A. 研究目的

HDL コレステロール(HDL-C)の基準分析法は、超遠心法(Ultracentrifugation 法、UC 法と略)とされる。国立循環器病研究センターの脂質基準分析室は、米国の Centers for Disease Control and Prevention (CDC) が主催する Cholesterol Reference Method Laboratory Network (CRMLN) に参加している正式のメンバーである。このネットワークを通じて、1997 年 5 月から 2014 年 1 月までの17年間にわたり、継続してUC法の標準化を行ってきた。UC 法は、これまでに大規模疫学共同研究や臨床試験等の場で HDL-C の目標値を提供する役割を果たしてきた。UC 法は、本研究においても適用される。しかしながら、本法の測定精度の実態についての論文や学会報告は極めて少ない。そこで、われわれは、UC 法の測定精度を明らかにすることを目的として、これまでの標準化成績を集計し、論文化した。分担研究報告書では、HDL-C の基準分析法である UC 法の測定精度を中心に述べる。

B. 研究方法

本研究班の 2 年目に当たる平成 26 年度内に行った研究課題とその主な内容は以下の通りである。

【脂質標準化システムの構築】

脂質標準化システムは、CDC が実施しているシステムとネットワークを構成する脂質基準分析室(例:国立循環器病研究センター)が実施しているシステムに大別することができ、いずれも試薬メーカーと臨床検査室を対象に標準化が行われる。

【UC 法の操作方法】

UC 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超遠心法による HDL-C と見なす。本研究班では、この測定法により HDL-C の目標値を確定した。

C. 研究結果、及び、D. 考察

【脂質標準化システムの構築と内容】

CDC が実施しているシステム: 試薬メーカーを対象とする脂質標準化システムは、CDC の web site(http://www.cdc.gov/labstandards/crmln.html)に掲載されている。その内容は、総コレステロールでは Total cholesterol certification protocol for manufacturers-revised-(October 2004)、HDL コレステロールでは HDL cholesterol certification protocol for manufacturers (November 2002)、LDL コレステロールでは LDL cholesterol certification protocol for manufacturers (June 2006)として世界中に公開されている。国立循環器病研究センターを通じて、試薬メーカーを対象とする標準化プログラムにより標準化を実施し、判定基準を満たした試薬メーカーの名称等は、CDC の web site において総コレステロールでは Analytical systems certified for total cholesterol、HDL コレステロールでは Analytical systems certified for HDL cholesterol、LDL コレステロールでは Analytical systems certified for LDL cholesterol として公示されている。次に、臨床検査室を対象とする脂質標準化システムは、総コレステロールのみが対象であり、その内容は Certification protocol for clinical laboratories (May 2004)で公開されている(4)。国立循環器病研究センターを通じて、臨床検査室を対象とする標準化プログラムにより標準化を実施し、判定基準を満たしたわが国の臨床検査室の名称等は、List of international clinical laboratories certified for total cholesterol として CDC で公示されている。

国立循環器病研究センターが実施しているシス

テム: 試薬メーカーを対象とする脂質の標準化は、CDC のプログラムと同じ内容が適用されている。次に、臨床検査室を対象とする脂質標準化システムは、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・ｱｲｿﾄｰﾌﾟ希釈・質量分析計で確定されている点に特徴がある。

【UC 法の 17 年間の測定精度のまとめ】
UC 法に対する最新の評価成績: 本研究班では約 200 人を対象に採血を実施して、HDL-C の正確な測定値を UC 法で求める。この測定に備えて、国立循環器病研究センターの脂質基準分析室では UC 法の測定体制が常時整っている。2014 年 7 月に実施された CDC による UC 法に対する最新の評価成績を、表 1 に示した。

CDC のネットワーク(CRMLN)を構成する脂質基準分析室に適用される判定基準を、表 2 に示した。

1997 年 5 月から 2014 年 1 月までの 17 年間における UC 法の測定精度を正確度(Accuracy)と精密度(Precision)に 2 分して、表 3 に示した。それによれば、対象例数が 626 例の正確度の回帰式(y=Osaka, x=CDC)で見ると、Slope=−0.008(95%CI: −0.013, −0.003; p=0.001)、Intercept=0.540(95%CI: 0.296, 0.784; p<0.001)で、r−square=0.017 であった。正確度の分布図を図 1 に示した。一方、精密度の回帰式(y=Osaka, x=CDC)で見ると、Slope=0.002(95%CI: −0.00005, 0.0036; p=0.056)、Intercept=0.270(95%CI: 0.179, 0.360; p<0.001)で、r−square=0.006 であった。精密度の分布図を図 2 に示した。

臨床検査室と試薬メーカーに適用される HDL-C の判定基準を、表 4 に示した。この判定基準が、認証試験に適用される。

1997 年 5 月から 2014 年 1 月までの 17 年間における UC 法の分析経過を、図 3 に示した。

E. 結論
CDC における 17 年間の標準化成績を解析することにより、HDL-C の基準分析法である超遠心法(Ultracentrifugation 法)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 HDL-C の目標値を確定した。

F. 健康危険情報
なし

G. 研究発表
1. 論文発表
(1)Miller WG, Myers GL, Sakurabayashi I, et al. Seven direct methods for measuring HDL and LDL cholesterol compared with ultracentrifugation reference measurement procedures. Clin Chem 2010;56:977−986.

(2) Miida T, Nishimura K, Okamura T, et al. Validation of homogeneous assays for

HDL-cholesterol using fresh samples from healthy and diseased subjects. Atherosclerosis 2014;233:253-259.

(3) Nakamura M, Yokoyama S, Kayamori Y, et al. HDL cholesterol performance using an ultracentrifugation reference measurement procedure and the designated comparison method. Clin Chim Acta 2015;439:185-190.

(4) Nakamura M, Iso H, Kitamura A, et al. Total cholesterol performance of Abell-Levy-Brodie-Kendall reference measurement procedure: Certification of Japanese in-vitro diagnostic assay manufacturers through CDC's Cholesterol Reference Method Laboratory Network. Clin Chim Actaに投稿中

2. 学会発表

なし

H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

表1 Network survey PS0714 - HDL-C

Pool ID	CDC目標値	大阪測定値	S.D.	Bias (mg/dL)
172	50.6	50.8	0.3	0.2
152	32.6	33.0	0.9	0.4
371	50.9	50.6	0.1	-0.3

単位: mg/dL

表 2 Performance criteria applied to CRMLN lipid reference laboratory using ultracentrifugation method

Lipid	Imprecision criterion	Accuracy criterion
HDL-C	Standard deviation ≤ 1 mg/dL	bias ≤ 1 mg/dL

CRMLN: Cholesterol Reference Method Laboratory Network.
HDL-C: High-density lipoprotein cholesterol.

表 3 Regression analysis of the bias between Osaka (y) and CDC (x) and imprecision for HDL-C over time (unit: mg/dL)

Parameter	HDL-C Method	Number of samples	Slope (95%CI)	Intercept (95%CI)	R^2	Time period
Accuracy	UC	626	-0.008	0.540	0.017	May 1997 to January 2014
			(-0.013, -0.003)	(0.296, 0.784)		(17 years)
			p=0.001	p<0.001		
Precision	UC	626	0.002	0.270	0.006	May 1997 to January 2014
			(-0.00005, 0.0036)	(0.179, 0.360)		(17 years)
			p=0.056	p<0.001		

UC: Ultracentrifugation.
HDL-C: High-density lipoprotein cholesterol.
CV: Coefficient of variation. CI: Confidence interval.

表 4 Performance criteria applied to clinical laboratory and manufacturer for HDL-C

Parameter	Criterion
R^2	> 0.975
Bias at 40 mg/dL	≤ 5 %
Bias at 60 mg/dL	≤ 5 %
Average % Bias	≤ 5 %
Average absolute % Bias	≤ 5 %
Among-run CV	≤ 4 %
t-test of bias	Not significant at α=5%
Within-method outliers	1 allowed
Between-method outliers	None allowed, but may eliminate one sample

HDL-C: High-density lipoprotein cholesterol. CV: Coefficient of variation.
CV: Coefficient of variation.

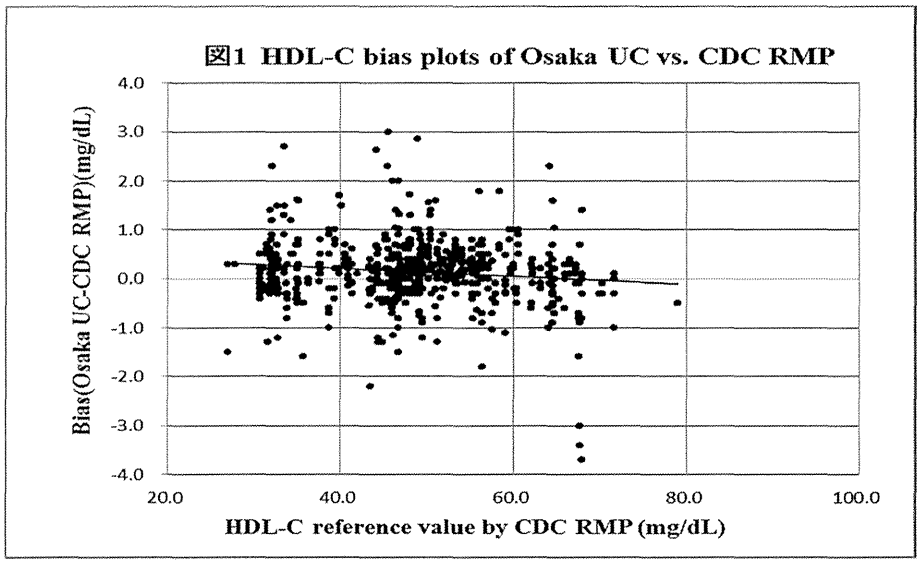
図1 HDL-C bias plots of Osaka UC vs. CDC RMP
Bias(Osaka UC-CDC RMP)(mg/dL)
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
20.0
40.0
60.0
80.0
100.0
HDL-C reference value by CDC RMP (mg/dL)

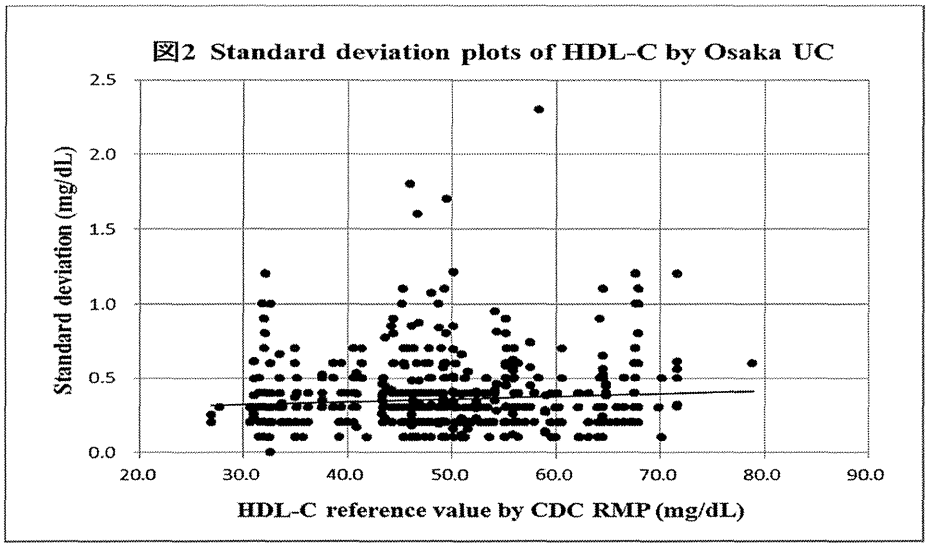
図2 Standard deviation plots of HDL-C by Osaka UC
Standard deviation (mg/dL)
2.5
2.0
1.5
1.0
0.5
0.0
20.0
30.0
40.0
50.0
60.0
70.0
80.0
90.0
HDL-C reference value by CDC RMP (mg/dL)

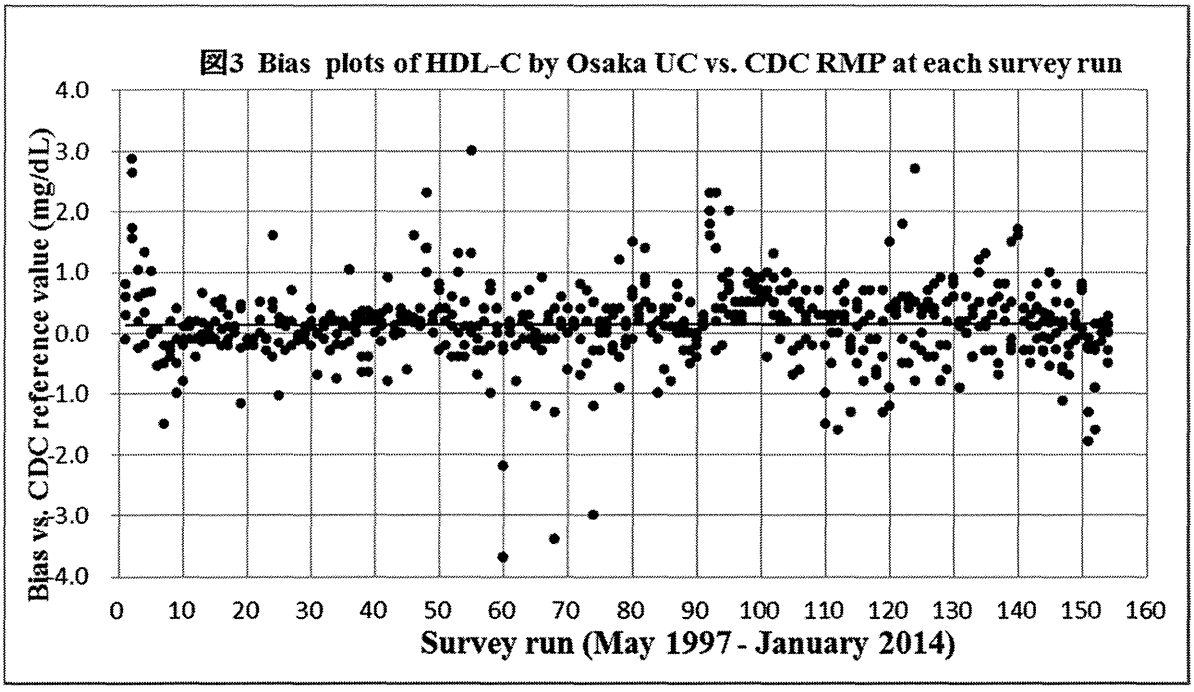
図3 Bias plots of HDL-C by Osaka UC vs. CDC RMP at each survey run
Bias vs. CDC reference value (mg/dL)
4.0
3.0
2.0
1.0
0.0
-1.0
-2.0
-3.0
-4.0
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
Survey run (May 1997 - January 2014)

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
Hirayama A, et al.	Effects of Evolocumab (AMG145), a Monoclonal Antibody to PCSK9, in Hypercholesterolemic, Statin-Treated Japanese Patients at High Cardiovascular Risk - Primary Results From the Phase 2 YUKAWA Study-	Circ J	78(5)	1073-1082	2014
The STABILITY Investigators,	Darapladib for Preventing Ischemic Events in Stable Coronary Heart Disease.	NEJM	370(18)	1702-1711	2014
Teramoto T, et al.	Efficacy, safety, tolerability, and pharmacokinetic profile of evacetrapib administered as monotherapy or in combination with atorvastatin in Japanese patients with dyslipidemia.	Am J Cardiol.	113(12)	2021-2029	2014
Teramoto T, et al.	Lipid and Blood Pressure Control for the Prevention of Cardiovascular Disease in Hypertensive Patients:A Subanalysis of the OMEGA Study.	J Atheroscler Thromb.	21		2014
Ikeda Y, et al.	Low-Dose Aspirin for Primary Prevention of Cardiovascular Events in Japanese Patients 60 Years or Older With Atherosclerotic Risk Factors. A Randomized Clinical Trial.	JAMA	312(23)	2510-2520	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	動脈硬化性疾患のための脂質異常症の管理：最新の疫学知見と日米のガイドラインから	東京都医師会雑誌	67（10）	1283-1290	201

【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
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Sugiyama D, et al.	The Relationship between Lectin-Like Oxidized Low-Density Lipoprotein Receptor-1 Ligands Containing Apolipoprotein B and the Cardio-Ankle Vascular Index in Healthy Community Inhabitants: The KOBE Study.	J Atheroscler Thromb. 2014.			Epub 2014/11/07.

【藤吉　朗】

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Hisamatsu T, et al.	Lipoprotein particle profiles compared with standard lipids in association with coronary artery calcification in the general Japanese population	Atherosclerosis	236	237-243	2014
Maryam Zaid, et al.	High-density lipoprotein particle concentration and subclinical atherosclerosis of the carotid arteries in Japanese men	Atherosclerosis	239	444-450	2014

【三井田　孝】

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
Yamaguchi S, et al.	Selective evaluation of high density lipoprotein from mouse small intestines by an in situ perfusion technique.	J Lipid Res	55(5)	905-918	2014
Idei M, et al.	The mean postprandial triglyceride concent- ration is an independent risk factor of carotid atherosclerosis in patients with type 2 diabetes.	Clin Chim Acta	430	134-139	2014
Shoji H, et al.	Lipid profile and atherogenic indices soon after birth in Japanese preterm infants.	Acta Paediatr	103(1)	22-26	2014
Nagasaka H, et al.	Changes of lipoproteins in phenylalanine hydroxylase-deficient children for the first early of life.	Clin Chim Acta	433	1-4	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
Haraguchi Y, et al.	Serum myeloperoxidase/paraoxonase 1 ratio as potential indicator of dysfunctional high-density lipoprotein and risk stratification in coronary artery disease.	Atherosclerosis.	234(2)	288-94.	2014

Nishimura K, et al.	Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the framingham risk score: the suita study.	J Atheroscler Thromb.	21(8)	784-98	2014
Tsukinoki R, et al.	Blood pressure, low-density lipoprotein cholesterol, and incidences of coronary artery disease and ischemic stroke in Japanese: the Suita study.	American journal of hypertension.	27(11)	1362-9.	2014

【山下　静也】

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
Okubo M, et al.	Serum apolipoprotein B-48 concentrations are associated with reduced estimated glomerular filtration rate and increased proteinuria	J Atheroscler Thromb	21(9)	974-982	2014
Masuda D, et al.	Reference interval of apolipoprotein B-48 concentration in healthy Japanese individuals	J Atheroscler Thromb	21(6)	618-627	2014
Kuroda M, et al.	Lipoprotein subfractions highly associated with renal damage in familial LCAT deficiency	Arterioscler Thromb Vasc Biol	34(8)	1756-1762	2014
Edahiro R, et al.	Association of lifestyle-related factors with circadian onset patterns of acute myocardial infarction: a prospective observational study in Japan	BMJ Open	4(6)	e005067	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
中村 雅一	LDL cholesterol performance of beta quantification reference measurement procedure	Clinica Chimica Acta	431	288-293	2014
中村 雅一	HDL cholesterol performance using an ultracentrifugation reference measurement procedure and the designated comparison method	Clinica Chimica Acta	439	185-190	2015

Ⅴ．研究成果の刊行物・別刷

Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

Effects of Evolocumab (AMG 145), a Monoclonal Antibody to PCSK9, in Hypercholesterolemic, Statin-Treated Japanese Patients at High Cardiovascular Risk

– Primary Results From the Phase 2 YUKAWA Study –

Atsushi Hirayama; Narimon Honarpour; Masayuki Yoshida; Shizuya Yamashita; Fannie Huang; Scott M. Wasserman; Tamio Teramoto

Background: YUKAWA is a 12-week, randomized, double-blind, placebo-controlled, phase 2 study evaluating the efficacy and safety of evolocumab (AMG 145) in statin-treated Japanese patients at high cardiovascular risk.

Methods and Results: 310 eligible patients receiving stable statin (±ezetimibe) therapy were randomized to 1 of 6 treatments: placebo every 2 weeks (Q2W) or monthly (QM), evolocumab 70 mg or 140 mg Q2W, or evolocumab 280 mg or 420 mg QM. The primary endpoint was the percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) measured by preparative ultracentrifugation (UC). Secondary endpoints included percentage changes in other lipid parameters and the proportion of patients with LDL-C <1.8 mmol/L. Mean (SD) age was 62 (10) years; 37% were female; and the mean (SD) baseline LDL-C was 3.7 (0.5) mmol/L (by UC). Mean (SE) changes vs. placebo in LDL-C were greatest in the high-dose groups: −68.6 (3.0) % and −63.9 (3.2) % with 140 mg Q2W and 420 mg QM dosing, respectively. Up to 96% of evolocumab-treated patients achieved LDL-C <1.8 mmol/L. Adverse events (AEs) were more frequent in evolocumab (51%) vs. placebo (38%) patients; 4 patients taking evolocumab discontinued treatment because of an AE. There were no significant differences in AE rates based on dose or dose frequency.

Conclusions: In Japanese patients at high cardiovascular risk with hypercholesterolemia on stable statin therapy, evolocumab significantly reduced LDL-C and was well tolerated during this 12-week study. (*Circ J* 2014; **78:** 1073–1082)

Key Words: Dyslipidemia; Hypercholesterolemia; Low-density lipoprotein cholesterol; PCSK9 antibody

Cardiovascular disease (CVD) remains the leading cause of death globally, with over 17 million deaths per year.[1] In Japan, CVD-associated deaths from heart disease and stroke are the second and third highest causes of death, respectively.[2] The incidence of coronary artery disease (CAD), a leading contributor to CVD incidence, increases in Japanese patients as low-density lipoprotein cholesterol (LDL-C) levels rise.[3,4] Although treatment with statins lowers the risk of CVD events,[5–10] high-risk patients may still fail to reach LDL-C goals,[1] leaving them vulnerable to subsequent cardiovascular events. Nearly half of the high-risk Japanese patients have not reached their Japan Atherosclerosis Society (JAS)-guideline LDL-C goal.[11,12]

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a secreted protein that binds to the LDL receptor (LDLR), preventing it from recycling to the cell surface.[13] This results in less available LDLR and higher circulating LDL-C levels.[13] Inhibition of PCSK9 with anti-PCSK9 antibodies increases hepatic LDLR recycling, which enhances LDL-C clearance from the serum.[14,15] Evolocumab is a fully human monoclonal antibody

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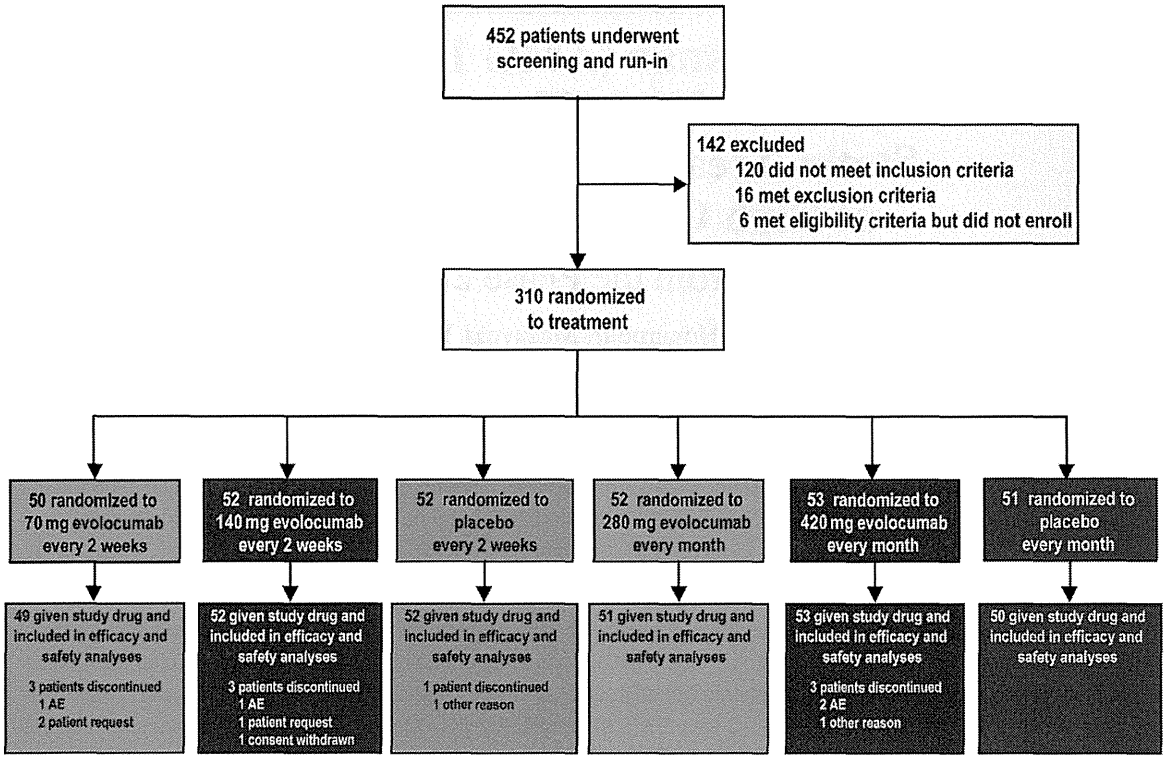

Figure 1. Disposition of patients in YUKAWA (Stud**Y** of LDL-Cholesterol Reduction **U**sing a Monoclonal PCS**K**9 **A**ntibody in Japanese Patients **W**ith **A**dvanced Cardiovascular Risk).

against PCSK9[14] that inhibits the binding of PCSK9 to LDLRs. In global phase 2 studies, evolocumab monotherapy reduced LDL-C measured by preparative ultracentrifugation (UC) by up to 53% vs. placebo,[16] and combination therapy with statins resulted in reductions of up to 66% vs. placebo.[17] Studies in patients with familial hypercholesterolemia[18,19] and statin intolerance[20] have shown similar efficacy. YUKAWA (Stud**Y** of LDL-Cholesterol Reduction **U**sing a Monoclonal PCS**K**9 **A**ntibody in Japanese Patients **W**ith **A**dvanced Cardiovascular Risk) is the first study to examine the efficacy and tolerability of evolocumab in hypercholesterolemic Japanese patients at high cardiovascular risk and on baseline statin therapy.

Methods

Patient Population and Study Design

YUKAWA is a 12-week, phase 2, randomized, multicenter, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy and safety of every 2 weeks (Q2W) or monthly (QM) evolocumab when used in combination with a statin in Japanese patients (NCT01652703). The study was carried out in 42 study centers in Japan. Briefly, patients were eligible if they were 20–80 years of age (inclusive) and classified as high risk for cardiovascular events. Patients were considered high risk if they had any of the following: history of CAD or cerebral infarction; a diagnosis of heterozygous familial hypercholesterolemia, arteriosclerosis obliterans/peripheral artery disease, or type 2 diabetes mellitus ≥3 months prior to randomization; a fasting plasma glucose >6.1 mmol/L ≥3 months prior to randomization; or the presence of ≥3 additional risk factors relating to age, smoking history, family history of CAD, and past diagnosis of hypertension or reduced high-density lipoprotein (HDL).[12,21] Inclusion/exclusion criteria are summarized in **Supplementary File 1**. Patients were required to be on stable statin therapy for ≥4 weeks prior to LDL-C screening. Baseline lipid requirements at screening were fasting LDL-C ≥3.0 mmol/L and fasting triglycerides ≤4.5 mmol/L.

Randomization and Study Blinding

Prior to randomization, all patients received a placebo injection to assess tolerance and acceptability of subcutaneous (SC) administration. Eligible patients who tolerated placebo injections were assigned equally to 1 of 6 treatment arms: SC placebo, evolocumab 70 mg, or evolocumab 140 mg Q2W; or SC placebo, evolocumab 280 mg, or evolocumab 420 mg QM (**Figure 1**). Baseline stratification factors included screening LDL-C (<3.4 mmol/L vs. ≥3.4 mmol/L) and a diagnosis of heterozygous familial hypercholesterolemia (yes vs. no). Treatment assignment and on-treatment laboratory lipid-panel values were blinded; dosing frequency was not blinded.

Study Endpoints

The primary efficacy endpoint was percentage change from baseline in LDL-C at week 12. Secondary endpoints assessed at week 12 were absolute change in LDL-C, percentage changes from baseline in other lipid parameters, and the proportion of patients who reached LDL-C <1.8 mmol/L. For endpoint assessments, LDL-C was measured by UC. Safety endpoints included the incidence of adverse events (AEs), laboratory values and vital signs, electrocardiography (ECG) parameters,

Table 1. Demographics and Baseline Characteristics of the Study Population[a]

	Placebo			Evolocumab					All patients
	Q2W (n=52)	QM (n=50)	Total (n=102)	70 mg Q2W (n=49)	140 mg Q2W (n=52)	280 mg QM (n=51)	420 mg QM (n=53)	Total (n=205)	Total (n=307)
Demographics									
Age, years, mean (SD)	60.2 (10.1)	60.9 (9.8)	60.5 (9.9)	64.1 (9.7)	60.8 (9.2)	61.6 (9.6)	61.3 (9.9)	61.9 (9.6)	61.5 (9.7)
Female, n (%)	16 (30.8)	14 (28.0)	30 (29.4)	24 (49.0)	20 (38.5)	23 (45.1)	17 (32.1)	84 (41.0)	114 (37.1)
Cardiac risk factors, n (%)									
CAD	15 (28.8)	15 (30.0)	30 (29.4)	12 (24.5)	13 (25.0)	9 (17.6)	13 (24.5)	47 (22.9)	77 (25.1)
PAD or CVD	7 (13.5)	7 (14.0)	14 (13.7)	8 (16.3)	4 (7.7)	7 (13.7)	9 (17.0)	28 (13.7)	42 (13.7)
T2DM	16 (30.8)	18 (36.0)	34 (33.3)	19 (38.8)	21 (40.4)	25 (49.0)	18 (34.0)	83 (40.5)	117 (38.1)
Hypertension	40 (76.9)	36 (72.0)	76 (74.5)	40 (81.6)	34 (65.4)	35 (68.6)	41 (77.4)	150 (73.2)	226 (73.6)
Elevated WC[b]	33 (63.5)	34 (68.0)	67 (65.7)	34 (69.4)	33 (63.5)	34 (66.7)	34 (64.2)	135 (65.9)	202 (65.8)
Current smoker	11 (21.2)	16 (32.0)	27 (26.5)	11 (22.4)	12 (23.1)	15 (29.4)	14 (26.4)	52 (25.4)	79 (25.7)
Metabolic syndrome[c]	17 (32.7)	12 (24.0)	29 (28.4)	13 (26.5)	14 (26.9)	11 (21.6)	16 (30.2)	54 (26.3)	83 (27.0)
≥2 cardiovascular risk factors	24 (46.2)	26 (52.0)	50 (49.0)	32 (65.3)	25 (48.1)	30 (58.8)	33 (62.3)	120 (58.5)	170 (55.4)
High-intensity statin use (global definition)[d]	2 (3.8)	3 (6.0)	5 (4.9)	6 (12.2)	2 (3.8)	3 (5.9)	3 (5.7)	14 (6.8)	19 (6.2)
High-intensity statin use (Japan-specific definition)[e]	14 (26.9)	14 (28.0)	28 (27.5)	14 (28.6)	11 (21.2)	10 (19.6)	10 (18.9)	45 (22.0)	73 (23.8)
Baseline lipids (mean [SD])									
UC LDL-C, mmol/L	3.7 (0.5)	3.7 (0.6)	3.7 (0.5)	3.7 (0.5)	3.6 (0.6)	3.6 (0.5)	3.6 (0.5)	3.7 (0.5)	3.7 (0.5)
Calculated LDL-C, mmol/L	3.7 (0.5)	3.6 (0.6)	3.7 (0.5)	3.7 (0.6)	3.6 (0.6)	3.6 (0.5)	3.6 (0.5)	3.6 (0.6)	3.6 (0.6)
Lp(a), nmol/L[f]	32.0 (17.5, 65.5)	35.0 (13.0, 66.0)	33.5 (16.0, 66.0)	29.0 (14.0, 56.0)	32.0 (11.0, 67.0)	27.0 (12.0, 53.0)	48.0 (20.0, 82.0)	33.5 (12.0, 66.0)	33.5 (13.0, 66.0)
TC, mmol/L	5.8 (0.6)	5.8 (0.6)	5.8 (0.6)	5.8 (0.7)	5.7 (0.7)	5.7 (0.7)	5.7 (0.6)	5.7 (0.7)	5.8 (0.6)
HDL-C, mmol/L	1.4 (0.3)	1.4 (0.3)	1.4 (0.3)	1.4 (0.4)	1.4 (0.3)	1.4 (0.4)	1.4 (0.4)	1.4 (0.3)	1.4 (0.3)
TG, mmol/L	1.6 (0.6)	1.6 (0.6)	1.6 (0.6)	1.6 (0.7)	1.5 (0.5)	1.4 (0.5)	1.6 (0.7)	1.5 (0.6)	1.5 (0.6)
VLDL-C, mmol/L[f]	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)	0.7 (0.5, 0.9)	0.7 (0.4, 0.9)	0.6 (0.5, 0.8)	0.6 (0.5, 0.7)	0.7 (0.5, 0.9)	0.6 (0.5, 0.8)	0.6 (0.5, 0.9)
Non-HDL-C, mmol/L	4.4 (0.6)	4.4 (0.7)	4.4 (0.6)	4.4 (0.7)	4.3 (0.7)	4.3 (0.6)	4.3 (0.6)	4.3 (0.7)	4.3 (0.6)
ApoB, g/L	1.2 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)	1.1 (0.2)
ApoA1, g/L	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.2)	1.6 (0.3)	1.6 (0.2)	1.6 (0.2)	1.6 (0.3)
TC:HDL-C	4.4 (0.9)	4.3 (1.1)	4.3 (1.0)	4.4 (1.2)	4.3 (1.0)	4.2 (1.0)	4.2 (1.0)	4.3 (1.0)	4.3 (1.0)
ApoB:ApoA1	0.8 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)	0.7 (0.2)
PCSK9, ng/ml	389.4 (121.2)	411.3 (101.1)	400.1 (111.8)	402.6 (129.1)	392.6 (125.8)	411.5 (137.9)	416.6 (143.9)	405.9 (133.8)	404.0 (126.8)

All percentages based on n. [a]Study population includes all randomized patients who received ≥1 dose of investigational product. [b]Elevated waist circumference (WC) defined as ≥85 cm for men, ≥90 cm for women. [c]JAS 2012 criteria. [d]Daily simvastatin 80 mg, atorvastatin ≥40 mg, rosuvastatin ≥20 mg, or any statin plus ezetimibe. [e]Daily atorvastatin ≥10 mg, pitavastatin ≥2 mg, rosuvastatin ≥5 mg, simvastatin ≥20 mg, lovastatin ≥40 mg, fluvastatin ≥80 mg, pravastatin ≥40 mg, or any statin plus ezetimibe. [f]Median (Q1, Q3).
Apo, apolipoprotein; CAD, coronary artery disease; CVD, cerebrovascular disease; HDL-C, high-density lipoprotein cholesterol; JAS, Japanese Atherosclerosis Society; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein A; PAD, peripheral arterial disease; PCSK9, proprotein convertase subtilisin/kexin type 9; Q1, first quartile; Q2W, every 2 weeks; Q3, second quartile; QM, monthly; SD, standard deviation; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; UC, ultracentrifugation; VLDL-C, very low-density lipoprotein cholesterol.

and incidence of anti-evolocumab antibodies.

Statistical Analysis

Analyses were conducted on data for randomized patients who received ≥1 dose of evolocumab or placebo. The primary endpoint was analyzed using an analysis of covariance model, including treatment group and the stratification factor of screening LDL-C. A last observation carried forward approach was used to impute missing values. Secondary endpoints were evaluated similarly to the primary endpoint; LDL-C response was assessed using a logistic regression, which included terms for treatment group and screening LDL-C. Secondary endpoint analyses were not adjusted for multiple comparisons. Analysis of the percentage change from baseline to the average of weeks 10 and 12 for lipid parameters of interest was performed using a repeated measures model and observed data, which included treatment group, the stratification factor of screening LDL-C, scheduled visit, and the interaction of treatment with scheduled visit.

AEs and serious AEs were recorded throughout the study and were coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA v16.0). Laboratory parameters were summarized using descriptive statistics for each treatment group at each scheduled visit. Rates of anti-evolocumab antibody formation were tabulated by treatment group.

Results

Patient disposition is summarized in **Figure 1**. Of the 452

Table 2. Efficacy at 12 Weeks

	Evolocumab Q2W		Placebo Q2W (n=52)	Evolocumab QM		Placebo QM (n=50)
	70 mg (n=49)	140 mg (n=52)		280 mg (n=51)	420 mg (n=53)	
LDL-C						
Mean (SE) percentage change vs. placebo in UC LDL-C; P value[a,b]	−52.9 (3.0); <0.001	−68.6 (3.0); <0.001	N/A	−58.2 (3.2); <0.001	−63.9 (3.2); <0.001	NA
Change in UC LDL-C vs. placebo (mmol/L; SE); P value[b]	−2.0 (0.1); <0.001	−2.5 (0.1); <0.001	NA	−2.1 (0.1); <0.001	−2.3 (0.1); <0.001	NA
Achieved LDL-C (mmol/L; mean [SD])[c]	1.5 (0.8)	0.9 (0.5)	3.6 (0.5)	1.5 (0.5)	1.2 (0.7)	3.6 (0.8)
LDL-C <2.6 mmol/L at week 12 (n [%])[d]	44 (94)	49 (98)	2 (4)	48 (94)	49 (96)	1 (2)
LDL-C <1.8 mmol/L at week 12 (n [%]; P value)[d]	31 (66); <0.001	48 (96); <0.001	0 (–)	41 (80); <0.001	42 (82); <0.001	0 (–)
Other lipid parameters						
Lp(a), mean (SE) % change vs. placebo; P value[a,b]	−41.5 (4.9); <0.001	−50.6 (4.9); <0.001	NA	−39.6 (4.9); <0.001	−32.3 (4.9); <0.001	NA
Achieved Lp(a), mean (SD), nmol/L	30.8 (42.5)	30.9 (42.3)	53.4 (58.5)	29.4 (41.9)	52.1 (68.1)	67.7 (87.0)
TC, mean (SE) % change vs. placebo; P value[a,b]	−36.2 (2.2); <0.001	−45.3 (2.1); <0.001	NA	−36.3 (2.3); <0.001	−40.2 (2.3); <0.001	NA
Achieved TC mean (SD), mmol/L	3.7 (0.9)	3.1 (0.6)	5.8 (0.7)	3.7 (0.7)	3.5 (0.8)	5.8 (0.8)
HDL-C, mean (SE) % change vs. placebo; P value[a,b]	4.4 (3.2); 0.17	9.1 (3.1); 0.004	NA	16.3 (3.1); <0.001	13.2 (3.1); <0.001	NA
Achieved HDL-C, mean (SD), mmol/L	1.6 (0.4)	1.6 (0.4)	1.5 (0.4)	1.6 (0.4)	1.6 (0.4)	1.4 (0.3)
TG, mean (SE) percentage change vs. placebo; P value[a,b]	−14.3 (6.3); 0.025	−16.6 (6.2); 0.009	NA	−17.1 (6.5); 0.009	−20.2 (6.4); 0.002	NA
Achieved TG, mean (SD), mmol/L	1.4 (0.6)	1.3 (0.6)	1.6 (0.9)	1.3 (0.5)	1.4 (0.7)	1.7 (0.8)
VLDL-C, median (Q1, Q3) % change vs. placebo; P value[a,b]	−22.2 (−42.4, −1.9); 0.002	−21.2 (−40.6, −1.7); 0.002	NA	−25.1 (−47.8, −2.4); 0.015	−24.1 (−46.4, −1.8); 0.004	NA
Achieved VLDL-C, median (Q1, Q3), mmol/L	0.5 (0.3, 0.6)	0.4 (0.3, 0.5)	0.6 (0.4, 1.0)	0.4 (0.3, 0.6)	0.5 (0.3, 0.6)	0.7 (0.4, 0.9)
Non-HDL-C, mean (SE) % change vs. placebo; P value[a,b]	−49.5 (2.7); <0.001	−62.6 (2.7); <0.001	NA	−53.5 (3.0); <0.001	−58.1 (3.0); <0.001	NA
Achieved Non-HDL-C, mean (SD), mmol/L	2.2 (0.9)	1.5 (0.5)	4.3 (0.7)	2.0 (0.6)	1.9 (0.8)	4.4 (0.9)
ApoB, mean (SE) % change vs. placebo; P value[a,b]	−46.8 (2.6); <0.001	−60.7 (2.5); <0.001	NA	−47.4 (2.8); <0.001	−53.4 (2.8); <0.001	NA
Achieved ApoB, mean (SD), g/L	0.6 (0.2)	0.4 (0.1)	1.1 (0.2)	0.6 (0.2)	0.5 (0.2)	1.1 (0.2)
ApoA1, mean (SE) % change vs. placebo; P value[a,b]	4.0 (2.4); 0.100	6.3 (2.4); 0.009	NA	9.3 (2.2); <0.001	9.6 (2.2); <0.001	NA
Achieved ApoA1, mean (SD), g/L	1.7 (0.3)	1.7 (0.3)	1.6 (0.3)	1.7 (0.3)	1.7 (0.3)	1.5 (0.2)
TC:HDL-C, mean (SE) % change vs. placebo; P value[a,b]	−37.2 (2.7); <0.001	−47.0 (2.6); <0.001	NA	−45.3 (2.9); <0.001	−46.7 (2.9); <0.001	NA
Achieved TCmean (SD), mmol/L	2.5 (0.8)	2.0 (0.4)	4.2 (1.1)	2.3 (0.5)	2.3 (0.9)	4.3 (1.2)
ApoB:ApoA1, mean (SE) % change vs. placebo; P value[a,b]	−47.5 (3.0); <0.001	−61.4 (2.9); <0.001	NA	−52.2 (3.1); <0.001	−57.8 (3.0); <0.001	NA
Achieved ApoB:ApoA1, mean (SD), g/L	0.4 (0.2)	0.2 (0.1)	0.7 (0.2)	0.4 (0.1)	0.3 (0.2)	0.7 (0.2)

[a]For least-squares mean percentage change from baseline in lipid parameters for each treatment group, see Supplementary File 1. [b]Least-squares mean difference within each dose frequency vs. matching placebo. [c]Calculated LDL-C. [d]Percentage calculated from n at week 12. NA, not applicable; SE, standard error. Other abbreviations as in Table 1.

patients screened for YUKAWA, 310 (69%) were randomized to treatment (2:1 evolocumab:placebo) (**Figure 1**). Baseline characteristics of the study population are reported in **Table 1**. Briefly, 37% were female; mean (standard deviation; SD) age was 62 (10) years; 55% were identified as having 2 or more cardiovascular risk factors, 38% had type 2 diabetes mellitus, and 25% had CAD. The mean (SD) baseline LDL-C values were 3.7 (0.5) mmol/L for placebo patients (total), 3.6 (0.6) mmol/L for evolocumab 140 mg Q2W, and 3.6 (0.5) mmol/L for evolocumab 420 mg QM. Baseline statin use was consistent with contemporary Japanese practice (**Table S1**).

All evolocumab treatment groups showed statistically significant (P<0.001) mean changes from baseline in LDL-C vs. placebo at week 12, with the highest evolocumab doses within each dose frequency (140 mg Q2W and 420 mg QM) providing the greatest efficacy (**Table 2**). Mean (standard error; SE) percentage changes vs. placebo at week 12 were −68.6 (3.0) % 140 mg Q2W and −63.9 (3.2) % 420 mg QM (both P<0.001; **Table 2**), reflecting mean (SE) changes from baseline of −71.3 (2.2) % and −63.9 (2.3) %, respectively (**Table S2**). Subgroup efficacy results were consistent with these findings (**Figure 2**). Reductions in calculated LDL-C were apparent by week 2 in the evolocumab treatment groups and continued through the end of study (**Figure 3**). The most robust and sustained reductions were seen in the 140 mg Q2W and 420 mg QM groups.

The least-squares mean percentage change in LDL-C was

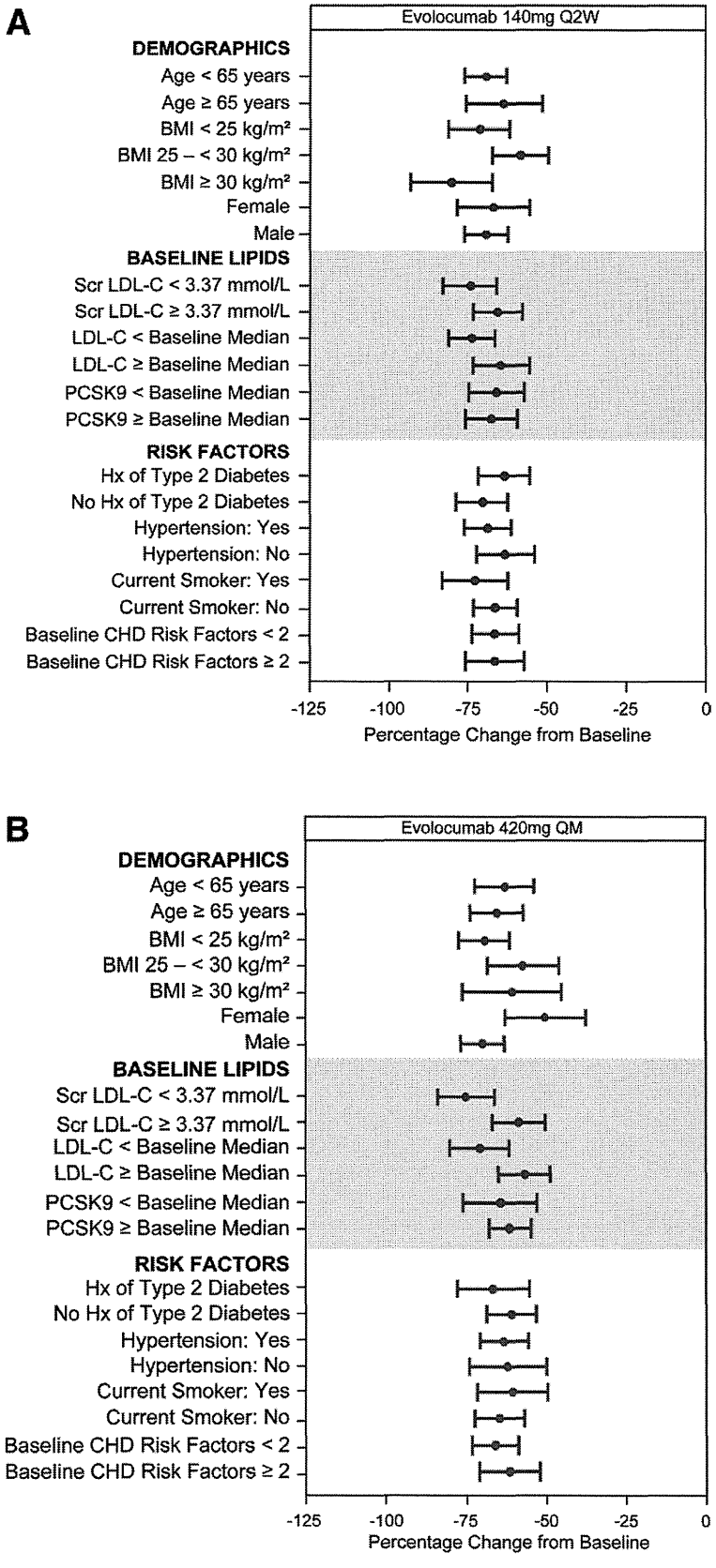

Figure 2. Mean percentage change in LDL-C measured by ultracentrifugation in the main subgroups given evolocumab either 140 mg SC Q2W (**A**) or 420 mg SC QM (**B**). Values reported are least-squares mean differences (95% CI) compared with matching placebo. Values less than 0 favor evolocumab, whereas those greater than 0 favor placebo. BMI, body mass index; CI, confidence interval; LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly; SC, subcutaneous; Scr, screening; Hx, history.

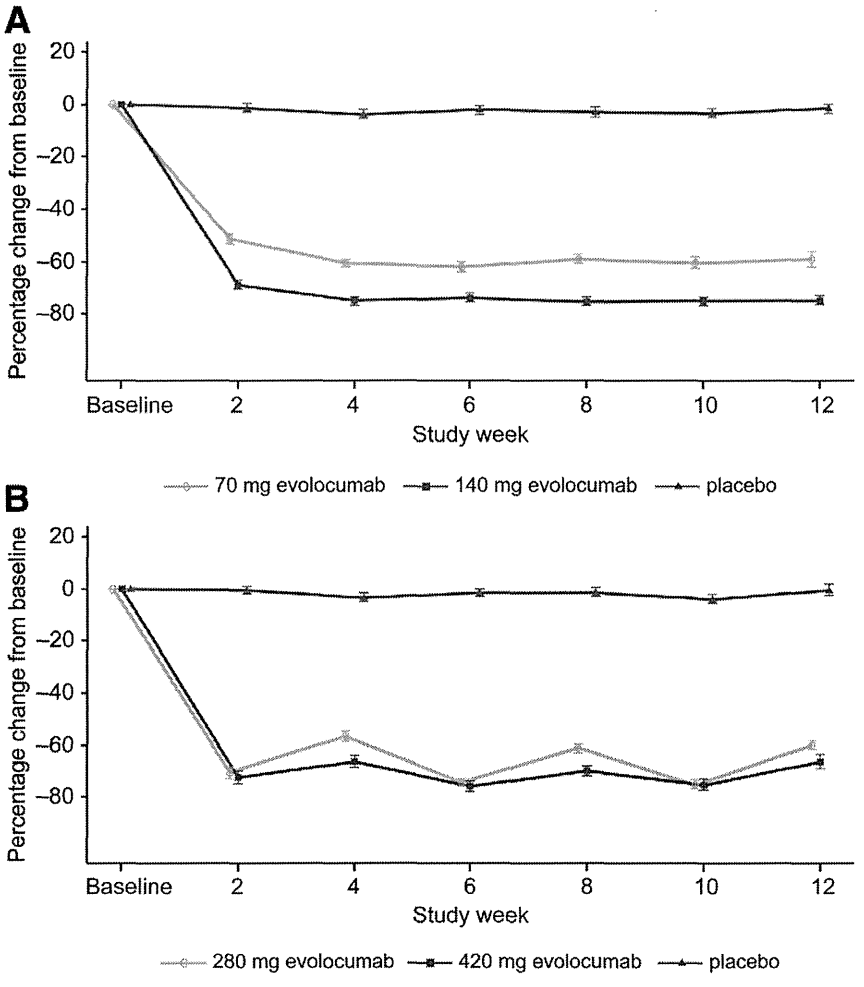

Figure 3. Mean percentage change in calculated LDL-C concentration from baseline by visit Q2W (**A**) or QM (**B**). Error bars indicate standard error (SE). Results are based on observed data. LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

also calculated for the mean of weeks 10 and 12, as this measure can be more reflective of the time-averaged reduction in LDL-C than the week 12 assessment alone.[22] LDL-C assessments at study visits between day 1 and week 12 used Friedewald's calculation. As a result, the mean LDL-C at weeks 10/12 reflects the average calculated LDL-C. Mean (SE) weeks 10/12 percentage changes vs. placebo were −71.7 (2.6) % 140 mg Q2W and −68.7 (2.6) % 420 mg QM (both P<0.0001), reflecting mean (SE) percentage changes from baseline by treatment group of −74.9 (1.8) % and −70.9 (1.9) %, respectively (**Table S3**).

Comparable LDL-C reductions were achieved with these doses in patients receiving intensive and non-intensive statin therapy. In patients receiving intensive statin therapy (global definition, see **Table 1**, footnote), mean (SE) changes in LDL-C of −63.8% (11.3) and −66.0% (10.8) were observed at week 12 with 140 mg Q2W and 420 mg QM dose groups, respectively. In those receiving non-intensive statin therapy, mean (SE) changes in LDL-C were −71% (2.2) and −63.7% (2.3) at week 12 for the 140 mg Q2W and 420 mg QM dose groups, respectively. Although the sample size for intensive statin use (global definition) was small (n=14 on evolocumab), similar results were seen when using the Japan-specific definition of intensive statin use (see **Table 1**, footnote), which classified more patients as receiving intensive statin therapy (n=45 on evolocumab). This suggests that the effect of evolocumab 140 mg Q2W and 420 mg QM does not change substantially with the intensity of background statin therapy. Appreciable differences in efficacy based on a history of heterozygous familial hypercholesterolemia were also not observed in this study; however, relatively few patients with this diagnosis received evolocumab (n=11). Based on a recently completed global phase 2 study evaluating evolocumab in patients with heterozygous familial hypercholesterolemia,[18] efficacy and safety results are expected to be similar to those seen in patients without familial hypercholesterolemia.[16,17,20]

Therapeutic monoclonal antibodies such as evolocumab demonstrate non-linear pharmacokinetics. Dosing evolocumab at QM intervals compared with Q2W can provide similar time-averaged reductions in PCSK9. In assessing PCSK9 suppression for this study, the evolocumab 140 mg Q2W group demonstrated mean (SE) unbound PCSK9 reductions of 83.2% (2.2) at week 2, 77.8% (2.7) at week 10, and 77.0% (3.0) at week 12 (2 weeks after the last dose of evolocumab 140 mg Q2W). In the evolocumab 420 mg QM group, mean reductions of unbound PCSK9 from baseline were 98.8% (0.3) at week 2, 94.2% (2.5) at week 10, and 50.6% (4.4) by week 12 (4 weeks after the last dose of 420 mg evolocumab QM).

Statistically significant improvements (P<0.05) were also seen in all evolocumab treatment groups for total cholesterol (TC), triglycerides, very low-density lipoprotein cholesterol (VLDL-C), non-HDL cholesterol (non-HDL-C), apolipopro-

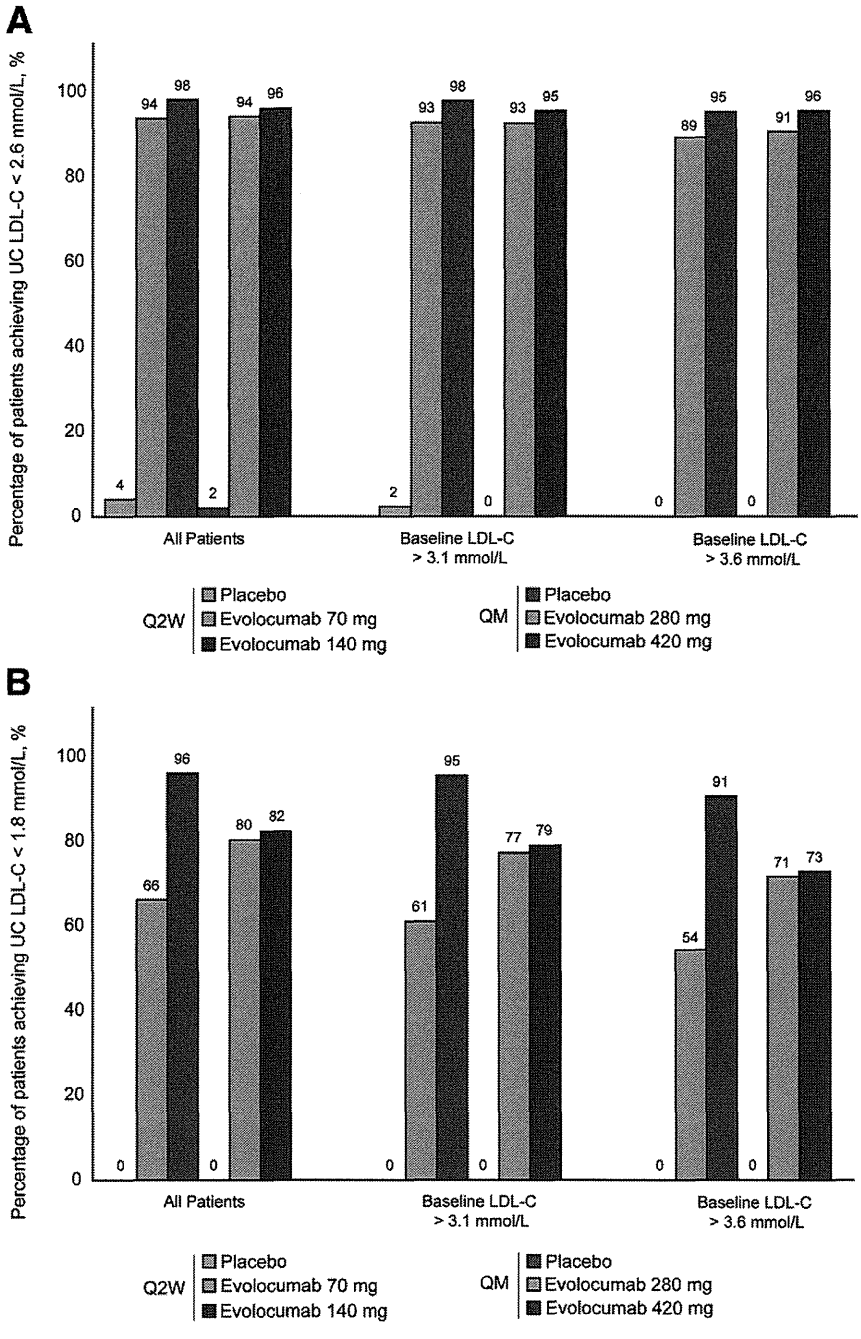

Figure 4. Frequency of attaining week-12 LDL-C targets measured by ultracentrifugation and stratified by baseline LDL-C. Percentage of patients reaching (**A**) LDL-C <2.6mmol/l or (**B**) LDL-C <1.8mmol/L. Percentages are based on the number of patients within each subgroup. LDL-C, low-density lipoprotein cholesterol.

tein B (ApoB), lipoprotein a (Lp[a]), the ApoB:ApoA1 ratio, and the TC:HDL-C ratio, and in all but the evolocumab 70mg Q2W group for HDL-C and ApoA1 at week 12 (**Table 2**, **Table S2**). Favorable changes were also seen in other lipids for the mean of weeks 10 and 12 (**Table S3**).

The majority (94% to 98%) of patients in the evolocumab treatment groups achieved the most stringent JAS-recommended LDL-C goal of <2.6mmol/L[12] at week 12. Goal achievement was highest in the 140mg Q2W and 420mg QM groups (98% and 96%, respectively, vs. 3% placebo; **Figure 4A**). The majority of evolocumab-treated patients also achieved LDL-C levels <1.8mmol/L (**Figure 4B**).

Although more AEs were reported in evolocumab-treated (51%) vs. placebo-treated (38%) patients (**Table 3**), most were Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or 2 (mild or moderate),[23] and no imbalances in AEs were observed with respect to dose or dose frequency. Nasopharyngitis was the most frequent AE; 4 (2%) patients in the evolocumab treatment group reported serious AEs (**Table 3**), none of which was considered related to the study drug. These AEs were carcinoid tumor of the cecum with a pre-randomization history of anal bleeding (drug was withdrawn); fracture of left clavicle, ribs, and ankle (dose was altered or withheld); prostate cancer (dose was unchanged); and worsening of arteriosclerosis (dose was unchanged). In total, 4 evolocumab-treated patients discontinued treatment because of any AE,

Table 3. Incidence of Adverse Events in Patients

n (%)	Placebo Q2W (n=52)	Evolocumab 70 mg Q2W (n=49)	Evolocumab 140 mg Q2W (n=52)	Placebo QM (n=50)	Evolocumab 280 mg QM (n=51)	Evolocumab 420 mg QM (n=53)
All treatment-emergency AEs[a]	18 (34.6)	24 (49.0)	28 (53.8)	21 (42.0)	21 (41.2)	31 (58.5)
Leading to drug discontinuation	0	1 (2.0)	1 (1.9)	0	0	2 (3.8)
Serious AEs[b]	0	0	1 (1.9)	0	1 (2.0)	2 (3.8)
Leading to drug discontinuation	0	0	0	0	0	1 (1.9)
Potential injection-site reactions[c]	1 (1.9)	1 (2.0)	2 (3.8)	0	0	1 (1.9)
Binding antibodies detected[d]	1 (1.9)	0	0	0	0	0
AST or ALT >3x ULN	0	1 (2.0)	0	0	0	0
CK >5x ULN	0	0	0	1 (2.0)	1 (2.0)	0
Positively adjudicated cardiovascular events[e]	1 (1.9)	0	0	1 (2.0)	0	0
All-cause mortality	0	0	0	0	0	0

All percentages are based on n. [a]The most common treatment-emergency AE for both the placebo and evolocumab group was nasopharyngitis. [b]Serious AEs: fracture, carcinoid tumor of the cecum, prostate cancer, and arteriosclerosis. [c]Pain, bruising, erythema, hemorrhage, or pruritus at injection site. [d]No neutralizing antibodies to evolocumab detected. [e]The 2 positively adjudicated cardiovascular events were percutaneous coronary revascularizations.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal. Other abbreviations as in Table 1.

Table 4. Adverse Events [n (%)] Stratified by Lowest Post-Baseline LDL-C Score

n (%)	LDL-C <0.65 mmol/l		LDL-C <1.04 mmol/l		LDL-C ≥1.04 mmol/l	
	Placebo[a] (n=0)	Evolocumab (n=90)	Placebo[a] (n=0)	Evolocumab (n=157)	Placebo (n=102)	Evolocumab (n=48)
Treatment-emergency AEs	NA	49 (54.4)	NA	79 (50.3)	39 (38.2)	25 (52.1)
Serious AEs	NA	1 (1.1)	NA	3 (1.9)	0 (0.0)	1 (2.1)
Myalgia	NA	2 (2.2)	NA	3 (1.9)	1 (1.0)	1 (2.1)
CK >5xULN	NA	0 (0.0)	NA	1 (0.6)	1 (1.0)	0 (0.0)
CK >10xULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)
AST or ALT >3xULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	1 (2.1)
Total bilirubin >2xULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)
Positively-adjudicated cardiovascular events	NA	0 (0.0)	NA	0 (0.0)	2 (2.0)	0 (0)

All percentages based on n. LDL-C categories are based on patient's lowest, post-baseline LDL-C. [a]No placebo patients achieved these 2 post-baseline LDL-C levels.
Abbreviations as in Tables 1,3.

only 1 of which was serious (carcinoid tumor of the cecum with pre-randomization history of anal bleeding; not considered treatment related). Incidences of positively adjudicated cardiovascular events and elevations in creatine kinase (CK) and aminotransferases were comparable between placebo- and evolocumab-treated patients (**Table 3**). Binding antibodies to evolocumab were not detected in any evolocumab-treated patients (**Table 3**). Incidences of AEs, serious AEs, myalgia, and positively adjudicated cardiovascular events, as well as CK and aminotransferase elevations, were comparable between placebo-treated and evolocumab-treated patients irrespective of lowest post-baseline LDL-C (**Table 4**).

Discussion

Results from YUKAWA suggest that evolocumab dosed Q2W or QM yields significant reductions in LDL-C and other lipids (**Table 2**). Congruent with global evolocumab phase 2 results,[16–18,20] the greatest and most sustained LDL-C reductions were seen in the highest dose groups (140 mg Q2W and 420 mg QM; **Table 2**, **Table S2**). As mentioned before, time-averaged reductions in LDL-C can be estimated using the mean of weeks 10 and 12. When comparing the mean reduction at weeks 10 and 12 between the 140 mg Q2W and 420 mg QM groups, results were also similar (**Table S3**). Favorable changes were seen in additional lipid parameters at both week 12 and the mean of weeks 10 and 12, with the 140 mg Q2W and 420 mg QM doses resulting in the greatest changes. Most (94–98%) of the YUKAWA patients on evolocumab Q2W or QM achieved the JAS-recommended lipid target of <2.6 mmol/L.[12] In this study, the mean (SD) baseline LDL-C was 3.7 (0.5) mmol/L, with no patients having an LDL-C <2.6 mmol/L. At 12 weeks, up to 98% of patients receiving evolocumab achieved an LDL-C <2.6 mmol/L (**Figure 4**).

Because of the less potent and lower doses of statins used in Japan, fewer patients in YUKAWA were on high-intensity statin therapy compared with the LAPLACE-TIMI-57[17] or RUTHERFORD[18] global phase 2 studies, in which evolocumab was administered with a background of statin therapy (**Table 1**). Compared with LAPLACE-TIMI 57, the prevalence of diabetes, hypertension, and smoking were higher in YUKAWA.[17] Despite these differences, and consistent with results of the evolocumab phase 1b study performed in Japanese patients,[24] changes in LDL-C and other lipid parameters in the YUKAWA patients were comparable to those seen in the other evolocumab phase 2 studies at week 12.[17,18] Additionally, reductions in LDL-C did not appear to be significantly affected by factors such as age, weight, baseline lipid concentrations, or