ステムは、総コレステロールではCDCと同じプログラムが適用されているが、HDLコレステロール、LDLコレステロール、及び、トリグリセライドは、国立循環器病研究センターで独自に開発されたプログラムが運用されており、それらは同センターのweb siteで公表されている。HDLコレステロールでは臨床検査室を対象としたHDLコレステロールの標準化プログラム(2012年06月)として、LDLコレステロールでは臨床検査室を対象としたLDLコレステロールの標準化プログラム(2012年06月)として、トリグリセライドでは臨床検査室を対象としたトリグリセライド(中性脂肪)の標準化プログラム(2012年06月)として公開されている。中でも、トリグリセライドの標準化は、わが国では最初のプログラムであり、その目標値はCDCに標準化されたｶﾞｽｸﾛﾏﾄｸﾞﾗﾌｰｱｲｿﾄｰﾌﾟ希釈・質量分析計で求められている点に特徴がある。

【BQ法に対する最新の評価成績】

BQ法は、バックグラウンド1.006の比重下で超遠心後に上清に浮上するカイロミクロンとVLDLをチューブスライサーで除去し、下層部分をBottom fraction(BF)と称する。BF中のコレステロールをBFC、BF中のHDLをヘパリンマンガン分離法で分離・測定したコレステロールをHDL-Cと見なす。LDL-C値は、LDL-C=BFC-HDL-Cとして求められる。2013年10月の評価成績(表1)によれば、国立循環器病研究センターのBFCの3濃度の検体の精密度(CV)は0.33%、正確度を示す平均値はCDCに対して-0.10mg/dLを示し、同様にしてHDL-Cでは精密度(CV)が0.74%、正確度は0.05mg/dL、LDL-Cでは精密度(CV)が0.27%、正確度は-0.29mg/dlを示した。これらの評価成績は、いずれも基準分析室に課される判定基準(表2)を満たす。以上の成績から、国立循環器病研究センターの脂質基準分析室はBQ法の標準化状態にあると判断され、本研究班における測定準備態勢が完了している。

【BQ法の基本的な測定精度について】

① 国立循環器病研究センター(以下、国循)における過去15年間の測定精度を、表3に示した。CDC(x)と国循(y)の相関関係は、BFCでは y=0.988x+1.794(R2=0.997)、HDL-Cでは y=0.980x+1.118(R2=0.994)、LDL-Cでは y=0.987x+1.200(R2=0.997)を示し、両者間に高い相関性が認められた。

② 国循で得られた3要素(BFC, HDL-C, LDL-C)の測定成績を表2の判定基準に基づいて判定した場合の合格率は、精密度ではBFCで280検体中の267で95.4%、HDL-Cで280検体中の267で同じく95.4%、LDL-Cで280検体中の257で91.8%を示し、一方、正確度では同様にして91.4%、94.6%、89.6%であった。

③ 1997年05月から2012年10月までの15年間に測定された70回のサーベイで用いられた計280検体の分析において、各サーベイ毎に検体の正確性をCDCに対する%バイアスで図2に示した。それによれば、測定開始当初と比較したとき、国循のLDL-C値は次第に低値を示す傾向が認められたが、測定結果に大きな影響を与えるものではなかった。

④ CDCの目標値に対する国循のバイアスの大きさを3要素(BFC, HDL-C, LDL-C)別に図1のA, B, Cに示した。図1Aは、122.3mg/dLから223.7mg/dLの濃度域におけるBFCのバイアスの分布図である。x軸にはCDCの目標値を、y軸にはCDCとの差の大きさを濃度(mg/dL)で示した。その結果、Y=-0.012x+1.759(R2=0.042, p value=0.001)であった。Xの係数のp valueと95%信頼限界はそれぞれ0.001と(-0.019, -0.005)であり、y切片のp valueと95%信頼限界はそれぞれ0.004と(0.551, 2.968)であった。図1Bは、27.0mg/dLから72.4mg/dLの濃度域におけるHDL-Cのバイアスの分布図である。x軸にはCDCの目標値を、y軸にはCDCとの差の大きさを濃度(mg/dL)で示した。その結果、Y=-0.020x+1.112(R2=0.063, p value<0.001)であった。Xの係数のp valueと95%信頼限界はそれぞれ<0.001と(-0.029, -0.011)であり、y切片のp valueと95%信頼限界はそれぞれ<0.001と(0.671, 1.553)であった。図1Cは、71.5mg/dLから173.3mg/dLの濃度域におけるLDL-Cのバイアスの分布図である。x軸にはCDCの目標値を、y軸にはCDCとの差の大きさを濃度(mg/dL)で示した。その結果、Y=-0.013x+1.186(R2=0.059, p value<0.001)であった。Xの係数のp valueと95%信頼限界はそれぞれ<0.001と(-0.020, -0.007)であり、y切片のp valueと95%信頼限界はそれぞれ0.004と(0.376, 1.996)であった。以上の成績から、CDCとのバイアスで見ると標準化は順調に進展した。

⑤ BQ法における3要素(BFC, HDL-C, LDL-C)別に、BFC(x軸)とLDL-C(y軸)の関係を図3のDに、

BFC(x 軸)と HDL-C(y 軸)の関係を図 3 の E に、また、LDL-C(x 軸)と HDL-C(y 軸)の関係を図 3 の F に示した。図 3D は、y=1.088x-0.208(R2=0.652, p value<0.001)であった。X の係数の p value と 95%信頼限界はそれぞれ<0.001 と(0.994, 1.182)であり、y 切片の p value と 95%信頼限界はそれぞれ<0.001 と(-0.289, -0.128)であった。図 3E は、y=0.480x+0.513(R2=0.057, p value<0.001)であった。X の係数の p value と 95%信頼限界はそれぞれ<0.001 と(0.250, 0.711)であり、y 切片の p value と 95%信頼限界はそれぞれ<0.001 と(0.316, 0.710)であった。また、図 3F は、y=-0.441x+0.299(R2=0.087, p value<0.001)であった。X の係数の p value と 95%信頼限界はそれぞれ<0.001 と(-0.609, -0.273)であり、y 切片の p value と 95%信頼限界はそれぞれ 0.004 と(0.098, 0.499)であった。以上の結果から、BQ 法の 3 要素の中では、BF の分離、すなわち超遠心の技術が最も重要であり、LDL-C 値の正確性に与える影響が大きいことが明らかとなった。一方、BFC と HDL-C の関係では相関係数はプラスに、また、LDL-C と HDL-C の関係では相関係数はマイナスの傾向が認められるが、いずれも LDL-C の正確性に与える影響は大きくはなかったことが明らかとなった。

E．結論

CDC における 15 年間の標準化成績を解析することにより、LDL-C の基準分析法である BQ 法(Beta quantification)の測定精度を明らかにした。この研究成果を活用して本研究班における検体の分析を担当する。

F．健康危険情報

なし

G．研究発表

論文発表

(1) Nakamura M, et al. Revised system to evaluate measurement of blood chemistry data from the Japanese National Health and Nutrition Survey and Prefectural Health and Nutrition Surveys. J Epidemiol. 23 ; 28-34, 2013

(2) Nagai Y, et al. Rationale, design, and baseline features of a randomized controlled trial to assess the effects of statin for the secondary prevention of stroke: the Japan Statin Treatment Against Recurrent Stroke (J-STARS). International J of Stroke 9(2) ; 232-239, 2014

(3) Oliveira MJ, et al. Evaluation of four different equations for calculating LDL-C with eight different direct HDL-C assays. Clin Chim Acta 21(2) ; 135-40, 2013

(4) Yokoyama S, et al. High-density lipoprotein levels have markedly increased over the past twenty years in Japan. J Atheroscler Thromb21(2) ; 151-60, 2013

(5) Miida T, et al. Validation of homogeneous assays for HDL-cholesterol using fresh samples from healthy and diseased subjects. Atherosclerosis 233(1) ; 235-9, 2014

(6) Nakamura M, Kayamori Y, Iso H, et al. LDL cholesterol performance of beta quantification reference measurement procedure. Clinica Chimica Acta 2014, available online.

＊下線論文は主要論文なので、「研究成果の刊行に関する一覧表」に掲載する。

H．知的所有権の出願・登録

なし

表 1　BQ 法に対する最新の評価成績

Osaka 1013 (October 2013) LDL cholesterol survey

Bottom Fraction

Sample ID	BF CDC RV	BF S.D.	BF Osaka mean	S.D.	%CV	% Bias vs CDC	Absolute % Bias	Bias vs CDC	Bias Limit Range	
BQ47	163.18	2.07	163.51	0.52	0.32	0.20	0.20	0.33	-2.12	1.85
BQ55	184.38	2.25	184.39	0.56	0.31	0.00	0.00	0.00	-2.40	2.74
BQ57	209.33	1.79	208.69	0.75	0.36	-0.31	0.31	-0.64	-3.03	3.28
		Mean =		**0.61**	**0.33**	**-0.03**	**0.17**	**-0.10**		

HDL Cholesterol

Sample ID	HDLC CDC RV	HDLC S.D.	HDLC Osaka mean	S.D.	%CV	% Bias vs CDC	Absolute % Bias	Bias vs CDC	Bias Limit Range*		Bias (4% RV) Limit Range*	
BQ47	64.51	1.05	64.38	0.52	0.80	-0.21	0.21	-0.14	-2.00	2.00	-2.58	2.58
BQ55	55.84	1.07	56.01	0.62	1.10	0.31	0.31	0.17	-2.00	2.00	-2.23	2.23
BQ57	51.60	1.83	51.73	0.16	0.31	0.24	0.24	0.13	-2.00	2.00	-2.06	2.06
		Mean =		**0.43**	**0.74**	**0.11**	**0.25**	**0.05**				

LDL Cholesterol

Sample ID	LDLC CDC RV	LDLC S.D.	LDLC Osaka mean	S.D.	%CV	% Bias vs CDC	Absolute % Bias	Bias vs CDC	Bias Limit Range	
BQ47	99.06	2.16	99.14	0.20	0.20	0.08	0.08	0.08	-1.98	1.98
BQ55	128.55	2.20	128.38	0.19	0.15	-0.14	0.14	-0.18	-2.57	2.57
BQ57	157.73	1.73	156.96	0.72	0.46	-0.49	0.49	-0.77	-3.15	3.15
		Mean =		**0.37**	**0.27**	**-0.18**	**0.23**	**-0.29**		

Shaded rows indicate cases where results exceed Proposal A criteria
Bold numbers indicate cases where results exceed Proposal B criteria
HDLC Bias Limit Range* - Use the HDLC limit range that is smaller

表 2 CRMLN 脂質基準分析室に要求される判定基準

Lipid	Precision	Accuracy
BFC	CV ≤ 1.5 %	± (CDC LDL-C reference value x 0.02 + HDL-C bias vs. CDC) [max = ±2 mg/dL or 0.04 (HDL-C reference value) if smaller]
HDL-C	SD ≤ 1 mg/dL	± CDC HDL-C reference value x 0.04
LDL-C	CV ≤ 1.5 %	± CDC LDL-C reference value x 0.02

CRMLN: Cholesterol Reference Method Laboratory Network. BQ RMP: Beta quantification reference measurement procedure.

CDC: US Centers for Disease Control and Prevention. SD: Standard deviation. CV: Coefficient of variation.

BFC: Bottom fraction cholesterol. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol.

表 3 国立循環器病研究センターの測定精度

Statistical item	BFC	HDL-C	LDL-C
Mean precision as %CV (SD)	0.60 (0.342)	1.01 (0.605)	0.85 (0.461)
Mean bias as % (SD)	-0.12 (0.853)	0.45 (1.708)	-0.34 (1.148)
Pass rate for imprecision (N)	95.4% (267)	95.4% (267)	91.8% (257)
Pass rate for bias (N)	91.4% (256)	94.6% (256)	89.6% (251)
Absolute bias (%)	0.63 ± 0.589	1.23 ± 1.270	0.86 ± 0.830
Bias in mg/dL (95%CI)	0.34 (0.14, 0.53)	-0.16 (-0.26, -0.07)	0.49 (0.32, 0.66)
Limits of agreement in mg/dL	-2.87 - 3.54	-1.76 - 1.43	0.31 - 0.66
Slope (95%CI)	0.988 (0.981, 0.995)	0.980 (0.971, 0.989)	0.987 (0.980, 0.993)
Intercept (95%CI)	1.794 (0.581, 3.006)	1.118 (0.676, 1.560)	1.200 (0.388, 2.011)
Correlation coefficient as R^2	0.997	0.994	0.997

CRMLN: Cholesterol Reference Method Laboratory Network.

SD: Standard deviation. CI: Confidense interval. N: Number.

BFC: Bottom fraction cholesterol. HDL-C: High-density lipoprotein cholesterol. LDL-C: Low-density lipoprotein cholesterol.

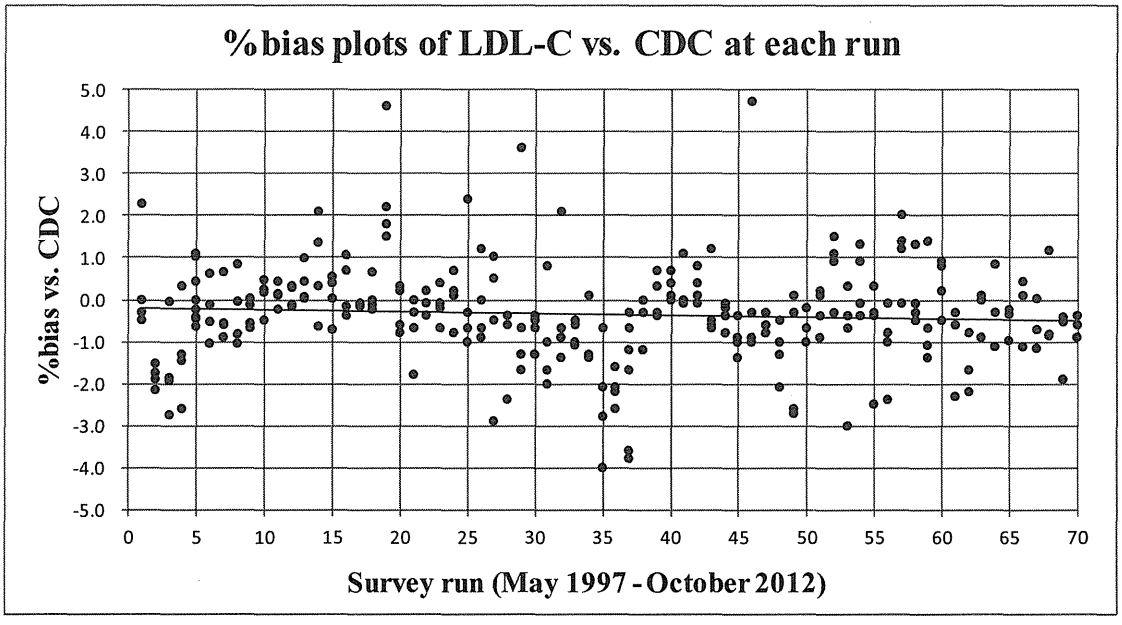
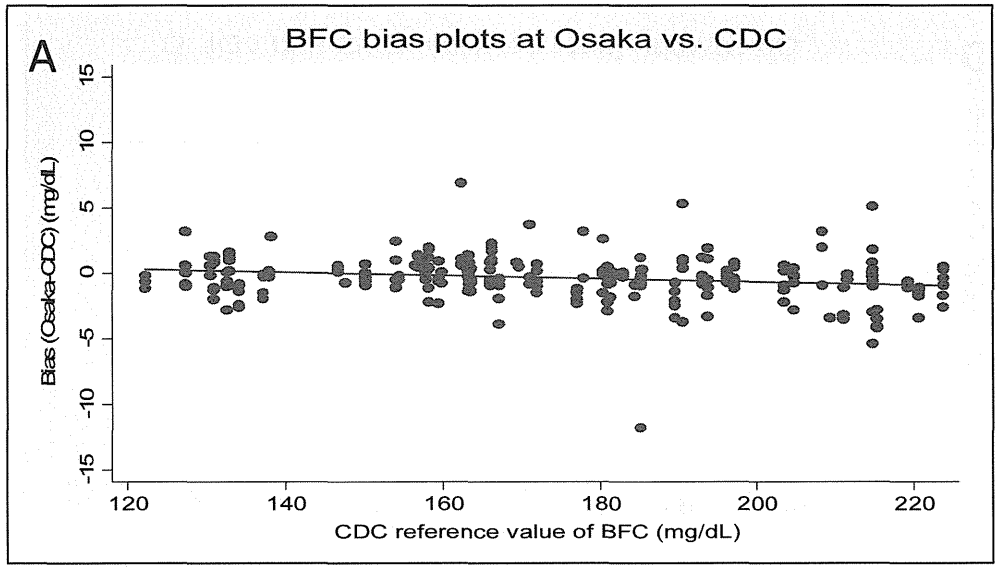
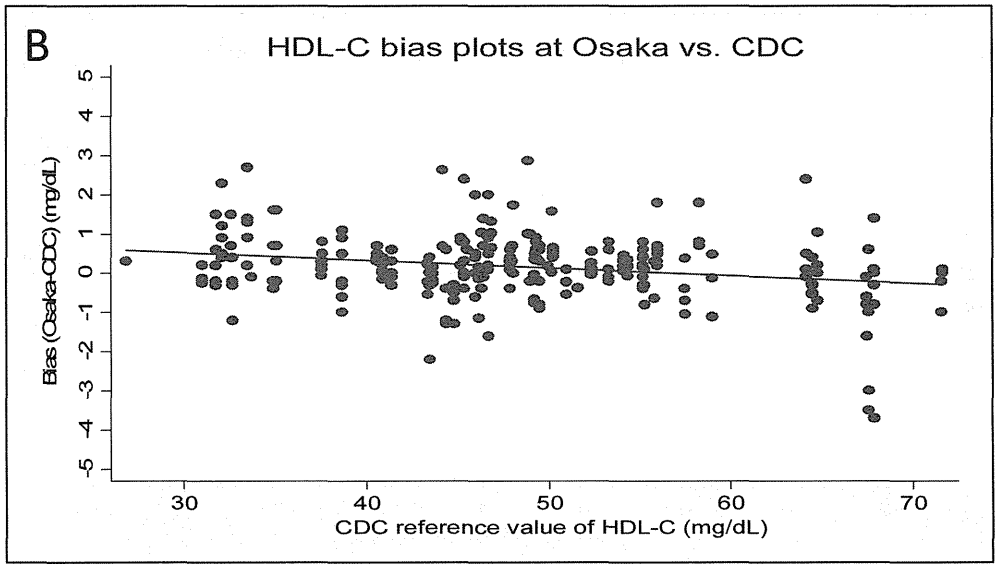


図. 2. 1997年5月から2012年12月の期間におけるバイアスの変動





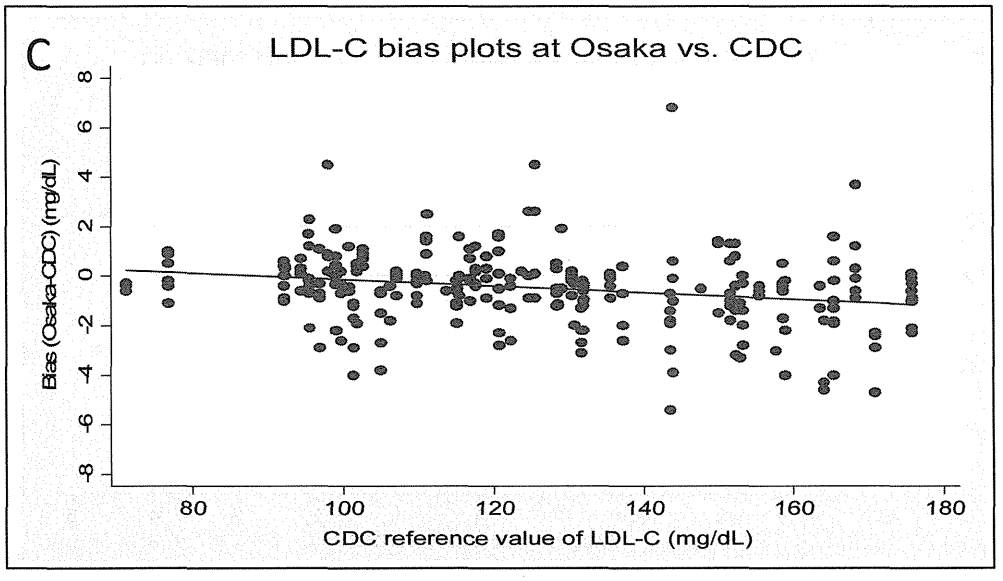
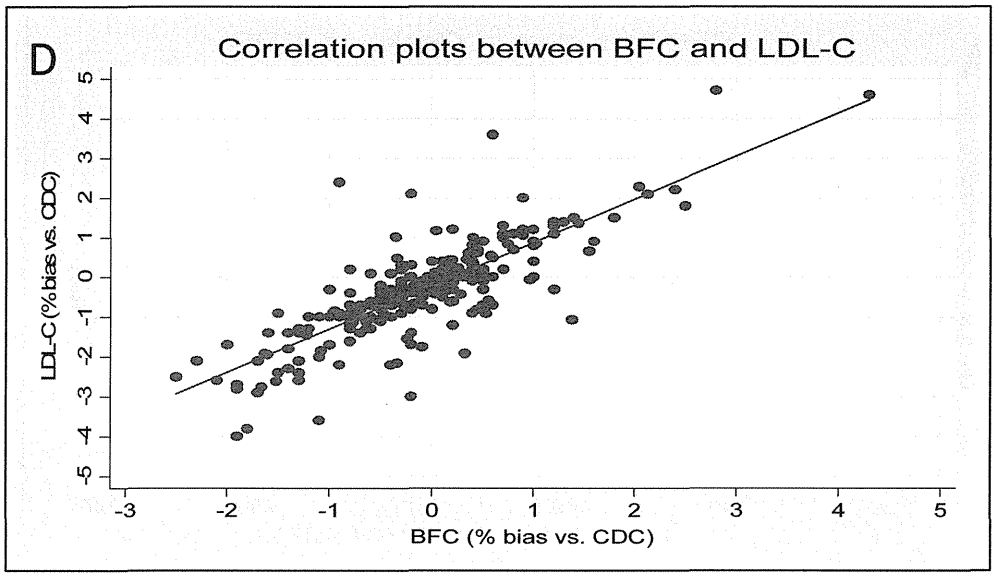
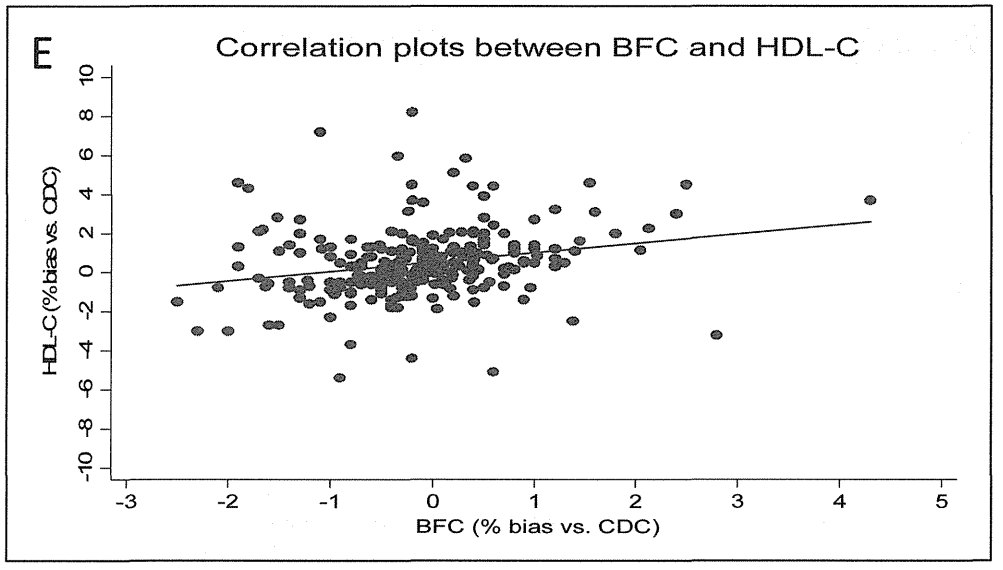


図 1　BFC, HDL-C, LDL-Cのバイアスの分布状況





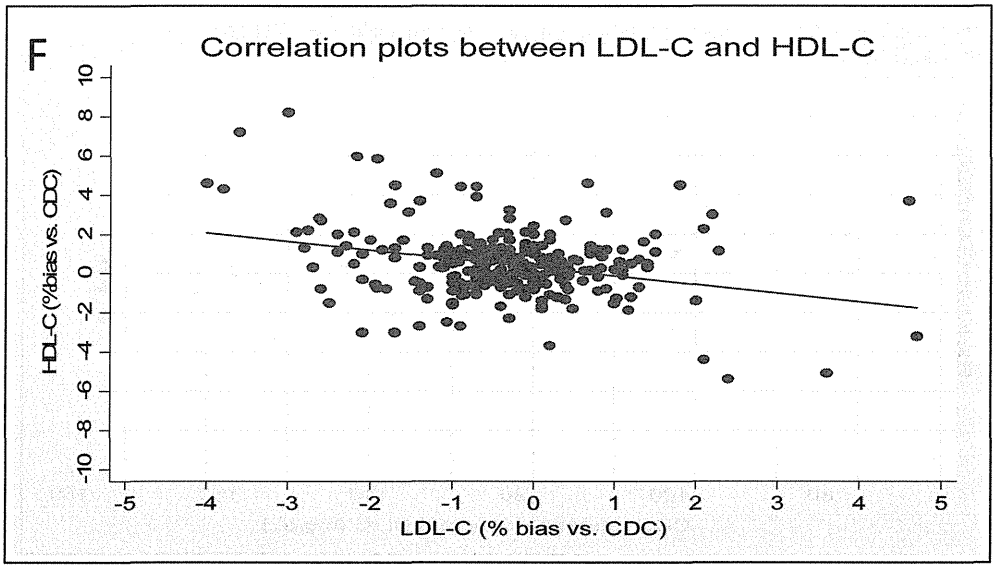


図. 3. BFCとLDL-C、BFCとHDL-C、及び、LDL-CとHDL-Cの関係を示す相関図

Ⅳ．研究成果の刊行に関する一覧表

研究成果の刊行に関する一覧表

【寺本　民生】

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Teramoto T, et al.	Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version.	J Atheroscler Thromb	20(6)	517-523	2013
Teramoto T, et al.	Diagnostic criteria for dyslipidemia.	J Atheroscler Thromb	20(8)	655-660	2013
Daida H, et al.	The relationship between low-density lipoprotein cholesterol levels and the incidence of cardiovascular disease in high-risk patients treated with pravastatin.	Int Heart J	55(1)	39-47	2014

【岡村　智教】

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
岡村智教 杉山大典	動脈硬化性疾患の絶対リスクの評価と脂質管理目標	日本臨床	71 (増刊号3)	29-35	2013
杉山大典、 岡村智教	わが国の虚血性心疾患の疫学	医学のあゆみ	245(13)	1115-1121	2013

【宮本　恵宏】

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ohara T, Kokubo Y, Toyoda K, Watanabe M, Koga M, Nakamura S, Nagatsuka K, Minematsu K, Nakagawa M, Miyamoto Y.	Impact of Chronic Kidney Disease on Carotid Atherosclerosis According to Blood Pressure Category: The Suita Study.	Stroke.	44	3537-9	2013

【北村　明彦】

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Chei CL, Yamagishi K, Kitamura A, Kiyama M, Imano H, Ohira T, Cui R, Tanigawa T, Sankai T, Ishikawa Y, Sato S, Hitsumoto S, Iso H; CIRCS Investigators.	High-density lipoprotein subclasses and risk of stroke and its subtypes in Japanese population: the Circulatory Risk in Communities Study.	Stroke	44(2)	327-33	2013

【三井田　孝】

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
三井田孝、西村邦宏	LDLコレステロール直接法の現在の課題	日本臨床社	脂質異常症-基礎・臨床研究の最新知見-（日本臨床臨時増刊）	日本臨床社	東京	2013	439-443
三井田孝、平山　哲	LDL-C直接法とβ-quantification法.	医歯薬出版	動脈硬化のすべて（医学のあゆみ臨時増刊）	医歯薬出版	東京	2013	1146-1147

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Miida T, et al.	Validation of homogeneous assays for HDL-cholesterol using fresh samples from healthy and diseased subjects.	Atherosclerosis	233(1)	253-259	2014

【西村　邦宏】

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nishimura K, et al.	Predicting Coronary Heart Disease by Using Risk Factor Categories for a Japanese Urban Population and Comparison with the Framingham Risk Score: Suita Study	J Atherosclerosis Thrombosis	in press		

【山下　静也】

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ
山下静也	原発性高カイロミクロン血症	平野勉	日本臨床	日本臨床社	東京	2013	71(9)1578-1583

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Masuda D, Yamashita S, et a.	Reference Interval for the Apolipoprotein B-48 Concentration in Healthy Japanese Individuals.	J Atheroscler Thromb.	14 Feb 26.	[Epub ahead of print]	2014

【中村　雅一】

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Nakamura M, et al.	Revised system to evaluate measurement of blood chemistry data from the Japanese National Health and Nutrition Survey and Prefectural Health and Nutrition Surveys.	J Epidemiol.	23	28-34	2013
Oliveira MJ, et al.	Evaluation of four different equations for calculating LDL-C with eight different direct HDL-C assays.	Clin Chim Acta	423	135-40	2013
Nakamura M, et al.	LDL cholesterol performance of beta quantification reference measurement procedure.	Clinica Chimica Acta			Available online 28 February 2014

Ⅴ．研究成果の刊行物・別刷

Committee Report 1

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan — 2012 Version

Tamio Teramoto, Jun Sasaki, Shun Ishibashi, Sadatoshi Birou, Hiroyuki Daida, Seitaro Dohi, Genshi Egusa, Takafumi Hiro, Kazuhiko Hirobe, Mami Iida, Shinji Kihara, Makoto Kinoshita, Chizuko Maruyama, Takao Ohta, Tomonori Okamura, Shizuya Yamashita, Masayuki Yokode and Koutaro Yokote

Committee for Epidemiology and Clinical Management of Atherosclerosis

Among the various atherosclerotic cardiovascular diseases (CVDs), these guidelines primarily deal with cerebrovascular disease, peripheral arterial disease (PAD) and coronary artery disease (CAD), which occur in association with atherosclerosis and is closely related to dyslipidemia.

1. Comprehensive Risk Management for the Prevention of Atherosclerotic CVD

To prevent CVD, it is important to manage dyslipidemia in addition to other risk factors. For this purpose, we propose comprehensive risk management for the prevention of CVD. Risk factors that should be considered include dyslipidemia, hypertension, diabetes mellitus, smoking, chronic kidney disease (CKD), a family history of premature CAD, a history of CAD, noncardiogenic cerebral infarction, PAD, age and sex. In this article, we describe the comprehensive management of CVD.

2. Diagnostic Criteria for Dyslipidemia

It has been shown in epidemiological studies conducted in Japan, as well as in Western countries, that the incidence of CAD increases in association with increases in the levels of LDL-cholesterol (LDL-C)[1] and triglycerides (TGs)[2, 3] and decreases in the level of HDL cholesterol (HDL-C)[4-7]. Currently in Japan, the incidence of CAD is much lower than that observed in Western countries[2, 3, 8, 9]; however, this incidence is anticipated to increase in the near future due to the recent Westernization of the Japanese lifestyle. Therefore, the current guidelines provide screening criteria for dyslipidemia to prevent CVD with a specific emphasis on the prevention of CAD, as shown in **Table 1**.

Received: November 2, 2012
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Regarding the diagnosis of dyslipidemia, the total cholesterol (TC), TG and HDL-C levels should be measured after an overnight fast. The LDL-C level is then calculated using the Friedewald formula (LDL-C=TC−HDL-C−TG/5).

This formula cannot be used if blood is collected without fasting or if the TG is ≥400 mg/dL. In such cases, using the non HDL-C level is recommended, which is calculated by subtracting the HDL-C level from the TC level. Data obtained in Japan indicate that the non HDL-C level is approximately 30 mg/dL higher than the LDL-C level. This view is shared by the National Cholesterol Education Program (NCEP). When lipids are evaluated based on the non HDL-C level, the target value of non HDL-C is determined by adding 30 mg/dL to the value of LDL-C (**Table 2**).

The incidence and mortality of CAD increase continuously in association with increases in the LDL-C level. At present, the incidence of CAD is lower in Japanese individuals than in Westerners. To maintain this low rate, efforts directed toward early prevention are required. Therefore, from the perspective of the prevention and treatment of CAD, the current guidelines propose an LDL-C level of 140 mg/dL as the reference value when screening Japanese individuals for hyper-LDL cholesterolemia. This value was selected because it corresponds to a TC level of 220 mg/dL, at which point the relative risk is approximately 1.5-fold higher than that observed at a TC level of <180 mg/dL, according to the NIPPON DATA80[10]. Since the LDL-C goal may vary depending on concomitant risk factors, an LDL-C level between 120 and 139 mg/dL is defined as indicating borderline hyper-LDL cholesterolemia.

Hypo-HDL cholesterolemia has also been established to be a risk factor for CVD. The current guidelines define an HDL-C level of <40 mg/dL as indicating hypo-HDL cholesterolemia, as determined in

Table 1. Dyslipidemia: Diagnostic Criteria for Screening (Fasting*)

Low-density lipoprotein cholesterol (LDL-C)	≥140 mg/dL	Hyper-LDL cholesterolemia
	120-139 mg/dL	Borderline hyper-LDL cholesterolemia**
High-density lipoprotein cholesterol (HDL-C)	<40 mg/dL	Hypo-HDL cholesterolemia
Triglycerides (TG)	≥150 mg/dL	Hypertriglyceridemia

• The LDL-C level is calculated using the Friedewald formula (TC − HDL-C − TG/5) (for TG <400 mg/dL).
• If the TG level is ≥400 mg/dL or non-fasting blood is used, the non HDL-C (TC − HDL-C) level should be used with a cutoff value of LDL-C + 30 mg/dL.
*Fasting is defined as deprivation of food for at least 10 to 12 hours; however, the ingestion of noncaloric beverages, such as water and tea, is allowed.
**If a patient is found to have borderline hyper-LDL cholesterolemia during screening, he/she should be examined for any high-risk conditions and the need for treatment should be considered.

Table 2. Lipid Management Targets for Patients with Different Risk Levels

Therapeutic principle	Management category	Lipid management target (mg/dL)			
		LDL-C	HDL-C	TG	Non HDL-C
Primary prevention Drug therapy should be considered after lifestyle modification	Category I	<160	≥40	<150	<190
	Category II	<140			<170
	Category III	<120			<150
Secondary prevention Drug therapy should be considered, together with lifestyle modification	History of CAD	<100			<130

• For patients at low absolute risk, such as the young, the relative risk chart (Supplementary Table) should be used and changes in the absolute risk should be monitored carefully while encouraging the patient to modify their lifestyle.
• These values should be considered general, not mandatory, goals.
• A 20%-30% reduction in the level of LDL-C is considered to be a prime target for pharmacological intervention.
• The management target for the non HDL-C level is the secondary target to be used after a patient with hypertriglyceridemia has achieved the management target for the LDL-C level. The non HDL-C level should be used if blood is collected after meals or if the TG level is ≥400 mg/dL.
• For patients in any category, the management goals should generally be achieved via lifestyle modification.
• For patients in category I, drug therapy should be considered if the LDL-C level is ≥180 mg/dL.

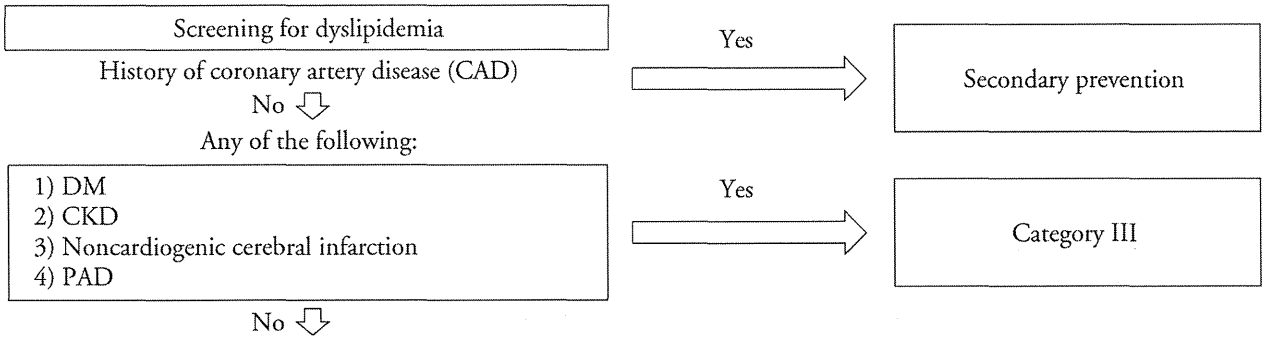
our previous guidelines. A number of studies have demonstrated sex differences in the HDL-C levels; however, it remains unclear whether these sex differences are reflected in the diagnosis of hypo-HDL cholesterolemia.

Hypertriglyceridemia has been found to occur in association with various conditions. Although some researchers insist that more intensive management is required in patients with certain diseases, such as diabetes mellitus, the current guidelines define a TG level of ≥150mg/dL as indicating hypertriglyceridemia, based on epidemiological data obtained during screenings of the general population.

3. Risk Stratification Based on Absolute Risk

The current guidelines stratify the risk of CVD for primary prevention according to the absolute risk calculated based on the results of the NIPPON DATA80[11]. This study identified age, sex, diabetes mellitus, current smoking, systolic blood pressure and the TC level as risk factors and determined the absolute risk of death from CAD depending on the degree or existence of these factors.

How absolute risk categories should be determined is based on clinical consensus and/or conventional wisdom. The U.S. NCEP Adult Treatment Panel III classifies a 10-year risk of death from CAD or the development of nonfatal myocardial infarction of ≥20% (based on the Framingham score) as high risk[12], whereas European guidelines classify a 10-year risk of death from CVD (including strokes and CAD) of ≥5% as high risk[13]. The current guidelines classify



Management categories based on absolute risk for the primary prevention of CAD

10-year probability (absolute risk) of CAD death derived from NIPPON DATA80	Additional risk factors	
	No additional risk factors	One or more of the following: (1) Hypo-HDL cholesterolemia (HDL-C < 40 mg/dL) (2) Family history of premature CAD in first-degree relatives (a man aged < 55 years or a women aged < 65 years) (3) Impaired glucose tolerance
< 0.5%	Category I	Category II
≥ 0.5%–< 2.0%	Category II	Category III
≥ 2.0%	Category III	Category III

This flow chart is not applicable to patients with FH.

Fig. 1. Flow chart for setting management targets for LDL cholesterol

patients with a 10-year risk of death from CAD of ≥ 2% as belonging to the high-risk group (category Ⅲ), those with a risk of ≥ 0.5% to < 2% as belonging to the intermediate-risk group (category Ⅱ) and those with a risk of < 0.5% as belonging to the low-risk group (category Ⅰ), considering that there is little evidence of an association between hypercholesterolemia and cerebrovascular diseases in Japanese individuals. Since diabetes mellitus, CKD and a history of noncardiogenic cerebral infarction or PAD are considered to be important risk factors, patients with any of these conditions are classified as belonging to the high-risk group (**Fig. 1**).

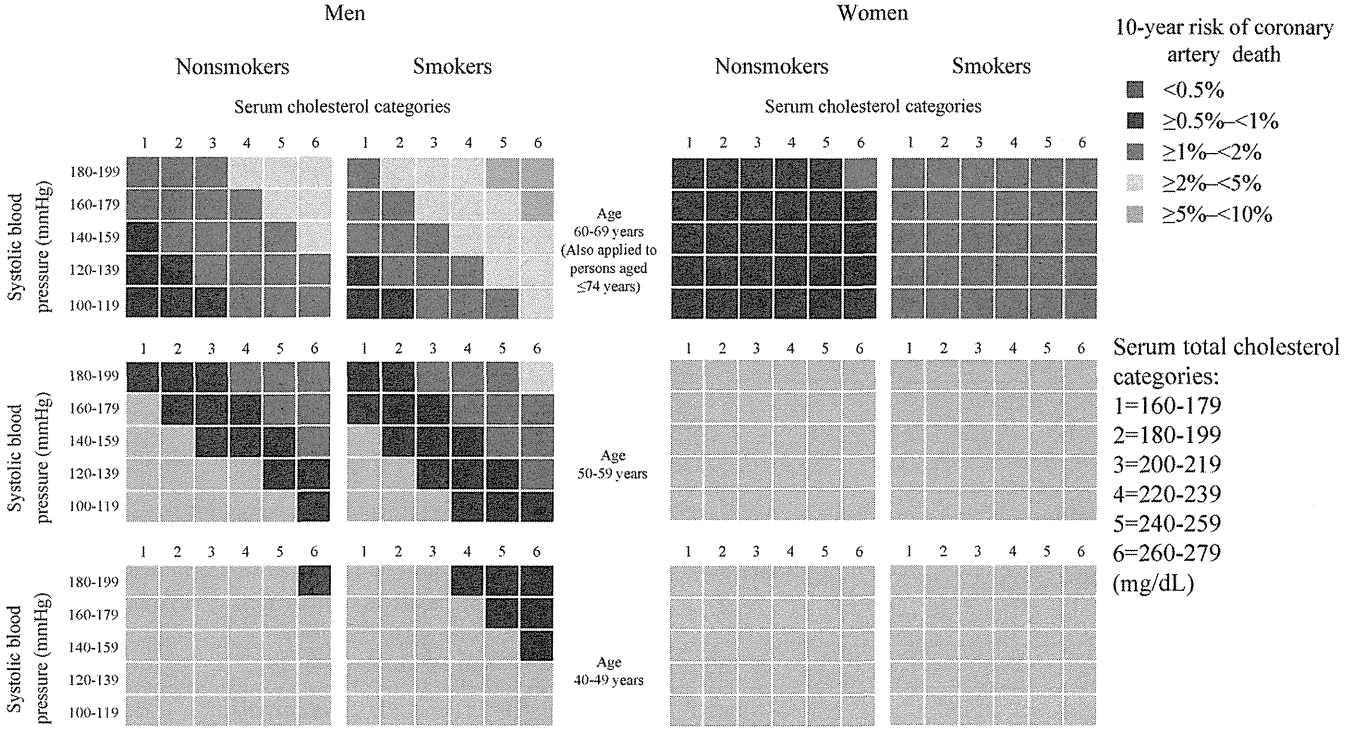
The 10-year absolute risk of CAD-related death should be determined based on the risk assessment chart provided in the NIPPON DATA80[11]. However, since this chart does not include hypo-HDL cholesterolemia, a family history of premature CAD or impaired glucose tolerance, the category should be raised if the patient meets one or more of these criteria (**Fig. 2**).

The chart obtained from the NIPPON DATA80 addresses the risk of CAD-related death in individuals between 40 and 79 years of age. While the current guidelines are intended for adults younger than 65 years of age, they can also be applied to persons between 65 and 74 years of age. To calculate the absolute risk for individuals ≥ 70 and < 75 years of age, the table for individuals between 60 and 69 years of age should be used. For adults < 40 years of age, the table for individuals between 40 and 49 years of age should be used.

When assessing the absolute risk, it should be noted that the absolute risk greatly depends on age. If a low absolute risk is obtained for a young individual with a risk factor, such as hypertension or smoking, the risk factors should be managed appropriately. When secondary prevention is required, each risk factor should be dealt with separately, as outlined in the previous guidelines.

4. Management Targets for Dyslipidemic Patients

The management targets for dyslipidemic patients are presented by category in **Table 2**. For primary prevention, drug therapy should be considered after lifestyle factors have been improved for a certain



The section of hyperglycemia from the NIPPON DATA80 risk assessment chart is omitted here. These charts cannot be applied to high-risk patients, such as those with DM or CKD.

Fig. 2. Absolute risk assessment charts for death from coronary artery disease (primary prevention).

Absolute risk should be reassessed at least once a year since it may be affected by either risk factors or aging.

Step 1: The applicable portion of the above figures should be assessed based on gender, age, the present smoking status, systolic blood pressure (mmHg) and the TC level (mg/dL).
Absolute risk ≥ 2% → Category III
Absolute risk < 2% → To Step 2
Step 2: Any of the following conditions: hypo-HDL-cholesterolemia (< 40 mg/dL), a family history of CAD and/or impaired glucose tolerance
Absolute risk ≥ 0.5% < 2% + Yes → Category III
Absolute risk ≥ 0.5% < 2% + No → Category II
Absolute risk < 0.5% + Yes → Category II
Absolute risk < 0.5% + No → Category I
Supplementary notes
(1) The TC category 160-179 mg/dL should be used in patients with a TC level of < 160.
(2) The TC category 260-279 mg/dL should be used in patients with a TC level of ≥ 280 mg/dL.
(3) The systolic blood pressure category of 100-119 mmHg should be used in patients with a systolic blood pressure of < 100 mmHg, while the systolic blood pressure category of 180-199 mmHg should be used in patients with a systolic blood pressure of ≥ 200 mmHg.
(4) The guidelines cannot be applied to persons 75 years of age or older. "The Elderly." For patients < 40 years of age, the relative risk chart (Supplementary Table) should be used.
(5) Blood pressure should be managed according to the guidelines established by the Japanese Society of Hypertension, while diabetes mellitus should be managed according to the guidelines established by the Japan Diabetes Society.
(6) It is desirable to encourage smokers to stop smoking irrespective of the level of absolute risk.

period and the response has been evaluated. For individuals in category I low absolute risk group), the management target for the LDL-C level is set at < 160 mg/dL. The target for individuals in category II is set at < 140 mg/dL, while that for individuals in category III (high absolute risk group) is set at < 120 mg/dL. It should be noted that achieving these targets is recommended but not obligatory. A meta-analysis of preventive clinical trials demonstrated that a 20%-30% reduction in the LDL-C level results in a decrease in the incidence of CAD of approximately 30%. Based on this finding, a 20%-30% decrease in

the LDL-C level can be considered a target. For secondary prevention, since the patient has already been diagnosed with CAD, the administration of drug therapy targeting an LDL-C level of <100 mg/dL is recommended in addition to lifestyle modification.

For the management of hypertriglyceridemia and hypo-HDL cholesterolemia, targeting a TG level of < 150 mg/dL and an HDL-C level of ≥40 mg/dL is recommended, as in the previous guidelines.

Some researchers have the opinion that stricter targets should be established for high-risk patients (such as those with diabetes mellitus or CKD) or those who require secondary prevention, depending on the patient's condition and severity of disease; however, there is insufficient evidence to support setting such goals. Nevertheless, the current guidelines also suggest that high-risk patients be stratified according to risk factors and that lower targets be established for such patients.

5. Treatment

Dyslipidemia should be treated with lifestyle modification, including smoking cessation and the administration of diet and/or exercise therapy. In primary prevention patients, drug therapy should only be considered when the lipid management targets are not achieved after sufficient effort has been made to improve lifestyle factors. In patients with a history of CAD, the use of drug therapy should be considered simultaneously with lifestyle modification.

When drug therapy is provided for patients with hyper-LDL cholesterolemia, statins are the first drug of choice. Resin, probucol and/or ezetimibe are used in combination with statins or selected when statins cannot be administered. The combination of statins and EPA is useful for treating high-risk patients with hyper-LDL cholesterolemia. For treating hypertriglyceridemia accompanied by hypo-HDL cholesterolemia, drugs such as fibrates and nicotinic acid derivatives should be considered.

6. High-Risk Conditions for CVD

The current guidelines include CKD in addition to a history of CAD (secondary prevention), diabetes mellitus, noncardiogenic cerebral infarction and PAD as high-risk conditions based on the findings of epidemiological studies, including evidence showing that the presence of CKD increases the incidence of CAD by at least two-fold. The previous guidelines classified a history of cerebral infarction as a high-risk condition, while the current guidelines classify a history of noncardiogenic cerebral infarction as a high-risk condition because cardiogenic cerebral infarctions are not caused by atherosclerotic disease.

7. Familial Hypercholesterolemia

Familial hypercholesterolemia occurs in approximately one in 500 individuals and is associated with a high risk of CAD. The current guidelines reference the diagnostic criteria for FH reported by the 2011 Primary Hyperlipidemia Research Group and set a target of an LDL-C level of <100 mg/dL or a decrease in the LDL-C level of at least 50%.

8. Evaluation of CVD

To prevent CVD, the presence or absence and severity of atherosclerosis must be evaluated before symptoms occur and risk factors must be managed or treated with the objective of preventing progression or possibly achieving regression. For this purpose, correctly staging CVD is important. At present, the degree of atherosclerosis is primarily evaluated using imaging techniques. Invasive techniques include angiography (to assess the severity of stenosis) as well as angioscopy and intravascular ultrasonography (to qualitatively assess the vessel walls). Noninvasive techniques include transcutaneous ultrasonography of the arteries, such as the carotid artery, to qualitatively and quantitatively evaluate the degree of atherosclerosis. Carotid artery ultrasonography is often used in general practice because the extent of carotid sclerosis has been shown to be correlated with the risk of cerebrovascular disease and/or CAD. The development of multidetector CT (MDCT) has allowed for easier detection of coronary artery lesions. At present, carotid artery ultrasonography and MDCT are less invasive and easier to perform than other imaging modalities. In the near future, developing guidelines for the assessment of atherosclerosis that can be employed before the onset of symptoms is necessary. At present, however, assessing the degree of atherosclerotic lesions using the above-mentioned imaging techniques is associated with some limitations. CVD should be diagnosed based on a clear understanding of these limitations.

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 1) published in Japanese in June 2012.

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References

1) Imano H, Noda H, Kitamura A, Sato S, Kiyama M, Sankai T, Ohira T, Nakamura M, Yamagishi K, Ikeda A, Shimamoto T, Iso H: Low-density lipoprotein cholesterol and risk of coronary heart disease among Japanese men and women: the Circulatory Risk in Communities Study (CIRCS). Prev Med, 2011; 52: 381-386
2) Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T: Comparison of fatal coronary heart disese occurrence based on population surveys in Japan and the USA. Int J Epidemiol, 2000; 29: 837-844
3) Menotti A, Blackburn H, Kromhout D, Nissinen A, Fidanza F, Giampaoli S, Buzina R, Mohacek I, Nedeljkovic S, Aravanis C, Toshima H: Changes in population cholesterol levels and coronary heart disease deaths in seven countries, Eur Heart J, 1997; 18: 566-571
4) Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB: Prediction of coronary heart disease using riskfactor categories. Circulation, 97: 1837-1847, 1998
5) Kitamura A, Iso H, Naito Y, Iida M, Konishi M, Folsom AR, Sato S, Kiyama M, Nakamura M, Sankai T: High-density lipoprotein cholesterol and premature coronary heart disease in urban Japanese men, Circulation, 1994; 89: 2533-2539
6) Matsuzaki M, Kita T, Mabuchi H, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H; J-LIT Study Group: Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia: primary prevention cohort study of the Japan Lipid Intervention Trial (J-LIT). Circ J, 2002; 66: 1087-1095
7) Mabuchi H, Kita T, Matsuzaki M, Matsuzawa Y, Nakaya N, Oikawa S, Saito Y, Sasaki J, Shimamoto K, Itakura H; J-LIT Study Group. Japan Lipid Intevention Trial: Large scale cohort study of the relationship between serum cholesterol concentration and coronary events with low-dose simvastatin therapy in Japanese patients with hypercholesterolemia and coronary heart disease: secondary prevention cohort study of the Japan Lipid Intervention Tr(la J-LIT). Circ J, 2002; 66: 1096-1100
8) Verschuren WM, Jacobs DR, Bloemberg BP, Bloemberg BPM, Kromhout D, Menotti A, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Karvonen MJ, Nedelijković S, Nissinen A, Toshima H: Serum total cholesterol and long-term coronary heart disease mortality in different cultures: twenty five-year follow-up of the seven countries study. JAMA, 1995; 274: 131-136
9) Hirobe K, Terai T, Fujioka S, Goto K, Dohi S; 3M-Study Project Committee of the Japan Association of Occupational Physicians "San-yu-kai": Morbidity of Myocardial Infarction Multicenter Study in Japan (3M Study): study design and event rates for myocardial infarction and coronary death by age category in Japanese workers. Circ J, 2005; 69: 767-773
10) Okamura T, Tanaka H, Miyamatsu N, Hayakawa T, Kadowaki T, Kita Y, Nakamura Y, Okayama A, Ueshima H; NIPPON DATA80 Research Group. The relationship

between serum total cholesterol and all-cause or cause-specific mortality in a 17.3-year study of a Japanese cohort. Atherosclerosis, 2007; 190: 216-223
11) NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J, 2006; 70: 1249-1255
12) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA, 2001; 285: 2486-2497
13) Catapano AL,Reiner Z, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Perrone Filardi P, Riccardi G, Storey RF, Wood D; ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Atherosclerosis, 2011; 217 Suppl 1: S1-44

Supplementary Table. Relative Risk Charts for the Young, etc. with a Low Absolute Risk (based on the risk charts of the NIPPON DATA80)

			Nonsmokers			
Systolic blood pressure						
Second-degree or higher hypertension (≥160 mmHg)	2.2	2.8	3.6	4.6	5.8	7.4
First-degree hypertension (140-159 mmHg)	1.7	2.2	2.8	3.5	4.5	5.7
Normal (≤140)	1.0*	1.3	1.6	2.1	2.6	3.4
TC category (mg/dL)	160-179	180-199	200-219	220-239	240-259	260+
			Smokers			
Systolic blood pressure						
Second-degree or higher hypertension (≥160 mmHg)	3.2	4.1	5.2	6.6	8.4	10.7
First-degree hypertension (140-159 mmHg)	2.5	3.1	4.0	5.1	6.5	8.2
Normal (≤140 mmHg)	1.4	1.8	2.3	3.0	3.8	4.8
TC category (mg/dL)	160-179	180-199	200-219	220-239	240-259	260+

Committee Report 3

Diagnostic Criteria for Dyslipidemia

Executive Summary of the Japan Atherosclerosis Society (JAS) Guidelines for the Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases in Japan — 2012 Version

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Committee for Epidemiology and Clinical Management of Atherosclerosis

Epidemiological studies conducted in Japan as well as Western countries have shown that higher levels of LDL-cholesterol (LDL-C)[1], total cholesterol (TC)[2-7], non HDL-cholesterol (non HDL-C)[8], and triglyceride (TG)[9, 10] and lower levels of HDL-C[5, 11-13] are associated with a higher risk of coronary artery disease (CAD) (**Fig. 1**). At present, the absolute risk (incidence and mortality) of CAD in Japan is much lower than that observed in Western countries[14-17]; however, due to recent increases in the LDL-C and TC levels in Japanese individuals as a result of Westernization of the Japanese lifestyle[18, 19], and the findings of a report showing that the incidence of CAD is increasing in some regions of Japan[19, 20], there is concern that the incidence of CAD will rise throughout Japan. Therefore, these guidelines define diagnostic criteria for assessing dyslipidemia during screening to prevent the development of arteriosclerosis from the perspective of preventing CAD, as shown in **Table 1**.

According to the diagnostic procedures, first, the TC, TG and HDL-C levels are measured in the morning after overnight fasting to calculate the LDL-C level using the Friedewald formula (LDL-C = TC − HDL-C − TG/5). This formula cannot be used in a non-fasting state or when the TG level is ≥ 400 mg/dL because large errors in the LDL-C level may occur. Although direct measurement methods for determining the LDL-C level have been applied clinically, significant problems have been found concerning variations in accuracy and the results obtained between kits, especially in cases of high TG levels[21]. Therefore, using the non HDL-C level is recommended when the TG level is ≥ 400 mg/dL. The non HDL-C level is calculated by subtracting the HDL-C level from the TC level.

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Lipid standardization in clinical laboratories in Japan has been judged internationally to be very accurate for the TC levels and fairly accurate for the HDL-C levels[22]. Nevertheless, the accuracy of TG and LDL-C measurements remains inadequate[22, 23]; thus, further standardization is warranted.

1. Hyper-LDL Cholesterolemia

The Framingham study and many other epidemiological studies conducted in Western countries have shown that the incidence and mortality of CAD increase in association with increases in the levels of TC and LDL-C. In addition, in Japan, epidemiological studies, such as the NIPPON DATA80[2], Suita[24], JALS[25], CIRCS[1], Hiroshima/Nagasaki[7], MHW Primary Hyperlipidemia[26], Okinawa cohort[27] and Ehime epidemiological[10] studies and epidemiological studies conducted in 76 workplaces in Japan (the 3M Study)[4], have confirmed that the relative risk of CAD increases continuously in association with increases in the levels of LDL-C and TC.

The NIPPON DATA80, a prospective epidemiological study conducted in Japan, demonstrated that the relative risk of CAD-related death in individuals with a TC level of 200-219 mg/dL, 220-239 mg/dL, 240-259 mg/dL and ≥ 260 mg/dL is 1.4-, 1.6-, 1.8- and 3.8-fold higher, respectively, than that observed in individuals with a TC level of 160-179 mg/dL (**Fig. 1a**)[2]. In men, in particular, mortality from CAD increases continuously in association with increases in the TC (LDL-C) levels, with no distinct threshold.

Meanwhile, studies conducted in Western countries regarding interventions for hypercholesterolemia, including lifestyle modification, have revealed that