke (Fig. 1B). Similar percentages were observed within each area of clinical expertise. "Yes" was selected by 98.0% of participants in the category of neurology/neurosurgery/stroke medicine for both questions, the highest value among the five categories.

Question 3: In relation to statin use, do you have concerns related to any of the following? (multiple answers)

Overall, participants were most concerned about muscle disorders (66.4%, 332 of 500, Fig. 2), followed by the risk of new onset diabetes (22.0%, 110 of 500). Muscle disorders were the greatest concern of physicians in all areas of clinical expertise. Concerns about the risk of hemorrhagic stroke were answered by 16.8% (84 of 500). A total of 15.6% (78 of 500) of responders expressed no concern about using statins. Physicians with expertise in diabetes, metabolism, and endo-

Q5. What are your target values for LDL-C management after pharmacotherapy for dyslipidemia, by patient category?

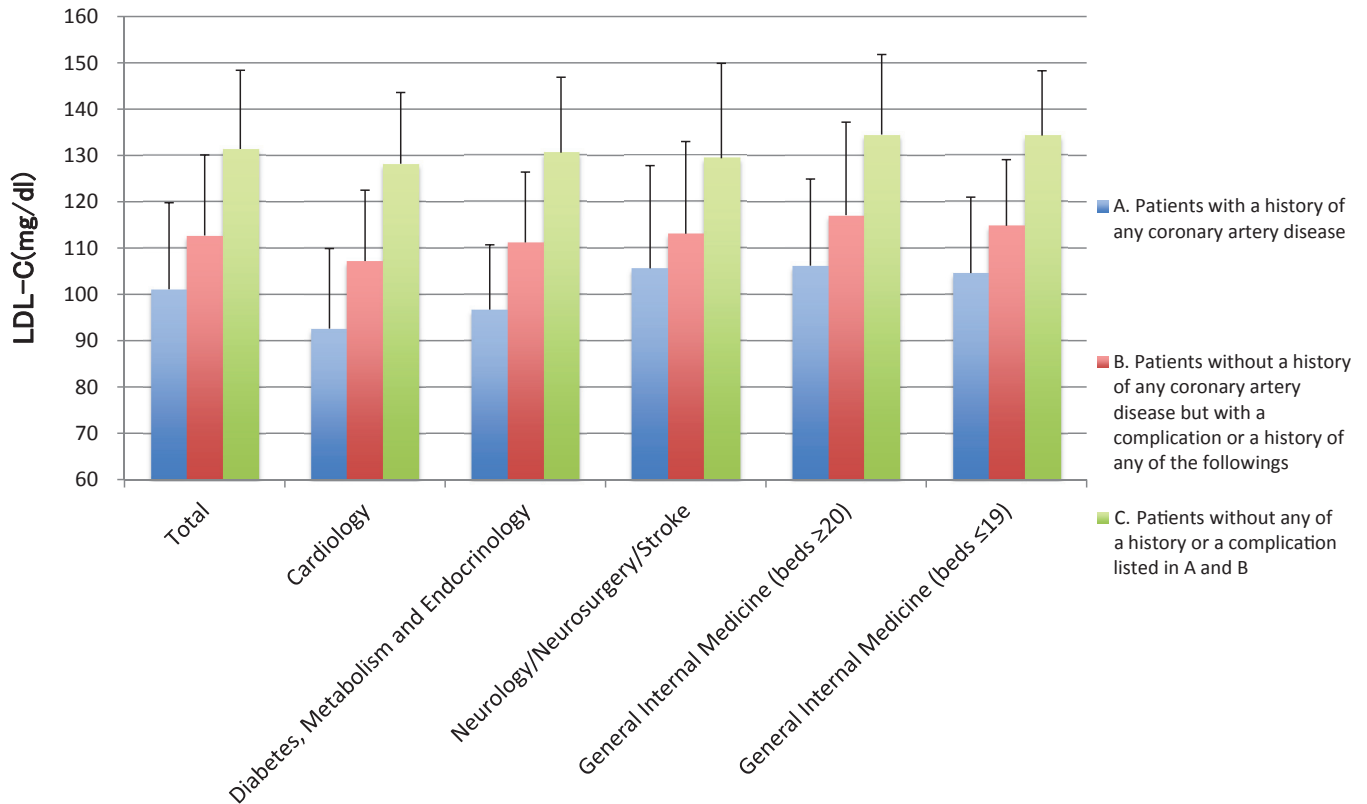


Fig. 4. Target LDL-C levels reported by survey participants

Mean target level of LDL-C (mg/dL) reported by the participants in each area of clinical expertise for patients with a history of CAD (A). Mean target level of LDL-C (mg/dL) reported by the participants in each area of clinical expertise for patients without a history of CAD but with a complication or a history of any of the following: diabetes, chronic kidney disease, non-cardiogenic cerebral infarction, or peripheral arterial disease (B). Mean target level of LDL-C (mg/dL) reported by the participants in each area of clinical expertise for patients without a history of CAD or a history or complication of diabetes, chronic kidney disease, non-cardiogenic cerebral infarction, or peripheral arterial disease (C).

Data presented as mean ± SD.

LDL-C, low density lipoprotein cholesterol; CAD, coronary artery disease

crinology tended to be more concerned about the increased risk of new onset diabetes (32.0%, 32 of 100), and physicians with expertise in cardiology tended to be less concerned about using statins (23.0%, 23 of 100) (**Fig. 2**).

Question 4: What percentages of your patients who try statin therapy are unable to continue because of adverse effects (muscle symptoms, etc.)?

Overall, 68.2% (341 of 500) of participants answered with ≥ 0.1 to $< 5\%$ and 18.0% (90 of 500) answered with ≥ 5 to $< 10\%$ (**Fig. 3**). The same trend was seen when results were stratified by area of clinical expertise.

Question 5: What are your target values for LDL-C management after pharmacotherapy for dyslipidemia, by patient category?

In patients with a history of CAD, the overall mean target level was 101.1 ± 18.7 mg/dL (**Fig. 4**). By specialty, the mean target level for physicians with expertise in cardiology was lowest of all the areas of clinical expertise (92.6 ± 17.3 mg/dL). In patients with a history or complications of diabetes, chronic kidney disease, non-cardiogenic cerebral infarction, or peripheral arterial disease, the overall mean target level was 112.7 ± 17.4 mg/dL (**Fig. 4**). Just as in patients with CAD, the mean target level for physicians with expertise in cardiology was lowest of all the areas of clinical expertise (107.2 ± 15.3 mg/dL). The overall mean tar-

Q6. In your opinion, what LDL-C levels are safe?

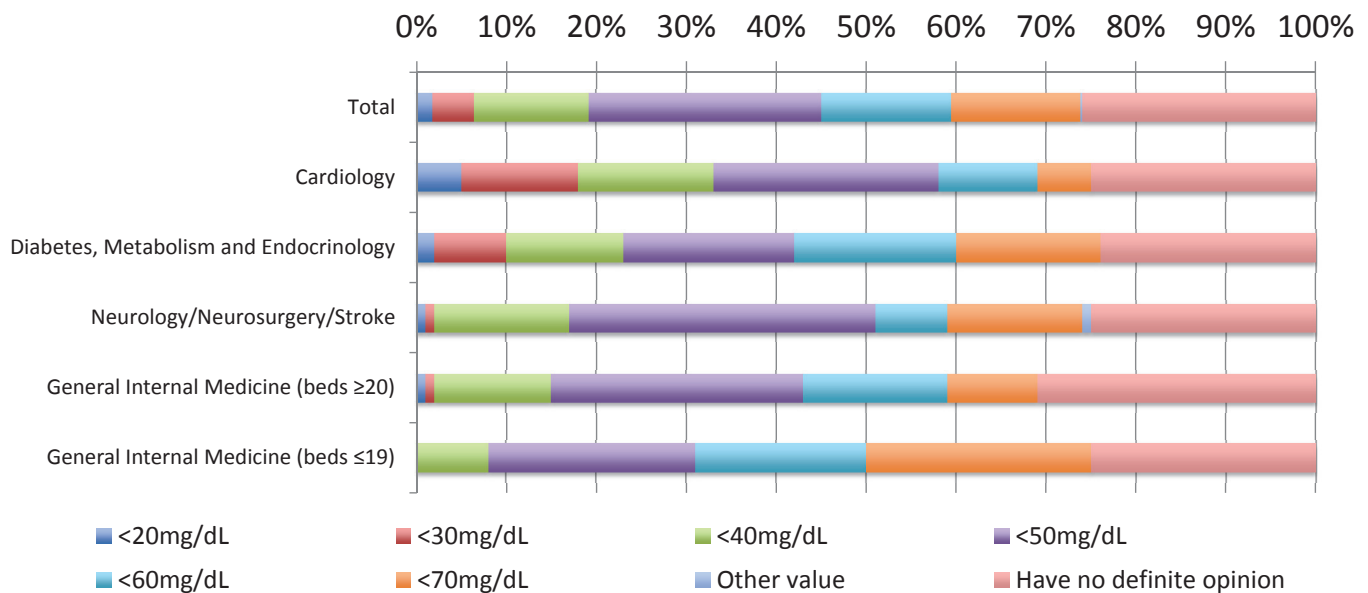


Fig. 5. Concerns about LDL-C target levels among survey participants

Participants reported the target LDL-C level at which they had concerns for patient safety. LDL-C, low density lipoprotein cholesterol

get LDL-C level in patients without a medical history or complications was 131.4 ± 17.0 mg/dL; the mean target level was around 130 mg/dL for physicians in any field.

Question 6: In your opinion, what LDL-C levels are safe?

The largest number of participants expressed concern about safety at LDL-C below 50 mg/dL (25.8%, 129 of 500) (**Fig. 5**). About a quarter of all participants noted concern at LDL-C levels below 60 mg/dL or below 70 mg/dL, half of all participants noted concern below 20 mg/dL, 30 mg/dL, 40 mg/dL or 50 mg/dL, and the remaining participants (26.0%, 130 of 500) stated that they had no particular concern about LDL-C level. Physicians with expertise in cardiology tended to choose lower LDL-C levels, and clinic physicians with expertise in general internal medicine (at clinics with ≤ 19 beds) tended to select higher levels.

Question 7: In your opinion, how much does LDL-C level affect ASCVD risk?

A total of 93.8% (469 of 500) of all participants answered either “affects the risk significantly” (51.0%) or “affects the risk moderately” (42.8%, **Fig. 6**). When results were stratified by area of clinical expertise, physicians with clinical expertise in cardiology chose the

answer “affects the risk significantly” more often than those with other areas of clinical expertise (64.0 %, 64 of 100), and physicians in general internal medicine (at hospitals with ≥ 20 beds) chose the answer “affects the risk moderately” more often than participants with other areas of clinical expertise (55.0%, 55 of 100).

Question 8: How do you use “non-HDL cholesterol” levels?

Sixty-two percent (310 of 500) of participants said that they did not use the non-HDL cholesterol level (**Fig. 7**), 20.4% (102 of 500) used non-HDL cholesterol level “as a risk index of ASCVD,” and 11.4% (57 of 500) said they used it “as a therapeutic efficacy index.” Stratified by subgroup, over 30% of physicians with clinical expertise in cardiology or in diabetes, metabolism, and endocrinology used non-HDL cholesterol “as a risk index of ASCVD” higher than among physicians with expertise in neurology/neurosurgery/stroke medicine or general internal medicine.

Question 9: Are you aware of the Risk Management Chart¹¹, and do you use it in your practice?

Most participants (62.6%; 313 of 500) knew about the risk management chart¹¹, and about 20% of those who were aware of the chart had used the chart (12.0%, 60 of 500) (**Fig. 8**). The chart was used by physicians

Q7. In your opinion, how much does LDL-C level affect ASCVD risk?

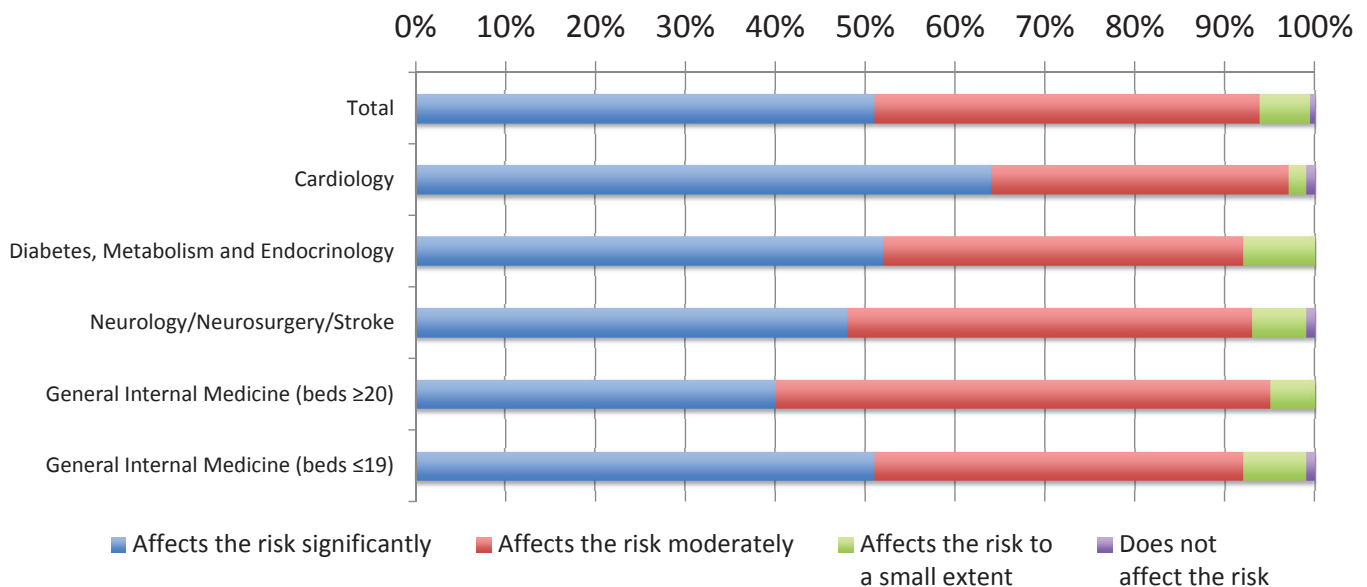


Fig. 6. Opinions about the effect of LDL-C level on risk of ASCVD among survey participants

Participants provided their opinions on how much LDL-C levels affect the risk of ASCVD. LDL-C, low density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease

with clinical expertise in cardiology, in diabetes, metabolism, and endocrinology, or in general internal medicine (at hospitals with ≥ 20 beds). Awareness of the chart tended to be low among physicians with expertise in neurology/neurosurgery/stroke medicine and general internal medicine (≤ 19 beds).

Of the physicians who were not considered to specialize in dyslipidemia treatment (physicians with expertise in neurology/neurosurgery/stroke medicine and general internal medicine), 53 were not affiliated with any of the nine academic societies detailed in entry F9, nor did they have specialist accreditation from any of the 11 academic societies listed in F10. Of those, 29 were general practitioners in clinics that had no beds, and those 29 tended to be less familiar with the Risk Management Chart: one uses it (3.4%); 11 know about it but do not use it (37.9%); 17 do not know about it (58.6%).

Question 10: Please choose the response that most accurately represents your clinical situation regarding familial hypercholesterolemia (FH)

A total of 65.4% (327 of 500) of participants had treated patients with FH (42.2%, 211 of 500) or had referred patients with FH to physicians at another medical institution (23.2%, 116 of 500) (Fig. 9). The percentage who had treated patients with FH was higher

in physicians with clinical expertise in cardiology, in diabetes, metabolism, and endocrinology (61.0% in both groups, 305 of 500) than other groups. The percentage who had not examined any patients with suspected FH tended to be higher among physicians with expertise in neurology/neurosurgery/stroke medicine. Among the 29 participants with no academic society affiliation and no specialist accreditation who worked at clinics with no beds, 13 selected “Familiar with the concept of FH, but have no patients in whom that condition is suspected” and 1 selected “I do not know about FH.” The mean number of patients with dyslipidemia for this group was about 100 (mean $102.1 \pm$ SD 47.1) per participant.

Question 11: When you diagnose FH in adult patients (15 years of age or older), do you perform the following? (multiple answers)

Out of 211 participants who responded “had treated patients with FH” in Question 10, 91.9% (194 of 211) asked patients about a family history of FH, 89.1% (188 of 211) asked about a family history of hyper-LDL cholesterol, and 81.5% (172 of 211) asked about a family history of premature CAD. Only 45.0% (95 of 211) examined X-ray photographs of the Achilles tendon (Fig. 10). The same tendency was observed in analysis subdivided by area of clinical

Q8. How do you use “non-HDL cholesterol” levels?

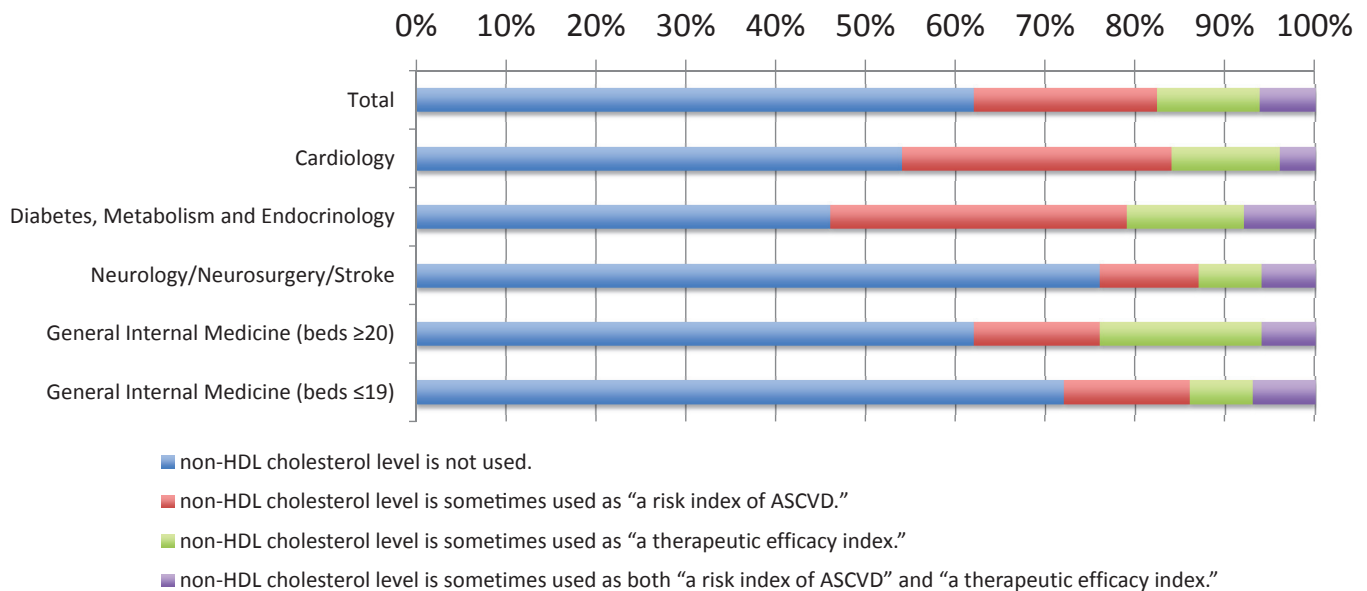


Fig. 7. Use of non-HDL-C levels by survey participants for estimating risk of ASCVD

Participants reported how they use non-HDL-C levels to assess the risk of ASCVD.

non-HDL-C, non high density lipoprotein cholesterol; ASCVD, atherosclerotic cardiovascular disease

expertise. About half of all physicians examined the X-ray photographs of the Achilles tendon, but the percentage who performed palpation of the Achilles tendon was notably higher among physicians with expertise in cardiology (77.0%, 35 of 61), diabetes, metabolism and endocrinology (77.0%, 35 of 61), and neurology/neurosurgery/stroke (38.0%, 8 of 21) than among physicians with other areas of medical expertise (25%, 17 of 68).

Question 12: Please compare your impressions of patient profiles and treatment for dyslipidemia and atherosclerotic cardiovascular diseases inside and outside Japan (multiple answers)

About half of participants (51.8%, 259 of 500) agreed with the statement “Compared with Westerners, stroke is a common atherosclerotic cardiovascular disease among Japanese” (Fig. 11). The next most common answer was “Compared with Westerners, Japanese are less likely to develop atherosclerotic cardiovascular diseases” (38.2%, 191 of 500). Stratified by area of clinical expertise, physicians with expertise in cardiology were most likely to agree with the statement “Compared with Westerners, Japanese are less likely to develop atherosclerotic cardiovascular diseases” (51.0%, 51 of 100). Physicians with expertise in neurology/neurosurgery/stroke were about twice as

likely as other participants to agree with the statement “Japanese with low LDL-C are more likely to develop cerebral hemorrhage” (24%, 24 of 100). Physicians with expertise in diabetes, metabolism, and endocrinology and general internal medicine (self-employed practitioners at clinics or small hospitals with ≤19 beds) were about twice as likely as other participants to agree with the statement “Japanese are more likely to be affected by lifestyle habits” (28% and 25%, 28 of 100 and 25 of 100, respectively).

Discussion

We found no extreme differences among specialists in the different fields, although there were some variations in responses to this questionnaire survey. In general, target LDL-C values tended to be lowest among physicians with expertise in cardiology and diabetes, metabolism and endocrinology. For secondary prevention in patients with CAD, the physicians who specialized in cardiology or in diabetes, metabolism, and endocrinology considered LDL-C levels 100 mg/dL or less to be the upper cutoff line, while specialists in neurology/neurosurgery/stroke and physicians in general internal medicine tended to aim for LDL-C values above 100 mg/dL (Fig. 4). For primary prevention in high-risk patients, specialists in all fields aimed for the

Q9. Are you aware of the Risk Management Chart, and do you use it in your practice?

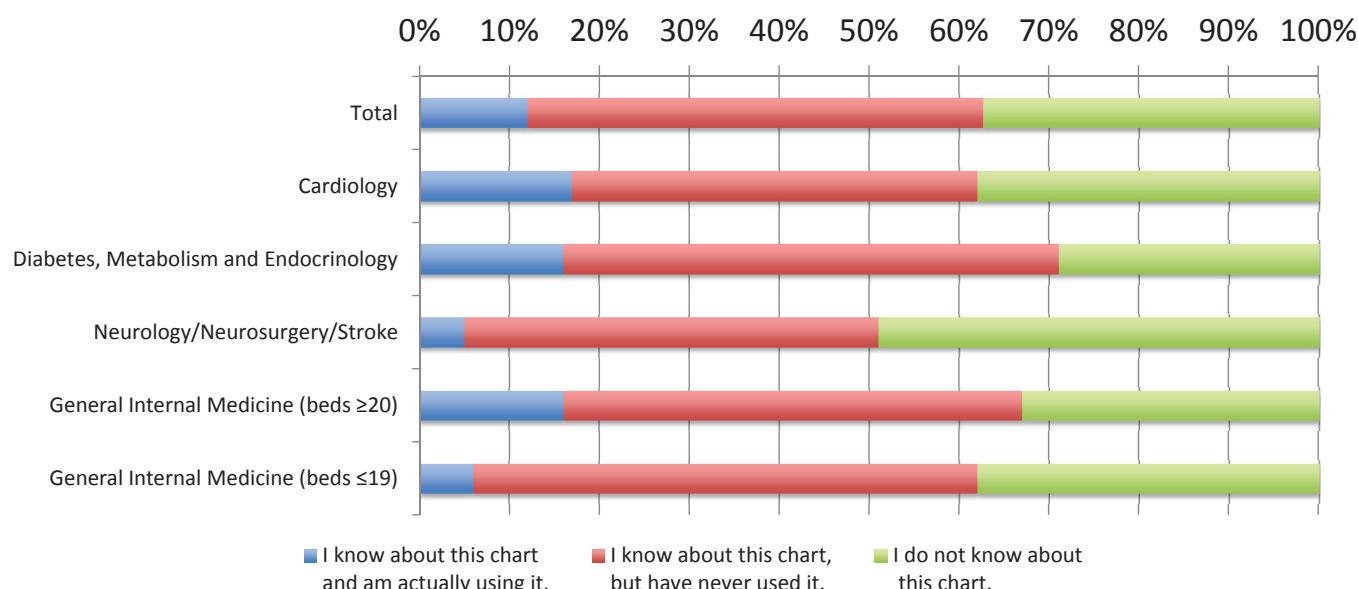


Fig. 8. Use of the Risk Management Chart by survey participants

The chart is a decision-making tool to help manage the risk of atherosclerotic cardiovascular disease.

target level listed in the official JAS guidelines (<120 mg/dL), but there was a tendency toward lower values among cardiologists. For primary prevention in patients without comorbidities, all practitioners tended to aim for LDL-C of approximately 130 mg/dL, which was higher than the target level in patients with moderate CV risk¹⁰. Even though the incidence rate of CAD is steadily increasing in Japan in recent years, it is still much lower than in the US and Europe. The idea that aggressive lipid-lowering therapy should be applied for patients who already have CAD is closer to “medical treatment” rather than “preventive medicine”. In Japan, physicians other than specialists in cardiology tend to consider the main purpose of lipid-lowering therapy to be the primary prevention of ASCVD. This survey suggested that specialists in cardiology tend to practice lipid lowering treatment more aggressively than those with other areas of medical expertise, which may be because they generally treat secondary prevention patients. The increasing number of patients who are candidates for secondary prevention of ASCVD could predispose these specialists to develop a mindset toward ASCVD therapy similar to that seen in the US and Europe. In addition, there may be important differences between Japan and the West with regard to real-world treatment, the attitudes of Japanese physicians about the importance of LDL-C lowering, and the

seriousness of adverse events. These differences may be due at least in part to the fact that similar levels of LDL-C and event reduction are provided by statin therapy with lower doses in Japan than in the West^{12, 13}.

Regarding safety considerations, overall the most common response for the lower limit of LDL-C was 50 mg/dL, with somewhat lower values supported by the cardiologists (Fig. 5). Specialists in neurology/neurosurgery/stroke tended to aim toward higher values, although concern about “increase in the risk of hemorrhagic stroke” (Q3) was no more frequent in these specialists than in others (Fig. 2). Less aggressive LDL-C target setting by this physician population seems to be partially related to their sense that Japanese patients are generally at low risk for CV events even without achieving the currently recommended lipid levels. The most common concern about adverse reactions to statins was in relation to muscular disorders, and was noted by approximately 70% of participants (Fig. 2). There was almost no difference across the various specialties in the percentage of patients who stopped statin therapy because of adverse events (Q4). Less than 5% of physicians accounted for at least 75% of these discontinued cases.

The percentage of patients with dyslipidemia who are treated as having FH is relatively high among physicians with expertise in cardiology and diabetes, metab-

Q10. Please choose the response that most accurately represents your clinical situation regarding FH

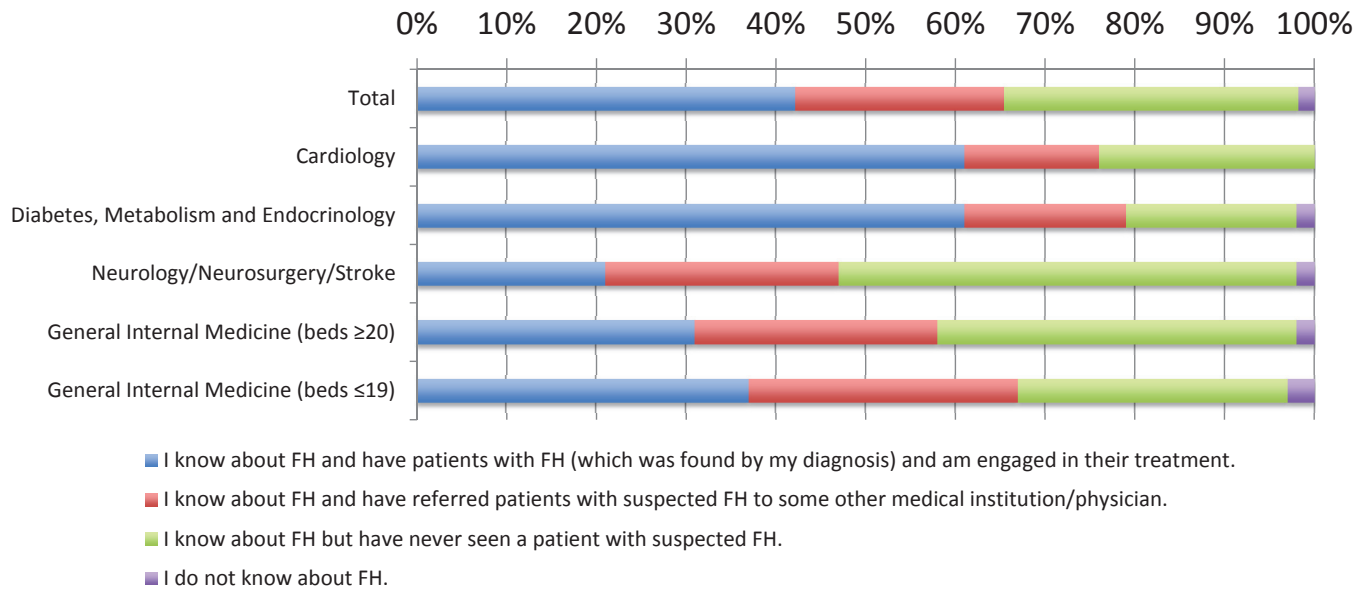


Fig. 9. Experience treating familial hypercholesterolemia among survey participants

Participants were asked about whether they are aware of FH, whether they have referred FH patients to other physicians, and whether they have treated FH patients.

FH, familial hypercholesterolemia

olism and endocrinology. This may be because many patients with FH are diagnosed after cardiovascular events have already developed and the patients are being followed by these two groups of physicians. In addition, the social awareness of FH is low and the rate of FH diagnosis has been reported at less than 1%¹⁴. However, we found that most physicians know about FH and two-third of physicians have patients with FH or have referred patients with suspected FH (Fig. 9). Of the general practitioners in clinics without hospital beds, about half said that they were “Familiar with the concept of FH but have no patients in whom that condition is suspected.” Moreover, the method of diagnosing FH is not sufficiently widespread among physicians (Q11). Within this physician population in our study, the mean number of people under treatment for dyslipidemia was approximately 100 patients/month. This is not a small number. It should be noted that, currently in Japan, researchers estimate there is 1 person heterozygous for FH for every 200 to 500 people in the overall Japanese population¹⁵. Thus, it is likely that general practitioners in Japan may be treating undiagnosed FH patients. In our survey, most responders at clinics without hospital beds seemed to be surgeons and internists in other specialties, such as gastroenter-

ology. Clearly, FH is not yet widely understood in Japan; we strongly recommend that knowledge of FH be extended to these non-specialists.

The Comprehensive Risk Management Chart was originally developed by 13 Japanese academic societies as a tool for risk management for the efficient prevention of ASCVD¹¹. The chart was designed specifically for use by general practitioners. This survey showed that about two-thirds of all participants were aware of this chart, which leaves one-third to be reached by future educational efforts (Fig. 8). Among the specialists, the lowest level of chart awareness was among physicians specializing in neurology/neurosurgery/stroke (51.0%, 51 of 100). The awareness of this chart must be raised among physicians, including those with this area of expertise, in order to properly prevent ASCVD in Japan. Improvements in metabolic syndrome profiles have already been noted under the Nationwide Lifestyle Intervention Program provided through Japanese national health insurance^{16, 17}. We hope that active use of the Comprehensive Risk Management Chart will provide similar improvement in the prevention and management of ASCVD.

Two-thirds of all participants did not use non-HDL cholesterol level, which provides a risk index of

Q11. When you diagnose FH in adult patients (15 years of age or older), do you perform the following? (multiple answers)

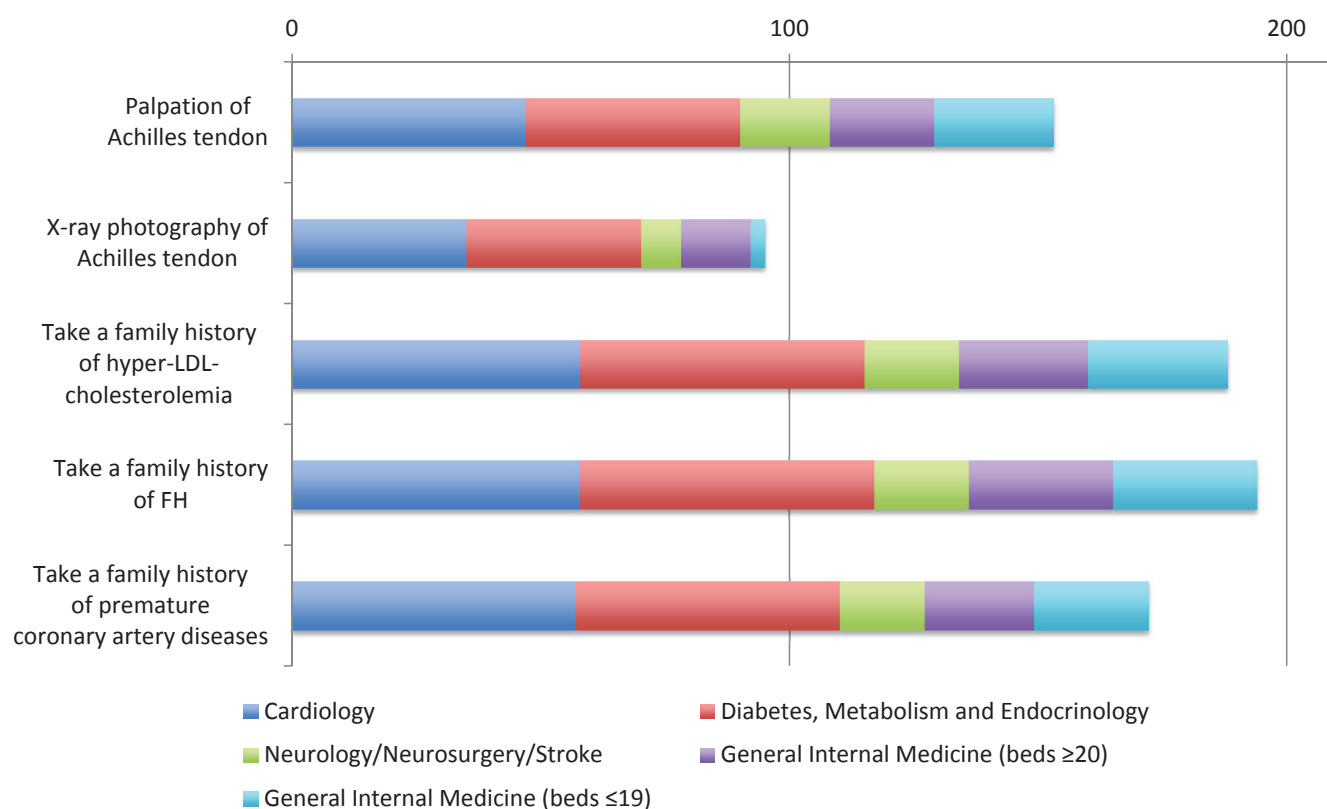


Fig. 10. Examinations performed by participants when diagnosing FH

Participants were asked about whether they investigated family history, and whether they palpated or x-rayed the Achilles tendon, when diagnosing FH. Multiple answers were allowed.

FH, familial hypercholesterolemia

ASCVD independent from LDL-C level (Fig. 7). This level of awareness was higher among physicians with expertise in cardiology and diabetes, metabolism, and endocrinology than among other groups. It is necessary to raise awareness of this index in order to further suppress residual CV risk.

It is crucial to develop interactive programs to educate physicians in best-practice treatment of dyslipidemia for the prevention of ASCVD. The JAS Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases were revised and published in 2017¹⁰⁾, and it is our goal to ensure that they are widely understood and actively implemented by physicians across Japan, including those who do not specialize in cardiovascular medicine. In the survey described here, we looked at the current status of lipid management by physicians for prevention of ASCVD. Next we plan to explore ways to encourage physicians to apply the new

JAS guidelines in their daily practice, especially when assessing CV risk, setting lipid targets, and using current and novel drugs. Case conferences and discussions on how to choose the best lipid-lowering drugs for selected patients may be essential for building our understanding of dyslipidemia and atherosclerosis. In particular, as the PCSK9 inhibitors enter the market, it becomes more feasible to reduce LDL-C below the levels targeted in the current guidelines. It is very possible that these treatments may provide major prevention of ASCVD. It is also essential to educate medical journalists to write accurately and responsibly on the treatment of ASCVD. We thus plan to develop interactive educational programs focusing on the management of dyslipidemia, and to offer these programs as training courses on a regular basis.

Limitation of the current study: This web-based survey was limited to CareNet members. Because par-

Q12. Please compare your impressions of patient profiles and treatment for dyslipidemia and atherosclerotic cardiovascular diseases inside and outside Japan (multiple answers)

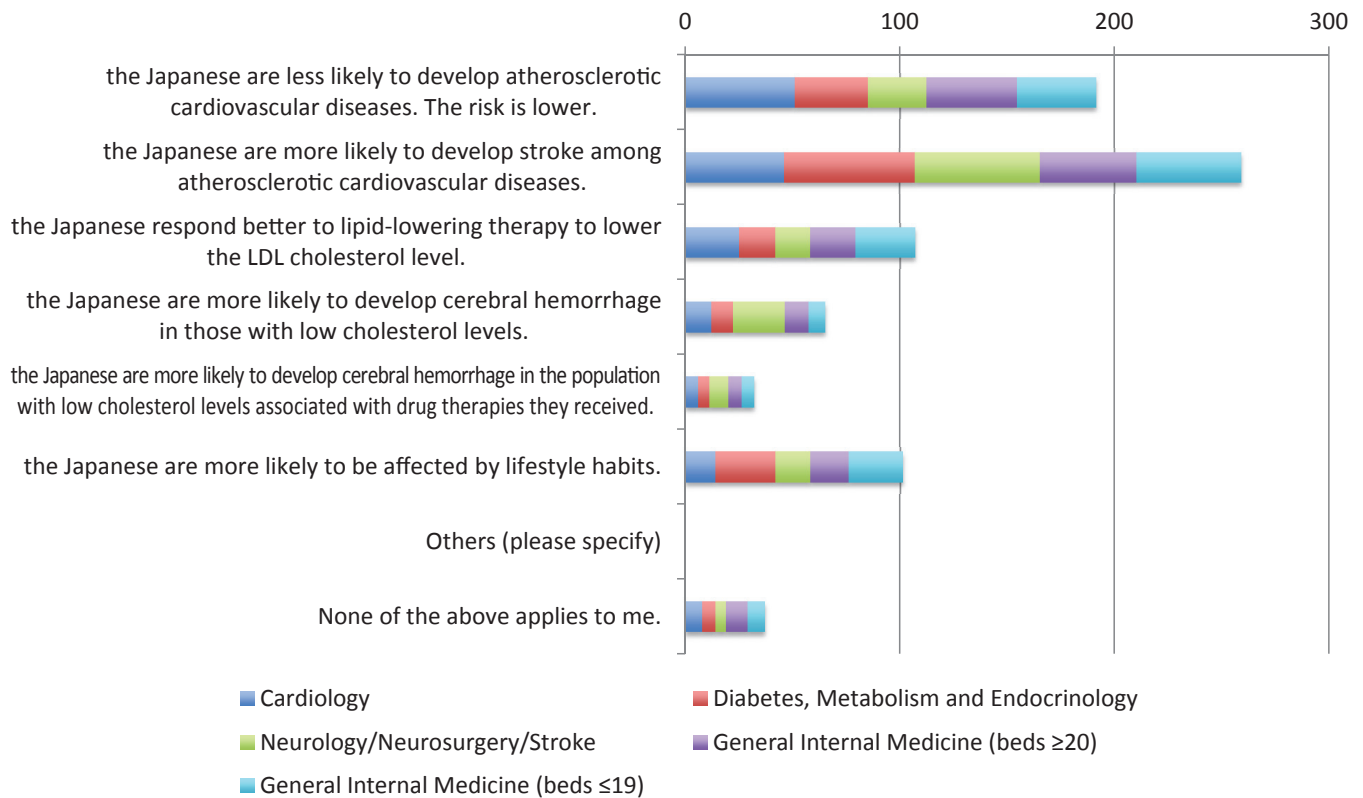


Fig. 11. Opinions on differences in dyslipidemia and cardiovascular disease between Japanese and Western patients
Participants were asked about characteristics of Japanese patients compared with Western patients. Multiple answers were allowed.

ticipants were required to access the Internet, the survey responses may be biased toward physicians who are comfortable with this type of survey. In addition, the sample was only 100 people per specialty, and only 500 people overall; this may be rather small to obtain an accurate overview of the actual situation in Japan.

Conclusion

We surveyed attitudes toward lipid management among selected physicians in Japan. Our findings suggest that awareness of target values for lipid management and of adverse reactions to statin therapy appears to vary somewhat depending on the participant's medical specialty. We also found that FH is probably underdiagnosed in Japan today. Appropriate treatment of ASCVD may require further education on lipid management for physicians who are not specialists in CV health.

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