Table 1. Diabetic Patients with a Higher Risk of Developing CAD

- Microangiopathy (retinopathy, nephropathy, etc.)
- Persistent poor glycemic control*
- Smoking
- Non-cardiogenic cerebral infarction/PAD
- Metabolic syndrome
- More than one major risk factor

*; HbA1c ≥ 8.4% (NGSP)

cerebral infarction/PAD[75], (5) metabolic syndrome[76] and (6) more than one major risk factor (**Table 1**)[65, 66, 74].

All patients with DM should aim for LDL-C levels of < 120 mg/dL as part of their primary CAD prevention. In patients with the previous characteristics, it is essential to follow intensive and strict management measures to reach the target values. Patients with DM who have more than one of these characteristics are expected to be at an extremely high risk of CAD, and the secondary prevention target values could be considered.

Lipid management in secondary prevention patients with DM is described in Chapter 11 of "Coronary Artery Disease."

Footnotes

This is an English version of the guidelines of the Japan Atherosclerosis Society (Chapter 12) published in Japanese in June 2012.

Acknowledgements

We are grateful to the following people and societies for their collaboration and valuable contributions: Dr. Hidenori Arai (The Japan Geriatrics Society), Dr. Kiminori Hosoda (Japan Society for the Study of Obesity), Dr. Hiroyasu Iso (Japan Epidemiological Association), Dr. Atsunori Kashiwagi (Japan Diabetes Society), Dr. Masayasu Matsumoto (The Japan Stroke Society), Dr. Hiromi Rakugi (The Japanese Society of Hypertension), Dr. Tetsuo Shoji (Japanese Society of Nephrology) and Dr. Hiroaki Tanaka (Japanese Society of Physical Fitness and Sports Medicine). We also thank Dr. Shinji Koba, Dr. Manabu Minami, Dr. Tetsuro Miyazaki, Dr. Hirotoshi Ohmura, Dr. Mariko Harada-Shiba, Dr. Hideaki Shima, Dr. Daisuke Sugiyama, Dr. Minoru Takemoto and Dr. Kazuhisa Tsukamoto for supporting this work.

References

1) Kannel WB, Mcgee DL: Diabetes and glucose tolerance as risk factors for cardiovascular disease: The Framingham study. Diabetes Care, 1979; 2: 120-126
2) Vaccaro O, Stamler J, Neaton JD: Sixteen-year coronary mortality in black and white men with diabetes screened for the Multiple Risk Factor Intervention Trial (MRFIT). Int J Epidemiol, 1998; 27: 636-641
3) Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M: Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med, 1998; 339: 229-234
4) The Emerging Risk Factors Collaboration: Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet, 2010; 375: 2215-2222
5) Ueshima H (editor): Cardiovascular evidence from NIPPON DATA. Japan Medical Journal, 2008
6) Fujishima M, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Yoshitake T: Diabetes and cardiovascular disease in a prospective population survey in Japan. The Hisayama study. Diabetes, 1996; 45 (Suppl 3): S14-S16
7) Yokoyama H, Matsushima M, Kawai K, Hirao K, Oishi M, Sugimoto H, Takeda H, Minami M, Kobayashi M, Sone H: Low incidence of cardiovascular events in Japanese patients with Type 2 diabetes in primary care settings: a prospective cohort study (JDDM 20). Diabet Med, 2011; 28: 1221-1228
8) Sone H, Tanaka S, Tanaka S, Iimuro S, Oida K, Yamasaki Y, Oikawa S, Ishibashi S, Katayama S, Ohashi Y, Akanuma Y, Yamada N; Japan Diabetes Complicatios Study Group: Serum levels of triglycerides is a potent risk factor comparable to LDL cholesterol for coronary heart disease in Japanese patients with Type 2 diabetes: Subanalysis of the Japan Diabetes Complications Study (JDCS). J Clin Endocrin Metab, 2011; 96: 3448-3456
9) Laing SP, Swerdlow AJ, Slater SD, Burden AC, Morris A, Waugh NR, Gatling W, Bingley PJ, Patterson CC: Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes. Diabetologia, 2003; 46: 760-765
10) Orchard TJ, Olson JC, Erbey JR, Williams K , Forrest KYZ, Kinder LS, Ellis D, Becker DJ: Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 diabetes. 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications study. Diabetes Care, 2003; 26: 1374-1379
11) Nesto RW, Phillips RT, Kett KG, Hill T, Perper E, Young E, Leland OS: Angina and exertional myocardial ischemia in diabetic and nondiabetic patients: Assessment by exercise thallium scintigraphy. Ann Intern Med, 1988; 108: 170-175
12) Goraya TY, Leibson CL, Palumbo PJ, Weston SA, Killian JM, Pfeifer EA, Jacobsen SJ, Frye RL, Roger VL: Coronary atherosclerosis in diabetes mellitus. A population based autopsy study. J Am Coll Cardiol, 2002; 40: 946-953

13) Ledru F, Ducimetiere P, Battaglia S, Courbon D, Beverelli F, Guize L, Guermonprez JL, Diebold B: New diagnostic criteria for diabetes and coronary artery disease: Insights from an angiographic study. J Am Coll Cardiol, 2001; 37: 1543-1550
14) Hoff JA, Quinn L, Sevrukov A, Lipton RB, Daviglus M, Garside DB, Ajmere NK, Gandhi S, Kondos GT: The prevalence of coronary artery calcium among diabetic individuals without known coronary artery disease. J Am Coll Cardiol, 2003; 41: 1008-1012
15) Iso H, Imano H, Kitamura A, Sato S, Naito Y, Tanigawa T, Ohira T, Yamagishi K, Iida M, Shimamoto T: Type 2 diabetes and risk of non-embolic ischaemic stroke in Japanese men and women. Diabetologia, 2004; 47: 2137-2144
16) Kobayashi S: The Japanese stroke databank 2009. Nakayama Shoten, 2009; 78-79
17) Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, Antman EM: Diabetes and mortality following acute coronary syndromes. JAMA, 2007; 298: 765-775
18) Takara A, Ogawa H, Endoh Y, Mori F, Yamaguchi J, Takagi A, Koyanagi R, Shiga T, Kasanuki H, Hagiwara N: Long-term prognosis of diabetic patients with acute myocardial infarction in the era of acute revascularization. Cardiovascular Diabetology, 2010; 366: 9: 1-7
19) Kasai T, Miyauchi K, Kajimoto K, Kubota N, Kurata T, Daida H: Influence of diabetes on >10-year outcomes after percutaneous coronary intervention. Heart Vessels, 2008; 23: 149-154
20) Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CDA: Cause of stroke recurrence is multifactorial patterns: risk factors and outcomes of stroke recurrence in the south London stroke register. Stroke, 2003; 34: 1457-1463
21) Shinohara Y, Gotoh F, Tohgi H, Hirai S, Terashi A, Fukuuchi Y, Otomo E, Itoh E, Matsuda T, Sawada T, Yamaguchi T, Nishimaru K, Ohashi Y: Antiplatelet cilostazol is beneficial in diabetic and/or hypertensive ischemic stroke patients. Subgroup analysis of the cilostazol stroke prevention study. Cerebrovasc Dis, 2008; 26: 63-70
22) Murabito JM, Agostino RBD, Silbershatz H, Wilson PWF: Intermittent claudication. A risk profile from the Framingham heart study. Circulation, 1997; 96: 44-49
23) Huxley R, Barzi F, Woodward M: Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ, 2006; 322: 73-78
24) Doi Y, Ninomiya T, Hata J, Fukuhara M, Yonemoto K, Iwase M, Iida M, Kiyohara Y: Impact of glucose tolerance status on development of ischemic stroke and coronary heart disease in a general Japanese population. The Hisayama study. Stroke, 2010; 41: 203-209
25) Fuller JH, Shipley MJ, Rose G, Jarrett RJ, Keen H: Coronary-heart-disease risk and impaired glucose tolerance. The Whitehall study. Lancet, 1980; 1: 1373-1376
26) Tominaga M, Eguchi H, Manaka H, Igarashi K, Kato T, Sekikawa A: Impaired glucose tolerance is a risk factor for cardiovascular disease, but not impaired fasting glucose. The Funagata diabetes study. Diabetes Care, 1999; 22: 920-924
27) DECODE study group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med, 2001; 161: 397-405
28) Nakagami T; DECODA Study Group: Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. Diabetologia, 2004; 47: 385-394
29) Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR, Holman RR: Risk factors for coronary artery disease in non-insulin dependent diabetes mellitus: United Kingdom Prospective Diabetes Study (UKPDS: 23). BMJ, 1998; 316: 823-828
30) Murakami K, Ishibashi S, Yamada N, Akanuma Y: Lipoprotein(a) as a coronary risk factor in Japanese patients with Type II (non-insulin-dependent) diabetes mellitus. Relation with apolipoprotein(a) phenotypes. Diabetologia, 1998; 41: 1397-1399
31) Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, Hallè JP, Young J, Rashkow A, Joyce C, Nawaz S, Yusuf S: Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA, 2001; 286: 421-426
32) Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR; UKPDS Group: Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). Kidney Int, 2003; 63: 225-232
33) Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY: Diabetic retinopathy and the risk of coronary heart disease. The atherosclerosis risk in communities study. Diabetes Care, 2007; 30: 1742-1746
34) Davis TME, Millns H, Stratton IM, Holman RR, Turner RC: Risk factors for stroke in type 2 diabetes mellitus. United Kingdom Prospective Diabetes Study (UKPDS 29). Arch Intern Med, 1999; 159: 1097-1103
35) Ciccarone E, Castelnuovo AD, Assanelli D, Archetti §S, Ruggeri G, Salcuni N, Donati MB, Capani F, Iacoviello L: Homocysteine levels are associated with the severity of peripheral arterial disease in Type 2 diabetic patients. J Thromb Haemost, 2003; 1: 2540-2547
36) Gæde P, Vedel P, Larsen N, Jensen GVH, Parving HH, Pedersen O: Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med, 2003; 348: 383-393
37) Gæde P, Lund-Andersen H, Parving HH, Pedersen O: Effect of a multifactorial intervention on mortality in type 2 diabetes. N Engl J Med, 2008; 358: 580-591
38) Araki S, Haneda M, Koya D, Hidaka H, Sugimoto T, Isono M, Isshiki K, Chin-Kanasaki M, Uzu T, Kashiwagi A: Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes. Diabetes, 2007; 56: 1727-1730
39) Berardis DG, Sacco M, Strippoli GFM, Pellegrini F, Graziano G, Tognoni G, Nicolucci A: Aspirin for primary prevention of cardiovascular events in people with diabetes: meta-analysis of randomised controlled trials. BMJ, 2009; 339: b4531
40) Lonn E, Yusuf S, Hoogwerf B, Pogue J, Yi Q, Zinman B,

Bosch J, Dagenais G, Mann JFE, Gerstein HC: Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes. Results of the HOPE study and MICRO-HOPE study. Diabetes Care, 2002; 25: 1919-1927
41) Iso H, Date C, Yamamoto A, Toyoshima H, Wtanabe Y, Kikuchi S, Koizumi A, Wada Y, Kondo T, Inaba Y, Tamacoshi A: Smoking cessation and mortality from cardiovascular disease among Japanese men and women: the JACC Study. Am J Epidemiol, 2005; 161: 170-179
42) Kuller LH, Ockene JK, Meilahn E, Wentworth DN, Svendsen KH, Neaton JD: Cigarette smoking and mortality. MRFIT research group. Prev Med, 1991; 20: 638-654
43) Manson JE, Greenland P, LaCroix AZ, Stefanick ML, Mouton CP, Oberman A, Perri MG, Sheps DS, Pettinger MB, Siscovick DS: Walking compared with vigorous exercise for the prevention of cardiovascular events in women. N Engl J Med, 2002; 347: 716-725
44) Noda H, Iso H, Toyoshima H, Date C, Yamamoto A, kikuchi S, Koizumi A, Kondo T, Watanabe Y, Wada Y, Inaba Y, Tamakoshi A: Walking and sports participation and mortality from coronary heart disease and stroke. J Am Coll Cardiol, 2005; 46: 1761-1767
45) Ornish D, Scherwitz LW, Billings JH, Gould KL, Merritt TA, Sparler S, Armstrong WT, Ports TA, Kirkeeide RL, Hogeboom C, Brand RJ: Intensive lifestyle changes for reversal of coronary heart disease. JAMA, 1998; 280: 2001-2007
46) Angermayr L, Melchart D, Linde K: Multifactorial lifestyle interventions in the primary and secondary prevention of cardiovascular disease and type 2 diabetes mellitus-a systematic review of randomized controlled trials. Ann Behav Med, 2010; 40: 49-64
47) Pi-Sunyer FX, Maggio CA, McCarron DA, Reusser ME, Stern JS, Haynes RB, Oparil S, Kris-Etherton P, Resnick LM, Chait A, Morris CD, Hatton DC, Metz JA, Snyder GW, Clark S, McMahon M: Multicenter randomized trial of a comprehensive prepared meal program in type 2 diabetes. Diabetes Care, 1999; 22: 191-197
48) Pastors JG, Franz M, Warshaw H, Kulkarni K, Daly A: The evidence for the effectiveness of medical nutrition therapy in diabetes management. Diabetes Care, 2002; 25: 608-613
49) Thomas D, Elliott EJ, Naughton GA: Exercise for type 2 diabetes mellitus (Review). Cochrane Database Syst Rev, 2006; CD002968
50) Al-Delaimy WK, Manson JE, Solomon CG, Kawachi I, Stampfer MJ, Willett WC, Hu FB: Smoking and risk of coronary heart disease among women with type 2 diabetes mellitus. Arch Intern Med, 2002; 162: 273-279
51) Hu FB, Stampfer MJ, Solomon C, Liu S, Colditz GA, Speizer FE, Willett WC, Manson JE: Physical activity and risk for cardiovascular events in diabetic women. Ann Intern Med, 2001; 134: 96-105
52) Heart Protection Study Collaborating Group: Heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomized placebo-controlled trial. Lancet, 2003; 361: 2005-2016
53) Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, Thomasan MJ, Mackness MI, Charlton-Menys V, Fuller JH: Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. Lancet, 2004; 364: 685
54) Cholesterol Treatment Trialists' (CTT) Collaborators: Efficacy of cholesterol-lowering therapy in 18686 people with diabetes in 14 randomised trials of statins: a meta-analysis. Lancet, 2008; 371: 117-125
55) FIELD study investigators: Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet, 2005; 366: 1849-1861
56) Action to Control Cardiovascular Risk in Diabetes Study Group: Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med, 2008; 358: 2545-2559
57) ACCORD Study Group: Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med, 2010; 362: 1563-1574
58) Oikawa S, Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K: Suppressive effect of EPA on the incidence of coronary events in hypercholesterolemia with impaired glucose metabolism: Sub-analysis of the Japan EPA lipid intervention study (JELIS). Atherosclerosis, 2009; 206: 535-539
59) Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, Wanner C, Krane V, Cass A, Craig J, Neal B, Jiang L, Hooi LS, Levin A, Agodoa L, Gaziano M, Kasiske B, Walker R, Massy ZA, Feldt-Rasmussen B, Krairittichai U, Ophascharoensuk V, Fellström B, Holdaas H, Tesar V, Wiecek A, Grobbee D, Zeeuw Dd, Gronhagen-Riska C, Dasgupta T, Lewis D, Herrington W, Mafham M, Majoni W, Wallendszus K, Grimm R, Pedersen T, Tobert J, Armitage J, Baxter A, Bray C, Chen Y, Chen Z,Hill M, Knott C, Parish S, Simpson D, Sleight P, Young A, Collins R; SHARP Investigators: The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of heart and renal protection): a randomised placebo-controlled trial. Lancet, 2011; 377: 2181-2192
60) Japan Atherosclerosis Society (JAS) (edit): Guidelines for prevention of atherosclerotic cardiovascular diseases 2007
61) Li C, Ford ES, Tsai J, Zhao G, Balluz LS, Gidding SS: Serum non-high-density lipoprotein cholesterol concentration and risk of death from cardiovascular disease among U.S. adults with diagnosed diabetes: the third national health and nutrition examination survey linked mortality study. Cardiovasc Diabetol, 2011; 10: 46-58
62) 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
63) American diabetes association: Clinical practice recommendations 2011. Diabetes Care, 2011; 34 (Suppl 1): S29-S31
64) Reiner Z, Catapano AL, Backer GD, Graham I, Taskinen

MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D: ESC/EAS 172 guidelines for the management of dyslipidemias: The task force for the management of dyslipidemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J, 2011; 32: 1769-1818
65) Mabuchi H: J-LIT chart 1. Primary prevention of coronary artery disease in Japanese population: coronary risk factors. Domyaku Koka, 2001; 29: 296
66) Mabuchi H: Overlap of risk factors and coronary events. The Lipid, 2007; 18: 63-72
67) Oikawa S, Kita T, Mabuchi H, Matsuzaki M, Matsuzawa Y, Nakaya N, Saito Y, Sasaki J, Shimamoto K, Itakura H: Risk of coronary events in Japanese patients with both hypercholesterolemia and type 2 diabetes mellitus on low-dose simvastatin therapy: Implication from Japan Lipid Intervention Trial (JLIT). Atherosclerosis, 2007; 191: 440-446
68) Kashiwagi A, Kida Y, Harada N, Kikkawa R: Macrovascular complications as risk factors for diabetic retinopathy: Microvascular and macrovascular complications. Folia ophthalmologica Japonica, 2000; 51: 7-10
69) Yokoyama H, Oishi M, Kawai K, Sone H: Reduced GFR and microalbuminuria are independently associated with prevalent cardiovascular disease in type 2 diabetes: JDDM study 16. Diabet Med, 2008; 25: 1426-1432
70) Ito H, Takeuchi Y, Ishida H, Antoku S, Abe M, Mifune M, Togane M: High frequencies of diabetic micro-and macroangiopathies in patients with type 2 diabetes mellitus with decreased estimated glomerular filtration rate and normoalbuminuria. Nephrol Dial Transplant, 2010; 25: 1161-1167
71) Stratton IM, Adler AI, Neil HAW, Matthews DR, Manley SE, Cull CA, Hadden D, Turner RC, Holman RR: Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ, 2000; 321: 405-412
72) Nishimura R, Nakagami T, Sone H, Ohashi Y, Tajima N: Relationship between hemoglobin A1c and cardiovascular disease in mild-to-moderate hypercholesterolemic Japanese individuals: subanalysis of a large-scale randomized controlled trial. Cardiovasc Diabetol, 2011; 10: 58-63
73) Nakanishi S, Yamada M, Hattori N, Suzuki G: Relationship between HbA1c and mortality in a Japanese population. Diabetologia, 2005; 48: 230-234
74) Kadota A, Hozawa A, Okamura T, Kadowaki T, Nakamura K, Murakami Y, Hayakawa T, Kita Y, Okayama A, Nakamura Y, Kashiwagi A, Ueshima H: Relationship between metabolic risk factor clustering and cardiovascular mortality stratified by high blood glucose and obesity. NIPPON DATA90, 1990-2000. Diabetes Care, 2007; 30: 1533-1538
75) Krempf M, Parhofer KG, Steg G, Bhatt DL, Ohman EM, Röther J, Goto S, Pasquet B, Wilson PWF: Cardiovascular event rates in diabetic and nondiabetic individuals with and without established atherothrombosis [from the Reduction of Atherothrombosis for Continued Health (REACH) registry]. Am J Cardiol, 2010; 105: 667-671
76) Ninomiya T, Kubo M, Doi Y, Yonemoto K, Tanizaki Y, Rahman M, Arima H, Tsuruya K, Iida M, Kiyohara Y: Impact of metabolic syndrome on the development of cardiovascular disease in a general Japanese population. The Hisayama study. Stroke, 2007; 38: 2063-2069

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 –

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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

Received February 2, 2014; revised manuscript received March 11, 2014; accepted March 13, 2014; released online March 21, 2014
Time for primary review: 18 days

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This paper was presented at the 78th Annual Scientific Meeting of the Japanese Circulation Society, Late Breaking Clinical Trials 1-3 (March 21, 2014, Tokyo, Japan).

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ISSN-1346-9843 doi:10.1253/circj.CJ-14-0130

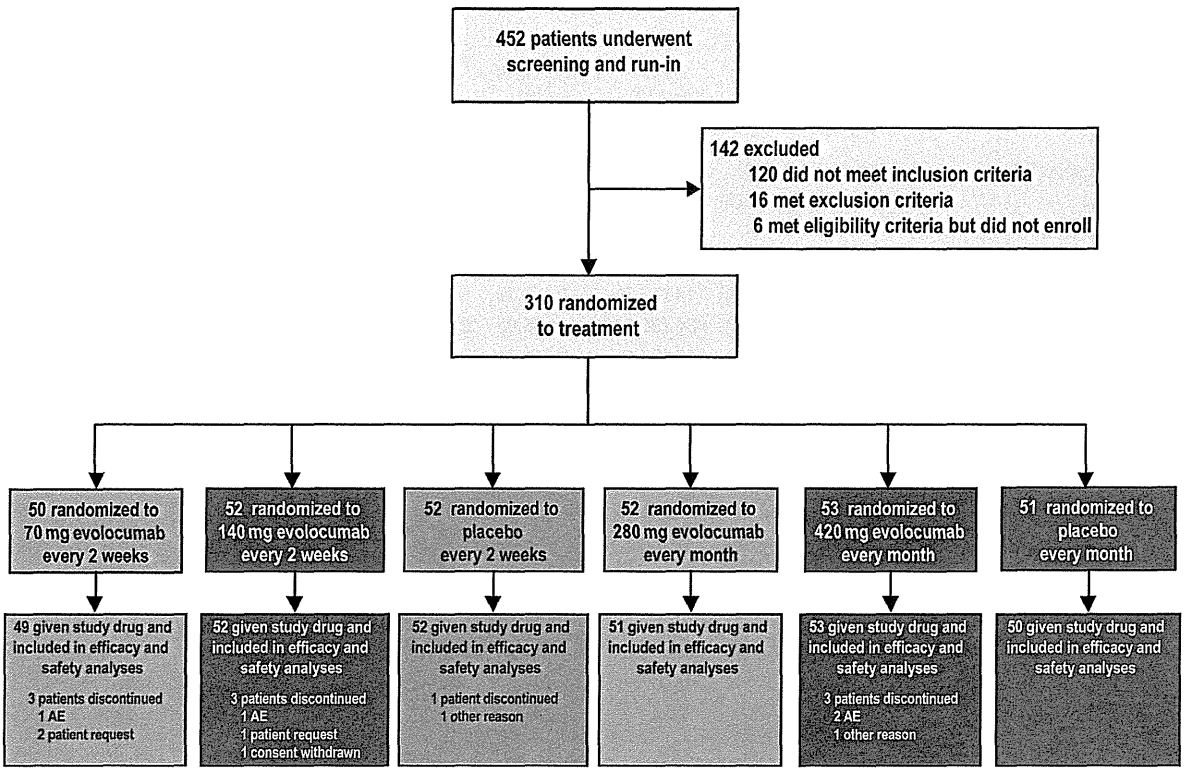

Figure 1. Disposition of patients in YUKAWA (Stud**Y** of LDL-Cholesterol Reduction **U**sing a Monoclonal PCS**K**9 **A**ntibody in Japanese Patients **W**ith **A**dvanced Cardiovascular Risk).

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	Evolocumab QM		Placebo QM
	70 mg (n=49)	140 mg (n=52)	(n=52)	280 mg (n=51)	420 mg (n=53)	(n=50)
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

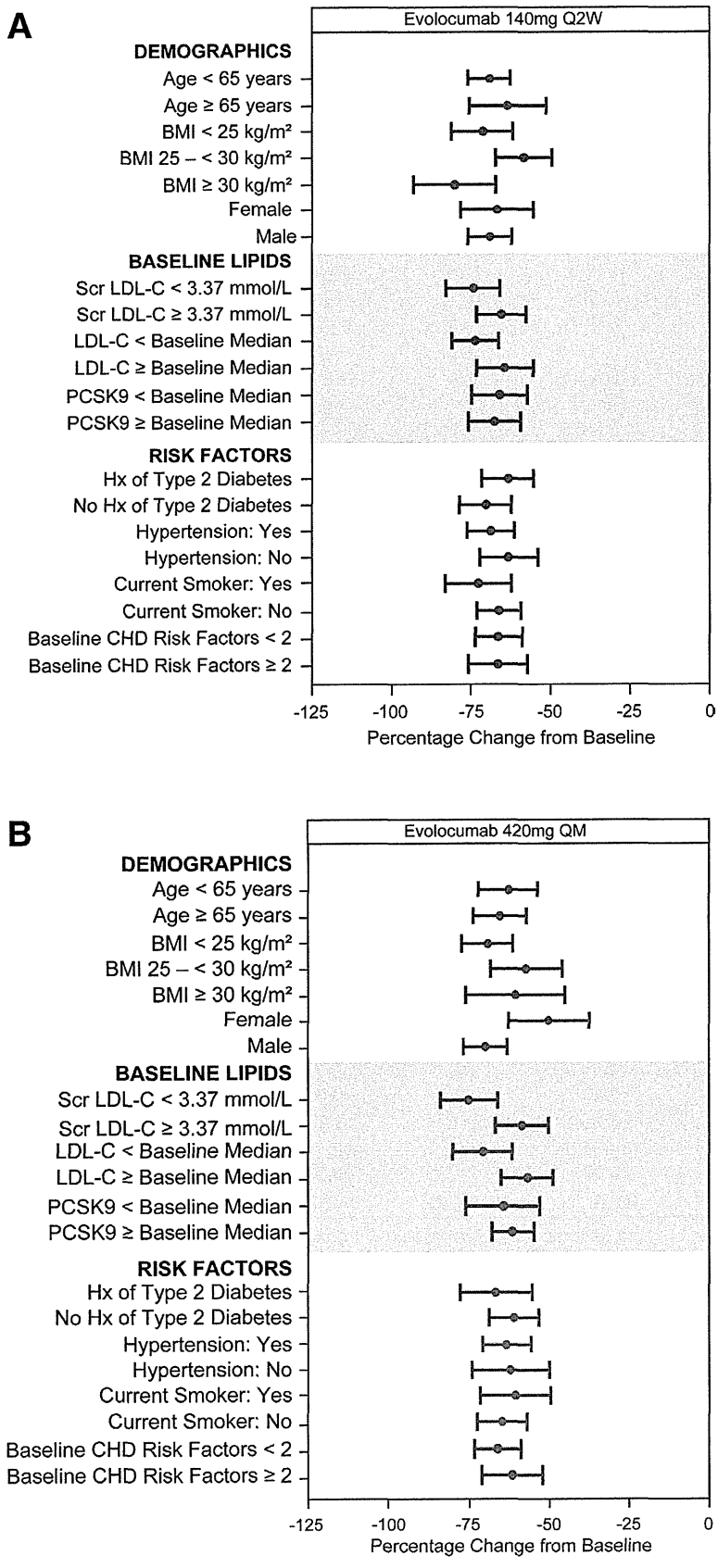

Figure 2. Mean percentage change in LDL-C measured by ultracentrifugation in the main subgroups given evolocumab either 140mg SC Q2W (**A**) or 420mg SC QM (**B**). Values reported are least-squares mean differences (95% CI) compared with matching placebo. Values less than 0 favor evolocumab, whereas 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.

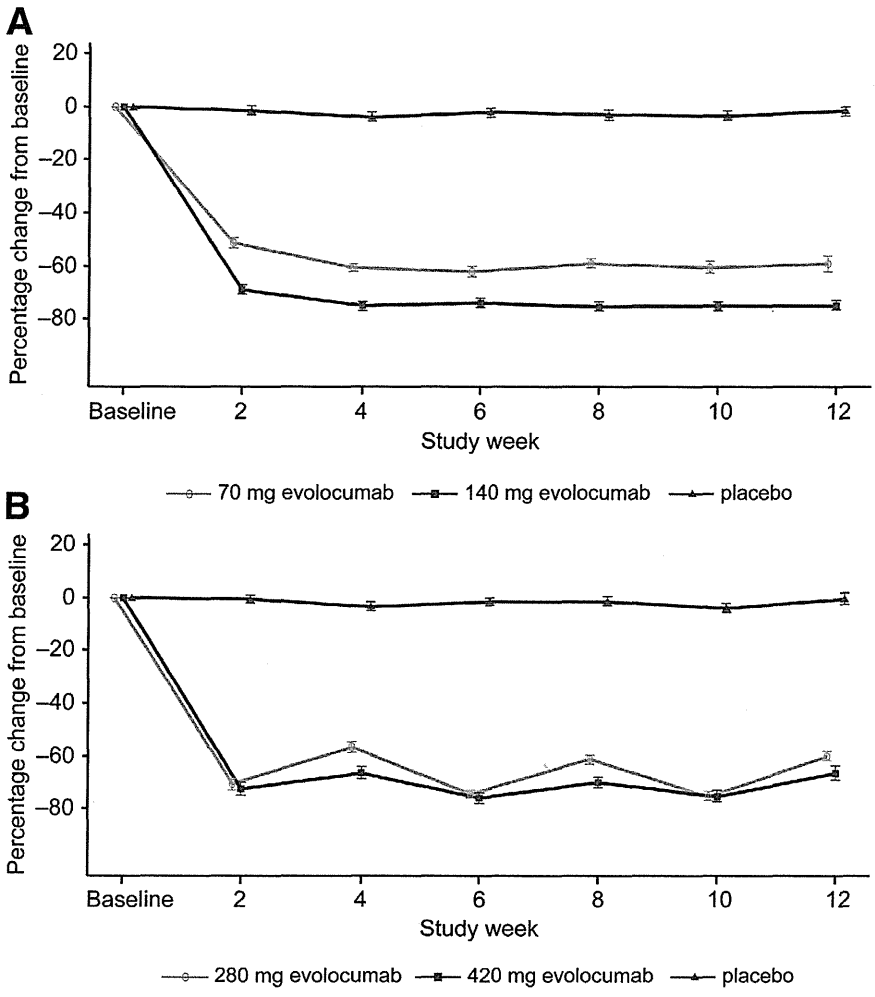

Figure 3. Mean percentage change in calculated LDL-C concentration from baseline by visit Q2W (**A**) or QM (**B**). Error bars indicate standard error (SE). Results are based on observed data. LDL-C, low-density lipoprotein cholesterol; Q2W, every 2 weeks; QM, monthly.

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-

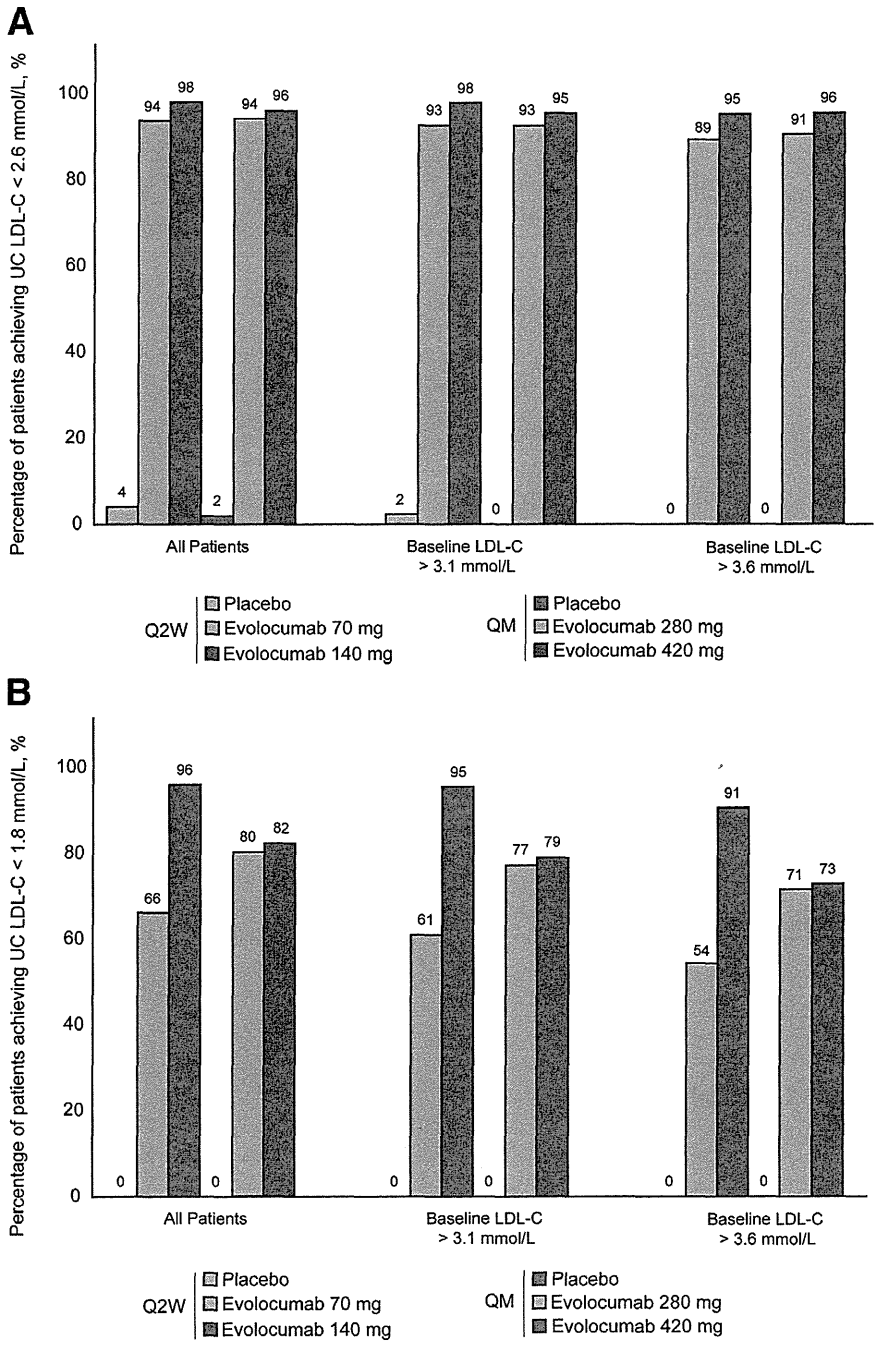

Figure 4. Frequency of attaining week-12 LDL-C targets measured by ultracentrifugation and stratified by baseline LDL-C. Percentage of patients reaching (**A**) LDL-C <2.6mmol/l or (**B**) LDL-C <1.8mmol/L. Percentages are based on the number of patients within each subgroup. LDL-C, low-density lipoprotein 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 >5×ULN	NA	0 (0.0)	NA	1 (0.6)	1 (1.0)	0 (0.0)
CK >10×ULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	0 (0.0)
AST or ALT >3×ULN	NA	0 (0.0)	NA	0 (0.0)	0 (0.0)	1 (2.1)
Total bilirubin >2×ULN	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

CV risk factors (**Figure 2**).

Although AEs were more frequent in patients receiving evolocumab vs. placebo, the majority were CTCAE grade 1 or 2 (mild or moderate), and showed no appreciable relationship to dose or dose frequency. Serious AEs were infrequent (2% evolocumab vs. 0% placebo), and none was considered to be treatment related. In addition, elevations in CK (0.5% evolocumab; 1.0% placebo) and aspartate aminotransferase (AST) and alanine aminotransferase (ALT; 0.5% evolocumab, 0% placebo) were rare. As evolocumab is a monoclonal antibody, patients were actively monitored for hypersensitivity- and immunogenicity-related side effects, such as injection-site reactions and antidrug antibodies:[25] 4 patients in the evolocumab group reported potential injection-site reactions, and none of the evolocumab-treated patients was found to have antidrug antibodies (binding or neutralizing). One patient in the placebo group was reported to have a positive evolocumab-binding antibody titer at the week 12 visit. This finding likely reflects non-specific evolocumab-binding antibodies that were detected by a highly sensitive assay. This case was not associated with any reported AE or alteration in patient treatment.

Intracerebral hemorrhage and cognitive impairment have been reported as potential causes of concern in the context of lipid reduction with statins.[26,27] A recent longer term study of evolocumab in approximately 1,100 subjects did not identify a difference in the incidence of either hemorrhagic stroke or cognitive impairment between the evolocumab (plus standard of care) arm vs. standard of care alone, irrespective of achieved LDL-C.[28] Similarly, in YUKAWA, there were no reported cases of hemorrhagic stroke or cognitive impairment over the study period. Rates of other AEs, serious AEs, myalgia, and CK and AST/ALT elevations were comparable between patients who achieved low (<1.04 mmol/L) or very low (<0.65 mmol/L) LDL-C levels. These results suggest that evolocumab can be used effectively and safely to reduce LDL-C in Japanese patients. As YUKAWA was a 12-week study, the long-term safety of achieving low and very low LDL-C will be better understood once longer term data are available for Japanese patients.

Current guidelines for lipid management recommend targeting either specific LDL-C concentrations (<2.6 mmol/L or <1.8 mmol/L),[29–31] or a percentage reduction in LDL-C (≥50%) for high-risk patients.[32] However, patients receiving statin therapy may not be able to achieve these goals,[33–35] and patient risk for CVD could be lowered with additional LDL-C reduction using other therapies.[30,31,33] In this study, the baseline LDL-C for high-risk patients was 3.7 mmol/L, despite stable use of background statin therapy. After 12 weeks of treatment with evolocumab, patients showed LDL-C reductions of up to 69%, and most (up to 96%) of the evolocumab-treated patients achieved LDL-C levels <1.8 mmol/L. Stable LDL-C reductions of the magnitude described here have not been seen with other classes of non-statin therapies.[36,37]

Close to half of high-risk Japanese patients are not at recommended LDL-C levels.[11,12] Thus, long-term use of evolocumab is poised to become an important treatment option for patients at high cardiovascular risk and/or unable to achieve their lipid goal. The YUKAWA study results suggest that novel, antibody-based therapies such as evolocumab may be used effectively and safely to reduce LDL-C in Japanese patients. Results from a large, ongoing cardiovascular outcomes trial will help elucidate whether the additional LDL-C lowering seen with evolocumab is associated with a reduction in cardiovascular events.[38]

Conclusions

Evolocumab Q2W or QM in combination with background statin therapy demonstrated robust efficacy and was well tolerated in a 12-week study in high-cardiovascular-risk Japanese patients with hypercholesterolemia. The greatest LDL-C reductions from baseline were observed with the 140 mg Q2W and 420 mg QM dosages. These findings support the continued investigation of evolocumab treatment in Japanese patients in a similarly designed phase 3 study currently underway (NCT01953328).

Acknowledgments

Statistical programming support was provided by Wei Cui, MS, of Amgen Inc and Qingwen Zhao, MS, on behalf of Amgen Inc. Editorial support was provided by Annalise M. Nawrocki, PhD, of Amgen Inc.

Disclosures

This study was funded by Amgen, Inc.

Atsushi Hirayama received honoraria from Bayer Pharmaceutical Co, Astellas Pharma Inc, Daiichi-Sankyo Pharmaceutical Co. Sanofi K.K., Sanwa Kagaku Kenkyusho Co, Boehringer Ingelheim Japan, Kyowa Hakko Kirin Co Ltd, Takeda Pharmaceutical Co Ltd, Kowa Co Ltd, Kissei Pharmaceutical Co Ltd, MSD K.K., Shionogi Pharmaceutical Co, Eizai Co Ltd, Chugai Pharmaceutical Co, Pfizer Japan, Otsuka Pharmaceutical Co, Tanabe Mitsubishi Pharmaceutical Co, Novartis Pharma K.K., and Astra Zeneca Co and received research support to institution from Astellas Pharmaceutical Co, Astra-Zeneca K.K., Eisai Co, Ltd, MSD, Otsuka Pharmaceutical Co Ltd, ONO Pharmaceutical Co Ltd, Kissei Pharmaceutical Co Ltd, Kyowa Hakko Kirin Co Ltd, Goodman Co Ltd, KOWA Pharmaceutical Co Ltd, Sanofi K.K., Shionogi & Co Ltd, Genzyme Japan K.K., Zeon Medical Inc, Daiichi Sankyo Co Ltd, Dainippon Sumitomo Pharma Co Ltd, Takeda Pharmaceutical Co Ltd, Mitsubishi Tanabe Pharma Corporation, Chugai Pharmaceutical Co Ltd, Toa Eiyo Ltd, Nippon Boehringer Ingelheim Co Ltd, Nihon Medi-Physics Co Ltd, Medtronic Japan Co Ltd, Novartis Pharma K.K., Pfizer Japan Inc, and Mochida Pharmaceutical Co Ltd. Shizuya Yamashita received honoraria from MSD, Bayer, and Kowa; served on advisory boards for Skylight Biotech, Kowa, Otsuka, and Amgen; received research support from MSD, Bayer, Astellas, Kowa, Shionogi, Otsuka Pharmaceutical Co, Kissei, and Boehringer. Tamio Teramoto received support from Astellas K.K., MSD K.K., Kowa K.K., Kissei K.K., Daiichi Sankyo K.K., Pfizer K.K., Bayer K.K., GSK K.K., Shionogi K.K., and Kobayashi K.K. Narimon Honarpour, Fannie Huang, and Scott M. Wasserman are employees of Amgen Inc and own Amgen stock/stock options. Masayuki Yoshida has no disclosures to report.

References

1. Global Atlas on Cardiovascular Disease Prevention and Control 2011. http://www.paho.org/hq/index.php?option=com_docman&task=doc_view&gid=21049&Itemid= (accessed 9 December, 2013).
2. Iso H. Lifestyle and cardiovascular disease in Japan. *J Atheroscler Thromb* 2011; **18:** 83–88.
3. Imano H, Noda H, Kitamura A, Sato S, Kiyama M, Sankai T, et al. 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.
4. Saito I, Folsom AR, Aono H, Ozawa H, Ikebe T, Yamashita T. Comparison of fatal coronary heart disease occurrence based on population surveys in Japan and the USA. *Int J Epidemiol* 2000; **29:** 837–844.
5. Downs JR, Clearfield M, Tyroler HA, Whitney EJ, Kruyer W, Langendorfer A, et al. Air Force/Texas Coronary Atherosclerosis Prevention study (AFCAPS/TEXCAPS): Additional perspectives on tolerability of long-term treatment with lovastatin. *Am J Cardiol* 2001; **87:** 1074–1079.
6. Ridker P, MacFadyen J, Fonseca F, Genest J, Gotto A, Kastelein J, et al. Number needed to treat with rosuvastatin to prevent first cardiovascular events and death among men and women with low low-density lipoprotein cholesterol and elevated high-sensitivity C-reactive protein: Justification for the use of statins in prevention: An intervention trial evaluating rosuvastatin (JUPITER). *Circ Cardiovasc Qual Outcomes* 2009; **2:** 616–623.
7. Sever PS, Chang CL, Gupta AK, Whitehouse A, Poulter NR, ASCOT Investigators. The Anglo-Scandinavian Cardiac Outcomes Trial:

11-year mortality follow-up of the lipid-lowering arm in the UK. *Eur Heart J* 2011; **32:** 2525–2532.
8. Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, et al. Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia: West of Scotland Coronary Prevention Study Group. *N Engl J Med* 1995; **333:** 1301–1307.
9. Shurtleff D. Some characteristics related to the incidence of cardiovascular disease and death: Framingham study, 18-year follow-up. *In*: Kannel WB, Gordon T, editors. Washington, D.C.: Department of.Health, Education, and Welfare, 1974.
10. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, et al. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): A prospective randomised controlled trial. *Lancet* 2006; **368:** 1155–1163.
11. Kurihara Y, Douzono T, Kawakita K, Fujita S, Nachi S, Nagasaka Y. A Large-scale, long-term, prospective post-marketing surveillance of pitavastatin (LIVALO® Tablet). *Jpn Pharmacol Ther* 2007; **35:** 9–40.
12. Teramoto T, Sasaki J, Ishibashi S, Birou S, Daida H, Dohi S, 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* 2013; **20:** 517–523.
13. Horton JD, Cohen JC, Hobbs HH. PCSK9: A convertase that coordinates LDL catabolism. *J Lipid Res* 2009; **50:** S172–S177.
14. Chan JC, Piper DE, Cao Q, Liu D, King C, Wang W, et al. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. *Proc Natl Acad Sci USA* 2009; **106:** 9820–9825.
15. Ni YG, Condra JH, Orsatti L, Shen X, Di Marco S, Pandit S, et al. A proprotein convertase subtilisin-like/kexin type 9 (PCSK9) C-terminal domain antibody antigen-binding fragment inhibits PCSK9 internalization and restores low density lipoprotein uptake. *J Biol Chem* 2010; **285:** 12882–12891.
16. Koren MJ, Scott R, Kim JB, Knusel B, Liu T, Lei L, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 as monotherapy in patients with hypercholesterolaemia (MENDEL): A randomised, double-blind, placebo-controlled, phase 2 study. *Lancet* 2012; **380:** 1995–2006.
17. Giugliano RP, Desai NR, Kohli P, Rogers WJ, Somaratne R, Huang F, et al. Efficacy, safety, and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolaemia (LAPLACE-TIMI 57): A randomised, placebo-controlled, dose-ranging, phase 2 study. *Lancet* 2012; **380:** 2007–2017.
18. Raal F, Scott R, Somaratne R, Bridges I, Li G, Wasserman SM, et al. Low-density lipoprotein cholesterol-lowering effects of AMG 145, a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease in patients with heterozygous familial hypercholesterolemia: The Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) randomized trial. *Circulation* 2012; **126:** 2408–2417.
19. Stein EA, Honarpour N, Wasserman SM, Xu F, Scott R, Raal FJ. Effect of the proprotein convertase subtilisin/kexin 9 monoclonal antibody, AMG 145, in homozygous familial hypercholesterolemia. *Circulation* 2013; **128:** 2113–2120.
20. Sullivan D, Olsson AG, Scott R, Kim JB, Xue A, Gebski V, et al. Effect of a monoclonal antibody to PCSK9 on low-density lipoprotein cholesterol levels in statin-intolerant patients: The GAUSS randomized trial. *JAMA* 2012; **308:** 2497–2506.
21. Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, et al. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb* 2007; **14:** 45–50.
22. Robinson J, Rogers WJ, Nedergaard BS, Fialkow J, Neutel JM, Ramstad D, et al. Rationale and design of LAPLACE-2: A phase 3, randomized, double-blind, placebo- and ezetimibe-controlled trial evaluating the efficacy and safety of AMG 145 in subjects with hypercholesterolemia on background statin therapy. *Clin Cardiol* 2014 January 30, doi:10.1002/clc.22252 [Epub ahead of print].
23. Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf (accessed 9 December, 2013).
24. Teramoto T, Shaywitz A, Hamilton L, Crispino C, Xu R, Emery M, et al. A phase 1, randomized, double-blind, placebo-controlled study of AMG 145 comparing the pharmacokinetics, pharmacodynamics, and safety in healthy Japanese and Caucasian subjects. *In*: Proceedings of 45th Annual Scientific Meeting of the Japan Atherosclerosis Society, Tokyo, Japan, 2013.
25. Foltz IN, Karow M, Wasserman SM. Evolution and emergence of therapeutic monoclonal antibodies. What cardiologists need to know. *Circulation* 2013; **127:** 2222–2230.
26. Cholesterol Treatment Trialists (CTT) Collaboration, Baigent C, Blackwell L, Emberson J, Holland L, Reith C, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: A meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010; **376:** 1670–1681.
27. Jukema JW, Cannon CP, de Craen AJ, Westendorp RG, Trompet S. The controversies of statin therapy: Weighing the evidence. *J Am Coll Cardiol* 2012; **60:** 875–881.
28. Koren MJ, Giugliano RP, Raal FJ, Sullivan D, Bolognese M, Langslet G, et al. Efficacy and Safety of Longer-Term Administration of Evolocumab (AMG 145) in Patients With Hypercholesterolemia: 52-Week Results From the Open-Label Study of Long-Term Evaluation Against LDL-C (OSLER) Randomized Trial. *Circulation* 2014; **129:** 234–243.
29. Anderson TJ, Grégoire J, Hegele RA, Couture P, Mancini GBJ, McPherson R, et al. 2012 Update of the Canadian Cardiovascular Society Guidelines for the Diagnosis and Treatment of Dyslipidemia for the Prevention of Cardiovascular Disease in the Adult. *Can J Cardiol* 2013; **29:** 151–167.
30. Grundy SM. An International Atherosclerosis Society Position Paper: Global recommendations for the management of dyslipidemia. *J Clin Lipidol* 2013; **7:** 561–565.
31. Perk J, De Backer G, Gohlke H, Graham I, Reiner Ž, Verschuren M, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). *Eur Heart J* 2012; **33:** 1635–1701.
32. Stone NJ, Robinson J, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*, 2013 November 12, doi:10.1161/01.cir.0000437738.63853.7a [Epub ahead of print].
33. LaRosa JC, Grundy SM, Waters DD, Shear C, Barter P, Fruchart J-C, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med* 2005; **352:** 1425–1435.
34. Pedersen TR, Faergeman O, Kastelein JJ, Olsson AG, Tikkanen MJ, Holme I, et al. High-dose atorvastatin vs usual-dose simvastatin for secondary prevention after myocardial infarction: The IDEAL Study: A randomized controlled trial. *JAMA* 2005; **294:** 2437–2445.
35. Santos RD, Waters DD, Tarasenko L, Messig M, Jukema JW, Chiang CW, et al. A comparison of non-HDL and LDL cholesterol goal attainment in a large, multinational patient population: The Lipid Treatment Assessment Project 2. *Atherosclerosis* 2012; **224:** 150–153.
36. Matsue Y, Matsumura A, Suzuki M, Hashimoto Y, Yoshida M. Differences in action of atorvastatin and ezetimibe in lowering low-density lipoprotein cholesterol and effect on endothelial function: Randomized controlled trial. *Circ J* 2013; **77:** 1791–1798.
37. Okada K, Kimura K, Iwahashi N, Endo T, Himeno H, Fukui K, et al. Clinical usefulness of additional treatment with ezetimibe in patients with coronary artery disease on statin therapy: From the viewpoint of cholesterol metabolism. *Circ J* 2011; **75:** 2496–2504.
38. Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER). http://clinicaltrials.gov/ct2/show/NCT01764633. (accessed 29 August, 2013).

Supplementary Files

Supplementary File 1

Inclusion/Exclusion criteria

Supplementary File 2

Table S1. Baseline lipid-lowering therapy

Table S2. Efficacy at 12 weeks

Table S3. Efficacy: mean of weeks 10 and 12

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-14-0130

Original Article

Lipid and Blood Pressure Control for the Prevention of Cardiovascular Disease in Hypertensive Patients: A Subanalysis of the OMEGA Study

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Aim: The aim of this analysis was to investigate the relationships between dyslipidemia, achieved blood pressure (BP) values and the lipid levels, as well as the control of four cardiovascular risk factors (BP, low-density lipoprotein: LDL cholesterol, hemoglobin A1c: HbA1c and smoking) and the incidence of cardiovascular disease (CVD), in Japanese patients receiving antihypertensive therapy.
Methods: A total of 13,052 patients with no history of CVD were included in this subanalysis of the prospective observational OMEGA study in Japanese hypertensive patients treated with olmesartan. Multivariable Cox regression models were used to evaluate the relationship with the risk of CVD.
Results: The incidence of CVD during the 36-month study period was 5.59/1,000 patient-years among the patients with dyslipidemia (n=6,297) and 5.57/1,000 patient-years among the patients without dyslipidemia (n=6,755), with no significant differences between the two groups. Higher achieved BP values tended to be associated with an increased CVD risk in both the patients with and without dyslipidemia. In addition, the risk of CVD tended to be higher in the patients with an achieved LDL cholesterol level of ≥120 mg/dL than in those with an LDL level of <120 mg/dL (trend p=0.0005) and in the patients with an achieved high-density lipoprotein cholesterol level of <60 mg/dL than in those with an HDL level of ≥60 mg/dL (trend p=0.0017). Furthermore, the risk of CVD was higher among the patients with fewer controlled risk factors than among those with control of all four risk factors (trend p<0.0001).
Conclusions: In order to prevent CVD in olmesartan-treated hypertensive patients with no history of CVD, it is important to control both the lipid and BP levels and aim for comprehensive risk factor control.

J Atheroscler Thromb, 2015; 22:62-75.

Key words: Cardiovascular event, Dyslipidemia, Hypertension, Comprehensive risk factor control, Olmesartan medoxomil

Introduction

Atherosclerotic cardiovascular disease (CVD) is a leading underlying cause of death in Japan, whose population is aging rapidly. Therefore, effective strategies for preventing CVD are urgently needed.

One such strategy is to aggressively control both dyslipidemia and hypertension. Dyslipidemia is an important risk factor for CVD, and epidemiologic studies have shown that higher low-density lipoprotein (LDL) cholesterol[1)] and non-high-density lipoprotein (HDL) cholesterol levels[2)] and lower HDL

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Received: March 30, 2014
Accepted for publication: July 13, 2014

cholesterol levels[3-5] are associated with an increased incidence of coronary heart disease (CHD). Another important risk factor for CVD is hypertension. Hypertension is closely related to cerebrovascular disorders[6, 7]; individuals with higher blood pressure (BP) values are more likely to develop cerebrovascular diseases[8, 9]. Furthermore, the coexistence of dyslipidemia and hypertension increases the risk of arteriosclerosis[4].

Among hypercholesterolemic patients with hypertension, aggressive LDL cholesterol-lowering treatment may prevent the incidence or recurrence of ischemic heart disease and stroke[10]. In addition, diet therapy combined with pravastatin treatment is effective in the primary prevention of CVD, reducing the risk of cerebral infarction by 46%, in Japanese patients with mild-to-moderate dyslipidemia complicated by hypertension[11]. However, few reports have addressed the relationship between the achieved BP value, lipid levels and incidence of CVD in Japanese patients in clinical practice.

The Japan Atherosclerosis Society *Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases* recommend the comprehensive control of dyslipidemia, hypertension and other risk factors, such as diabetes mellitus and smoking, in order to prevent atherosclerotic disease[12]. However, few reports have addressed the relationship between comprehensive risk factor control and the incidence of CVD in Japanese patients in clinical practice.

The Olmesartan Mega Study to Determine the Relationship Between Cardiovascular Endpoints and Blood Pressure Goal Achievement (OMEGA study) is a large-scale prospective observational study designed primarily to evaluate the relationships between the achieved BP, metabolic syndrome, lifestyle factors (e.g. dietary habits), other risk factors and the incidence of CVD in Japanese hypertensive patients treated with olmesartan medoxomil. We previously reported the relationships between the achieved BP, dietary habits, metabolic syndrome and the incidence of CVD[13]. In addition, we reported that diabetes mellitus is an important risk factor for CVD, cerebrovascular events (stroke) and CHD and that dyslipidemia is an important risk factor for CHD[14]. In addition, previous reports have described the relationships between diabetes mellitus, achieved BP, hemoglobin A1c (HbA1c, National Glycohemoglobin Standardization Program) and the incidence of CVD[15].

Aim

Our aim was to investigate the relationships between the incidence of CVD and dyslipidemia, achieved BP and the lipid levels in patients with no history of CVD using data obtained from the OMEGA study. The relationship between the comprehensive control of four CVD risk factors (BP, LDL cholesterol, HbA1c and smoking) and the incidence of CVD was also analyzed.

Methods

The OMEGA study was conducted as a prospective, large-scale observational study from July 2005 to March 2010 by Sankyo Co., Ltd. (presently Daiichi Sankyo Co., Ltd.). The study protocol was approved by the Ethics Committee of Sankyo Co., Ltd., as well as the Ministry of Health, Labour and Welfare of Japan before commencement, and conformed with the pharmaceutical affairs laws of Japan. Furthermore, the study conformed to the Helsinki Declaration of 1975 as revised in 1983 and was carried out at registered medical institutions according to Good Postmarketing Study Practices in Japan. The survey data were collected via the Internet using a validated electronic data-capturing system (PostMaNet; Fujitsu FIP, Tokyo, Japan). The protocol for the OMEGA study is described briefly below. Further details of the protocol are available in a previous publication[16].

Patients

Male and female outpatients 50-79 years of age with essential hypertension who had not been previously treated with olmesartan were enrolled in the OMEGA study. The exclusion criteria were a history of myocardial infarction, stroke, coronary artery bypass grafting or percutaneous coronary intervention within six months prior to enrollment, as well as scheduled coronary intervention, congenital or rheumatic heart disease, severe arrhythmia, severe hepatic or renal disease, cancer that was currently under treatment and pregnancy or the potential to become pregnant.

The patients were enrolled using the central registration system. Written informed consent was obtained from each patient, and a questionnaire survey regarding lifestyle and habits was conducted prior to the start of the study. This subanalysis was carried out in order to investigate the incidence of initial CVD in patients without a history of the disorder.

Observation Items and Period

The observation items included the following information: patient characteristics, lifestyle factors and habits; exposure to olmesartan and concomitant

drugs; concomitant therapies; BP; pulse rate; laboratory results; and incidence of CVD. The observation period was three years from the start of treatment with olmesartan. Observation was continued even if the olmesartan treatment was discontinued and terminated if a patient was lost to follow-up or withdrew their consent. The method of BP measurement was not specified, and the BP values were obtained according to the routine procedures used at each institution. Data for the BP, pulse rate and laboratory tests were collected before study initiation and every six months thereafter. If available, any applicable values measured in daily clinical practice during the study period were also collected.

Events

Cardiovascular disease was defined as a composite of the following events: stroke (cerebral infarction, cerebral hemorrhage or subarachnoid hemorrhage), CHD (myocardial infarction, cardiac intervention or hospitalization for angina) and sudden death. CVD was defined as a composite endpoint comprising the above three endpoints.

The diagnostic criteria for the various endpoints have been previously described in detail[13, 16].

Definition of Dyslipidemia

In this subanalysis, patients who met either of the following conditions were considered to have dyslipidemia and those who met neither condition were considered to be without dyslipidemia: patients who had been diagnosed by their physician as having dyslipidemia at the start of the study and those who were receiving treatment with any lipid-lowering drugs at the start of the study.

Statistical Analysis

The patient characteristics of the dyslipidemia and non-dyslipidemia groups were compared using the *t*-test for continuous variables and the chi-squared test for categorized variables. Data for BP, LDL cholesterol and HDL cholesterol were analyzed by comparing the values obtained at baseline and each visit using the Dunnett-Hsu test. The incidence of CVD during the study period was compared between the dyslipidemia and non-dyslipidemia groups using the log-rank test. The relationships between the achieved BP values and lipid levels and the risk of CVD were evaluated using the Cox proportional hazards model, including the achieved BP values or lipid levels as time-dependent covariates and sex, age, family history of coronary arthery disease, HbA1c (time-dependent covariate), dyslipidemia (only in comparisons between the dyslipidemia and non-dyslipidemia groups), body mass index and smoking as adjusted factors. BP was classified using cut-off values of 130/85 mmHg and 140/90 mmHg, in accordance with the JSH 2009 criteria[17]. In the analyses of the relationships between the lipid levels and the risk of CVD, the achieved BP value was also applied as a time-dependent adjusted factor. The lipid levels were classified using the following cut-off values: LDL cholesterol <120 mg/dL, 140 mg/dL and 160 mg/dL, and HDL cholesterol <40 mg/dL and 60 mg/dL, in accordance with the Japan Atherosclerosis Society Guidelines for the Prevention of Atherosclerotic Cardiovascular Diseases 2012[12].

The relationship between comprehensive risk factor control and the risk of CVD was evaluated using the Cox proportional hazards model, including each risk factor (LDL cholesterol, BP, HbA1c and smoking) or the number of controlled risk factors as covariates, adjusted for sex, age, family history of coronary arthery disease and body mass index.

The degree of control of LDL cholesterol (adequately controlled: <120 mg/dL), BP (adequately controlled: $<140/90$ mmHg) and HbA1c (adequately controlled: $<6.9\%$) was assessed based on the mean measurements obtained during the study period. The degree of control of smoking (adequately controlled: non-smoking) was assessed based on the results of the patient questionnaire obtained at baseline, which classified patients as either 'non-smokers' (including subjects who answered 'never smoked' or 'quit smoking more than one year ago') or 'smokers' (including subjects who answered 'quit smoking within the past year' or 'currently smoking'). Since almost half of the study patients were elderly, the target BP for elderly patients defined by the JSH 2009 criteria[17] ($<140/90$ mmHg) was used as a target.

All statistical analyses were performed using the SAS version 9.2 software program (SAS Institute Inc., Cary, NC, USA), with a two-sided significance level of 0.05.

Results

Patients

A total of 15,313 patients were enrolled from 2,219 institutions across Japan, and baseline data for 15,255 patients were collected. Of these individuals, 534 were excluded: 51 patients who were later found to not have met the inclusion or exclusion criteria, six patients who received no dose of olmesartan, 244 patients for whom no on-treatment data were available (e.g. those who did not return to the institution after their first visit), 82 patients with no case report

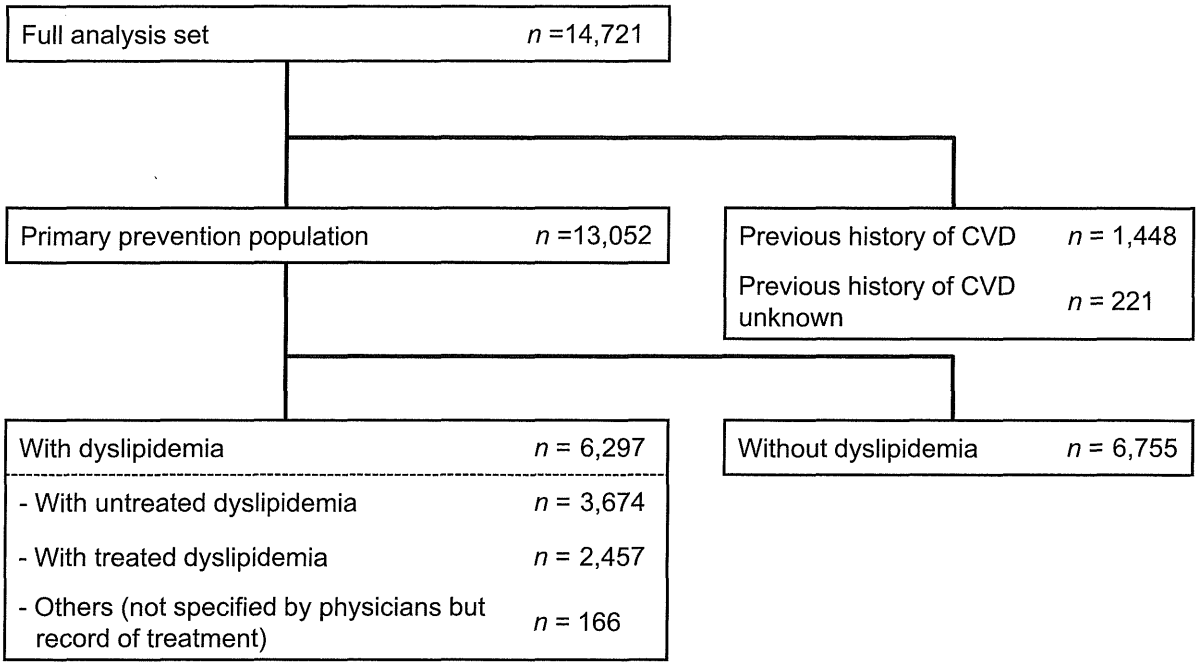

Fig. 1. Composition of the patients in the OMEGA study. CVD, cardiovascular disease.

form data at six months, 63 patients who withdrew their consent during the first six months of the study and 88 patients who were later found to have enrolled after the specified period of enrollment. Of the remaining 14,721 patients, 13,052 had no history of CVD, and their data were accordingly included in the sub-analysis (**Fig. 1**).

Patient Characteristics

The patient characteristics at baseline are summarized in **Table 1A**. A total of 6,297 patients (48.2%) had dyslipidemia. The proportion of women was higher in the dyslipidemia group than in the non-dyslipidemia group. However, there were no differences in age between the two groups. In the dyslipidemia group, the duration of hypertension was significantly longer, although the systolic BP (SBP) and diastolic BP (DBP) values were both lower. Meanwhile, the LDL cholesterol and non-HDL cholesterol values were higher in the dyslipidemia group, whereas the HDL cholesterol values were similar between the groups. In addition, the patients with dyslipidemia were more likely to have diabetes mellitus and hepatic and/or renal impairment. **Table 1B** shows the patient characteristics at baseline according to the comprehensive risk factor control category. The mean age ranged from 61.0 to 65.9 years, the mean body mass index ranged from 24.56 to 24.96 kg/m^2 and the mean duration of hypertension ranged from 4.21 to 4.77 years.

Exposure to Olmesartan and Concomitant Drugs

The daily dose of olmesartan at baseline was 17.2 ± 5.6 mg in the dyslipidemia group versus 17.3 ± 5.4 mg in the non-dyslipidemia group. At 36 months, the daily doses were 17.3 ± 8.6 mg and 17.2 ± 8.3 mg, respectively. The proportion of patients who were still receiving treatment with olmesartan at 36 months was similar between the dyslipidemia group and non-dyslipidemia group (91.3% and 90.9%, respectively).

The proportion of patients who received any antihypertensive drugs other than olmesartan prior to the start of the survey was 53.3% in the dyslipidemia group and 43.6% in the non-dyslipidemia group. Meanwhile, the number of antihypertensive drugs, including olmesartan, used at baseline and at 36 months was similar between the groups (1.5 ± 0.7 and 1.6 ± 0.9, respectively, in the dyslipidemia group, compared with 1.4 ± 0.7 and 1.6 ± 0.9, respectively, in the non-dyslipidemia group). **Table 2** shows the rate of use of olmesartan and concomitant antihypertensive drugs at baseline, after six months and at study completion. The percentage of patients taking olmesartan was similar between those with and without dyslipidemia at all time points. The percentage of patients taking antihypertensive drugs other than olmesartan increased by approximately 10% after six months and approximately 15% at study completion, compared

Table 1A. Patient characteristics at baseline[§1]

	Non-dyslipidemia group	Dyslipidemia group	p[§2]
n	6755	6297	
Male	3,716 (55.0)	2,726 (43.3)	<0.0001
Female	3,039 (45.0)	3,571 (56.7)	
Age (years)	64.7 ± 8.2	64.3 ± 8.1	0.0248
Body mass index (kg/m^2)	24.30 ± 3.58	25.26 ± 3.59	<0.0001
Duration of hypertension (years)[§3]	4.35 ± 4.21	4.97 ± 4.23	<0.0001
Blood pressure immediately before treatment (mmHg)			
Systolic	159.1 ± 17.9	157.1 ± 17.4	<0.0001
Diastolic	90.1 ± 12.2	88.7 ± 11.9	<0.0001
Pulse rate (beats/min) immediately before treatment	73.9 ± 10.6	74.0 ± 10.7	0.9154
Coexisting diseases			
Diabetes mellitus	1,186 (17.6)	1,856 (29.5)	<0.0001
Heart disease	121 (1.8)	112 (1.8)	0.9565
Cerebrovascular disease	12 (0.2)	14 (0.2)	0.5673
Hepatic disease	561 (8.3)	1,013 (16.1)	<0.0001
Renal disease	333 (4.9)	546 (8.7)	<0.0001
Malignant neoplasm	33 (0.5)	24 (0.4)	0.3525
Smoking status			
Current smoker	1,348 (20.0)	1,084 (17.2)	<0.0001
Stopped smoking ≤ 1 year ago	222 (3.3)	179 (2.8)	
Stopped smoking > 1 year ago	1,385 (20.5)	1,179 (18.7)	
Never smoked	3,450 (51.1)	3,632 (57.7)	
Unknown	350 (5.2)	223 (3.5)	
HDL cholesterol (mg/dL)	57.98 ± 15.17	57.99 ± 15.83	0.9883
LDL cholesterol (mg/dL)	114.80 ± 26.96	131.48 ± 35.13	<0.0001
Non-HDL cholesterol (mg/dL)	137.67 ± 29.10	163.99 ± 36.81	<0.0001
Triglycerides (mg/dL)	116.89 ± 60.12	171.00 ± 117.73	<0.0001
HbA1c (NGSP value) (%)	6.22 ± 1.26	6.56 ± 1.40	<0.0001
Receiving statin therapy at start of treatment	0 (0.0)	2221 (35.3)	<0.0001

HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.
[§1]Values expressed as *n* (%) or mean ± SD.
[§2]Chi-squared test for categorical data and unpaired *t*-test for quantitative data.
[§3]Duration ≥ 10 years was treated as a duration of hypertension of 10 years.

with that observed at baseline among the patients with and without dyslipidemia.

The proportion of dyslipidemic patients using any lipid-lowering drugs slightly increased from baseline (41.7%) to 36 months (53.7%). Most of the lipid-lowering drugs used during the study period were statins (35.3% at baseline and 46.0% at 36 months). In the non-dyslipidemia group, the proportion of patients who used any lipid-lowering drugs at 36 months was 7.9% (statins: 6.5%).

Changes in Blood Pressure and Lipid Levels

The changes in BP from baseline to 36 months in the dyslipidemia and non-dyslipidemia groups are shown in **Fig. 2**. The SBP/DBP values in the dyslipidemia group were significantly decreased at six months (137.6 ± 14.1/79.1 ± 9.8 mmHg) compared to that noted at baseline (157.1 ± 17.4/88.7 ± 11.9 mmHg), and the lower BP values were maintained at 36 months (134.2 ± 13.2/76.1 ± 9.4 mmHg) (p<0.0001 at six and 36 months, compared with baseline). In addition, the SBP/DBP values in the non-dyslipidemia group also decreased significantly from baseline (159.1 ± 17.9/90.1 ± 12.2 mmHg) to six months (137.5 ± 14.1/79.2 ± 9.8 mmHg) and 36 months (134.0 ± 13.1/76.6 ± 9.3 mmHg) (p<0.0001 at six and 36 months, compared with baseline).

The changes in the LDL and HDL cholesterol levels from baseline to 36 months in the dyslipidemia and non-dyslipidemia groups are shown in **Fig. 3**.

Table 1B. Patient characteristics at baseline according to the comprehensive risk factor control category[§1]

	No. of controlled risk factors				
	4	3	2	1	0
n	1,974	4,181	4,070	2,207	583
Male	931 (47.2)	1,917 (45.9)	1 968 (48.4)	1 153 (52.2)	453 (77.7)
Female	1,043 (52.8)	2,264 (54.1)	2,102 (51.6)	1,054 (47.8)	130 (22.3)
Age (years)	65.9 ± 7.8	65.0 ± 8.1	64.4 ± 8.2	63.5 ± 8.1	61.0 ± 7.8
Body mass index (kg/m^2)	24.56 ± 3.43	24.66 ± 3.54	24.92 ± 3.72	24.96 ± 3.76	24.70 ± 3.56
Duration of hypertension[§2]	4.77 ± 4.25	4.74 ± 4.22	4.73 ± 4.22	4.41 ± 4.26	4.21 ± 4.15
Blood pressure immediately before treatment (mmHg)					
Systolic	153.8 ± 17.2	156.2 ± 17.0	159.0 ± 17.6	162.3 ± 17.7	164.9 ± 18.7
Diastolic	87.5 ± 11.6	88.4 ± 11.5	89.5 ± 12.1	91.6 ± 12.5	94.3 ± 12.9
Pulse rate (beats/min) immediately before treatment	72.6 ± 10.0	73.3 ± 10.1	74.7 ± 10.9	74.7 ± 11.3	76.3 ± 11.7
Coexisting diseases					
Dyslipidemia	891 (45.1)	2,024 (48.4)	1,941 (47.7)	1,026 (46.5)	238 (40.8)
Diabetes mellitus	366 (18.5)	911 (21.8)	1,018 (25.0)	592 (26.8)	149 (25.6)
Heart disease	40 (2.0)	78 (1.9)	74 (1.8)	37 (1.7)	4 (0.7)
Cerebrovascular disease	6 (0.3)	8 (0.2)	6 (0.1)	4 (0.2)	2 (0.3)
Hepatic disease	225 (11.4)	506 (12.1)	508 (12.5)	264 (12.0)	71 (12.2)
Renal disease	136 (6.9)	237 (5.7)	270 (6.6)	179 (8.1)	54 (9.3)
Malignant neoplasm	9 (0.5)	19 (0.5)	19 (0.5)	8 (0.4)	2 (0.3)
Smoking status					
Current smoker	0 (0.0)	455 (10.9)	890 (21.9)	653 (29.6)	434 (74.4)
Stopped smoking ≤ 1 year ago	0 (0.0)	91 (2.2)	152 (3.7)	104 (4.7)	54 (9.3)
Stopped smoking > 1 year ago	636 (32.2)	961 (23.0)	685 (16.8)	282 (12.8)	0 (0.0)
Never smoked	1,338 (67.8)	2,601 (62.2)	2,166 (53.2)	977 (44.3)	0 (0.0)
Unknown	0 (0.0)	73 (1.7)	177 (4.3)	191 (8.7)	95 (16.3)
Not reported	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
HDL cholesterol (mg/dL)	60.18 ± 16.71	58.35 ± 15.36	57.39 ± 15.26	57.13 ± 15.17	53.88 ± 14.19
LDL cholesterol (mg/dL)	111.89 ± 30.30	121.85 ± 31.49	127.16 ± 32.99	132.28 ± 32.62	124.97 ± 32.58
Non-HDL cholesterol (mg/dL)	137.84 ± 33.72	149.44 ± 34.36	155.41 ± 35.88	161.28 ± 36.50	156.30 ± 35.68
Triglycerides (mg/dL)	133.42 ± 84.65	142.92 ± 94.03	147.31 ± 99.56	153.6 ± 115.17	158.58 ± 96.95
HbA1c (NGSP value) (%)	5.94 ± 0.91	6.21 ± 1.13	6.56 ± 1.37	7.01 ± 1.75	7.01 ± 1.86
Receiving statin therapy at start of treatment	440 (22.3)	799 (19.1)	653 (16.0)	285 (12.9)	39 (6.7)

HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NGSP, National Glycohemoglobin Standardization Program.
[§1]Values expressed as *n* (%) or mean ± SD.
[§2]Duration ≥ 10 years was treated as a duration of hypertension of 10 years.

Consequently, the LDL cholesterol levels in the dyslipidemia group were significantly decreased at 36 months (115.6 ± 27.9 mg/dL) compared to that observed at baseline (131.5 ± 35.1 mg/dL, $p < 0.0001$). The LDL cholesterol levels in the non-dyslipidemia group also decreased significantly from baseline (114.8 ± 27.0 mg/dL) to 36 months (111.7 ± 25.8 mg/dL, $p < 0.0001$); however, the difference was smaller than that seen in the dyslipidemia group. In contrast, the high-density cholesterol levels did not change significantly during the study period in either the dyslipidemia group (58.0 ± 15.8 mg/dL at baseline and 58.0 ± 15.1 mg/dL at 36 months, $p = 0.9932$) or non-dyslipidemia group (58.0 ± 15.2 mg/dL at baseline and 57.8 ± 15.1 mg/dL at 36 months, $p = 0.8257$).

Incidence of Cardiovascular Disease

The incidence of CVD, stroke and CHD during the study period was 5.59, 2.40 and 3.29 per 1,000 patient-years, respectively, in the dyslipidemia group, and 5.57, 3.06 and 2.11 per 1,000 patient-years, respectively, in the non-dyslipidemia group. The rate of CHD differed significantly between the two groups ($p = 0.0323$), whereas the frequency of CVD and