Atherosclerotic Cardiovascular Risk in Japan

Shuko Nojiri[1] and Hiroyuki Daida[2]

[1]Clinical Research Support Center, Juntendo University, Tokyo, Japan. [2]Department of Cardiovascular Medicine, Juntendo University Graduate School of Medicine Tokyo, Japan.

ABSTRACT: Increased global mortality is associated with atherosclerosis, which appears to be independent of race. Cardiovascular disease is one of the leading causes of mortality and morbidity in Japan. Atherosclerosis, an inflammatory disease characterized by abnormal lipid accumulation and inflammation in the arterial wall, is the main underlying cause of cardiovascular disease. Numerous cardiovascular risk scores have been developed and are used to prioritize patients' treatment needs. The predictive performance of risk scores established in Western nations needs to be examined in Japanese populations. For secondary prevention, it is imperative to control hypertension, hyperlipidemia, diabetes mellitus, smoking, and local interventions. In this review, we present a historical overview of atherosclerotic risk research and the risk factors for atherosclerosis in Japan and compare the situation in Japan with that in Western nations. In addition, we discuss relevant cardiovascular risk assessment tools in the context of clinical practice in Japan.

KEYWORDS: Cardiovascular risk, atherosclerosis, Japanese

Introduction

There is a global epidemic of cardiovascular disease (CVD) caused by atherosclerosis. The number of cases of CVD increased to 17.3 million in 2013, according to the Global Burden of Disease Study 2013.[1] The World Health Organization (WHO) recently issued its 2013-2020 Global Action Plan for the Prevention and Control of Noncommunicable Diseases, and it called on WHO member states to target a 25% reduction in CVD risk factors, including hypertension, diabetes mellitus (DM), and obesity by 2025.[2] In addition, the American Heart Association (AHA) and World Heart Federation recently published a scientific statement that WHO recommended for "The Heart of 25 by 25" CVD goals.[3]

Many longitudinal, epidemiological studies have provided valuable insights into the natural history and risk factors of CVD in Japan. The age-adjusted annual incidence rates of acute myocardial infarction (AMI) per 100 000 persons in those aged 25 to 74 years were 58.2 for men and 18.0 for women in Takashima County, Shiga,[4] and 54.6 for men and 7.2 for women in Nagaoka, Niigata, Japan, based on cases of AMI, according to the WHO-MONICA project.[5] The CVD mortality rate in Japan has decreased over the past 50 years at a faster rate than the Organisation for Economic Co-operation and Development (OECD) average rate, reaching the lowest at 171 per 100 000 persons, which is 43% lower than the OECD average rate of 299 per 100 000 persons.[6] The Japanese population has one of the highest life expectancies in the world, which is estimated to be 86.35 years (95% uncertainty interval [UI]: 86.28-86.41) for women and 79.94 years (95% UI: 79.88-80.00) for men in 2015, and healthy life expectancies for women and men in 2015 were 76.28 years (95% UI: 73.33-78.85) and 71.54 years (95% UI:

69.14-73.67), respectively.[7] Data from Japanese elderly individuals who have a multimorbidity status, including CVDs, will serve as a good model for how to deal with an aging society in Western populations in the future. Systematically assessing and quantifying modifiable CVD risk factors are crucial in the Japanese population. From the global perspective, various CVD risk prediction models have been developed over the past decades, and some of these models have played a role in the development of clinical guidelines for therapeutic management. Risk assessment tools can serve to identify individuals who would benefit from risk factor intervention. With the aforementioned in mind, this review discusses research regarding short-term and long-term risk assessments, and we aimed to compare common risk scores and epidemiological studies among nations. We highlight some key cardiovascular epidemiological studies concerning the increase in the coronary atherosclerotic CVD risk in Japan, and we describe the potential direction of strategies to remedy this situation in the future.

Cardiovascular Risk and Risk Factors in Japan

Although dietary fat intake and serum total cholesterol levels have steadily increased in Japan because of westernization,[8] Japan has an extraordinarily lower mortality rate for CVD than that reported in other countries.[6,9] A low saturated fat intake, high fish diet, containing omega-3 fatty acid, and soy bean intake may contribute to lower mortality and morbidity rates for CVD observed in Japan.[10,11] These hypotheses have been confirmed by cross-cultural studies of CVD, autopsy studies, and studies of the subclinical stages of coronary atherosclerosis measured by coronary artery calcification (CAC).[12–16] The

identified CAD risk factors are smoking, high cholesterol level, high blood pressure, DM, and low physical activity in addition to overweight, diet, dyslipidemia, and genetic factors associated with the development of atherosclerosis in Japan[10,16–18] The Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic CVDs in Japan define the risk factors of CVD in Japan as DM/impaired glucose tolerance, chronic kidney disease, noncardiogenic cerebral infarction/peripheral artery disease, age and sex, dyslipidemia, hypertension, smoking, and a family history of premature CAD in a first-degree relative.[19]

Cardiovascular Risk: Metabolic Syndrome and DM

A cluster of multiple risk factors, including DM and metabolic syndrome (MetS), have been reported.[20,21] Metabolic syndrome and type 2 DM confer an increased risk of CVD, and obesity has been focused on globally because it is an established risk factor for DM and strongly related to MetS. In Japan, MetS is defined as an increased waist circumference and the presence of 2 or more additional risk factors.[22] The criteria of MetS in Japan are as follows: waist circumferences ≥85 cm in men and ≥90 cm in women. Additional criteria include the presence of 2 other abnormal parameters among dyslipidemia, hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C) level, hypertension, and hyperglycemia. According to the National Health and Nutrition Survey in Japan in 2013, 23.6% of adult men and 9.1% of adult women were diagnosed as having MetS.[23] The association between the body mass index (BMI) and cardiovascular risk has been reported in several large population studies in Japan, such as the Japan Collaborative Cohort (JACC) study and Japan Public Health Center (JPHC) study.[24,25] In the Japan Arteriosclerosis Longitudinal Study-Existing Cohorts Combine (JALS-ECC) study, a meta-analysis of 16 Japanese cohorts using individual data, the hazard ratio for myocardial infarction (MI) was 3.16 (95% confidence interval [CI], 1.66-6.01) for a BMI of 27.5 kg/m² or greater versus a BMI less than 21.0 kg/m² only in men.[26] According to an 18-year prospective cohort study (9087 Japanese people aged 40-69 years), high blood pressure, high triglyceride level, and low HDL-C level were associated with increased risks of CVD or stroke, and there was a dose-response relationship between the number of metabolic risk factors and incidence of ischemic heart disease (IHD) or stroke.[27] Liu et al[28] reported that the United States has a significantly higher prevalence of MetS than Japan, in which an estimated 13% of excess CVD mortality could be explained by differences in MetS according to the National Health and Nutrition Examination Survey (NHANES) III and NIPPON DATA studies. Compared to Westerners, Japanese people are less obese, but increases in BMI have been reported in Japanese populations. In addition, childhood obesity has been reported in Japan in a cross-sectional study,[29] and future cardiovascular risks associated with obesity from early ages should not be overlooked in the long term.

With regard to the prevalence of prediabetes and DM in Japan, the prevalence of strongly suspected DM between 1997 and 2012 has considerably increased from 9.9% to 15.2% in male adults and from 7.1% to 8.7% in female adults, according to a national survey using the glycated hemoglobin A1c level. Furthermore, the prevalence of prediabetes increased from 8.0% to 12.1% and from 7.9% to 13.1% in men and women, respectively.[30] The American Diabetes Association recommends screening people at an increased risk based on age and BMI, not their DM risk,[31] and the potential consequences of this policy in terms of prediabetes on cardiovascular morbidity and mortality are a subject of debate. The levels of glycated hemoglobin A1c, impaired fasting glucose, and impaired glucose tolerance are associated with increases in the risk of CVD, according to meta-analyses, the JPHC study, and Funagata Diabetes Study.[32–34] However, the effect of a prediabetes status on the actual CVD risk in Japan has been inconclusive. As for DM, there are differences in the prevalence of its complications, cardiovascular risk factors, and pathophysiology of the disease between Asians and Europeans.[35,36] The risk of type 2 DM becomes significant at a low BMI for Asians than for Europeans, and obesity cannot solely explain the cause of DM in Japan. The association between hyperglycemia and the risk of CVD is well understood from results of the Hisayama study, Circulatory Risk in Communities Study (CIRCS), and JPHC study.[37–39] The population attributable fraction (PAF) represents the proportional reduction in population disease or mortality that would occur if exposure to a risk factor was reduced.[40] The PAFs of CVD due to DM increased over time: 2.8% in 1992-1995, 5.6% in 1996-1999, and 12.4% in 2000-2003 according to CIRCS (Japanese residents aged 40-69 years),[38] which could have predicted the increasing burden of CVD in the future.

Non–HDL-C and Beyond Low-Density Lipoprotein Cholesterol

The marker non–HDL-C estimates the cholesterol concentration of all apolipoprotein B (apoB)-containing lipoproteins, including very-low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), low-density lipoprotein (LDL), and lipoprotein(a) [Lp(a)].[41] The non–HDL-C level can represent cholesterol levels in atherogenic lipoproteins, and it may be a useful lipid marker for predicting the onset of future cardiovascular-related events in daily clinical practice. Japanese epidemiological data regarding the association between non–HDL-C and fatal and/or nonfatal CVD have been accumulated, such as the Hisayama study, Suita study, Ibaraki Prefectural Health study, NIPPON DATA, and pooled analyses.[42–46] Apolipoprotein B represents all atherogenic apoB-containing lipoproteins, including chylomicrons, chylomicron remnants, VLDL, IDL, LDL, and Lp(a) particles containing one molecule of apoB, and so on, and these lipoproteins have been identified as possible predictors of CAD; however, limited research has been performed regarding these new risk markers, such as the apoB/apoA-I ratio, in Japan.[47]

An increase in the concentration of small, dense LDL (sd LDL) particles is also an interesting topic because of a possible association between these particles and atherogenesis, in addition to observations that altering the LDL size decreases CAD events independent of any effect of lowering the LDL concentration itself. A community-based study of 851 individuals without CVD demonstrated that the overall association of CAC with nuclear magnetic resonance–measured lipoprotein indices and LDL particles was not superior to standard lipid profiles for predicting CAD.[48] Hirano et al used a simple precipitation assay for sd LDL directly in serum to determine the importance of screening familial combined hyperlipidemia, and they found that sd LDL particles were a significant risk factor of CAD events.[49,50] In a cross-sectional study of 481 Japanese Americans who were not using lipid-lowering medication, sd LDL-C was positively correlated with BMI, fasting glucose level, insulin level, 2-hour glucose level, homeostatic model assessment-insulin resistance (HOMA-IR), high-sensitivity C-reactive protein (hs-CRP) level, and intima-media thickness (IMT) after adjusting for age and sex.[51] The Framingham Offspring Study could not conclude that sd LDL particles are an independent risk factor of future CVD, although they suggested that sd LDL particles could add information about the residual risk in patients with established CVD.[52] More data and prospective studies are needed before sd LDL particles, apoB, apoA-I, apoB/apoA-I ratio, or LDL particle counts can be used as predictive markers or treatment targets in the Japanese population.

Even with very aggressive reductions in the levels of LDL-C by a statin, residual cardiovascular risk remains.[53,54] In the Asia-Pacific Region Study (220 660 participants), the isolated, low HDL-C level was significantly associated with an increased risk of CVD.[55] A low HDL-C level is another independent risk factor for CVD. Hirata et al[56] conducted a pooled analysis of the association of isolated, low levels of HDL-C with cardiovascular mortality in Japan, and compared with normal HDL-C levels, non-isolated, low HDL-C levels were significantly associated with an increased risk of CVD (hazard ratio, 1.37; 95% CI, 1.04-1.80); however, isolated, low HDL-C levels were not significantly associated with an increased risk of CVD. Further investigation with a longer follow-up period is needed to confirm the association of isolated, low levels of HDL-C with cardiovascular mortality.

Inflammatory Biomarkers

Inflammatory cells, inflammatory cytokines, and inflammatory responses from vascular cells are related to the pathogenesis of various stages of atherosclerosis, such as the initiation and progression of atheroma, plaque instability, and rupture. In addition, it has been widely accepted that in the hyperglycemic state, pathways triggered by advanced glycated end products and mediated by the nuclear factor-κB lead to increased oxidative status and impaired nitric oxide production. Then, numerous substances, such as growth factors, cytokines, and procoagulant factors, increase and alter processes to induce and promote atherogenesis.[57,58]

C-reactive protein is an acute-phase protein and a marker of systemic inflammation, which increases in response to injury, infection, and the inflammatory process of atherogenesis.[59,60] Regarding the relationship of subclinical atherosclerosis, the Electron-Beam Tomography and Risk Assessment among Japanese and US Men in the Post World War II Birth Cohort (ERA-JUMP) study found an association between inflammatory markers (CRP and fibrinogen) with carotid IMT and CAC in the general male population,[61] and in another cross-sectional study of the general population (2056 subjects), IMT significantly increased with the increasing hs-CRP quartile, but this relationship disappeared after adjusting for other cardiovascular risk factors.[62] The CRP level is a possible biomarker of subclinical atherosclerosis in the general population; however, this may be easily confounded by age and cardiovascular risk factors, such as obesity, smoking, and blood pressure.[63] In addition, the effect of comorbid illnesses (eg, rheumatoid arthritis and liver-related diseases) on the hs-CRP level as a risk marker for CVD has been still unknown. There is a positive association between the CRP level and CVD risk according to the JACC study, Hisayama study, and a meta-analysis in East Asians.[64–66] The Centers for Disease Control and Prevention/AHA statement recommends the use of hs-CRP in the diagnosis and management of CVD.[67] In patients at an intermediate risk for CVD (10%-20% at 10 years according to the Framingham risk score), the hs-CRP level may help physicians perform further evaluation and primary prevention. In patients with established atherosclerotic CVD, the hs-CRP level may be useful as an independent marker of prognosis, but not for the application of secondary prevention measures. In Japan, JAS indicated cardiovascular risk factors or markers to consider, such as the CRP level, inflammation-related markers, homocysteine, and coagulation/fibrinolytic factors as nonlipid factors.[19] The CRP screening may provide an appropriate timing of targeting preventive interventions, such as statin and aspirin therapy; however, more data are needed to use the CRP level as a screening tool in Japan. Other expected biomarkers are interleukin 6, myeloperoxidase, interleukin 18, tumor necrosis factor α, transforming growth factor β, soluble intercellular adhesion molecule 1, P-selectin, lipoprotein-associated phospholipase A2, matrix metalloproteinases, pentraxin 3, and amyloid A.[68–74]

Risk Assessment Tools for CVD

There are several reliable risk-estimating tools to identify individuals who are at a high risk of a cardiovascular event to effectively implement prevention strategies. The Framingham CVD risk score is used in clinical practice, and patient education tools have been developed in some regions, such as Europe, New Zealand, the United States, and United Kingdom.[75–77] Most risk-estimation tools are based on conventional risk factors, such as age, sex, smoking, blood pressure, and cholesterol

level (total and high-density or low-density fractions), and they seemingly tend to include additional risk factors, such as overweight; DM; chronic kidney disease; individuals with a low HDL cholesterol level; individuals with increased hs-CRP, triglyceride, fibrinogen, apoB, and Lp(a) levels; psychosocial risk factors; and a family history of CVD. There are several risk assessment tools in addition to the Framingham risk score, modified Framingham risk score, Prospective Cardiovascular Münster (PROCAM) score, Systematic Coronary Risk Evaluation, United Kingdom Prospective Diabetes Study tool for DM, Reynolds risk score, and Progetto CUORE score.[78–84] However, each of the studies had different inclusion criteria, methods of case ascertainment, and end point definition. In a 2010 report in asymptomatic adults, the American College of Cardiology (ACC) Foundation/AHA Task Force on Practice Guidelines recommended obtaining global risk scores and details regarding a patient's family history of CVD for cardiovascular risk assessment.[85] Global risk scores can be computed to establish the 10-year risk of CVD based on risk factors, such as age, sex, family history of premature CVD, increased total or LDL-C level, decreased HDL-C level, smoking, hypertension, DM, obesity, and sedentary lifestyle. The Adult Panel III study recommended that Framingham's estimate of the 10-year risk (point scores) should be used for CAD risk evaluation. For external validity, the risk scores were established by different parameters in different geographic regions, and it is necessary to develop and validate applicable risk prediction tools in the Japanese population. The Framingham risk score has been reported to overestimate the coronary risk among Japanese American men, Hispanic men, and native Americans.[86] The assumption of risk homogeneity among different regions cannot be realistic in most epidemiologic studies. Population-level risk assessment results are not always applicable to an individual's risk because unmeasured background factors vary among individuals.

In Japan, a risk assessment chart for the 10-year probability of death due to coronary heart disease, stroke, and all CVD in men and women using traditional risk factors (ie, systolic blood pressure, smoking habit, serum total cholesterol level, and serum glucose level) has been developed[87] and adopted for clinical use. The NIPPON DATA risk chart for MI showed a positive relationship between total cholesterol and MI; however, the limitations of this study were that more detailed cholesterol data, such as the HDL-C and LDL-C levels, were not measured, and their end point was 10-year death probabilities, not the incidence probability. The Japan Public Health Center-based Prospective Study (n = 15 672) derived the risk equations for CAD and the incidence of ischemic stroke, in which the selected variables were age, sex, current smoker, systolic blood pressure, antihypertensive medication use, DM, and HDL-C and non–HDL-C.[88] In the Hisayama study, the CVD risk prediction model incorporated age, sex, systolic blood pressure, DM, LDL-C level, HDL-C level, and smoker.[89] The JALS study presented a 5-year AMI risk prediction model.[45] The

Suita study proposed the Suita Score, which incorporates age, sex, current smoker, DM, blood pressure, total cholesterol level, HDL-C level, and chronic kidney disease.[90] The Jichi Medical School study also developed an MI risk prediction tool, but this was limited by a lack of generalizability because most participants in the study were rural residents of retirement age or older.[91] Some cardiovascular risk assessment tools have been proposed based on clinical study data, such as those produced by postmarketing studies and randomized clinical trials. The MEGA risk prediction score can predict the 5-year risk for CVD with 5 levels of risk based on the total risk score, including treatment (diet and diet plus pravastatin), sex, age, baseline HDL-C and LDL-C levels, glucose abnormalities, hypertension, and smoking.[92] A 3-year risk assessment chart was constructed using a combination of all the risk factors in the prediction model from a postmarketing study for the angiotensin receptor blocker olmesartan.[93]

Further studies are needed to assess the effectiveness of using the risk scores to aid in the primary prevention of CVD in clinical practice, and the predictive accuracy of the risk score needs to be examined. Cardiovascular risk factors have been constantly changing in a different magnitude and direction in recent years, and the CVD risk prediction model at the population level needs to be justified over time. For example, a downward trend was observed for cigarette smoking, whereas other factors such as obesity, MetS, and DM have become more prevalent in Japan. Furthermore, the proposed risk models in Japan have a relatively short time prediction for CVDs in a limited population; indeed, attempting to predict lifetime cardiovascular risks would be a challenging work in the future. In addition, hypolipidemic drugs, such as statins, have contributed to high LDL-C levels in patients in Japan, so the actual benefit of statin therapy at various cutoff points in high-risk patients may be valuable information. According to the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk, clinical studies with long-term outcome data for groups predicted to be at a low 10-year risk have value because previous studies have indicated that the development of atherosclerosis proceeds over decades, and the effect of cumulative exposure to causal modifiable risk factors during cardiovascular events should be measured.[94] The recomendation is the long term assessment is important, to assess traditional CVD risk factors every 4 to 6 years in adults who are free from CVD (20 to 79 year of age) and estimate 10-year CVD risk every 4 to 6 years in adults (40 to 79 years of age) who are free from CVD. The long-term predicted risks for CVD among subjects who are at a low predicted short-term risk in Japan are still unknown. Other risk factors, such as obesity, comorbid status, inflammatory markers, and lifestyle, are not included in the present risk formulae in Japanese risk assessment tools, and the CVD risk may be underestimated or overestimated in the current assessment results. Hlatky et al provided criteria for evaluating novel markers of cardiovascular risk. As the degree of cardiovascular risk changes over time, the necessity of recalibrating existing risk equations is needed with a validation set.[95] Discrimination

analysis, which separates those who do and do not experience an outcome, and reclassification analysis would add value to the current risk equation model. Along with the development of new biomarkers and expanding the understanding of the pathophysiology of atherosclerosis, future CVD risk formulae should incorporate measures of factors, including different mechanistic pathways, beyond the current approach. In the Multi-Ethnic Study of Atherosclerosis (MESA; n = 6814), the coronary artery calcium score of 0 was the strongest modulator of the future risk, and it had the greatest effect on net reclassification of the risk.[96]

Conclusions

Asia, including Japan, has gained an important position in the clinical research community because of the potential for economic growth in the region. The incidence of IHD has generally been low in most Japanese populations; however, an increase in the incidence among urban, male populations has been observed.[97] The possibility of an earlier onset of obesity and assessment of accumulation of long-time exposure of risk factors, in addition to the complex clinical manifestations, should be considered in an elderly population in the following decades. An aging population is expected to lead to vast costs associated with medications for atherosclerotic diseases, making it important to develop proper risk prediction and substratification techniques. To develop an effective CVD prevention strategy in Japan, numerous issues need to be investigated, such as the cost-effectiveness and health benefits of treatments. Policymakers should be actively analyzing existing epidemiologic data from electronic databases, registry data, and large cohort studies to assess ongoing trends in the net cardiovascular risk. To obtain clinically meaningful information from observational studies, it is imperative to reduce any possible bias from the study planning stage and its evaluation, such as misclassification, unmeasured confounders, and selection bias.

A future study will be needed to define intermediate or unspecified subgroups that would benefit most from the use of novel biomarkers in early primary prevention. To develop new antiatherosclerotic strategies in Japan in the future, new evidence is required in the following areas: HDL-C therapy, new peroxisome proliferator–activated receptor agents, triglyceride therapies, anti-inflammatory agents, direct inhibitors of atherosclerotic plaque signaling, and antidiabetic agents.

Author Contributions

HD and SN wrote the first draft of the manuscript, contributed to the writing of the manuscript, agree with manuscript results and conclusions, jointly developed the structure and arguments for the paper, and made critical revisions and approved the final version.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

REFERENCES

1. Global Burden of Disease Study. http://www.healthdata.org/gbd. Published 2013.
2. WHO. *Global Action Plan for the Prevention and Control of NCDs 2013-2020*. http://www.who.int/nmh/events/ncd_action_plan/en/.
3. Sacco RL, Roth GA, Srinath Reddy K, et al. AHA/WHF scientific statement, the heart of 25 by 25: achieving the goal of reducing global and regional premature deaths from cardiovascular diseases and stroke. http://circ.ahajournals.org/content/early/2016/05/06/CIR.0000000000000395.full.pdf+html.
4. Yoshida M, Kita Y, Nakamura Y, et al. Incidence of acute myocardial infarction in Takashima, Shiga, Japan. *Circ J*. 2005;69:404–408.
5. Tanabe N, Saito R, Sato T, et al. Event rates of acute myocardial infarction and coronary deaths in Niigata and Nagaoka cities in Japan. *Circ J*. 2003;67:40–45.
6. OECD. *Cardiovascular Disease and Diabetes: Policies for Better Health and Quality of Care*. Paris, France: OECD Health Policy Studies, OECD Publishing; 2015.
7. GBD 2015 DALYs and HALE Collaborators. Global, regional, and national disability-adjusted life-years (DALYs) for 315 diseases and injuries and healthy life expectancy (HALE), 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1603–1658.
8. Ministry of Health Labor and Welfare. *The Fifth National Survey of Cardiovascular Diseases*. Tokyo, Japan: Chuo Houki; 2003.
9. Goto S, Ikeda Y, Chan JCN, et al. Risk-factor profile, drug usage and cardiovascular events within a year in patients with and at high risk of atherothrombosis recruited from Asia as compared with those recruited from non-Asian regions: a substudy of the REduction of Atherothrombosis for Continued Health (REACH) registry. *Heart Asia*. 2011;3:93–98.
10. Ueshima H. Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. *J Atheroscler Thromb*. 2007;14:278–286.
11. Hoy SM, Keating GM. Omega-3 ethylester concentrate: a review of its use in secondary prevention post-myocardial infarction and the treatment of hypertriglyceridaemia. *Drugs*. 2009;69:1077–1105.
12. Ueshima H, Sekikawa A, Miura K, et al. Cardiovascular disease and risk factors in Asia: a selected review. *Circulation*. 2008;118:2702–2709.
13. Takei H, Strong JP, Yutani C, et al. Comparison of coronary and aortic atherosclerosis in youth from Japan and the USA. *Atherosclerosis*. 2005;180:171–179.
14. Sekikawa A, Ueshima H, Kadowaki T, et al. Less subclinical atherosclerosis in Japanese men in Japan than in white men in the United States in the post-World War II birth cohort. *Am J Epidemiol*. 2007;165:617–624.
15. Abbott RD, Ueshima H, Rodriguez BL, et al. Coronary artery calcification in Japanese men in Japan and Hawaii. *Am J Epidemiol*. 2007;166:1280–1287.
16. Iso H. Changes in coronary heart disease risk among Japanese. *Circulation*. 2008;118:2725–2729.
17. van den Hoogen PC, Feskens EJ, Nagelkerke NJ, et al. The relation between blood pressure and mortality due to coronary heart disease among men in different parts of the world. Seven Countries Study Research Group. *N Engl J Med*. 2000;342:1–8.
18. Chan JC, Gagliardino JJ, Baik SH, et al. Multifaceted determinants for achieving glycemic control: the International Diabetes Management Practice Study (IDMPS). *Diabetes Care*. 2009;32:227–233.
19. The Japan Atherosclerosis Society (JAS). http://www.j-athero.org/en/publications/guideline2012.html.
20. Kaplan NM. The deadly quartet. Upper-body obesity, glucose intolerance, hypertriglyceridemia, and hypertension. *Arch Intern Med*. 1989;149:1514–1520.
21. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. *Diabetes Care*. 1991;14:173–194.
22. Committee to Evaluate Diagnostic Standards for Metabolic Syndrome. Definition and the diagnostic standard for metabolic syndrome [in Japanese]. *Nippon Naika Gakkai Zasshi*. 2005;94:794–809.
23. *Annual Report on Health Labour Welfare* [in Japanese]. Tokyo, Japan: Japan Ministry of Health Labour and Welfare; 2007.

24. Chei CL, Iso H, Yamagishi K, et al. Body mass index and weight change since 20 years of age and risk of coronary heart disease among Japanese: the Japan Public Health Center-Based Study. *Int J Obes (Lond)*. 2008;32:144–151.

25. Cui R, Iso H, Toyoshima H, et al; JACC Study Group. Body mass index and mortality from cardiovascular disease among Japanese men and women: the JACC study. *Stroke*. 2005;36:1377–1382.

26. Yatsuya H, Toyoshima H, Yamagishi K, et al; Japan Arteriosclerosis Longitudinal Study (JALS) Group. Body mass index and risk of stroke and myocardial infarction in a relatively lean population: meta-analysis of 16 Japanese cohorts using individual data. *Circ Cardiovasc Qual Outcomes*. 2010;3:498–505.

27. Iso H, Sato S, Kitamura A, et al. Metabolic syndrome and the risk of ischemic heart disease and stroke among Japanese men and women. *Stroke*. 2007;38: 1744–1751.

28. Liu L, Miura K, Fujiyoshi A, et al. Impact of metabolic syndrome on the risk of cardiovascular disease mortality in the United States and in Japan. *Am J Cardiol*. 2014;113:84–89.

29. Matsushita Y, Yoshiike N, Kaneda F, et al. Trends in childhood obesity in Japan over the last 25 years from the national nutrition survey. *Obes Res*. 2004;12: 205–214.

30. The National Health and Nutrition Survey in Japan. Tokyo, Japan. http://www. mhlw.go.jp/stf/houdou/0000106405.html. Published 2014.

31. American Diabetes Association (ADA). Guidelines. http://www.ndei.org/ ADA-diabetes-management-guidelines-cardiovascular-disease-CVD-management-lipids-BP.aspx.html. Published 2016.

32. Ford ES, Zhao G, Li C. Pre-diabetes and the risk for cardiovascular disease: a systematic review of the evidence. *J Am Coll Cardiol*. 2010;55:1310–1307.

33. Goto A, Noda M, Matsushita Y, et al. Hemoglobin a1c levels and the risk of cardiovascular disease in people without known diabetes. *Medicine*. 2015;94:e785.

34. Tominaga M, Eguchi H, Manaka H, et al. 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.

35. Chan JC, Malik V, Jia W, et al. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA*. 2009;301:2129–2140.

36. Huxley R, James WP, Barzi F, et al; Obesity in Asia Collaboration. Ethnic comparisons of the cross-sectional relationships between measures of body size with diabetes and hypertension. *Obes Rev*. 2008;9:53–61.

37. Doi Y, Ninomiya T, Hata J, et al. 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.

38. Hayama-Terada M, Muraki I, Imano H, et al; CIRCS Investigators. Diabetes trends and impact on risk of cardiovascular disease in middle-aged Japanese people: the CIRCS study. *Circ J*. 2016;80:2343–2348.

39. Saito I, Kokubo Y, Yamagishi K, et al. Diabetes and the risk of coronary heart disease in the general Japanese population: the Japan Public Health Center-based prospective (JPHC) study. *Atherosclerosis*. 2011;216:187–191.

40. WHO. Health statistics and information systems. http://www.who.int/health-info/global_burden_disease/metrics_paf/en/.

41. Nordestgaard BG, Tybjaerg-Hansen A. IDL, VLDL, chylomicrons and atherosclerosis. *Eur J Epidemiol*. 1992;8:92–98.

42. Imamura T, Doi Y, Ninomiya T, et al. Non-high-density lipoprotein cholesterol and the development of coronary heart disease and stroke subtypes in a general Japanese population: the Hisayama study. *Atherosclerosis*. 2014;233:343–348.

43. Okamura T, Kokubo Y, Watanabe M, et al. Low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol and the incidence of cardiovascular disease in an urban Japanese cohort study: the Suita study. *Atherosclerosis*. 2009;203:587–592.

44. Noda H, Iso F, Irie T, et al. Association between non high-density lipoprotein cholesterol concentrations and mortality from coronary heart disease among Japanese men and women: the Ibaraki Prefectural Health Study. *J Atheroscler Thromb*. 2010;17:30–36.

45. Tanabe N, Iso H, Okada K, et al. Serum total and non-high-density lipoprotein cholesterol and the risk prediction of cardiovascular events—the JALS-ECC. *Circ J*. 2010;74:1346–1356.

46. Ito T, Arima H, Fujiyoshi A, et al; NIPPON DATA90 Research Group. Relationship between non-high-density lipoprotein cholesterol and the long-term mortality of cardiovascular diseases: NIPPON DATA 90. *Int J Cardiol*. 2016;220:262–267.

47. Millán J, Pintó X, Muñoz A, et al. Lipoprotein ratios: physiological significance and clinical usefulness in cardiovascular prevention. *Vasc Health Risk Manag*. 2009;5:757–765.

48. Hisamatsu T, Fujiyoshi A, Miura K, et al; SESSA Research Group. Lipoprotein particle profiles compared with standard lipids in association with coronary artery calcification in the general Japanese population. *Atherosclerosis*. 2014;236:237–243.

49. Hirano T, Nohtomi K, Sato Y. Small dense LDL-cholesterol determined by a simple precipitation assay for screening familial combined hyperlipidemia. *Atherosclerosis*. 2009;205:603–607.

50. Nishikura T, Koba S, Yokota Y, et al. Elevated small dense low-density lipoprotein cholesterol as a predictor for future cardiovascular events in patients with stable coronary artery disease. *J Atheroscler Thromb*. 2014;21:755–767.

51. Maeda S, Nakanishi S, Yoneda M. Associations between small dense LDL, HDL subfractions (HDL2, HDL3) and risk of atherosclerosis in Japanese-Americans. *J Atheroscler Thromb*. 2012;19:444–452.

52. Libby P. Changing concepts of atherogenesis. *J Intern Med*. 2000;247:349–358.

53. Cannon CP, Braunwald E, McCabe CH, et al. Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med*. 2004;350:1495–1504.

54. LaRosa JC, Grundy SM, Waters DD, et al. Intensive lipid lowering with atorvastatin in patients with stable coronary disease. *N Engl J Med*. 2005;352:1425–1435.

55. Huxley RR, Barzi F, Lam TH, et al. Isolated low levels of high-density lipoprotein cholesterol are associated with an increased risk of coronary heart disease: an individual participant data meta-analysis of 23 studies in the Asia-Pacific region. *Circulation*. 2011;124:2056–2064.

56. Hirata T, Sugiyama D, Nagasawa SY, et al. A pooled analysis of the association of isolated low levels of high-density lipoprotein cholesterol with cardiovascular mortality in Japan [published online ahead of print October 5, 2016]. *Eur J Epidemiol*. doi:10.1007/s10654-016-0203-1

57. Tousoulis D, Papageorgiou N, Androulakis E, et al. Diabetes mellitus-associated vascular impairment: novel circulating biomarkers and therapeutic approaches. *J Am Coll Cardiol*. 2013;6:667–676.

58. Deodhar SD. C-reactive protein: the best laboratory indicator available for monitoring disease activity. *Cleve Clin J Med*. 1989;56:126–130.

59. Ishikawa T, Hatakeyama K, Imamura T, et al. Involvement of C-reactive protein obtained by directional coronary atherectomy in plaque instability and developing restenosis in patients with stable or unstable angina pectoris. *Am J Cardiol*. 2003;91:287–292.

60. Inoue T, Kato T, Uchida T, et al. Local release of C-reactive protein from vulnerable plaque or coronary arterial wall injured by stenting. *J Am Coll Cardiol*. 2005;46:239–245.

61. Nagasawa SY, Ohkubo T, Masaki K. Associations between inflammatory markers and subclinical atherosclerosis in middle-aged white, Japanese-American and Japanese men: the ERA-JUMP study. *J Atheroscler Thromb*. 2015;22:590–598.

62. Makita S, Nakamura M, Hiramori K. The association of C-reactive protein levels with carotid intima-media complex thickness and plaque formation in the general population. *Stroke*. 2005;36:2138–2142.

63. Mendall MA, Patel P, Ballam L, et al. C reactive protein and its relation to cardiovascular risk factors: a population based cross sectional study. *Br Med J*. 1996;312:1061–1065.

64. Iso H, Cui R, Date C, et al. C-reactive protein levels and risk of mortality from cardiovascular disease in Japanese: the JACC Study. *Atherosclerosis*. 2009;207: 291–297.

65. Arima H, Kubo M, Yonemoto K, et al. High-sensitivity C-reactive protein and coronary heart disease in a general population of Japanese: the Hisayama study. *Arterioscler Thromb Vasc Biol*. 2008;28:1385–1391.

66. Saito I, Maruyama K, Eguchi E. C-reactive protein and cardiovascular disease in East asians: a systematic review. *Clin Med Insights Cardiol*. 2015;8:35–42.

67. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511.

68. Zakynthinos E, Pappa N. Inflammatory biomarkers in coronary artery disease. *J Cardiol*. 2009;53:317–333.

69. Inoue K, Kodama T, Daida H. Pentraxin 3: a novel biomarker for inflammatory cardiovascular disease. *Int J Vasc Med*. 2012;2012:657025.

70. Ogasawara K, Mashiba S, Wada Y, et al. A serum amyloid A and LDL complex as a new prognostic marker in stable coronary artery disease. *Atherosclerosis*. 2004;174:349–356.

71. Zhang R, Brennan ML, Fu X, et al. Association between myeloperoxidase levels and risk of coronary artery disease. *JAMA*. 2001;286:2136–2142.

72. Blankenberg S, Tiret L, Bickel C, et al. Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina. *Circulation*. 2002;106: 24–30.

73. Oei HH, van der Meer IM, Hofman A, et al. Lipoprotein-associated phospholipase A2 activity is associated with risk of coronary heart disease and ischemic stroke: the Rotterdam Study. *Circulation*. 2005;111:570–575.

74. Pai JK, Pischon T, Ma J, et al. Inflammatory markers and the risk of coronary heart disease in men and women. *N Engl J Med*. 2004;351:2599–2610.

75. Perk J1, De Backer G, Gohlke H, et al; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012): the Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice. *Eur J Prev Cardiol*. 2012;19:585–667.

76. 1996 National Heart Foundation clinical guidelines for the assessment and management of dyslipidaemia. Dyslipidaemia Advisory Group on behalf of the scientific committee of the National Heart Foundation of New Zealand. *N Z Med J*. 1996;109:224–231.

77. Wallis EJ, Ramsay LE, Haq IU, et al. Coronary and cardiovascular risk estimation for primary prevention: validation of a new Sheffield table in the 1995 Scottish health survey population. *BMJ*. 2000;320:671–676.

78. Kannel WB, Castelli WP, Revotskie N, et al. Profile of the coronary-prone individual. Assessment of risk of developing coronary heart disease. The Framingham study. *Proc Annu Meet Med Sect Am Life Conv*. 1967;55:74–99.

79. Wilson PW, D'Agostino RB, Levy D, et al. Prediction of coronary heart disease using risk factor categories. *Circulation*. 1998;97:1837–1847.

80. Conroy RM, Pyorala K, Fitzgerald AP, et al. SCORE project group: estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J*. 2003;24:987–1003.

81. Assmann G, Cullen P, Schulte H. Simple scoring scheme for calculating the risk of acute coronary events based on the 10-year follow-up of the prospective cardiovascular Münster (PROCAM) study. *Circulation*. 2002;105:310–315.

82. Stevens RJ, Kothari V, Adler AI, et al. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). *Clin Sci (Lond)*. 2001;101:671–679.

83. Ridker PM, Paynter NP, Rifai N, et al. C-reactive protein and parental history improve global cardiovascular risk prediction: the Reynolds Risk Score for men. *Circulation*. 2008;118:2243–2251.

84. Ferrario M, Chiodini P, Chambless LE, et al; CUORE Project Research Group. Prediction of coronary events in a low incidence population. Assessing accuracy of the CUORE Cohort Study prediction equation. *Int J Epidemiol*. 2005;34:413–421.

85. Greenland P, Alpert JS, Beller GA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2010;56: 2182–2199.

86. D'Agostino RB Sr, Grundy S, Sullivan LM, et al; CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA*. 2001;286:180–187.

87. NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. *Circ J*. 2006;70:1249–1255.

88. Yatsuya H, Iso H, Li Y, et al. Development of a risk equation for the incidence of coronary artery disease and ischemic stroke for middle-aged Japanese—Japan Public Health Center-Based Prospective Study. *Circ J*. 2016;80:1386–1395.

89. Arima H, Yonemoto K, Doi Y, et al. Development and validation of a cardiovascular risk prediction model for Japanese: the Hisayama study. *Hypertens Res*. 2009;32:1119–1122.

90. Nishimura K, Okamura T, Watanabe M, et al. Predicting coronary heart disease using risk factor categories for a Japanese urban population, and comparison with the Framingham risk score: the Suita study. *J Atheroscler Thromb*. 2014;21: 784–798.

91. Matsumoto M, Ishikawa S, Kayaba K, et al; Jichi Medical School (JMS) Cohort Study Group. Risk charts illustrating the 10-year risk of myocardial infarction among residents of Japanese rural communities: the JMS Cohort Study. *J Epidemiol*. 2009;19:94–100.

92. Teramoto T, Ohashi Y, Nakaya N, et al; MEGA Study Group. Practical risk prediction tools for coronary heart disease in mild to moderate hypercholesterolemia in Japan: originated from the MEGA study data. *Circ J*. 2008;72:1569–1575.

93. Teramukai S, Okuda Y, Miyazaki S, et al. Dynamic prediction model and risk assessment chart for cardiovascular disease based on on-treatment blood pressure and baseline risk factors. *Hypertens Res*. 2016;39:113–118.

94. Goff DC Jr, Lloyd-Jones DM, Bennett G, et al. 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk: a Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63:2935–2959.

95. Hlatky MA, Greenland P, Arnett DK, et al. Criteria for evaluation of novel markers of cardiovascular risk: a scientific statement from the American Heart Association. *Circulation*. 2009;119:2408–2416.

96. Blaha MJ, Cainzos-Achirica M, Greenland P, et al. Role of coronary artery calcium score of zero and other negative risk markers for cardiovascular disease: the multi-ethnic study of atherosclerosis (MESA). *Circulation*. 2016;133:849.

97. Iso H. A Japanese health success story: trends in cardiovascular diseases, their risk factors, and the contribution of public health and personalized approaches. *EPMA J*. 2011;2:49–57.