mortality in type 2 diabetes: the Casale Monferrato study. Diabetologia. 2007;50:941–8.
32. Babazono T, Nyumura I, Toya K, Hayashi T, Ohta M, Suzuki K, et al. Higher levels of urinary albumin excretion within the normal range predict faster decline in glomerular filtration rate in diabetic patients. Diabetes Care. 2009;32:1518–20.
33. Ruggenenti P, Porrini E, Motterlini N, Perna A, Ilieva AP, Iliev IP, et al. Measurable urinary albumin predicts cardiovascular risk among normoalbuminuric patients with type2 diabetes. J Am Soc Nephrol. 2012;23:1717–24.
34. Yokoyama H, Oishi M, Kawai K, Sone H. Japan Diabetes Clinical Data Management Study Group. Reduced GFR and microalbuminuria are independently associated with prevalent cardiovascular disease in Type 2 diabetes: JDDM study 16. Diabet Med. 2008;25:1426–32.
35. Drury PL, Ting R, Zannino D, Ehnholm C, Flack J, Whiting M, et al. Estimated glomerular filtration rate and albuminuria are independent predictors of cardiovascular events and death in type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study. Diabetologia. 2011;54:32–43.
36. Toyama T, Furuichi K, Ninomiya T, Shimizu M, Hara A, Iwata Y, et al. The impacts of albuminuria and low eGFR on the risk of cardiovascular death, all-cause mortality, and renal events in diabetic patients: meta-analysis. PLoS One. 2013. doi:10.1371/journal.pone.0071810.
37. Furuichi K, Shimizu M, Toyama T, Koya D, Koshino Y, Abe H, et al. Japan Diabetic Nephropathy Cohort Study: study design, methods, and implementation. Clin Exp Nephrol. 2013. doi:10.1007/s10157-013-0778-8.
38. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al. Japan Renal Biopsy Registry: the first nationwide, web-based, and prospective registry system of renal biopsies in Japan. Clin Exp Nephrol. 2011;15:493–503.

Clin Exp Nephrol (2014) 18:201–205
DOI 10.1007/s10157-013-0898-1

REVIEW ARTICLE

WCN 2013 Satellite Symposium "Kidney and Lipids"

# Treatment and impact of dyslipidemia in diabetic nephropathy

**Tadashi Toyama · Miho Shimizu · Kengo Furuichi · Shuichi Kaneko · Takashi Wada**

Received: 20 September 2013 / Accepted: 21 October 2013 / Published online: 7 November 2013


**Abstract** Recent epidemiological research revealed that dyslipidemia is a risk factor for development and progression of diabetic nephropathy. Results from interventional studies revealed the possibility that anti-hyperlipidemic agents have a better effect on diabetic nephropathy through improvement of albuminuria and loss of renal function. In addition, dyslipidemia may be a consequence of albuminuria and renal dysfunction, thereby perpetuating kidney damage. Today, the proportion of diabetic patients receiving statins is increasing due to their beneficial effect on cardiovascular mortality. However, treatment for patients should be determined based on consideration of the risk and benefit of the treatment. More insight into the pathogenesis of diabetic nephropathy and the effects of life-style changes is required.

**Keywords** Diabetic nephropathy · Dyslipidemia · Cardiovascular disease · End-stage renal disease

T. Toyama · M. Shimizu · K. Furuichi · T. Wada (✉)
Division of Nephrology, Kanazawa University Hospital, Kanazawa, Japan
e-mail: twada@m-kanazawa.jp

S. Kaneko
Department of Disease Control and Homeostasis, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan

T. Wada
Department of Laboratory Medicine, Institute of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, Japan

## Introduction

In the past, epidemiological research in diabetes has found that albuminuria and renal dysfunction are dominant risk factors for the progression of diabetic nephropathy. Some interventional studies have revealed that strict glycemic control reduces the risk of development and progression of albuminuria [1, 2].

It is a crucial fact that diabetic patients are at high risk of cardiovascular events. To prevent these events, dyslipidemia should be carefully controlled because it is one of the well-known risk factors. Statins and fibrates are representative drugs for dyslipidemia. Besides reducing plasma cholesterol levels they are thought to have many pleiotropic effects including improvement of endothelial function and inflammation [3, 4]. However, treatment of patients with dyslipidemia is complicated because it is not a simple metabolic disorder but closely related to the patient's lifestyle. For this reason, lowering the level of cholesterol will not always result in a reduction of the risks.

Here, we focus on the treatment and impact of dyslipidemia on the progression of diabetic nephropathy.

## Dyslipidemia as a complication of diabetic nephropathy

One cross-sectional study implied that patients with diabetic nephropathy had significant increases in triglycerides and total cholesterol levels, reduced levels of apolipoprotein A (ApoA)-I and ApoA-II, and increased levels of ApoC-II and ApoC-III [5]. Other cross-sectional studies of patients from the Diabetic Control and Complications Trial/Epidemiology of Diabetic Interventions and Complications study group revealed that high levels of triglycerides, low-density lipoprotein (LDL) cholesterol, total

cholesterol, and ApoB are associated with albuminuria [6]. ApoB is thought to be related to cardiovascular events in some studies [7, 8]. In this way, the studies revealed the relationships between lipid profiles and diabetic nephropathy.

Cardiovascular events are also important complications in diabetic patients [9]. A meta-analysis reported the relationship between dyslipidemia and cardiovascular risk [10]; however, risks for diabetic patients are not well known.

## Dyslipidemia and loss of renal function

The 'lipid nephrotoxicity' hypothesis was advocated by Moorhead et al. in 1982 as a description of the effect of dyslipidemia on renal dysfunction [11]. Under this hypothesis, mesangial proliferation caused by accumulation of lipoprotein into mesangial cells induces glomerulosclerosis. This theory has been updated recently including the concept of inflammation stress modifying lipid homeostasis and tissue lipid accumulation [12]. With regard to diabetes and lipids, Hartroft [13] discovered in 1954 that intraluminal fat was found in both preglomerular and postglomerular vessels of diabetics patients with Kimmelstiel–Wilson lesions. In addition to this study, a lot of basic research has discovered the mechanisms between dyslipidemia and diabetic nephropathy [14]. Studies revealed that transforming growth factor-β signaling [15], renin–angiotensin system [16], S100A8/TLR4 signaling [17], and oxidative stress [18] may play an important role in the progression of diabetic nephropathies. Concerning the development of albuminuria, the importance of the deterioration of glycocalyx, which is on the surface of endothelium, was highlighted [19]. These factors orchestrated each other, thereby perpetuating the progression of diabetic nephropathy. Further studies will be required for a better understanding of diabetic nephropathy.

Some epidemiological studies of general cohorts have elucidated the relationships between dyslipidemia and loss of renal function. The Framingham Offspring Study which consists of 1,916 general population subjects with a follow-up of 9.5 years, revealed that low high-density lipoprotein (HDL) cholesterol levels are one of the risk factors for incident albuminuria [20]. An analysis of 1,440 general Japanese cohorts that participated in the Hisayama study revealed that metabolic syndrome defined as the presence of components including high triglyceride levels and low HDL cholesterol levels are associated with a risk of developing chronic kidney disease (CKD) [21]. A study of 4,483 healthy males revealed that dyslipidemia including high total cholesterol levels, high non-HDL cholesterol levels, and low HDL cholesterol levels are associated with a risk of renal dysfunction [22].

According to these facts, dyslipidemia may be one of the potential risk factors for loss of renal functions in a healthy subject.

## Relationships between dyslipidemia and progression or regression of diabetic nephropathy

The stages in diabetic renal disease were reported by Mogensen et al. [23] in 1983. According to their theory, elevated urinary albumin excretion and following persistent proteinuria are important manifestations of diabetic nephropathy, and many studies defined them as surrogate markers for end-stage renal disease.

Some cohort studies of diabetic patients have proven the risk factors associated with the progression or regression of the staging. Regarding the development of micro- and macroalbuminuria, a cohort study of 27,805 patients with type 1 diabetes followed up for 2.5 years revealed that, besides diabetes duration and glycosylated hemoglobin, dyslipidemia is a risk factor for developing albuminuria [24]. A cohort study of 574 patients with type 2 diabetes followed up for 7.8 years also revealed that, as well as high mean blood pressure and hyperglycemia, high plasma cholesterol levels are the main risk factors for development of dyslipidemia [25]. In this study, the participants with a combination of these three risk factors are a high-risk group for progression to diabetic nephropathy.

Associations between reduction of urinary albumin and dyslipidemia were reported in a cohort study of 386 patients with type 1 diabetes [26]. In this study, along with low levels of glycosylated hemoglobin and low systolic blood pressure, low levels of both cholesterol and triglycerides were independently associated with regression of microalbuminuria. Moreover, these factors had additive effects on regression of microalbuminuria.

A small number of studies reported an association between dyslipidemia and loss of renal functions. Regarding the rate of decline in glomerular filtration rate (GFR), a prospective study of 30 patients with type 1 diabetes revealed that high serum cholesterol, triglycerides and apolipoprotein B were correlated to a rapid decline in glomerular filtration rate [27].

As described above, evidence has been accumulated to suggest that dyslipidemia is one of the risk factors for progression and regression of diabetic nephropathy. However, as far as we knew, there have been few studies reporting the association with end-stage renal disease, or renal replacement therapy. A report of a scientific workshop sponsored by the National Kidney Foundation (NKF) and the US Food and Drug Administration (FDA) indicated that evidence was insufficient to use a change of albuminuria as a surrogate marker as a clinical endpoint [28].

Long-term follow-up studies are needed to demonstrate the causal relationships between dyslipidemia and end-stage renal disease from diabetic nephropathy.

## Treatment of dyslipidemia and diabetic nephropathy

With regard to the treatment of dyslipidemia in patients with diabetes, there were some interventional trials of anti-hypercholesterolemic agents including fibrates and statins.

The Diabetes Atherosclerosis Intervention Study (DAIS) is a randomized study that assessed the effect of fenofibrate on type 2 diabetic patients [29]. In this study, fenofibrate reduced the worsening of urine albumin excretion and the effects were mainly observed in the progression from normoalbuminuria to microalbuminuria. The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study also evaluated the effect of fenofibrate on type 2 diabetes [30]. From this study, it was proved that fenofibrate is effective in lowering the decline of the estimated glomerular filtration rate (eGFR) and reducing the progression of albuminuria. Additionally in this study, patients treated with fenofibrate had higher rates of regression of albuminuria than the placebo group. This evidence suggests that fenofibrate is effective in ameliorating diabetic nephropathy. In a meta-analysis of these two studies, the significant effect on the regression from microalbuminuria to normoalbuminuria was proved; however, progression from microalbuminuria to macroalbuminuria was not significant [31].

The effect of statins on diabetic nephropathy was examined in the Collaborative Atorvastatin Diabetes Study (CARDS) [32]. Treatment with atorvastatin was compared with a placebo in this study, and was associated with an improvement in annual changes in eGFR (0.18 mL/min/1.73 $m^2$/year). It is noteworthy that atorvastatin ameliorated eGFR without improving albuminuria, when comparing angiotensin-converting enzyme inhibitors which have renoprotective effects and prevent the onset of albuminuria [33].

There is still a lot of uncertainty about the effect of statins. The effect on renal protection was not demonstrated in the Study of Heart and Renal Protection (SHARP) which included 2,094 (33 %) patients with diabetes [34], and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) which included 3,638 (36 %) patients with diabetes [35]. A meta-analysis also showed that regression of albuminuria [31] and changes in eGFR [36] were not observed in patients with diabetes treated with statins.

There seems to be no definite answer for treatment of dyslipidemia in diabetic patients from the viewpoint of anti-hyperlipidemic agents. One of the supposed causes of inconsistency in results is that kidney diseases in patients with diabetes may not be uniform, but consist of many renal diseases [37]. In some cases, renal biopsies might be needed to assess the accurate risks [38].

Diabetic patients are at higher risk for cardiovascular mortality compared with non-diabetic patients [10, 39]. There is sufficient evidence, such as SHARP [34], to show that statins reduce the risk of cardiovascular events. Considering these facts, many diabetic patients might benefit from statin treatment. An increasing number of patients are now receiving this treatment. In the analysis of the National Health and Nutrition Examination Survey (NHANES) 2005–2006, 93.5 % of diabetic men aged 65–69 without cardiovascular disease received statins [40].

On the other hand, administration of statin may have adverse side-effects, including myopathy [41], renal toxicity [42], and incident diabetes [43]. A study comparing the risks and benefits of statins concluded that cardiovascular benefits outweigh the increased risk of new-onset diabetes [44]. It is beyond doubt that each patient's risk must be taken into account before administration of statins.

It is also important to consider changes in life-style; however, the difficulty lies in improving renal and cardiovascular events through life-style changes [45]. It remains a challenge for future research to examine the impact of life-style changes.

## Concluding remarks and future directions

In considering the complexity of the problem of diabetic nephropathy, many aspects of a patient's condition and treatment should be taken into account. Further insight into the pathogenesis of dyslipidemia, and the risk and benefits of each treatment may be beneficial for each patient.

**Acknowledgments** This study was supported in party by a Grant-in-Aid for Diabetic Nephropathy Research from the Ministry of Health, Labor and Welfare of Japan.

**Conflict of interest** The authors have declared that no conflict of interest exists.

## References

1. Ohkubo Y, Kishikawa H, Araki E, Miyata T, Isami S, Motoyoshi S, et al. Intensive insulin therapy prevents the progression of diabetic microvascular complications in Japanese patients with non-insulin-dependent diabetes mellitus: a randomized prospective 6-year study. Diabetes Res Clin Pract. 1995;28:103–17.
2. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med. 1993;329:977–86.
3. Fried LF. Effects of HMG-CoA reductase inhibitors (statins) on progression of kidney disease. Kidney Int. 2008;74:571–6.

4. Krysiak R, Gdula-Dymek A, Bachowski R, Okopien B. Pleiotropic effects of atorvastatin and fenofibrate in metabolic syndrome and different types of pre-diabetes. Diabetes Care. 2010;33:2266–70.
5. Attman PO, Knight-Gibson C, Tavella M, Samuelsson O, Alaupovic P. The compositional abnormalities of lipoproteins in diabetic renal failure. Nephrol Dial Transplant. 1998;13:2833–41.
6. Jenkins AJ, Lyons TJ, Zheng D, Otvos JD, Lackland DT, McGee D, et al. Lipoproteins in the DCCT/EDIC cohort: associations with diabetic nephropathy. Kidney Int. 2003;64:817–28.
7. McQueen MJ, Hawken S, Wang X, Ounpuu S, Sniderman A, Probstfield J, et al. Lipids, lipoproteins, and apolipoproteins as risk markers of myocardial infarction in 52 countries (the INTERHEART study): a case-control study. Lancet. 2008;372:224–33.
8. Sniderman AD, Williams K, Contois JH, Monroe HM, McQueen MJ, de Graaf J, et al. A meta-analysis of low-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and apolipoprotein B as markers of cardiovascular risk. Circ Cardiovasc Qual Outcomes. 2011;4:337–45.
9. Toyama T, Furuichi K, Ninomiya T, Shimizu M, Hara A, Iwata Y, et al. The impacts of albuminuria and low eGFR on the risk of cardiovascular death, all-cause mortality, and renal events in diabetic patients: meta-analysis. PLoS One. 2013;8:e71810.
10. Fox CS, Matsushita K, Woodward M, Bilo HJG, Chalmers J, Heerspink HJL, et al. Associations of kidney disease measures with mortality and end-stage renal disease in individuals with and without diabetes: a meta-analysis. Lancet. 2012;380:1662–73.
11. Moorhead JF, Chan MK, El-Nahas M, Varghese Z. Lipid nephrotoxicity in chronic progressive glomerular and tubulo-interstitial disease. Lancet. 1982;2:1309–11.
12. Ruan XZ, Varghese Z, Moorhead JF. An update on the lipid nephrotoxicity hypothesis. Nat Rev Nephrol. 2009;5:713–21.
13. Hartroft WS. Fat emboli in glomerular capillaries of choline-deficient rats and of patients with diabetic glomerulosclerosis. Am J Pathol. 1955;31(3):381–97.
14. Rutledge JC, Ng KF, Aung HH, Wilson DW. Role of triglyceride-rich lipoproteins in diabetic nephropathy. Nat Rev Nephrol. 2010;6:361–70.
15. Yamamoto T, Nakamura T, Noble NA, Ruoslahti E, Border WA. Expression of transforming growth factor beta is elevated in human and experimental diabetic nephropathy. Proc Natl Acad Sci USA. 1993;90:1814–8.
16. Tojo A, Onozato ML, Kurihara H, Sakai T, Goto A, Fujita T. Angiotensin II blockade restores albumin reabsorption in the proximal tubules of diabetic rats. Hypertens Res. 2003;26:413–9.
17. Kuwabara T, Mori K, Mukoyama M, Kasahara M, Yokoi H, Saito Y, et al. Exacerbation of diabetic nephropathy by hyperlipidaemia is mediated by Toll-like receptor 4 in mice. Diabetologia. 2012;55:2256–66.
18. Chen HC, Tan MS, Guh JY, Tsai JH, Lai YL. Native and oxidized low-density lipoproteins enhance superoxide production from diabetic rat glomeruli. Kidney Blood Press Res. 2000;23:133–7.
19. Kuwabara A, Satoh M, Tomita N, Sasaki T, Kashihara N. Deterioration of glomerular endothelial surface layer induced by oxidative stress is implicated in altered permeability of macromolecules in Zucker fatty rats. Diabetologia. 2010;53:2056–65.
20. O'Seaghdha CM, Hwang S-J, Upadhyay A, Meigs JB, Fox CS. Predictors of incident albuminuria in the Framingham Offspring cohort. Am J Kidney Dis. 2010;56:852–60.
21. Ninomiya T, Kiyohara Y, Kubo M, Yonemoto K, Tanizaki Y, Doi Y, et al. Metabolic syndrome and CKD in a general Japanese population: the Hisayama Study. Am J Kidney Dis. 2006;48:383–91.
22. Schaeffner ES, Kurth T, Curhan GC, Glynn RJ, Rexrode KM, Baigent C, et al. Cholesterol and the risk of renal dysfunction in apparently healthy men. J Am Soc Nephrol. 2003;14:2084–91.
23. Mogensen CE, Christensen CK, Vittinghus E. The stages in diabetic renal disease. With emphasis on the stage of incipient diabetic nephropathy. Diabetes. 1983;32(Suppl 2):64–78.
24. Raile K, Galler A, Hofer S, Herbst A, Dunstheimer D, Busch P, et al. Diabetic nephropathy in 27,805 children, adolescents, and adults with type 1 diabetes: effect of diabetes duration, A1C, hypertension, dyslipidemia, diabetes onset, and sex. Diabetes Care. 2007;30:2523–8.
25. Ravid M, Brosh D, Ravid-Safran D, Levy Z, Rachmani R. Main risk factors for nephropathy in type 2 diabetes mellitus are plasma cholesterol levels, mean blood pressure, and hyperglycemia. Arch Intern Med. 1998;158:998–1004.
26. Perkins BA, Ficociello LH, Silva KH, Finkelstein DM, Warram JH, Krolewski AS. Regression of microalbuminuria in type 1 diabetes. N Engl J Med. 2003;348:2285–93.
27. Mulec H, Johnsen SA, Wiklund O, Björck S. Cholesterol: a renal risk factor in diabetic nephropathy? Am J Kidney Dis. 1993;22:196–201.
28. Levey AS, Cattran D, Friedman A, Miller WG, Sedor J, Tuttle K, et al. Proteinuria as a surrogate outcome in CKD: report of a scientific workshop sponsored by the National Kidney Foundation and the US Food and Drug Administration. Am J Kidney Dis. 2009;54:205–26.
29. Ansquer J-C, Foucher C, Rattier S, Taskinen M-R, Steiner G. Fenofibrate reduces progression to microalbuminuria over 3 years in a placebo-controlled study in type 2 diabetes: results from the Diabetes Atherosclerosis Intervention Study (DAIS). Am J Kidney Dis. 2005;45:485–93.
30. Davis TME, Ting R, Best JD, Donoghoe MW, Drury PL, Sullivan DR, et al. Effects of fenofibrate on renal function in patients with type 2 diabetes mellitus: the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) Study. Diabetologia. 2011;54:280–90.
31. Slinin Y, Ishani A, Rector T, Fitzgerald P, MacDonald R, Tacklind J, et al. Management of hyperglycemia, dyslipidemia, and albuminuria in patients with diabetes and CKD: a systematic review for a KDOQI clinical practice guideline. Am J Kidney Dis. 2012;60:747–69.
32. Colhoun HM, Betteridge DJ, Durrington PN, Hitman GA, Neil HAW, Livingstone SJ, et al. Effects of atorvastatin on kidney outcomes and cardiovascular disease in patients with diabetes: an analysis from the Collaborative Atorvastatin Diabetes Study (CARDS). Am J Kidney Dis. 2009;54:810–9.
33. Ruggenenti P, Cravedi P, Remuzzi G. The RAAS in the pathogenesis and treatment of diabetic nephropathy. Nat Rev Nephrol. 2010;6:319–30.
34. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. 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;377:2181–92.
35. Rahman M, Baimbridge C, Davis BR, Barzilay J, Basile JN, Henriquez MA, et al. Progression of kidney disease in moderately hypercholesterolemic, hypertensive patients randomized to pravastatin versus usual care: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Am J Kidney Dis. 2008;52:412–24.
36. Sandhu S, Wiebe N, Fried LF, Tonelli M. Statins for improving renal outcomes: a meta-analysis. J Am Soc Nephrol. 2006;17:2006–16.
37. Sharma SG, Bomback AS, Radhakrishnan J, Herlitz LC, Stokes MB, Markowitz GS, et al. The modern spectrum of renal biopsy findings in patients with diabetes. Clin J Am Soc Nephrol. 2013;8:1–7.
38. Shimizu M, Furuichi K, Toyama T, Kitajima S, Hara A, Kitagawa K, et al. Long-term outcomes of Japanese type 2 diabetic patients with biopsy-proven diabetic nephropathy. Diabetes Care. 2013;36:3655–62.

39. Wei M, Gaskill SP, Haffner SM, Stern MP. Effects of diabetes and level of glycemia on all-cause and cardiovascular mortality. The San Antonio Heart Study. Diabetes Care. 1998;21:1167–72.
40. Robinson JG, Booth B. Statin use and lipid levels in older adults: National Health and Nutrition Examination Survey, 2001 to 2006. J Clin Lipidol. 2010;4:483–90.
41. Ballantyne CM, Corsini A, Davidson MH, Holdaas H, Jacobson TA, Leitersdorf E, et al. Risk for myopathy with statin therapy in high-risk patients. Arch Intern Med. 2003;163:553–64.
42. Alsheikh-Ali AA, Ambrose MS, Kuvin JT, Karas RH. The safety of rosuvastatin as used in common clinical practice: a postmarketing analysis. Circulation. 2005;111:3051–7.
43. Carter AA, Gomes T, Camacho X, Juurlink DN, Shah BR, Mamdani MM. Risk of incident diabetes among patients treated with statins: population based study. BMJ. 2013;346:f2610.
44. Wang K-L, Liu C-J, Chao T-F, Huang C-M, Wu C-H, Chen S-J, et al. Statins, risk of diabetes, and implications on outcomes in the general population. J Am Coll Cardiol. 2012;60:1231–8.
45. Multiple risk factor intervention trial research group. Mortality rates after 10.5 years for participants in the Multiple Risk Factor Intervention Trial. Findings related to a priori hypotheses of the trial. The Multiple Risk Factor Intervention Trial Research Group. JAMA. 1990;263:1795–801.

透析会誌 47(7):415〜419, 2014

委員会報告

# 糖尿病性腎症病期分類 2014 の策定（糖尿病性腎症病期分類改訂）について

糖尿病性腎症合同委員会
羽田 勝計[1,5] 宇都宮 一典[1,6] 古家 大祐[1,7] 馬場園 哲也[1,8]
守屋 達美[1,9] 槇野 博史[2,10] 木村 健二郎[2,11] 鈴木 芳樹[2,12]
和田 隆志[2,13] 小川 晋[2,14] 稲葉 雅章[3,15] 菅野 義彦[3,16]
重松 隆[3,17] 政金 生人[3,18] 土谷 健[3,19] 本田 佳子[4,20]
市川 和子[4,21] 幣 憲一郎[4,22]
[1]日本糖尿病学会 [2]日本腎臓学会 [3]日本透析医学会 [4]日本病態栄養学会（オブザーバー）
[5]旭川医科大学内科学講座病態代謝内科学分野
[6]東京慈恵会医科大学糖尿病・代謝・内分泌内科
[7]金沢医科大学糖尿病・内分泌内科学 [8]東京女子医科大学糖尿病センター内科
[9]北里大学健康管理センター [10]岡山大学病院
[11]聖マリアンナ医科大学腎臓・高血圧内科 [12]新潟大学保健管理センター
[13]金沢大学医薬保健学総合研究科血液情報統御学
[14]東北大学高等教育開発推進センター，東北大学病院腎・高血圧・内分泌科
[15]大阪市立大学大学院医学研究科代謝内分泌病態内科学
[16]東京医科大学腎臓内科学講座 [17]和歌山県立医科大学腎臓内科学 [18]矢吹病院
[19]東京女子医科大学第四内科 [20]女子栄養大学栄養学部実践栄養学科
[21]川崎医科大学附属病院栄養部 [22]京都大学医学部附属病院疾患栄養治療部

キーワード：糖尿病[性]腎症，慢性腎臓病，アルブミン尿，蛋白尿，糸球体濾過量

〈要旨〉
糖尿病性腎症合同委員会では，estimated glomerular filtration rates(eGFR)および chronic kidney disease(CKD)の概念の普及を鑑み，従来の糖尿病性腎症病期分類を改訂した．新たな糖尿病性腎症病期分類 2014 は，厚生労働省科学研究費腎疾患対策事業「糖尿病性腎症の病態解明と新規治療法確立のための評価法の開発」における研究成果を参考として作成した．主要変更点は，1．病期分類に用いる GFR を eGFR に変更する，2．第 3 期 A と B 区分を削除する，3．GFR 30 mL/分/1.73 $m^2$未満を尿アルブミン値に拘わらず腎不全とする，であるが，同時に，4．いずれの病期においても非糖尿病性腎臓病との鑑別が重要であることを表記した．

# Classification of Diabetic Nephropathy 2014

Joint Committee on Diabetes Nephropathy
Masakazu Haneda[1,5], Kazunori Utsunomiya[1,6], Daisuke Koya[1,7], Tetsuya Babazono[1,8], Tatsumi Moriya[1,9], Hirofumi Makino[2,10], Kenjiro Kimura[2,11], Yoshiki Suzuki[2,12], Takashi Wada[2,13], Susumu Ogawa[2,14], Masaaki Inaba[3,15], Yoshihiko Kanno[3,16], Takashi Shigematsu[3,17], Ikuto Masakane[3,18], Ken Tsuchiya[3,19], Keiko Honda[4,20], Kazuko Ichikawa[4,21], Kenichiro Shide[4,22]
[1]The Japanese Diabetes Society, [2]Japanese Society of Nephrology, [3]The Japanese Society for Dialysis Therapy, [4]Japan Society of Metabolism and Clinical Nutrition(Observer), [5]Department of Medicine, Division of Metabolism and Biosystemic Science, Asahikawa Medical University, [6]Department of Internal Medicine, Division of Diabetes, Endocrinology & Metabolism, Jikei University School of Medicine, [7]Department of Diabetology & Endocrinology, Kanazawa Medical University, [8]Department of Medicine, Diabetes Center ,Tokyo Women's Medical University School of Medicine, [9]Health Care Center, Kitasato University, [10]Okayama University Hospital, [11]Nephrology and Hypertension, Department of Internal Medicine, St. Marinna University School of Medicine, [12]Health Administra-

tion Center, Niigata University, [13]Division of Nephrology, Department of Laboratory Medicine, Kanazawa University, [14]Center for the Advancement of Higher Education, Tohoku University. Division of Nephrology, Endocrinology and Vascular Medicine, Tohoku University Hospital, [15]Department of Metabolism, Endocrinology, Molecular Medicine Faculty of Internal Medicine, Osaka City University Graduate School of Medicine, [16]Department of Nephrology, Tokyo Medical University, [17]Division of Nephrology, Department of Internal Medicine, Wakayama Medical University, [18]Department of Nephrology, Yabuki Hospital, [19]Department of Medicine IV, Tokyo Women's Medical University, [20]Laboratory of Medicine Nutrition, Applied Nutrition, Kagawa Nutrition University, [21]Nutrition Department, Kawasaki Medical School Hospital, [22]Department of Metabolism and Clinical Nutrition, Kyoto University Hospital

〈Abstract〉
The Committee on Diabetic Nephropathy revised the classification of diabetic nephropathy in view of the current status of eGFR and CKD in Japan. To make revisions for the classification of diabetic nephropathy 2014, the Committee carefully evaluated the report of the Research Group on Diabetic Nephropathy, Ministry of Health, Labour, and Welfare of Japan. The major revisions made were as follows：1. eGFR can be used for the evaluation of GFR；2. In stage 3（overt nephropathy), A and B were combined; 3. Stage 4（renal failure）was defined as GFR less than 30 mL/min/1.73 $m^2$, regardless of albuminuria；and 4. The importance of differential diagnosis was stressed in all stages.

## はじめに

糖尿病性腎症から慢性透析療法に導入される患者は，1998年から第1位となりその後は増加の一途を辿ったが，この数年はプラトーになりつつある．しかし，CKDのかなりの部分を糖尿病性腎症が占めており，未だに透析療法導入疾患の原疾患として他の腎臓病と比較しても突出していることも事実である[1]．その結果，慢性透析療法に係る医療費は増大しており，医学的かつ社会的問題であることが指摘されている．

糖尿病性腎症病期分類に関しては，旧厚生省糖尿病調査研究班で作成され[2]糖尿病性腎症合同委員会で改訂された分類[3]が，現在我が国で広く用いられている．しかし，CKDの概念が提唱され，CKDステージ分類[4]が登場した時点で，両者が乖離する症例が存在することが明らかとなった．これは従来の糖尿病性腎症病期分類がGFR（Ccr：creatinine clearance）も評価項目に入っているにも拘わらず主にアルブミン尿で分類され，一方CKDステージ分類はGFR（eGFR）のみで分類されていることに起因していた．現在，一般臨床ではGFRの評価にeGFRが繁用されるようになったこと，および2012年に新たにCKD重症度分類が策定されたことを受け[5]，糖尿病性腎症合同委員会では様々な議論を行い，糖尿病性腎症病期分類を改訂することとした．

## 糖尿病性腎症病期分類2014の策定（糖尿病性腎症病期分類改訂）（表）

改訂に先立ち，厚生労働省科学研究費腎疾患対策事業「糖尿病性腎症の病態解明と新規治療法確立のための評価法の開発」において，10施設，4,355例の「事前登録前向き試験」を行い，腎イベント（eGFR半減，透析導入），心血管イベント，総死亡を検討した[6,7]．その結果，以下の点が明らかとなった（尚，詳細は，厚生労働省ホームページおよび参考論文をご参照頂きたい）．

1．正常アルブミン尿を基準とすると，微量アルブミン尿・顕性アルブミン尿に進行するに従い，上記3イベントとも有意に増加した．
2．GFR 60 mL/分/1.73 $m^2$未満の腎機能低下例において，
　①腎イベントのリスクは微量アルブミン尿例で増加し，顕性アルブミン尿例でさらに増加する．
　②心血管イベントのリスクは微量アルブミン尿例，顕性アルブミン尿例で増加する．
　③総死亡のリスクは顕性アルブミン尿例で増加する．ただし，GFR 30 mL/分/1.73 $m^2$未満では，正常アルブミン尿例，微量アルブミン尿例ともイベントリスクが増加する．

以上の結果は，真の前向き観察研究ではないこと，参加施設および症例数が限られていること，海外に比べると心血管イベントが少ないこと，など課題を残していることは事実であるが，糖尿病性腎症の予後を知

表　糖尿病性腎症病期分類2014[注1]

| 病期 | 尿アルブミン値（mg/gCr）<br>あるいは<br>尿蛋白値（g/gCr） | GFR（eGFR）<br>（mL/分/1.73 m$^2$） |
|---|---|---|
| 第1期<br>（腎症前期） | 正常アルブミン尿（30未満） | 30以上[注2] |
| 第2期<br>（早期腎症期） | 微量アルブミン尿（30～299）[注3] | 30以上 |
| 第3期<br>（顕性腎症期） | 顕性アルブミン尿（300以上）<br>あるいは<br>持続性蛋白尿（0.5以上） | 30以上[注4] |
| 第4期<br>（腎不全期） | 問わない[注5] | 30未満 |
| 第5期<br>（透析療法期） | 透析療法中 | |

注1：糖尿病性腎症は必ずしも第1期から順次第5期まで進行するものではない．本分類は，厚労省研究班の成績に基づき予後（腎，心血管，総死亡）を勘案した分類である（URL：http://mhlw-grants.niph.go.jp/, Wada T, Haneda M, Furuichi K, Babazono T, Yokoyama H, Iseki K, Araki SI, Ninomiya T, Hara S, Suzuki Y, Iwano M, Kusano E, Moriya T, Satoh H, Nakamura H, Shimizu M, Toyama T, Hara A, Makino H；The Research Group of Diabetic Nephropathy, Ministry of Health, Labour, and Welfare of Japan. Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. Clin Exp Nephrol. 2013 Oct 17.[Epub ahead of print]）

注2：GFR 60 mL/分/1.73 m$^2$未満の症例はCKDに該当し，糖尿病性腎症以外の原因が存在し得るため，他の腎臓病との鑑別診断が必要である．

注3：微量アルブミン尿を認めた症例では，糖尿病性腎症早期診断基準に従って鑑別診断を行った上で，早期腎症と診断する．

注4：顕性アルブミン尿の症例では，GFR 60 mL/分/1.73 m$^2$未満からGFRの低下に伴い腎イベント（eGFRの半減，透析導入）が増加するため注意が必要である．

注5：GFR 30 mL/分/1.73 m$^2$未満の症例は，尿アルブミン値あるいは尿蛋白値に拘わらず，腎不全期に分類される．しかし，特に正常アルブミン尿・微量アルブミン尿の場合は，糖尿病性腎症以外の腎臓病との鑑別診断が必要である．

【重要な注意事項】本表は糖尿病性腎症の病期分類であり，薬剤使用の目安を示した表ではない．糖尿病治療薬を含む薬剤特に腎排泄性薬剤の使用に当たっては，GFR等を勘案し，各薬剤の添付文書に従った使用が必要である．

る上で我が国の症例を対象とした重要な研究であると考えられる．従って，今回の病期分類の改訂においては，上記成果を参考にした．

今回の改訂にあたっては，上記研究成果以外にも，下記の点も考慮した．

1．これまで行われた大部分のランダム化比較試験が，症例登録をアルブミン尿で規定しており，GFR主体の病期分類にすると治療エビデンスが殆ど存在しなくなること．
2．既に，「糖尿病透析予防指導管理料」加算が，現行の病期分類に基づいて行われていること．
3．「糖尿病性腎症治療薬に関する臨床評価ガイドライン（案）」が，現行の病期分類に基づいて策定されたこと．

以上を考慮し，糖尿病性腎症合同委員会で討論を重ねた結果，分類表自体は従来のものを踏襲することとした．ただし，CKD重症度分類の普及を鑑み，付表を作成した．尚，付表をヒートマップにしなかった理由は，上記研究では症例数が少ないことおよび透析療法中の症例が含まれていないことにある．また，この病期分類には，糖尿病症例に合併する全ての腎臓病が含まれ得るため，鑑別診断の重要性を（注）として記載した．鑑別診断に当たっては，腎生検の必要性を含め腎臓内科医との協調が必要である．さらに，進展過程が病期通りでない症例も存在するため，その旨も（注）に記載した．そのため，（注）が多い表となった．尚，糖尿病治療薬の増加を考慮し，下段に【重要な注意事項】を追記した．

糖尿病性腎症病期分類（改訂）の主要変更点を下記にまとめる．

1．病期分類に用いるGFRをeGFRに変更したこと．
2．病期を，正常アルブミン尿，微量アルブミン尿，顕性アルブミン尿，腎不全，と単純化したこと．
3．従来の3期AとB（顕性腎症前期・後期）の区

付表：糖尿病性腎症病期分類 2014 と CKD の重症度分類との関係

| アルブミン尿区分 | | A1 | A2 | A3 |
|---|---|---|---|---|
| | 尿アルブミン定量<br>尿アルブミン/Cr 比<br>(mg/gCr)<br>(尿蛋白定量)<br>(尿蛋白/Cr 比)<br>(g/gCr) | 正常アルブミン尿<br>30 未満 | 微量アルブミン尿<br>30-299 | 顕性アルブミン尿<br>300 以上<br>(もしくは高度蛋白尿)<br>(0.50 以上) |
| GFR 区分<br>(mL/分/1.73 $m^2$) | ≥90<br>60～89<br>45～59<br>30～44 | 第 1 期<br>(腎症前期) | 第 2 期<br>(早期腎症期) | 第 3 期<br>(顕性腎症期) |
| | 15～29<br><15 | 第 4 期<br>(腎不全期) | | |
| | (透析療法中) | 第 5 期<br>(透析療法期) | | |

分は行わないこと（1 g/日の蛋白尿で分類する根拠に乏しい）としたこと．

4．GFR 30 mL/分/1.73 $m^2$未満を全て腎不全としたこと（従来の定義を日本腎臓学会の分類[8]を参考に数値化した）．逆に腎不全以外は，GFR 30 mL/分/1.73 $m^2$以上と規定したこと．

5．括弧内の文言（早期腎症期など）を削除する案も検討したが，広く認知されていることに鑑み，今回は残すことにした．

6．いずれの病期も鑑別診断の重要性を強調したこと．

また，American Diabetes Association では，Clinical Practice Recommendations 2013 において，microalbuminuria と macroalbuminuria の区別を廃し，30 μg/mg Cr(＝mg/g Cr)以上のアルブミン尿を，Increased urinary albumin excretion と呼ぶことを提唱した[9]．しかし，Clinical Practice Recommendations 2014 では，この提唱を残しつつも，microalbuminuria を persistent albuminuria 30-299 mg/24h，macroalbuminuria を persistent albuminuria≧300 mg/24h と呼ぶことを新たに提唱している[10]．すなわち，米国では一般臨床で「微量アルブミン尿」，「顕性アルブミン尿」の呼称がなくなる訳であるが，論文から消去を求められている訳ではなく，我が国では現時点で広く用いられている用語であるため，拙速な追随は混乱を招くと考え，この呼称は残すこととした．

尚，現在我が国では多施設共同前向き研究として，JDCP study (Japan Diabetes Complication and the Prevention prospective study)，日本腎臓学会レジストリー研究，JDDM (Japan Diabetes Clinical Data Management Study Group) 研究や，ランダム化比較試験として，J-DOIT3 (Japan Diabetes Optimal Integrated Treatment study for 3 major risk factors of cardiovascular diseases) が進行中であり，これらの成果が得られ，今回改訂した病期分類をさらに改訂する必要があると判断された場合は，速やかに改訂作業を行う予定である．

## 結　語

従来の糖尿病性腎症病期分類と CKD ステージ分類との齟齬を解消すべく，糖尿病性腎症病期分類を改訂した．尚，本病期分類（改訂）は，既に 2014 年 1 月 10 日，糖尿病性腎症合同委員会構成学会のホームページに掲載した．また，改訂は今後も行われるであろうが故に，本報告をもって，本改訂分類を「糖尿病性腎症病期分類 2014」と呼称したい．

謝辞：糖尿病性腎症病期分類2014作成に当たって参考にさせて頂いた，厚生労働省科学研究費腎疾患対策事業「糖尿病性腎症の病態解明と新規治療法確立のための評価法の開発」にご協力頂いた先生方に深謝申し上げます．

利益相反情報についての開示

羽田　勝計　講演料（日本ベーリンガーインゲルハイム，田辺三菱製薬，ノボノルディスクファーマ，第一三共，大正製薬，サノフィ，MSD，アステラス製薬，協和発酵キリン，興和創薬，武田薬品工業，ノバルティスファーマ），奨学（奨励）寄付などの総額（アステラス製薬，第一三共，田辺三菱製薬，武田薬品工業，日本イーライリリー，ノボノルディスクファー

マ，MSD，日本ベーリンガーインゲルハイム）
宇都宮一典　講演料（ノバルティスファーマ，MSD，興和創薬，サノフィ，ノボノルディスクファーマ，協和発酵キリン），臨床研究費（受託研究費，共同研究費など）の総額（MSD，協和発酵キリン，興和創薬，田辺三菱製薬）
古家　大祐　講演料（田辺三菱製薬，大日本住友製薬，日本ベーリンガーインゲルハイム，MSD，ノボノルディスクファーマ，アステラス製薬，日本イーライリリー），臨床研究費（受託研究費，共同研究費など）の総額（MSD，アステラス製薬，協和発酵キリン，武田薬品工業，田辺三菱製薬，日本たばこ産業，日本ベーリンガーインゲルハイム，ノボノルディスクファーマ）
馬場園哲也　講演料（MSD）
守屋　達美　旅費，贈答品などの受領（アステラス製薬，武田薬品工業，ノボノルディスクファーマ，第一三共）
槇野　博史　（本人は）営利を目的とする企業：帝人ファーマ株式会社の治験調整医師，講演料（アステラス製薬，MSD，武田薬品工業，田辺三菱製薬，ファイザー，アヴィー，日本ベーリンガーインゲルハイム，第一三共，協和発酵キリン，大日本住友製薬，ノバルティスファーマ），臨床研究費（受託研究費，共同研究費など）の総額（岡山県地域医療実践研究事業），奨学（奨励）寄付などの総額（アステラス製薬，第一三共，MSD，武田薬品工業，協和発酵キリン，田辺三菱製薬）
木村健二郎　講演料（ノバルティスファーマ，大日本住友製薬），奨学（奨励）寄付などの総額（大塚製薬，協和発酵キリン，武田薬品工業，旭化成，バクスター）
和田　隆志　講演料（MSD，第一三共），奨学（奨励）寄付などの総額（中外製薬）
小川　晋　講演料（第一三共，日本イーライリリー，ノボノルディスクファーマ），臨床研究費（受託研究費，共同研究費など）の総額（第一三共）
稲葉　雅章　講演料（小野薬品工業，大正富山医薬品，中外製薬，MSD，協和発酵キリン，ファイザー，第一三共），臨床研究費（受託研究費，共同研究費など）の総額（バイエル薬品，協和メデックス），奨学（奨励）寄付などの総額（アステラス製薬，旭化成ファーマ，協和発酵キリン，第一三共，中外製薬，帝人ファーマ，田辺三菱製薬，武田薬品工業）
菅野　義彦　原稿料（大塚製薬，協和発酵キリン），奨学（奨励）寄付などの総額（中外製薬），旅費，贈答品などの受領（アボットジャパン）
重松　隆　講演料（バイエル薬品，中外製薬，協和発酵キリン），臨床研究費（受託研究費，共同研究費など）の総額（バイエル薬品）
政金　生人　講演料（協和発酵キリン）
土谷　健　講演料（中外製薬，バイエル薬品）
本田　佳子　講演料（ノボノルディスクファーマ），原稿料（医歯薬出版，メディカ出版）

## 参考文献

1) 日本透析医学会統計調査委員会．図説わが国の慢性透析療法の現況．
http://docs.jsdt.or.jp/overview/index.html
2) 平成3年度　糖尿病調査研究報告書．320頁．
3) 吉川隆一（世話人）　糖尿病性腎症に関する合同委員会報告．1．糖尿病性腎症病期分類厚生省案の改訂について．糖尿病 2001；44：623.
4) 日本腎臓学会．CKD診療ガイド．日腎会誌 2007；49：767.
5) 日本腎臓学会．CKD診療ガイド2012．日腎会誌 2012；54：1047.
6) 厚生労働科学研究補助金腎疾患対策研究事業「糖尿病性腎症の病態解明と新規治療法確立のための評価法の開発」平成21-23年度総合研究報告書，pp1-44
http:/mhlw-grants.niph.go.jp/
7) Wada T, Haneda M, Furuichi K, et al.; The Research Group of Diabetic Nephropathy, Ministry of Health, Labour, and Welfare of Japan. Clinical impact of albuminuria and glomerular filtration rate on renal and cardiovascular events, and all-cause mortality in Japanese patients with type 2 diabetes. Clin Exp Nephrol. 2013 Oct 17.[Epub ahead of print] PMID: 24132561
8) 日本腎臓学会．腎疾患患者の生活指導・食事療法に関するガイドライン．日腎会誌 1997；39：1-37.
9) American Diabetes Association. Clinical Practice Recommendations 2013. Diabetes Care 2013；36(Suppl 1)：S3, S35.
10) American Diabetes Association. Clinical Practice Recommendations 2014. Diabetes Care 2014；37(Suppl 1)：S4, S43-44.

Original Article

OPEN

# Combinations of olmesartan and a calcium channel blocker or a diuretic in elderly hypertensive patients: a randomized, controlled trial[1]

Toshio Ogihara[a], Takao Saruta[b], Hiromi Rakugi[c], Ikuo Saito[b], Kazuaki Shimamoto[d], Hiroaki Matsuoka[e], Kazuyuki Shimada[f], Sadayoshi Ito[g], Masatsugu Horiuchi[h], Tsutomu Imaizumi[i], Shuichi Takishita[j], Jitsuo Higaki[h], Shigehiro Katayama[k], Genjiroh Kimura[l], Satoshi Umemura[m], Nobuyuki Ura[n], Koichi Hayashi[b], Masato Odawara[o], Norio Tanahashi[k], Toshihiko Ishimitsu[e], Naoki Kashihara[p], Satoshi Morita[m], Satoshi Teramukai[q], for the COLM Investigators

See editorial comment on page 1967

**Objective:** The aim of the present study was to compare the cardiovascular effects of olmesartan, an angiotensin II receptor blocker, combined with a calcium channel blocker (CCB) or a diuretic, in a prospective, randomized, open-label, blinded endpoint trial.

**Methods:** Japanese hypertensive patients aged at least 65 to less than 85 years with SBP at least 140 mmHg and/or DBP at least 90 mmHg with antihypertensive treatment, or SBP at least 160 mmHg and/or DBP at least 100 mmHg without antihypertensive treatment were randomized to receive olmesartan with either a dihydropyridine CCB or a low-dose diuretic. If SBP and/or DBP remained at least 140 and/or at least 90 mmHg, the other antihypertensive drug was added. The primary endpoint was a composite of fatal and nonfatal cardiovascular events. The median follow-up time was 3.3 years.

**Results:** Blood pressure decreased similarly in both groups. The primary endpoint occurred in 116/2568 patients (4.5%) in the olmesartan plus CCB group and in 135/2573 patients (5.3%) in the olmesartan plus diuretic group [hazard ratio 0.83, 95% confidence interval (CI) 0.65–1.07, $P=0.16$]. Rates of all-cause death and cardiovascular deaths were similar. Among patients aged at least 75 years, the incidence of stroke tended to be lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group (hazard ratio 0.63, 95% CI 0.38–1.02, $P=0.059$, interaction $P=0.019$). Fewer patients in the olmesartan plus CCB group (8.2%, 211/2568) than in the olmesartan plus diuretic group (9.8%, 253/2573; $P=0.046$) experienced serious adverse events.

**Conclusion:** Despite no significant difference in cardiovascular events, the different safety profiles suggest that the combination of olmesartan and CCB may be preferable to that of olmesartan and diuretic.

**Keywords:** blood pressure, calcium channel blockers, diuretics, hypertension, olmesartan, randomized controlled trial

**Abbreviations:** ACCOMPLISH, Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; BP, blood pressure; CCB, calcium channel blocker; COLM, Combinations of OLMesartan; SAE, serious adverse event

## INTRODUCTION

Hypertension is a major risk factor for cardiovascular morbidity and mortality [1]. Tight control of blood pressure (BP) is recommended for the prevention of cardiovascular diseases [2] and often requires combinations of two or more antihypertensive drugs [3]. Current clinical guidelines for the management of hypertension list several combinations of drugs [4–6]. Only a few studies, however, such as the Avoiding Cardiovascular Events Through Combination Therapy in Patients Living With Systolic Hypertension (ACCOMPLISH) [7] and Combination Therapy of Hypertension to Prevent Cardiovascular Events

Journal of Hypertension 2014, 32:2054–2063

[a]Morinomiya University of Medical Sciences, Osaka, [b]Keio University, Tokyo, [c]Osaka University Graduate School of Medicine, Osaka, [d]Sapporo Medical University, Hokkaido, [e]Dokkyo Medical University, [f]Shin-Oyama City Hospital, Tochigi, [g]Tohoku Tohoku University Graduate School of Medicine, Miyagi, [h]Ehime University Graduate School of Medicine, Ehime, [i]Kurume University School of Medicine, Fukuoka, [j]University of the Ryukyus School of Medicine, Okinawa, [k]Saitama Medical University, Saitama, [l]Asahi Rousai Hospital, Aichi, [m]Yokohama City University Graduate School of Medicine, Kanagawa, [n]Sapporo Nishimaruyama Hospital, Hokkaido, [o]Tokyo Medical University, Tokyo, [p]Kawasaki Medical School, Okayama and [q]Kanazawa University Hospital, Ishikawa, Japan

Correspondence to Professor Toshio Ogihara, Morinomiya University of Medical Sciences, 1-26-16, Nankokita, Suminoe-ku, Osaka 559-8611, Japan. Tel: +81 6 6616 6911; fax: +81 6 6616 6912; e-mail: ogihara@morinomiya-u.ac.jp

The authors' contributions, members of the COLM Study Committees, and the list of investigators are presented in the Appendix.

[1] Some data from this report were presented as a late-breaking clinical trial at the 23rd European Meeting on Hypertension and Cardiovascular Protection (Milan, Italy), 16 June 2013.

**Received** 14 November 2013 **Revised** 20 May 2014 **Accepted** 20 May 2014



DOI:10.1097/HJH.0000000000000281

[8] trials, have directly compared the effects of different combinations.

Combinations of an angiotensin II receptor blocker (ARB) and a calcium channel blocker (CCB) or an ARB and a diuretic are widely used to treat hypertension, and both combinations are recommended in clinical guidelines [4–6]. No studies, however, have compared these combinations in terms of preventing cardiovascular disease.

With the aim of addressing this issue, we conducted the Combinations of OLMesartan (COLM) study to compare the effects of an ARB combined with a CCB with those of an ARB combined with a diuretic on cardiovascular endpoints in a high-risk cohort of Japanese elderly hypertensive patients. In this study, we used olmesartan as the ARB in both groups because it had good antihypertensive effects in several large-scale, international clinical trials [9–13].

## METHODS

### Study design

The rationale, study design, and implementation of the COLM study are described in more detail in our previous report [14]. This multicentre prospective, randomized, open-label blinded-endpoint trial was conducted between April 2007 and September 2011 at 707 primary care and cardiology centres in Japan. Patient recruitment was completed in September 2008. After randomization, all patients were followed up for at least 3 years until the trial was terminated at the prespecified time. The trial was conducted in accordance with the Declaration of Helsinki. The protocol was reviewed and approved by institutional review boards at each participating centre.

### Patients

Hypertensive patients aged at least 65 to less than 85 years with a history of cardiovascular disease or risk factors for cardiovascular disease, including diabetes mellitus or dyslipidemia, were eligible for the study. Patients were enrolled if their clinic-measured SBP was at least 140 mmHg and/or their DBP was at least 90 mmHg during treatment with one or more antihypertensive drugs at enrolment, or if their SBP was at least 160 mmHg and/or DBP was at least 100 mmHg without antihypertensive treatment. All patients provided written informed consent.

### Randomization and treatments

Patients were randomized 1 : 1 using a dynamic allocation method with stratification for sex, age ($\geq$75/<75 years), history of cardiovascular disease, BP (mild/moderate or severe hypertension according to the Japanese guideline for the management of hypertension [15]), prior use of antihypertensive agents, and centre. Randomization was conducted using a computerized system by the COLM study data centre, and the random allocation sequence was concealed until the end of the enrolment period. Patients were treated with olmesartan (5–40 mg/day) and either a long-acting dihydropyridine CCB [amlodipine (2.5 or 5 mg/day) or azelnidipine (8 or 16 mg/day)] or a low-dose diuretic (trichlormethiazide $\leq$1 mg, hydrochlorothiazide $\leq$12.5 mg, or indapamide $\leq$1 mg and other diuretics). Wherever possible, low doses of diuretics were preferred [16]. Medication was administered orally, once a day, usually after breakfast. The choice of which CCB and diuretic were used concomitantly with olmesartan was at the discretion of the investigator in charge of each patient [14].

### Study protocol

The target SBP and DBP were less than 140 and less than 90 mmHg, respectively, in both groups. For patients with BP exceeding these targets, the dose of each drug was to be increased. If the target BP was not achieved with maximal doses of the allocated drug, the other class of antihypertensive drug was added, followed by the addition of other antihypertensive drugs, including β-blockers, α-blockers, and angiotensin-converting enzyme (ACE) inhibitors. If the BP decreased excessively, the doses of antihypertensive agents other than the study drugs were reduced, or the other drugs were discontinued with the aim of continuing the combination for as long as possible [14].

### Outcomes

Measurement of BP, assessment of cardiovascular events, and laboratory tests were conducted at 1, 3, and 6 months after randomization, and then every 6 months thereafter. BP was measured at least twice at intervals of 1–2 min, and the mean value of two stable measurements that differed by less than 5 mmHg was used. The primary endpoint was a composite of fatal and nonfatal cardiovascular events. Cardiovascular events included sudden death; new occurrence or recurrence of cerebral infarction, cerebral haemorrhage, subarachnoid haemorrhage, or transient ischaemic attack; new occurrence or recurrence of myocardial infarction; coronary revascularization (percutaneous intervention or coronary artery bypass grafting); hospitalization for angina pectoris or heart failure; and renal events (doubling of serum creatinine, serum creatinine $\geq$2.0 mg/100 ml, and end-stage renal disease).

Secondary endpoints included cardiovascular death, nonfatal myocardial infarction, nonfatal stroke except transient ischaemic attack, all-cause deaths, composite of hard endpoints (cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke except transient ischaemic attack), new-onset diabetes, incidence of specific events (sudden death, cerebrovascular events, cardiac events, and renal events), new occurrence of atrial fibrillation, adverse events, and the proportion of patients who withdrew from the allocated treatment. Adverse events, classified as drug-related or nondrug-related and serious or nonserious, were monitored throughout the study. All events contributing to the primary and secondary endpoints and all serious adverse events (SAEs) reported by the participating physicians were adjudicated by the Endpoint Committee, which was blinded to the study group.

### Sample size

The rationale for the sample size is reported elsewhere [14]. Briefly, the incidence of cardiovascular events (i.e., the primary endpoint) was estimated to be 2% per year, and the relative difference in the incidence of cardiovascular events between the two groups was estimated to be 33%. Therefore, more than 2000 patients were needed for each

group to provide a significance level of 5% (two-sided) at a power of 80%.

### Statistical methods

All analyses were conducted according to the intention-to-treat principle. Time-to-event curves for cardiovascular events were plotted using the Kaplan–Meier method. Stratified log-rank tests were conducted with sex, age, and history of cardiovascular disease as strata. Hazard ratios and 95% confidence intervals (CIs) were calculated using the stratified proportional hazards model. Exploratory analyses of prespecified subgroup analyses were conducted, and interactions between treatment group and each subgroup were investigated. Patient characteristics at baseline, BP at the end of the trial, and the frequency of adverse events between two groups were compared using the *t*-test (for continuous variables) and Fisher's exact test (for categorical variables). The *t*-test was used to compare the change in BP, and the analysis of covariance adjusted by baseline data was conducted to compare the average change in heart rate between two groups. Two interim analyses were planned to either continue or discontinue the study on the basis of ethical and scientific considerations, with adjustment for repeated comparisons using the O'Brien–Fleming α-spending function, and the results were evaluated by the Independent Data Monitoring Committee. The prespecified significant levels for stopping criteria were 0.00001 for the first interim analysis and 0.003 for the second interim analysis. If these were met, the Data Monitoring Committee would ask the Steering Committee to either amend the study protocol or discontinue the study. For the primary endpoint, the significance level for the final analysis was set at 0.049 (two-sided) considering the two interim analyses. In other analyses, the level of significance was 0.05 (two-sided). All statistical analyses were done using SAS 9.1 (SAS Institute, Inc., Cary, North Carolina, USA).

## RESULTS

### Patients

Of 5658 patients assessed for eligibility, 489 patients met the exclusion criteria and 28 patients withdrew consent before enrolment. Therefore, 5141 patients were randomized. Overall, 46 patients in the olmesartan plus CCB group and 72 patients in the olmesartan plus diuretic group were lost to follow-up, leaving 2568 and 2573 patients in these groups, respectively (Fig. 1). The results of two interim analyses in October 2009 and December 2010 did not meet the prespecified early stopping criteria. The median follow-up period was 3.3 years (range 1 day to 4.3 years), and the follow-up rate was 98.0%. The baseline characteristics, including BP at randomization, are shown in Table 1. The mean age of patients was 73.6 years, and 51.6% were men. There were no significant differences in baseline characteristics between the two groups. Approximately 24% of patients had a history of cardiovascular diseases, including stroke (14.6%) and ischaemic heart disease (11.0%). Approximately 81% of patients were treated with antihypertensive agents at enrolment; the most common types were ARBs (49%) and CCBs (37%).

At 3 years, the mean number of antihypertensive drugs used, including the allocated drugs, was 2.1 in the olmesartan plus CCB group and 2.1 in the olmesartan plus diuretic group ($P=0.64$). The median number of drugs was two in both groups.

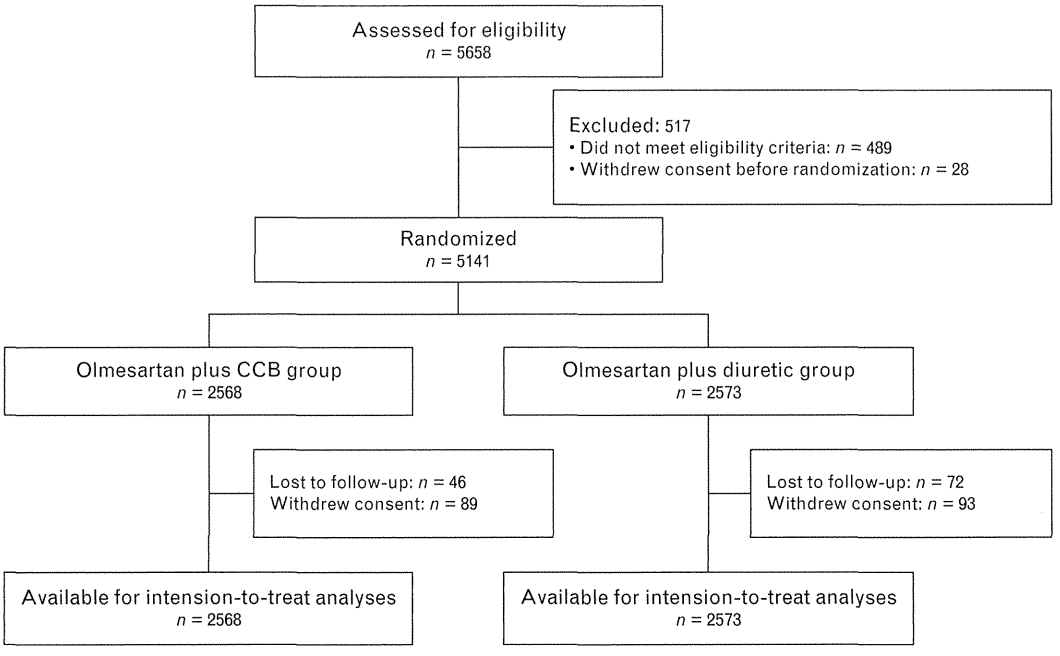


**FIGURE 1** Patient disposition.

**TABLE 1. Baseline characteristics of the study population according to treatment group**

| Characteristic | Olmesartan plus CCB ($n=2568$) | Olmesartan plus diuretic ($n=2573$) | *P*-Value |
|---|---|---|---|
| Sex | | | |
| Men | 1323 (51.5) | 1330 (51.7) | 0.91 |
| Women | 1245 (48.5) | 1243 (48.3) | |
| Age (years) | 73.6 ± 5.3 | 73.6 ± 5.4 | 0.74 |
| ≥75 years old | 1109 (43.2) | 1114 (43.3) | 0.95 |
| <75 years old | 1459 (56.8) | 1459 (56.7) | |
| BMI (kg/m$^2$) | 24.3 ± 3.5 | 24.2 ± 3.4 | 0.26 |
| eGFR (ml/min per 1.73 m$^2$) | 67.6 ± 19.0 | 67.3 ± 18.3 | 0.62 |
| SBP (mmHg) | 158.0 ± 12.7 | 158.0 ± 12.5 | 0.96 |
| DBP (mmHg) | 87.1 ± 10.8 | 86.9 ± 10.8 | 0.58 |
| Heart rate (bpm) | 73.1 ± 9.9 | 72.9 ± 9.3 | 0.49 |
| Cardiovascular history | | | |
| Stroke | 369 (14.4) | 382 (14.9) | 0.63 |
| Ischaemic heart disease | 286 (11.1) | 277 (10.8) | 0.68 |
| Cardiovascular risk factors | | | |
| Dyslipidemia | 1165 (45.5) | 1172 (45.8) | 0.84 |
| Diabetes mellitus | 684 (26.6) | 678 (26.4) | 0.82 |
| Smoking | 641 (25.1) | 648 (25.4) | 0.84 |
| Drinking | 1090 (42.8) | 1086 (42.5) | 0.88 |
| Use of antihypertensive drugs at enrolment[a] | | | |
| ARB | 1262 (49.2) | 1254 (48.9) | 0.84 |
| CCB | 977 (38.1) | 916 (35.8) | 0.08 |
| β-Blockers | 231 (9.0) | 191 (7.5) | 0.04 |
| ACE inhibitors | 149 (5.8) | 154 (6.0) | 0.76 |
| Diuretics | 146 (5.7) | 168 (6.6) | 0.20 |
| α-Blockers | 71 (2.8) | 70 (2.7) | 1.00 |
| Concomitant use of other drugs | | | |
| Statin | 704 (27.5) | 719 (28.1) | 0.64 |
| Antiplatelet drugs | 555 (21.7) | 561 (21.9) | 0.83 |
| Antidiabetic drugs | 472 (18.4) | 497 (19.4) | 0.37 |

Data are *n* (%) or mean ± standard deviation. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blocker; CCB: calcium channel blocker; eGFR: estimated glomerular filtration rate, calculated using the Japanese formula 194 × Cr − 1.094 × age − 0.287 (×0.739 for women).
[a]Excludes 16 patients for whom data were not collected after randomization ($n=2563$ in the olmesartan plus CCB group, $n=2562$ in the olmesartan plus diuretic group).

The following drugs were used in the olmesartan plus CCB group: amlodipine (44.9%) and azelnidipine (49.8%), and in the olmesartan plus diuretic group: trichlormethiazide (62.4%), indapamide (22.8%), hydrochlorothiazide (2.3%), and other thiazides (3.5%). The mean doses of olmesartan were 18.3 ± 8.1 and 18.5 ± 8.6 mg/day for patients in the olmesartan plus CCB and olmesartan plus diuretic groups, respectively.

## Blood pressure and heart rate

BP at baseline was approximately 158/87 mmHg, and was similar in both groups (Table 1). The time-course of changes in SBP and DBP was similar in both groups (Fig. 2). At the end of the trial, the mean SBP/DBP was 132.9 ± 12.6/73.2 ± 9.8 mmHg in the olmesartan plus CCB group and 132.9 ± 13.6/73.5 ± 9.8 mmHg in the olmesartan plus diuretic group, corresponding to mean reductions in SBP/DBP of 24.4 ± 16.4/13.8 ± 12.0 and 24.9 ± 17.3/13.7 ± 12.4 mmHg ($P=0.30/0.79$), respectively. There were no significant differences in mean SBP or DBP at each visit between the two groups.

Overall, 69.2% (1735/2568) of patients in the olmesartan plus CCB group and 70.5% (1759/2573) of patients in the olmesartan plus diuretic group ($P=0.30$) achieved the target BP levels (SBP <140 mmHg and DBP <90 mmHg).

Heart rate was 73.1 and 72.9 bpm ($P=0.49$) at baseline in the olmesartan plus CCB and olmesartan plus diuretic groups, respectively, and decreased slightly to 69.7 ± 11.2 and 70.5 ± 11.7 bpm, respectively, at 3 years. The decrease in heart rate was significantly greater in the olmesartan plus CCB group than in the olmesartan plus diuretic group ($P=0.01$), with a mean difference of 0.55 bpm.

## Primary outcome

Kaplan–Meier analysis of the time to the first primary endpoint is shown in Fig. 3. The incidence and hazard ratio of the primary endpoint are shown in Fig. 4. The primary endpoint occurred in 116/2568 patients (4.5%) in the olmesartan plus CCB group, and in 135/2573 patients (5.3%) in the olmesartan plus diuretic group (hazard ratio 0.83, 95% CI 0.65–1.07, $P=0.16$). The incidence of the primary endpoint per 1000 patient-years was 14.8 in the olmesartan plus CCB group and 17.6 in the olmesartan plus diuretic group. There were no significant differences in the rates of each type of event between the two groups (Fig. 4).

## Secondary and other prespecified endpoints

Overall, 64/2568 patients (2.5%) in the olmesartan plus CCB group (8.0/1000 patient-years) and 76/2573 patients (3.0%) in the olmesartan plus diuretic group (9.7/1000 patient-years) died during the study (hazard ratio 0.83, 95% CI 0.59–1.15, $P=0.27$). The rates of all-cause death and cardiovascular death were not significantly different between the two groups. The composite of hard endpoints occurred in 72/2568 patients (2.8%) in the olmesartan plus CCB

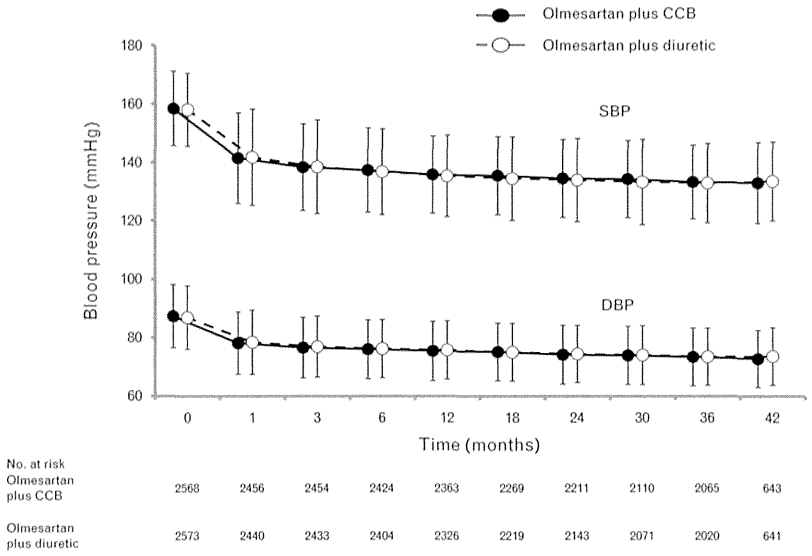


**FIGURE 2** Time-course of changes in blood pressure.

group and in 88/2573 patients (3.4%) in the olmesartan plus diuretic group (hazard ratio 0.80, 95% CI 0.58–1.09, $P=0.16$). The rates of new-onset atrial fibrillation and diabetes were not significantly different between the two groups (Fig. 4).

Table 2 shows the results of prespecified subgroup analyses. The incidence rates of the primary endpoint among older patients (≥75 years old), in patients without diabetes, and in patients without dyslipidemia were lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group; however, the interactions were not statistically significant.

Among older patients (≥75 years old), the incidence of the composite of hard endpoints was also lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group (hazard ratio 0.64, 95% CI 0.42–0.97, $P=0.03$), although the interaction was not significant ($P=0.12$). In this subgroup, the incidence of stroke was also lower in the olmesartan plus CCB group (hazard ratio 0.63, 95% CI 0.38–1.02, $P=0.059$) and the interaction between treatment and age subgroup was statistically significant ($P=0.019$).

## Safety and adverse events

A total of 77/2568 patients (3.0%) in the olmesartan plus CCB group and 131/2573 patients (5.1%) in the olmesartan plus diuretic group ($P<0.001$) were withdrawn because of SAEs. The incidence of SAEs was lower in the olmesartan plus CCB group (211/2568 patients, 8.2%) than in the olmesartan plus diuretic group (253/2573 patients, 9.8%) ($P=0.046$). The three most frequent SAEs were malignancy (olmesartan plus CCB vs. olmesartan plus diuretic: 2.5 vs.

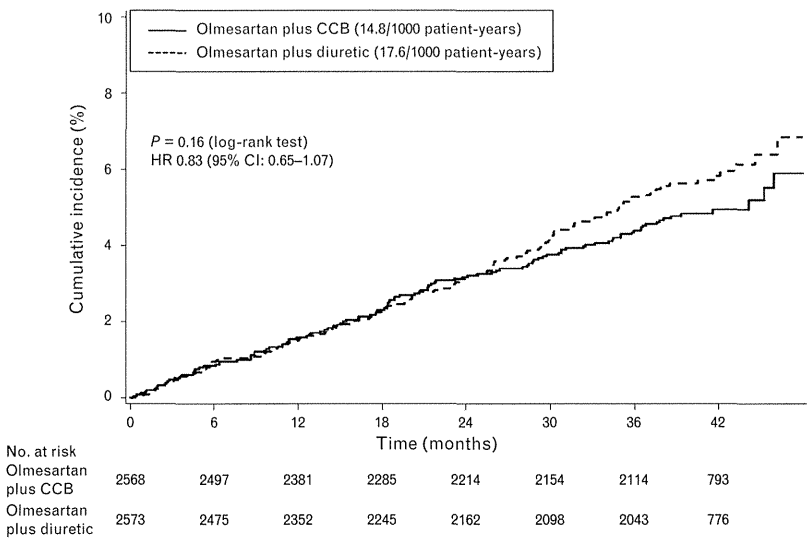


**FIGURE 3** Kaplan–Meier curves for the primary composite endpoint of fatal and nonfatal cardiovascular events.

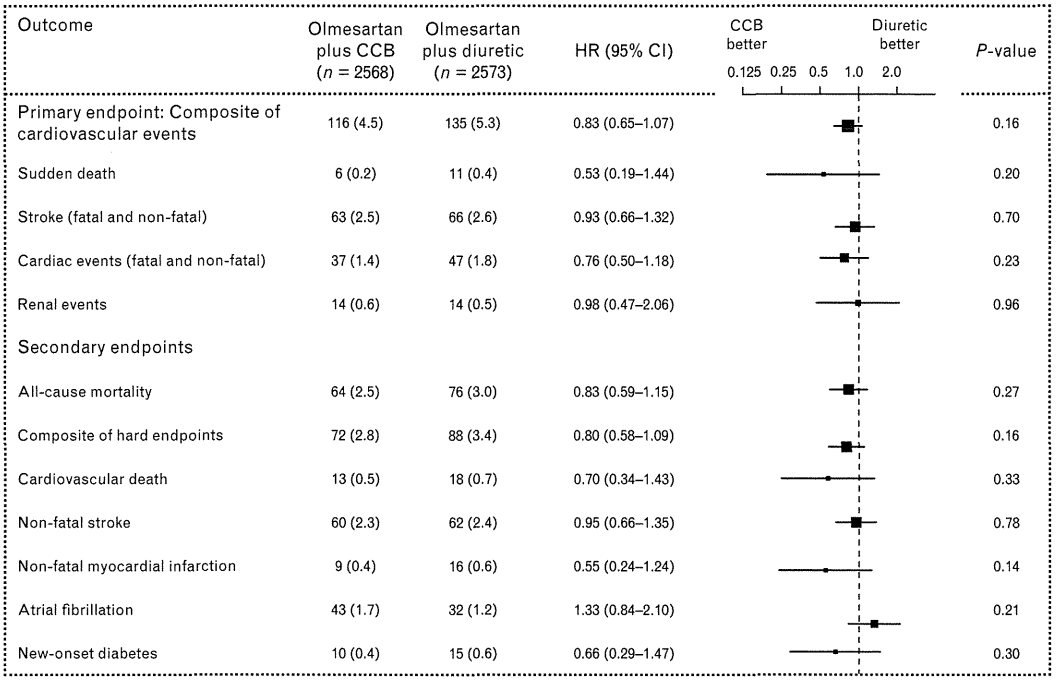


**FIGURE 4** Incidence rates and hazard ratios of the primary composite endpoint, of individual components of the primary endpoint, and of the secondary endpoints. The hazard ratios and 95% CIs were determined using a stratified Cox proportional hazards model taking into account sex, age, and baseline cardiovascular disease. The *P*-values were derived from a log-rank test, stratified by sex, age, and baseline cardiovascular disease. CCB, calcium channel blocker; CI, confidence interval.

**TABLE 2. Results of prespecified subgroup analyses for the primary endpoint**

| Subgroup | Olmesartan plus CCB ($n = 2568$) | Olmesartan plus diuretic ($n = 2573$) | Hazard ratio (95% CI) | *P*-Value | *P*-Value (interaction) |
|---|---|---|---|---|---|
| Sex | | | | | |
| Men | 63/1323 (4.8) | 76/1330 (5.7) | 0.82 (0.58–1.14) | 0.24 | 0.81 |
| Women | 53/1245 (4.3) | 59/1243 (4.7) | 0.87 (0.60–1.26) | 0.46 | |
| Age | | | | | |
| <75 years old | 58/1459 (4.0) | 55/1459 (3.8) | 1.03 (0.71–1.49) | 0.85 | 0.14 |
| ≥75 years old | 58/1109 (5.2) | 80/1114 (7.2) | 0.70 (0.50–0.99) | 0.04 | |
| BMI | | | | | |
| <25 (kg/m$^2$) | 76/1525 (5.0) | 93/1527 (6.1) | 0.81 (0.59–1.09) | 0.17 | 0.74 |
| ≥25 (kg/m$^2$) | 40/1022 (3.9) | 41/1018 (4.0) | 0.94 (0.60–1.45) | 0.78 | |
| eGFR | | | | | |
| <60 ml/min per 1.73 m$^2$ | 43/622 (6.9) | 52/642 (8.1) | 0.82 (0.55–1.24) | 0.35 | 0.94 |
| ≥60 ml/min per 1.73 m$^2$ | 47/1230 (3.8) | 55/1224 (4.5) | 0.83 (0.56–1.23) | 0.37 | |
| Diabetes mellitus | | | | | |
| Yes | 48/684 (7.0) | 42/678 (6.2) | 1.12 (0.74–1.69) | 0.58 | 0.06 |
| No | 68/1884 (3.6) | 93/1895 (4.9) | 0.71 (0.52–0.97) | 0.03 | |
| Dyslipidemia | | | | | |
| Yes | 68/1165 (5.8) | 66/1172 (5.6) | 1.01 (0.72–1.41) | 0.94 | 0.08 |
| No | 48/1398 (3.4) | 69/1390 (5.0) | 0.68 (0.47–0.98) | 0.03 | |
| History of cardiovascular disease | | | | | |
| Yes | 55/610 (9.0) | 59/615 (9.6) | 0.90 (0.62–1.30) | 0.58 | 0.61 |
| No | 61/1958 (3.1) | 76/1958 (3.9) | 0.78 (0.56–1.10) | 0.16 | |

Data are *n* of patients reaching the primary endpoint/total *n* (%). CCB, calcium channel blocker; CI, confidence interval; eGFR, estimated glomerular filtration rate.

3.1%; $P = 0.17$), gastrointestinal disorders (1.1 vs. 1.1%; $P = 0.79$), and infection (0.9 vs. 0.9%; $P = 0.76$). New-onset diabetes occurred in 10 patients (0.4%) in the olmesartan plus CCB group and 15 patients (0.6%) in the olmesartan plus diuretic group (hazard ratio 0.66, 95% CI 0.29–1.47, $P = 0.30$). Regarding laboratory events, the incidence of hyperuricaemia was greater in the olmesartan plus diuretic group than in the olmesartan plus CCB group (6.5 vs. 2.6%, $P < 0.001$).

## DISCUSSION

Over a median follow-up period of 3.3 years, there were no differences in the cardiovascular risk reduction conferred

using olmesartan, an ARB, in combination with either a CCB or a diuretic. The incidence of SAEs, however, was significantly lower in the olmesartan plus CCB group than in the olmesartan plus diuretic group. Patients in the present study were well matched in terms of age, obesity, history of cardiovascular disease, cardiovascular risk factors, and antihypertensive medications. BP at baseline and 3 years were similar in both groups, with comparable reductions in BP in both groups.

Several studies have examined the effects of combinations of antihypertensive drugs with different mechanisms of action. For example, the ACCOMPLISH trial showed that the combination of an ACE inhibitor and a CCB was superior to that of an ACE inhibitor and a diuretic for preventing cardiovascular events [7], and the Combination Therapy of Hypertension to Prevent Cardiovascular Events trial showed that the combination of a CCB and a diuretic was superior to that of a CCB and a β-blocker [8]. Among studies examining the efficacy of add-on antihypertensive drugs, the Losartan Intervention For Endpoint reduction in hypertension study showed that an ARB-based regimen with an add-on diuretic was superior to a β-blocker–based regimen with an add-on diuretic for preventing cardiovascular events [17], whereas the Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm showed that a CCB-based regimen with an add-on ACE inhibitor was superior to a β-blocker–based regimen with an add-on diuretic [18]. The results of these two studies suggested that the combination of an ARB and a diuretic or a CCB and an ACE inhibitor had some advantages over that of a β-blocker and a diuretic for treating hypertension. In the present study, we compared two widely used combinations of hypertensive drugs: an ARB and a CCB, and an ARB and a diuretic.

The primary endpoint, a composite of cardiovascular morbidity and mortality, and its individual components were not significantly different between the two groups in our study, indicating that both combinations conferred similar reductions in cardiovascular risk in elderly hypertensive patients, consistent with earlier studies showing that BP lowering is essential to reduce cardiovascular morbidity and mortality in hypertensive patients [19–21]. Although the present results do not support the conclusion of the ACCOMPLISH trial [7] that the combination of a renin–angiotensin system (RAS) inhibitor and a CCB is superior to that of a RAS inhibitor and diuretic, we could not consider a smaller relative risk reduction such as 19.6% in the ACCOMPLISH trial, because the present study was specifically powered to detect a relative risk reduction of 33% between the two groups [14]. Nevertheless, the reason why the present results do not support those of the ACCOMPLISH trial may be differences in the races of study patients and the use of an ACE inhibitor vs. an ARB. The higher salt sensitivity in the older Japanese patients (mean age: 73.6 years) in our study than that in the slightly younger predominantly white (83.5%) (mean age: 68.4 years) patients in the ACCOMPLISH trial may have caused greater efficacy of the combination of the RAS inhibitor and diuretic in our study relative to theirs. Another important issue is that stroke was the most common component of the primary endpoint (51.4%) in our study, whereas myocardial infarction (23.1%) and coronary revascularization (58.5%) were more common in the ACCOMPLISH trial. The different pattern of endpoints between the two trials may be related to differences in ethnicity and the severity of cardiac risk at enrolment. It is well known that the incidence of stroke is more strongly associated with BP than is myocardial infarction. Indeed, the two groups in our study achieved similar SBP with a similar incidence of stroke. Although the incidence of the primary endpoint was not significantly different between the two groups, the prespecified subgroup analyses showed that the incidence of stroke among patients aged at least 75 years tended to be lower in the olmesartan plus CCB group ($P=0.059$), with a statistically significant interaction ($P=0.019$), which should be confirmed in future studies.

There were more SAEs and also SAEs that required treatment discontinuation in the olmesartan plus diuretic group than in the olmesartan plus CCB group. Furthermore, hyperuricaemia was more common in the olmesartan plus diuretic group, even though low doses of diuretics were used. On the basis of these tolerability issues, we suggest that the combination of an ARB and CCB may be preferable to that of an ARB and diuretic for elderly hypertensive patients.

Guidelines for the treatment of hypertension currently recommend target SBP/DBP less than 140/less than 90 mmHg for general hypertensive patients [4–6]. To achieve such targets, it is often necessary to use multiple antihypertensive drugs of different classes. Consequently, numerous clinical trials have used two or more antihypertensive drugs [21,22]. In recent years, various combination antihypertensive drugs have been launched, and fixed combinations of two antihypertensive drugs are now widely used in clinical practice. In the United States, the combination of a RAS inhibitor and a diuretic or a CCB is the preferred one, whereas that of a CCB and β-blocker or a diuretic is an acceptable one [23]. These recommendations, however, are not fully supported by clinical evidence. Therefore, further studies are necessary to provide adequate clinical evidence to either support or change the current clinical recommendations. Additionally, it will also be necessary to determine the safety profiles and cardiovascular risk reduction associated with the use of other ARBs in combination with a β-blocker, CCB, or diuretic.

Some limitations warrant mention. First, we used the method of prospective, randomized, open-label blinded-endpoint trial, which may lead to some investigator bias. Because BP control was similar in both groups, however, it is unlikely that some investigator bias affected the main outcomes of this study. Regarding statistical power, the incidence of the primary endpoint was close to the expected incidence. Because the sample size was designed to detect a relative difference of 33%, however, more patients were necessary to detect the smaller than expected difference in the incidence of the primary endpoint. Another limitation is that we only enrolled Japanese elderly hypertensive patients, so the results may not be generalizable to other populations.

In conclusion, antihypertensive drugs are widely prescribed to reduce the risk of serious cardiovascular events in patients deemed to be at high risk of such events. The

current clinical guidelines for the management of hypertension advocate the use of multiple antihypertensive drugs in combination to help reach BP targets. Although there is abundant evidence supporting the use of combination therapy, very few studies have compared different combinations of drugs. We found no marked differences in the cardiovascular risk reduction by using olmesartan together with either a CCB or a diuretic. When considering the safety aspects, however, a regimen consisting of olmesartan and a CCB may be preferable to olmesartan in combination with a diuretic. Well designed studies are needed to compare the cardiovascular risk reduction profiles and safety profiles of combination regimens based on an ARB, ACE inhibitor, or CCB.

## ACKNOWLEDGEMENTS

We thank the collaborators and members of the COLM Study Group.

The present work was supported by a grant from Japan Heart Foundation. The Japan Heart Foundation had no input into the study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

### Conflicts of interest

T.O., T.S., H.R., I.S., K.Shimamoto., H.M., K.Shimada, S.I., M.H., T.I., S.T., J.H., S.K., G.K., N.U., K.H., M.O., N.T., T.I., S.U., N.K., and S.T. have received travel expenses, payment for speaking at meetings, or funding for research from one or more pharmaceutical companies that market antihypertensive drugs, including Daiichi Sankyo Co. Ltd. S.M. has no conflicts of interest to disclose.

## Appendix

### COLM study committees

Executive and Writing Committee: T. Saruta (Co-Chair, Keio University), T. Ogihara (Co-Chair, Morinomiya University of Medical Sciences), H. Rakugi (Secretary, Osaka University Graduate School of Medicine), and I. Saito (Keio University).

Steering Committee: K. Shimamoto (Sapporo Medical University), S. Ito (Tohoku University Graduate School of Medicine), H. Matsuoka (Dokkyo Medical University), K. Shimada (Shin-Oyama City Hospital), M. Horiuchi (Ehime University Graduate School of Medicine), T. Imaizumi (Kurume University School of Medicine), and S. Takishita (University of the Ryukyus School of Medicine).

Protocol Committee: K. Shimada (Shin-Oyama City Hospital), N. Ura (Sapporo Nishimaruyama Hospital), K. Hayashi (Keio University), and H. Rakugi (Osaka University Graduate School of Medicine).

Endpoint Committee: J. Higaki (Ehime University Graduate School of Medicine), M. Odawara (Tokyo Medical University), N. Tanahashi (Saitama Medical University), and G. Kimura (Asahi Rousai Hospital).

Independent Data Monitoring Committee: S. Katayama (Saitama Medical University), S. Umemura (Yokohama City University Graduate School of Medicine), T. Ishimitsu (Dokkyo Medical University), N. Kashihara (Kawasaki Medical School), and S. Morita (Yokohama City University Graduate School of Medicine).

Statistical Committee: I. Saito (Keio University) and S. Teramukai (Kanazawa University Hospital).

Ethics committee: Y. Uetsuka (Tokyo Women's Medical University), M. Fujikawa (Edogawa City Office), R. Nagao (Marunouchi Minami Law Office), and M. Ito (Chibaken Certified Public Tax Accountants' Association).

### COLM study investigators

T. Anno, S. Aoyama, N. Arima, Y. Bando, Y. Dohi, H. Fujioka, M. Fukuda, S. Fukuda, M. Fukuta, Y. Futamura, Y. Hirakawa, K. Imaeda, H. Imai, A. Imamura, M. Ito, O. Ito, T. Ito, T. Iwa, J. Izumi, Y. Kaga, K. Kanematsu, Y. Kato, Y. Kawata, T. Kitamura, K. Kobayashi, M. Koyasu, S. Kuwabara, M. Kuzuya, M. Maekawa, H. Mihara, F. Mitsuguchi, T. Murohara, T. Narita, K. Negi, Y. Numaguchi, T. Ohya, N. Okayama, K. Okuma, N. Ozaki, N. Ozeki, K. Sato, T. Sawada, Y. Seino, M. Suezawa, T. Suzuki, Y. Suzuki, N. Takahashi, R. Takahashi, N. Tanaka, Y. Wakida, H. Watanuki, M. Watarai, K. Yamada, S. Yamashita, M. Yoshikane (Aichi), M. Goto, Y. Ishida, H. Kimura, K. Takahashi, N. Yashima (Akita), Y. Abe, S. Fujiwara, H. Higashino, M. Kaizuka, O. Minami, Y. Ogiu, T. Osanai, T. Sasaki, A. Sato, K. Sugimoto, H. Takahashi, K. Tanabe (Aomori), D. Azuma, C. Ibuki, H. Inoya, T. Iyo, M. Kusaka, M. Ogawa, Y. Okubo, H. Rinno, M. Sano, T. Shishikura, H. Takahara, M. Takano, T. Takemura, S. Yamamoto, Y. Yonemitsu (Chiba), M. Hasui, T. Honda, M. Igase, S. Kimoto, K. Kohno, S. Kondo, T. Oonishi, H. Saeki, T. Sunayama, H. Takahashi, C. Wakisaka, H. Watanabe, K. Watanabe (Ehime), Y. Iwahori (Fukui), Alan H.C. Lau, S. Ando, H. Eguchi, M. Fujino, J. Fukui, T. Gondo, S. Hatakeyama, K. Hirano, Y. Hirooka, H. Ikeda, T. Inou, T. Jinnouchi, T. Kadokami, H. Kai, H. Kameo, M. Kaneyuki, A. Katoh, H. Kishikawa, H. Koiwaya, K. Kusaba, S. Maeda, S. Maki, M. Matsumoto, T. Matsumoto, J. Matsumura, S. Matsuo, H. Meno, S. Miki, J. Miyagi, T. Miyauchi, S. Mori, M. Nagashima, S. Nagata, R. Nakamura, T. Nakamura, H. Niiyama, K. Noda, M. Nohara, Y. Ohta, I. Onitsuka, T. Otonari, S. Ouma, T. Sakisaka, K. Saku, K. Sasaki, S. Sasaki, Y. Sawayama, M. Shihara, K. Shiota, K. Shirakawa, Y. Tachikawa, S. Takemura, T. Takeuchi, M. Tanabe, M. Tanaka, H. Tashiro, M. Tatsukawa, T. Tsuchihashi, T. Tsuiki, T. Tsutsui, Y. Uehara, H. Umei, T. Yamada, J. Yamagata (Fukuoka), T. Ajihara, K. Hagiwara, S. Imamura, M. Inoue, I. Konno, K. Konta, Y. Kubota, H. Kumakawa, T. Kuwana, H. Mitsuhashi, Y. Miyazaki, J. Nagashima, M. Nambu, T. Nishimaki, M. Sato, Y. Taneda, T. Tezuka, T. Yabuki (Fukushima), F. Ando, Y. Fuwa, S. Umeda (Gifu), O. Araki, Y. Furushima, Y. Hattori, H. Hirabayashi, M. Horigome, J. Hoshino, C. Iguchi, H. Inamura, H. Kawauchi, S. Kogure, H. Kubo, F. Naganuma, T. Nagao, T. Nagao, T. Nagata, H. Nakashima, Y. Shimizu, H. Shoda, M. Tachibana, K. Yabe (Gunma), R. Kuwashima, R. Mouri, T. Murakami, H. Muraoka, S. Nomura, F. Okuno, N. Sasaki, R. Sasaki, T. Satoh, M. Shirataki, H. Sugino, H. Takahashi, H. Takemoto (Hiroshima), J. Ashihara, T. Betsuyaku, T. Fujita, T. Haga, M. Hayashi, Y. Hayashi, K. Hirasawa, Y. Ishii, R. Ishimoto, T. Komakine, M. Kyuma, I. Maeda, H. Matsuda, T. Matsuki, T. Matsumoto, T. Mito, M. Mizutani, H. Morimoto, S. Natori, T. Nishimiya, M. Nishimura, H. Oimatsu, H. Ooiwa, S.

Saitoh, Y. Sasagawa, T. Segawa, H. Shuke, K. Sotozono, S. Takagi, S. Tanaka, M. Tashi, T. Tsubokura, Y. Ueno, K. Urabe, K. Yamauchi, H. Yoshida (Hokkaido), M. Amano, Y. Hiroumi, K. Iiyama, H. Kido, A. Kosaka, A. Nogami, M. Okada, M. Shigenobu, R. Shigeta, S. Takagi, T. Takamiya, T. Takemura, S. Tomimoto, T. Tsuboi (Hyogo), N. Abe, E. Akaogi, S. Iida, K. Ito, H. Jonouchi, T. Matsushima, H. Miura, M. Miyazaki, S. Okubo (Ibaraki), T. Araki, O. Iritani, K. Masuya, S. Morimoto, T. Nakahashi, Y. Wakasa, M. Yanagi (Ishikawa), Y. Abe, H. Ito, T. Kawakami, Y. Kawamorita, H. Okamoto, H. Omori, T. Suzuki, T. Yoshida (Iwate), K. Akiyama, S. Fujita, T. Hamamoto, K. Hasegawa, M. Hattori, H. Imachi, T. Ishida, H. Ishihama, K. Kaifu, H. Kishikawa, M. Kono, M. Kunishige, T. Maeta, H. Masugata, I. Matsumoto, N. Matsuoka, H. Miki, S. Mori, T. Morita, Y. Nishijima, E. Ohashi, Y. Okauchi, T. Okura, Y. Onishi, K. Ono, S. Senda, I. Seo, Y. Sugimoto, M. Tada, K. Yokoi, K. Yoshinare (Kagawa), K. Arikawa, Y. Hayashi, K. Iida, S. Miyata, H. Mizoguchi, A. Osako, S. Saishoji, I. Shimozono, S. Takenouchi, S. Tanaka (Kagoshima), T. Furuki, N. Hatori, T. Iwaki, E. Kametsu, T. Kawafune, I. Kobayashi, T. Kubo, I. Michishita, F. Nonaka, H. Numata, A. Ogata, K. Okubo, T. Sano, R. Sawada, T. Sekino, N. Shimizu, H. Shionoiri, H. Tsuchiya, Y. Watanabe, H. Yamamoto, G. Yasuda (Kanagawa), M. Aoki, Y. Iwasaki, H. Kawamoto, S. Kitagawa, M. Matsumoto, M. Nishinaga, M. Nishiyama, K. Tsuboi, I. Ueda, T. Yabe, H. Yamada, T. Yoshida (Kochi), K. Azuma, O. Doi, R. Fukami, Y. Horio, Y. Ichikawa, S. Ikeda, T. Inaba, S. Mimori, K. Ohmori, K. Sasaki, A. Sato, H. Toyama, Y. Toyama (Kumamoto), T. Hamasaki, H. Hayashi, T. Isono, S. Kageyama, K. Komaki, S. Matoba, H. Matsubara, T. Matubara, C. Nakagawa, D. Nishi, M. Nishi, K. Oiwa, H. Takamatsu, H. Takashima, T. Takegami, K. Takenaka, H. Yamada, Y. Yasuda (Kyoto), M. Horiguchi, J. Iemura, N. Isaka, T. Ishiga, T. Kato, T. Kitamura, M. Kobayashi, M. Setsuda, K. Shimono (Mie), M. Abe, T. Abe, Y. Abe, Y. Akino, H. Ebina, G. Hirasawa, K. Hirasawa, H. Kamada, M. Kishi, K. Kohama, S. Kyogoku, K. Matsuo, Y. Meguro, S. Miyasato, K. Morita, H. Nakagawa, Y. Otake, H. Saito, A. Sasaki, I. Sasaki, S. Sato, N. Uchida, Y. Utsumi, S. Yamaguchi (Miyagi), K. Hosokawa, Y. Ishiyama, S. Kariya, H. Komidori, M. Kuwabara, H. Ohta, S. Sonoda, M. Takii, N. Wake, N. Yokota (Miyazaki), A. Iijima, T. Shinozaki, T. Takeda (Nagano), A. Ito, H. Kawano, Y. Koide, H. Matsuoka, K. Nakao, K. Yamaguchi, A. Yamanaka (Nagasaki), Y. Furiya, T. Kimu, Y. Kuga, Y. Nishida, Y. Saito, K. Sugie, T. Takami, M. Yamasaki (Nara), Y. Kaneko, H. Kawabata, S. Nakayama (Niigata), Y. Abe, H. Ando, T. Fujino, K. Gotoh, T. Kakuma, I. Katsuragi, A. Kuroda, T. Masaki, K. Ninomiya, K. Okita, H. Ono, T. Watanabe, A. Yoshiiwa (Oita), K. Abe, S. Deguchi, F. Ikeda, H. Kataoka, N. Komai, K. Koten, K. Kusano, N. Maeda, H. Makino, S. Matano, T. Ohe, K. Shikata (Okayama), M. Gushiken, R. Hamada, K. Matsushima, T. Shimabukuro, S. Tohma (Okinawa), T. Akagi, F. Akai, T. Amatsu, N. Babaya, S. Ban, K. Fujii, M. Fujimoto, Y. Fujimura, S. Fukumoto, M. Funauchi, H. Hanada, K. Hasegawa, N. Hayashi, T. Hibuse, M. Higashida, H. Honde, A. Imagawa, Y. Imamura, S. Inoue, R. Ishii, K. Ishikawa, K. Ishitani, H. Ito, S. Kaito, A. Kamitani, K. Kamiya, N. Kasayuki, R. Kawanami, T. Kawasaki, Y. Kijima, K. Kinoshita, M. Kishibuchi, Y. Kitamura, M. Kobayashi, T. Kono, Y. Maeda, K. Masaki, H. Matsumoto, S. Matsuoka, R. Matsuwaka, K. Minamikata, M. Miyagawa, H. Miyamoto, M. Miyamoto, E. Miyazaki, K. Miyoshi, M. Mune, N. Nakagawa, Y. Nakagawa, F. Nakamura, T. Nakamura, K. Nakanishi, Y. Nakatani, J. Nariyama, H. Nishida, M. Nishino, M. Nishiyama, K. Nishizawa, R. Nohara, A. Nose, H. Ogasawara, R. Ogawa, Y. Ohno, M. Ojima, Y. Okuyama, H. Otani, S. Otani, H. Park, H. Saito, A. Sakai, H. Sakamoto, H. Sata, Y. Sekine, T. Shinozuka, T. Suga, K. Sugimoto, M. Sugiyama, K. Suyama, K. Suyama, J. Tachi, T. Takagi, C. Takaori, M. Takenaka, T. Tamai, K. Tanaka, Y. Tanaka, K. Tane, M. Taniura, N. Tatsuda, Y. Teramoto, K. Teranaka, S. Teranishi, J. Terasaki, K. Toki, K. Tsuji, Y. Tsuji, T. Tsunetoshi, K. Ujino, S. Umeki, N. Wakagi, N. Wakaki, K. Yamaguchi, Y. Yamamoto, S. Yanagitani, M. Yoshida, H. Yoshimoto, H. Yoshioka (Osaka), H. Ikeda, M. Matsumoto, K. Nagae, M. Nishiyama, K. Noda, M. Ohga (Saga), M. Akui, H. Aoki, J. Arafune, M. Arai, T. Arai, I. Asami, K. Eguchi, T. Fujino, H. Fujinuma, H. Fukata, J. Fukuda, T. Hamasaki, M. Haneda, I. Hisauchi, T. Hogi, M. Ichikawa, T. Iijima, H. Inoue, Y. Inoue, T. Kakinuma, H. Kanai, U. Kaneko, T. Kano, T. Katsumi, T. Kawashima, K. Kogure, O. Komuro, Y. Kubouchi, N. Kujirai, K. Kurokawa, T. Lee, K. Maeda, T. Majima, Y. Maruyama, S. Mashiba, K. Mashiko, K. Matsumoto, M. Matsuzawa, Y. Mitsugi, J. Morita, C. Nakajima, Y. Nakazato, Y. Nashida, H. Nasuhara, Y. Numajiri, T. Ogasawara, T. Okudaira, I. Osawa, N. Otani, A. Otsuka, Y. Ozawa, T. Sakai, Y. Sakai, K. Shimizu, T. Shinozaki, M. Shirai, K. Shiroma, H. Shuto, H. Suzuki, A. Tada, M. Takagi, K. Takahashi, N. Takahashi, A. Taniguchi, Y. Tonegawa, M. Toyoda, T. Tsuchiya, M. Uchida, H. Uchino, H. Wada, O. Wada, H. Yoshioka (Saitama), H. Horie, M. Ichikawa, K. Ikenoue, T. Kawashima, H. Mizuhara, S. Ono (Shiga), S. Ishikawa, K. Kawakami, S. Yano (Shimane), N. Kubota, A. Nakagawa, T. Shigemasa, S. Suwa (Shizuoka), T. Akabane, M. Amagai, Y. Asanobu, S. Horinaka, T. Iijima, K. Kasai, T. Kataoka, M. Kobayashi, T. Masuda, I. Nakano, M. Namekawa, A. Numabe, A. Ono, K. Sakata, I. Taguchi, T. Tomotsune, S. Toyoda (Tochigi), M. Arizumi, Y. Morimoto, A. Ota, S. Sawada, K. Yata (Tokushima), H. Akita, T. Akitsu, K. Amemiya, M. Ando, N. Aoki, J. Aoyagi, T. Baba, T. Degawa, S. Eto, K. Fujimoto, H. Fukuda, T. Furukawa, I. Goto, A. Hachiya, Y. Hanatani, K. Hara, T. Haruta, K. Hasegawa, T. Hatano, M. Hayashi, T. Hirano, M. Hiratsuka, Y. Horikawa, T. Horiuchi, M. Hosoya, K. Ichikawa, K. Iguchi, H. Imai, K. Ishibashi, K. Ishida, Y. Ishii, S. Ishiwata, T. Iwama, H. Kadota, S. Kaku, Y. Kamisaka, R. Kanbara, T. Kanematsu, A. Kashiwagi, I. Kawa, B. Kawai, M. Kawai, S. Kiuchi, T. Kiyozuka, S. Koba, H. Kobayashi, K. Koike, H. Kojima, E. Koshibu, Y. Koshibu, I. Kubo, K. Kuga, T. Kushiro, S. Miyakata, M. Miyakawa, F. Miyoshi, Y. Mochida, N. Moriyama, T. Myojo, M. Nagashima, H. Nakada, T. Nakai, T. Nakamura, Y. Nakaya, M. Nishizawa, S. Nishizawa, K. Oba, Y. Obu, N. Ohara, M. Okazaki, Y. Okazaki, K. Okumura, T. Ono, Y. Osamura, M. Otsuka, M. Ouchi, N. Sakamoto, Y. Sakata, S. Saneshige, M. Sasajima, T. Satoi, Y. Sengoku, K. Shibuya, H. Shimizu, K. Shimokado, M. Shoji, H. Tabata, A. Takahashi, H. Takakura, T. Takao, M. Taya, H. Tomonari, T. Tsunematsu, A. Uehata, T. Umezawa, H. Usui, T. Watanabe, Y. Yajima, F. Yamada, K. Yamada, A. Yamaguchi, T. Yamaguchi, K. Yamamoto, M. Yamamoto (Tokyo), T. Hamada, I.