Asymptomatic coronary heart disease in type 2 diabetic patients with vascular complications: a cross-sectional study

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TITLE

Asymptomatic coronary heart disease in type 2 diabetic patients with vascular complications: a cross-sectional study

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ABSTRACT

Background

Recent studies have suggested that microvascular and macrovascular diseases are associated with coronary events.

Objective

To test the hypothesis that asymptomatic coronary heart disease (CHD) may be present in many diabetic patients with vascular complications.

Design

From April 2009 to August 2010, we conducted a cross-sectional study to assess the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications at a national diabetes center in Japan. Eligibility criteria included type 2 diabetic patients with no known CHD and one or more of the following four criteria: 1) proliferative diabetic retinopathy or after photocoagulation; 2) estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or an estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria; 3) peripheral arterial disease; and 4) cerebrovascular disease. Each patient underwent a stress singlephoton emission computed tomography (SPECT); patients with myocardial perfusion abnormalities then underwent

coronary angiography.

Results

A total of 1008 patients with type 2 diabetes were screened, and 122 eligible patients consented to participate. Stress SPECT revealed myocardial perfusion abnormalities in 96 (79%) patients. Of the 112 patients who completed the study protocol, 59 (53%) had asymptomatic CHD with ≥ 50% diameter stenosis. Additionally, 35 (31%) patients had multivessel disease or left main disease, and 42 (38%) had a coronary artery with ≥ 75% diameter stenosis. In the multivariate logistic-regression analysis to identify coronary risk factors associated with asymptomatic CHD, the only significant predictor was a male sex (odds ratio, 6.18; 95% confidence interval, 2.30 to 16.64; $P < 0.001$).

Conclusions

Asymptomatic CHD with ≥ 50% diameter stenosis and myocardial perfusion abnormalities was detected in more than half of the type 2 diabetic patients with vascular complications.

ARTICLE SUMMERY

Article focus

・Many past studies have reported that some diabetic patients have asymptomatic CHD.

・No definite markers for effectively identifying the presence of asymptomatic CHD in diabetic patients presently exist.

・In recent studies, microvascular and macrovascular diseases were associated with the subsequent coronary events.

Key Messages

・Asymptomatic CHD with ≥ 50% diameter stenosis and myocardial perfusion abnormalities was detected in more than half of the type 2 diabetic patients with vascular complications.

・Traditional coronary risk factors might not be effective in screening for asymptomatic CHD among type 2 diabetic patients.

Strengths and limitations of this study

・This study is, to our knowledge, the first report that many type 2 diabetic patients with vascular complications have asymptomatic CHD with multivessel disease and severe stenosis in addition to myocardial ischemia on stress SPECT.

- We demonstrated that type 2 diabetic patients with advanced microvascular or macrovascular diseases had a far greater prevalence of myocardial perfusion abnormalities and asymptomatic CHDs, compared with previous data.

- This study was performed at a single center and was limited to a specific geographical area.

INTRODUCTION

Diabetes is a risk factor of coronary heart disease (CHD) which is a leading cause of mortality.[1] Many studies have revealed that some diabetic patients may have asymptomatic CHD, and a retrospective study and a small randomized trial suggested a possible benefit from CHD screening.[2, 3] In a large randomized controlled trial, however, routine screening for asymptomatic CHD among type 2 diabetic patients was of no benefit to the cardiac outcome.[4] In addition, traditional coronary risk factors such as hypertension and dyslipidemia were not associated with silent ischemia and asymptomatic CHD.[5, 6] Therefore, aggressive routine screening for asymptomatic CHD among all diabetic patients with or without these risk factors is not recommended at present. No definite markers for effectively identifying the presence of asymptomatic CHD in diabetic patients presently exist, and further investigations are needed.

In recent studies, microvascular and macrovascular diseases were associated with the subsequent coronary events. Diabetic retinopathy was associated with the onset of CHD and cardiovascular disease.[7-10] Patients with proliferative diabetic retinopathy (PDR) and after photocoagulation had a particularly high risk of cardiovascular disease.[11] An independent association was also observed between renal dysfunction and cardiovascular events,[12-16] and the risk of cardiovascular disease was increased when proteinuria developed.[17, 18] Moreover, many studies suggested that macrovascular diseases such as peripheral arterial disease (PAD) and

cerebrovascular disease were strongly associated with CHD.[19-21]

Thus, we hypothesized that asymptomatic CHD may be present in many type 2 diabetic patients with vascular complications such as advanced diabetic retinopathy, renal dysfunction, PAD, or cerebrovascular disease. The aim of this study was to assess the prevalence of asymptomatic CHD requiring treatment with antiplatelet agents or revascularization among type 2 diabetic patients with vascular complications and no known CHD.

METHODS

Study Design and Participants

From April 2009 to August 2010, we conducted a cross-sectional study, and patients were enrolled at the National Center for Global Health and Medicine in Tokyo, Japan. The institutional review boards approved this study, and all the patients provided their written informed consent. Eligibility criteria included type 2 diabetic patients without suggestive symptoms of CHD between the ages of 40 and 75 years. Additionally, all the patients had one or more of the following four criteria: 1) PDR or after photocoagulation; 2) renal dysfunction; 3) PAD; and 4) cerebrovascular disease. An ophthalmologist diagnosed the PDR or after photocoagulation. Renal dysfunction was defined as an estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or an estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria, corresponding to ≥ 30 mg/day or ≥ 30 mg/g of creatinine. The estimated GFR was calculated using the following formula,[22] as recommended by the Japanese Society of Nephrology: estimated GFR (mL/min/1.73 m^2) = 194 × $Cre^{-1.094}$ × $Age^{-0.287}$ (× 0.739 if patient is a woman). PAD was defined as an ankle-brachial index (ABI) < 0.9, confirmed peripheral artery stenosis based on radiological images, or after surgical treatment. Cerebrovascular disease was defined as stroke or transient ischemic attack. The exclusion criteria included 1) known CHD or suspected CHD; 2) the presence of antibodies to glutamic acid decarboxylase; 3) acute kidney

injury; and 4) a very poor prognosis and inappropriate conditions for testing. The inclusion criteria and exclusion criteria were confirmed using clinical records, laboratory data, questionnaires, and questioning by the physician.

Diagnostic Approach and Evaluation of Outcomes

We first performed stress singlephoton emission computed tomography (SPECT) in all the patients who met the study criteria; patients who exhibited myocardial perfusion abnormalities then underwent conventional coronary angiography (CAG), 64-slice multidetector-row computed tomography (MDCT) coronary angiography, or both examinations. We referred to the conventional CAG findings when the patients underwent both imaging procedures. The left main coronary artery, the left anterior descending coronary artery, the left circumflex coronary artery, and the right coronary artery were each assessed using the American Heart Association classification.[23] We diagnosed asymptomatic CHD when a coronary artery with ≥ 50% diameter stenosis was confirmed using coronary angiography. The primary end point of this study was the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications.

Stress SPECT

Electrocardiogram (ECG)-gated stress SPECT imaging was performed in all the patients using a dual-headed gamma camera (E.cam; Siemens, Munich, Germany). Patients underwent exercise stress (n = 75) according to the Bruce protocol. Exercise testing was terminated when the patients achieved a heart rate of 85% or more of the predicted maximal heart rate, a sufficient blood pressure response (such as a systolic blood pressure ≥ 250 mmHg), a feeling that further exercise was impossible, or significant severe ischemic changes on an ECG recording. Patients who were unable to perform the exercise (n = 47) underwent a pharmacologic stress test comprised of a 6-minute adenosine infusion protocol, as recommended by The Japanese Society of Nuclear Cardiology. Technetium-99m tetrofosmin SPECT imaging was performed using a 1-day protocol in 108 patients, and thallium-201 was used in 14 patients. Two experienced doctors of nuclear cardiology independently evaluated the images without knowing the details of the clinical information. We diagnosed myocardial perfusion abnormalities when one or more of the doctors pointed out the presence of abnormal myocardial perfusion on the stress SPECT images. For patients with myocardial perfusion abnormalities, ischemia was diagnosed when one or more of the doctors pointed out a reversible defect. Other abnormal myocardial perfusion abnormalities were diagnosed as scar.

Conventional CAG

When patients had severe coronary calcifications with coronary artery calcium (CAC) scores ≥ 400 Agatston units, an irregular heart rhythm, advanced renal dysfunction, severe myocardial ischemia on stress SPECT, or severe stenosis on MDCT coronary angiography, we aggressively conducted conventional CAG to assess the coronary arteries. Conventional CAG images were interpreted by two experienced cardiologists blinded to the detailed patient characteristics.

64-slice MDCT

In the absence of contraindications, the patients who had myocardial perfusion abnormalities underwent MDCT tests to determine their CAC scores followed by coronary angiography. The imaging was performed using 64-slice MDCT with a slice thickness of 0.5 mm (Aquilion64; Toshiba Medical Systems, Otawara, Japan). If necessary and tolerated, oral beta-blockers (metoprolol 40 mg to 100 mg) were provided before the scan to achieve a heart rate < 60 beats/min. We performed a nonenhanced prospective electrocardiographically gated scan to measure the CAC scores, which were calculated using the Agatston method (24). The MDCT coronary angiography was performed using 64 × 0.5 mm collimation and retrospective electrocardiographic gating. MDCT images were interpreted by an experienced cardiologist in cooperation with radiologists who were unaware of the detailed clinical backgrounds. All the

coronary arteries and side branches with a luminal diameter ≥ 2.0 mm were assessed.

Other Measurements

The rest and exercise stress ECG tests were assessed by a trained cardiologist who had no knowledge of the clinical findings of the patients. We diagnosed an abnormality on the rest ECG findings if ST segment abnormalities, T wave abnormalities, an abnormal Q wave, or a complete left bundle branch block were observed; ischemia was diagnosed on an exercise stress ECG if the exercise induced any ischemic changes.

The ABI and the baPWV were simultaneously measured (Form PWV/ABI; Colin Company, Komaki, Japan) to assess the presence of arteriosclerosis in the peripheral arteries.[25] The lowest ABI and the highest baPWV for the left and right sides were used in subsequent analyses.

To examine the progression of diabetic autonomic neuropathy, the degree of heart rate variability was evaluated using the coefficients of variance of RR intervals (CVRR) on ECG (FDX-4521; Fukuda Denshi, Tokyo, Japan).[26] The RR intervals were measured for 100 consecutive cardiac cycles while the patient maintained a supine position after having rested for several minutes, excluding patients with an arrhythmia. The CVRR was then calculated using the following formula: CVRR = (standard deviation of RR ÷ mean RR) × 100.

To estimate cardiac function such as the ejection fraction and the wall motion, we conducted

an echocardiography examination (Aplio 80; Toshiba Medical Systems, Otawara, Japan). The examinations were performed by a trained ultrasonographer and cardiologist who had no knowledge of the patients' clinical information. Doppler echocardiography was also performed to assess the peak Doppler velocities of the early (E) and late diastolic flows (A), the deceleration time (DT), and the E/A ratio for the mitral inflow. Moreover, tissue Doppler imaging of the mitral annulus was measured from the apical 4-chamber view. A sample volume was placed at the septal mitral annulus and the early (E') diastolic velocity was measured. We analyzed the E/E' ratio to assess the cardiac function.[27]

The carotid intima-media thickness (IMT) was evaluated using high-resolution B-mode ultrasound with a 10-MHz linear transducer (Aplio XG; Toshiba Medical Systems, Otawara, Japan).[28] A trained ultrasonographer and a doctor or a skilled doctor alone who were unaware of the patient' characteristics assessed the maximum carotid IMT. The maximum carotid IMT was defined as the thickest IMT for the left and right sides from the common carotid artery to the internal carotid artery.

Statistical Methods

Data are presented as the number (%), mean with standard deviation (SD), and median with lower and upper ends of the interquartile range (IQR). Continuous variables were compared

using t tests and Wilcoxon rank sum tests. Categorical variables were compared using chi-square tests. A multivariate logistic-regression analysis of coronary risk factors, such as age, sex, overweight or obesity, current smoking habit, hypertension, and dyslipidemia, was performed to identify coronary risk factors associated with asymptomatic CHD. P values < 0.05 according to a two sided test were considered statistically significant for all the tests. All analyses were performed using Stata software, version 11.1 (Stata Corp, College Station, Texas).

RESULTS

A total of 1008 patients with type 2 diabetes between the ages of 40 and 75 years were screened, and 219 met the inclusion criteria for this study. Of the 206 eligible patients without any exclusion criteria, 122 consented to participate (Figure 1). The clinical characteristics of this study population are presented in Table 1. The mean age was 64.1 ± 8.3 years, and 84 (68%) were men, and the mean A1C was 7.7 ± 1.5 %. The numbers of patients with PDR or after photocoagulation, renal dysfunction, PAD, and cerebrovascular disease were 76 (62%), 25 (20%), 21 (17%), and 46 (37%), respectively.

Of the 122 patients, 96 (79%) had myocardial perfusion abnormalities on stress SPECT: 70 (58%) had ischemia and 26 (21%) had scar. Of the 96 patients with myocardial perfusion abnormalities, 42 underwent conventional CAG, 83 underwent MDCT coronary angiography, and 39 underwent both examinations. Ten patients did not undergo either MDCT coronary angiography or CAG and were excluded from the analysis to determine the prevalence of asymptomatic CHD. Of the 112 patients who completed the study protocol, 59 (53%) had asymptomatic CHD (Figure 2A). Thus, more than half of the patients who met any one of the four inclusion criteria for vascular complications had asymptomatic CHD (Figure 2B). The prevalences of asymptomatic CHD among the patients who met only one criteria and among the patients who met more than one of the four inclusion criteria for vascular complications were not significantly different (P = 0.50). The prevalence of asymptomatic CHD in patients with

myocardial perfusion abnormalities on stress SPECT are shown in Figure 2C. The prevalences of asymptomatic CHD among patients with ischemia and among those with scar were not significantly different. The CAC scores for the patients with and for those without asymptomatic CHD were significantly different (Figure 2D).

The majority of patients with asymptomatic CHD had multivessel disease (Figure 3A). 59 Patients with asymptomatic CHD had 1.8 ± 0.8 vessels with ≥ 50% diameter stenosis: 24 (41%) patients had one-vessel disease, 22 (37%) had two-vessel disease, and 13 (22%) had three-vessel disease or left main disease. The maximum percent diameter stenosis in patients with asymptomatic CHD is shown in Figure 3B. 42 (71%) Patients had ≥ 75% diameter stenosis and 24 (41%) had ≥ 90% diameter stenosis. The analyses of the clinical variables among the patients with and those without asymptomatic CHD are shown in Table 2. Men, a current smoking habit, the Brinkman index, age at the time of diabetes diagnosis, the ejection fraction, the E/A ratio, the maximum carotid IMT, and the CAC scores differed significantly between the two groups in a univariate analysis. However, abnormal findings on the rest ECG, ischemic findings on the exercise stress ECG, and abnormal wall motion on echocardiography were not significantly different. When a multivariate logistic-regression analysis was performed to identify coronary risk factors independently associated with asymptomatic CHD, the only significant predictor was a male sex (odds ratio, 6.18; 95% confidence interval, 2.30 to 16.64; P

< 0.001). The result was similar when the duration of diabetes was added to the multivariate analysis.

DISCUSSION

This study is, to our knowledge, the first report that many type 2 diabetic patients with vascular complications have asymptomatic CHD with multivessel disease and severe stenosis in addition to myocardial ischemia on stress SPECT. Moreover, asymptomatic CHD was detected in more than half of the patients who met any one of the four inclusion criteria for vascular complications. Many past studies have reported that some diabetic patients have asymptomatic CHD. However, under which conditions the diabetic patients were most likely to have asymptomatic CHD was unclear. We demonstrated that type 2 diabetic patients with advanced microvascular or macrovascular diseases had a far greater prevalence of myocardial perfusion abnormalities and asymptomatic CHDs, compared with previous data.[5, 6] Because the diabetic complications had progressed, the patients might have had severe autonomic denervation of the heart, accounting for their asymptomatic presentation.[29] The statistical analysis revealed that asymptomatic CHD was more common among men than among women. However, other coronary risk factors were not associated with asymptomatic CHD. These results may be similar to those of previous studies.[5, 6] Thus, traditional coronary risk factors might not be effective in screening for asymptomatic CHD among type 2 diabetic patients. Further research will be required to identify possibly useful markers such as the ejection fraction, E/A ratio, maximum carotid IMT, and CAC scores.

Since diabetic patients with vascular complications often had asymptomatic CHD, excessive

stress on the hearts of such patients may be unusually dangerous. Additionally, hypoglycemia should certainly be avoided because not only hypoglycemia is associated with an increased risk of death,[30, 31] but also catecholamine hypersecretion as a result of hypoglycemia may lead to hazardous cardiac stress in patients with CHD. Appropriate glycemic goals to avoid hypoglycemia and inhibit complications are the problems that must be solved in the future.

Importantly, some patients without significant coronary stenosis exhibited abnormal findings, such as ischemia on stress ECG, abnormal wall motion on echocardiography, or myocardial perfusion abnormalities on stress SPECT. Although these facts might suggest the possibility of false-positive results, coronary microvascular dysfunction may be responsible for cardiac disorders because the patients had many coronary microvascular risk factors, such as diabetes, cigarette smoking, dyslipidemia, and hypertension.[32] Further investigation is needed for coronary microvascular dysfunction.

Our study had several limitations. First, this study was performed at a single center and was limited to a specific geographical area. Thus, large-scale studies at multiple centers throughout the world will be necessary to confirm these results. However, we believe that this is an extremely important study that may lead to numerous future trials and that may have a large influence on diabetic management. Second, we did not perform further tests in patients with normal myocardial perfusion on stress SPECT. Therefore, some patients with normal

myocardial perfusion might have had asymptomatic CHD. However, stress SPECT has a very high sensitivity for CHD and affects the decisions regarding future treatment.[33] Consequently, this diagnostic approach may enable unnecessary angiography to be effectively avoided. Third, the coronary arteries in some of the patients were evaluated using MDCT coronary angiography alone. In large-scale studies, a high rate of agreement between MDCT coronary angiography and conventional CAG has been confirmed.[34] Furthermore, conventional CAG was performed in most of the severe calcification cases with CAC scores ≥400 Agatston units, which could be problematic for MDCT coronary angiography.[35] The median CAC scores in the 44 patients who underwent MDCT coronary angiography alone was 149.0 (14.1-383.4) Agatston units. Thus, we assumed that the diagnosis of CHD was accurate.

In conclusion, this study revealed that asymptomatic CHD with myocardial perfusion abnormalities was detected in more than half of the type 2 diabetic patients with vascular complications. A relationship between CHD and sudden cardiac death has been revealed,[36] and we expect that the results of this study may contribute greatly to reducing myocardial infarction and sudden cardiac death among type 2 diabetic patients. However, the best approach to treating asymptomatic CHD remains unknown. Therefore, an appropriate randomized controlled trial is needed to determine the optimal management.

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Competing interests: None declared.

Ethical approval: This study was approved by the institutional review boards by the National Center for Global Health and Medicine in Tokyo, Japan.

Data sharing: No additional data available.

References

1. Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med.* 1998;339:229-34.

2. Sorajja P, Chareonthaitawee P, Rajagopalan N, Miller TD, Frye RL, Hodge DO, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging

treated with coronary artery bypass grafting. *Circulation*. 2005;112:I311-6.

3. Faglia E, Manuela M, Antonella Q, Michela G, Vincenzo C, Maurizio C, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *Am Heart J*. 2005;149:e1-6.

4. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, Taillefer R, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA*. 2009;301:1547-55.

5. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, Barrett EJ, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*. 2004;27:1954-61.

6. Scognamiglio R, Negut C, Ramondo A, Tiengo A, Avogaro A. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol.* 2006;47:65-71.

7. Rajala U, Pajunpaa H, Koskela P, Keinanen-Kiukaanniemi S. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. *Diabetes Care*. 2000;23:957-61.

8. Chew EY, Ferris FL, 3rd, Csaky KG, Murphy RP, Agron E, Thompson DJ, et al. The

long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. *Ophthalmology*. 2003;110:1683-9.

9. van Hecke MV, Dekker JM, Stehouwer CD, Polak BC, Fuller JH, Sjolie AK, et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. *Diabetes Care*. 2005;28:1383-9.

10. Cheung N, Wang JJ, Klein R, Couper DJ, Sharrett AR, Wong TY. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2007;30:1742-6.

11. Targher G, Bertolini L, Zenari L, Lippi G, Pichiri I, Zoppini G, et al. Diabetic retinopathy is associated with an increased incidence of cardiovascular events in Type 2 diabetic patients. *Diabet Med*. 2008;25:45-50.

12. Adler AI, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;63:225-32.

13. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med.* 2004;351:1296-305.

14. Patel UD, Young EW, Ojo AO, Hayward RA. CKD progression and mortality among older patients with diabetes. *Am J Kidney Dis*. 2005;46:406-14.

15. Tonelli M, Wiebe N, Culleton B, House A, Rabbat C, Fok M, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol*. 2006;17:2034-47.

16. Sukhija R, Aronow WS, Kakar P, Garza L, Sachdeva R, Sinha A, et al. Relation of microalbuminuria and coronary artery disease in patients with and without diabetes mellitus. *Am J Cardiol*. 2006;98:279-81.

17. Tonelli M, Jose P, Curhan G, Sacks F, Braunwald E, Pfeffer M, et al. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ*. 2006;332:1426.

18. Hallan S, Astor B, Romundstad S, Aasarod K, Kvenild K, Coresh J. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study. *Arch Intern Med*. 2007;167:2490-6.

19. Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol.* 2005;25:1463-9.

20. Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbidity and mortality implications. *Circulation*. 2006;114:688-99.

21. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;295:180-9.

22. Matsuo S, Imai E, Horio M, Yasuda Y, Tomita K, Nitta K, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;53:982-92.

23. Austen WG, Edwards JE, Frye RL, Gensini GG, Gott VL, Griffith LS, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;51:5-40.

24. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Jr., Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;15:827-32.

25. Koji Y, Tomiyama H, Ichihashi H, Nagae T, Tanaka N, Takazawa K, et al. Comparison of ankle-brachial pressure index and pulse wave velocity as markers of the presence of coronary artery disease in subjects with a high risk of atherosclerotic cardiovascular disease. *Am J Cardiol*. 2004;94:868-72.

26. Takebayashi K, Matsutomo R, Matsumoto S, Suetsugu M, Wakabayashi S, Aso Y, et al. Relationships between heart rate variability and urinary albumin excretion in patients

with type 2 diabetes. *Am J Med Sci*. 2006;331:72-8.

27. Ommen SR, Nishimura RA, Appleton CP, Miller FA, Oh JK, Redfield MM, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation*. 2000;102:1788-94.

28. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999;340:14-22.

29. Niakan E, Harati Y, Rolak LA, Comstock JP, Rokey R. Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy. *Arch Intern Med*. 1986;146:2229-30.

30. Bonds DE, Miller ME, Bergenstal RM, Buse JB, Byington RP, Cutler JA, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. *BMJ*. 2010;340:b4909.

31. Zoungas S, Patel A, Chalmers J, de Galan BE, Li Q, Billot L, et al. Severe hypoglycemia and risks of vascular events and death. *N Engl J Med*. 2010;363:1410-8.

32. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*.

2007;356:830-40.

33. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;107:2900-7.

34. Miller JM, Rochitte CE, Dewey M, Arbab-Zadeh A, Niinuma H, Gottlieb I, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;359:2324-36.

35. Budoff MJ, Dowe D, Jollis JG, Gitter M, Sutherland J, Halamert E, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;52:1724-32.

36. Zheng ZJ, Croft JB, Giles WH, Mensah GA. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;104:2158-63.

Figure legends

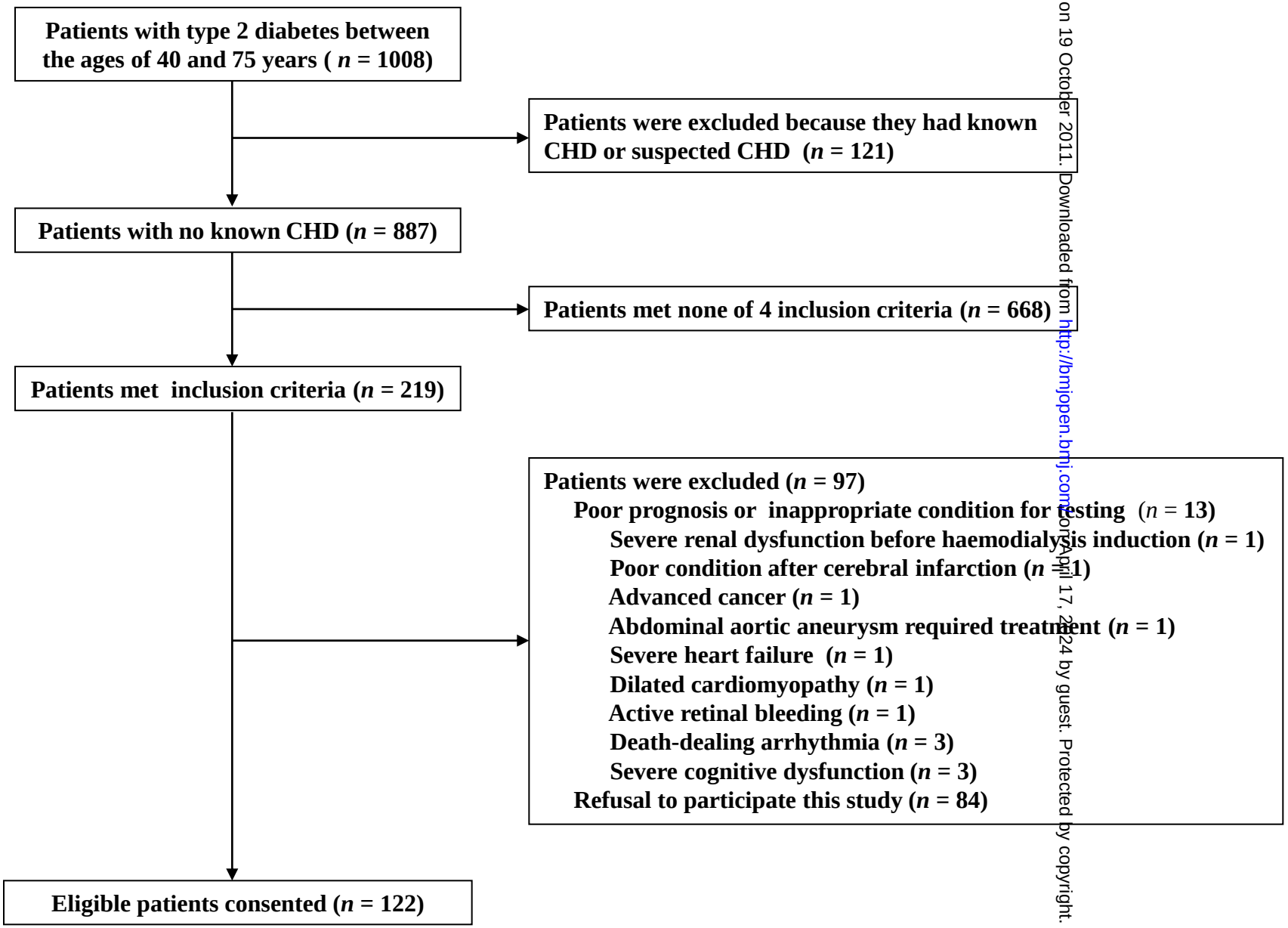
Figure 1. Flowchart of Study Participants.

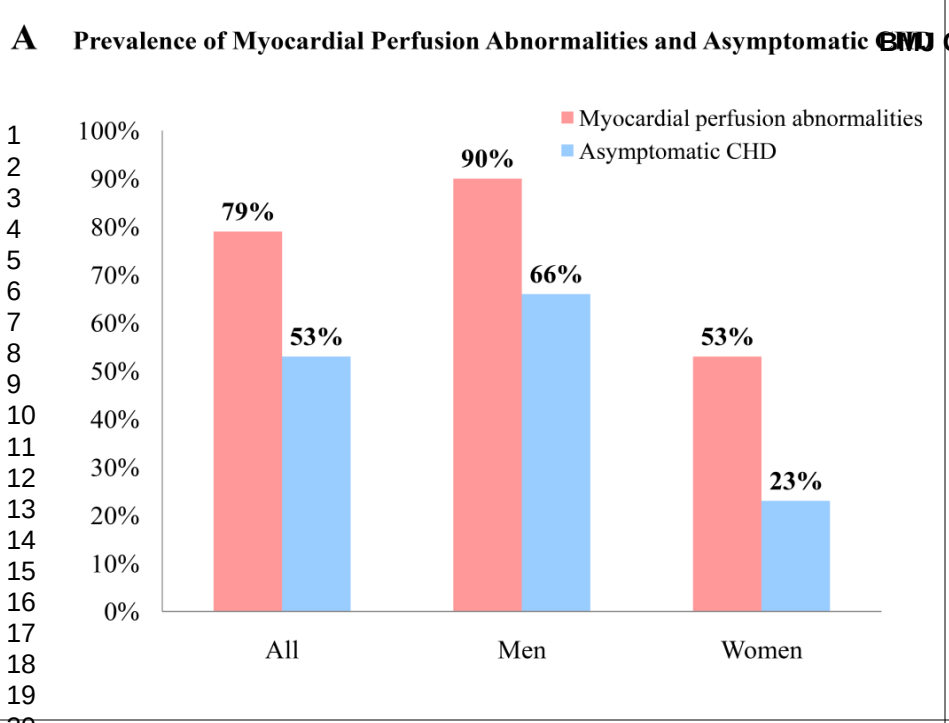
Figure 2. Prevalence of Myocardial Perfusion Abnormalities and Asymptomatic CHD (A). Prevalence of Asymptomatic CHD for Each of the Vascular Complications (B). Prevalence of Asymptomatic CHD in Patients with Ischemia or Scar (C). CAC Scores in Patients With or Without Asymptomatic CHD (D).

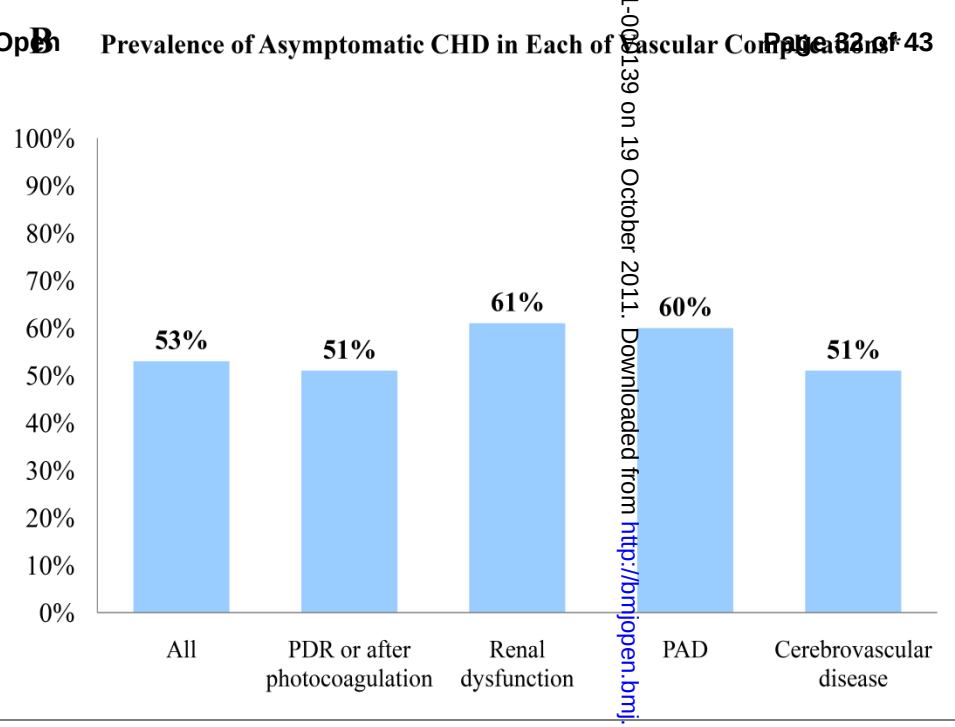
CHD = coronary heart disease, CAC = coronary artery calcium, PDR = proliferative diabetic retinopathy, GFR = glomerular filtration rate, and PAD = peripheral arterial disease.

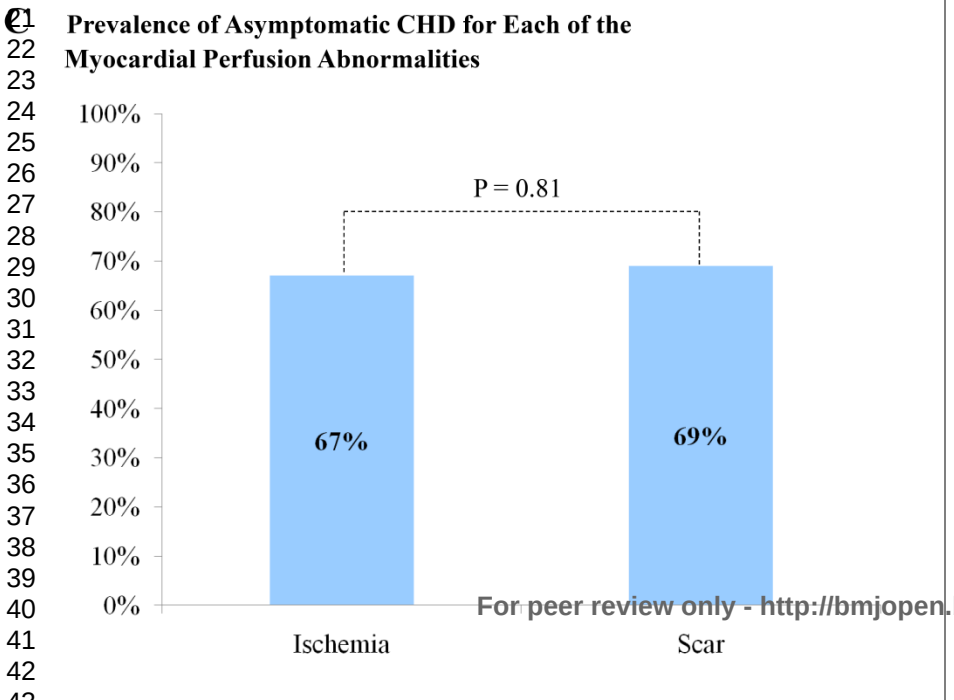
Figure 3. Number of Coronary Arteries* with ≥ 50% Diameter Stenosis in Patients with Asymptomatic CHD (A). Maximum Percent Diameter Stenosis in Patients with Asymptomatic CHD (B).

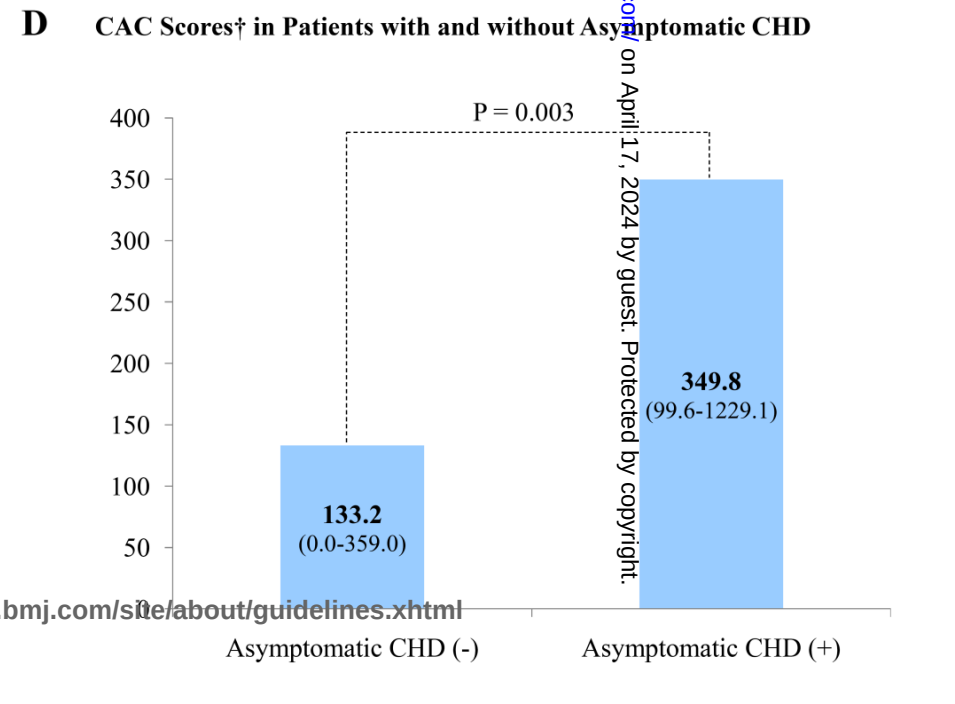
*The left main coronary artery, left anterior descending coronary artery, left circumflex coronary artery, and right coronary artery were each assessed. CHD = coronary heart disease.



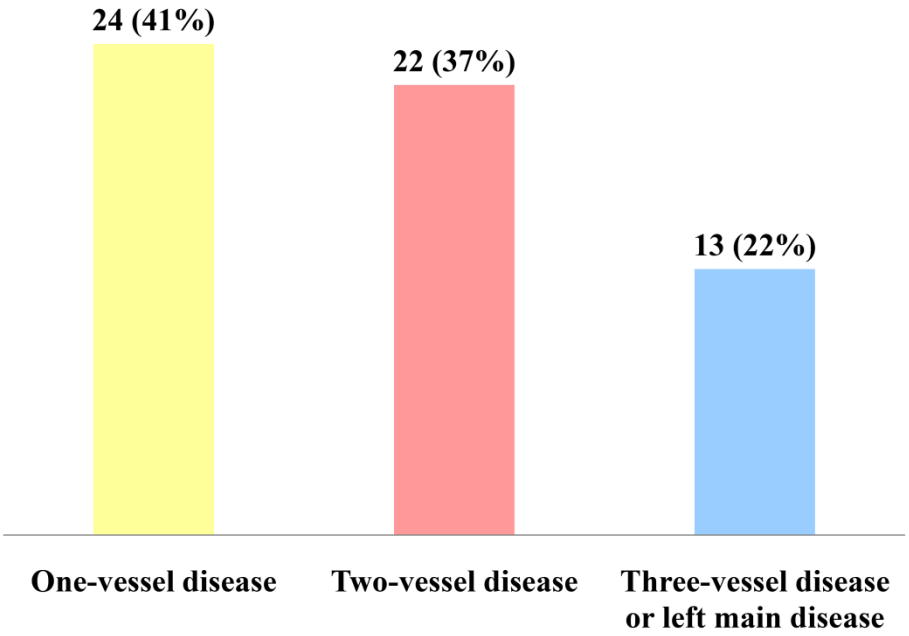








A **Number of Coronary Arteries*with ≥ 50% Diameter Stenosis in Patients with Asymptomatic CHD**



B **Maximum Percent Diameter Stenosis in Patients with Asymptomatic CHD**

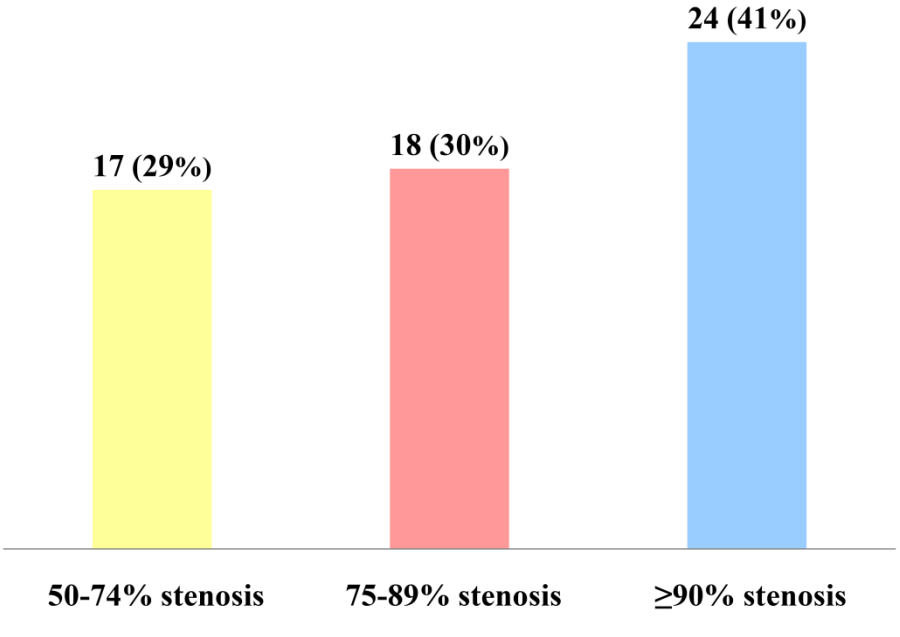


Table 1 Characteristics of Study Population*

	N	All	Men	Women
		122	84 (69%)	38 (31%)
Age (y.o.)	122	64.1 (8.3)	63.9 (8.3)	64.6 (8.5)
Weight (kg)	122	64.6 (12.4)	66.7 (12.1)	60.1 (12.2)
Body-mass index (kg/m^2)†	122	24.5 (4.0)	24.3 (3.7)	25.1 (4.5)
Waist (cm)	112	90.3 (11.2)	89.8 (10.7)	91.5 (12.5)
Smoking	122			
Non		47 (39%)	16 (18%)	31 (82%)
Former		37 (30%)	34 (41%)	3 (8%)
Current		38 (31%)	34 (41%)	4 (10%)
Brinkman index‡	122	440 (0-1000)	755 (175-1290)	0 (0-0)
History of cerebrovascular disease§	122	46 (37%)	32 (38%)	14 (36%)
Duration of diabetes (years)	122	16.0 (10.2)	16.5 (9.8)	15.2 (11.1)
Age at the time of diabetes diagnosis (y.o.)	122	49.0 (12.2)	48.4 (11.8)	50.4 (13.1)
Any diabetic retinopathy	122	97 (79%)	67 (79%)	30 (79%)
PDR or after photocoagulation	122	76 (62%)	50 (59%)	26 (68%)

A1C (%)	122	7.7 (1.5)	7.8 (1.7)	7.5 (1.2)
Treatment for diabetes	122			
Diet		7 (6%)	7 (8%)	0 (0%)
Oral agents		59 (48%)	37 (44%)	22 (58%)
Insulin		15 (12%)	13 (16%)	2 (5%)
Insulin + Oral agents¶		41 (34%)	21 (32%)	14 (37%)
Hypertension‖	122	95 (77%)	66 (78%)	29 (76%)
Treatment: ARB/ACE-I		88 (72%)	61 (72%)	27 (71%)
CCB		55 (45%)	37 (44%)	18 (47%)
Diuretics		16 (13%)	9 (10%)	7 (18%)
Others		4 (3%)	3 (3%)	1 (2%)
Dyslipidemia**	122	90 (73%)	60 (71%)	30 (79%)
Total cholesterol (mg/dL)		192.7 (39.0)	194.7 (42.4)	188.3 (30.9)
LDL cholesterol (mg/dL)		115.6 (40.5)	119.6 (43.8)	106.5 (30.4)
HDL cholesterol (mg/dL)		52.4 (14.8)	51.1 (13.5)	55.3 (17.2)
Triglyceride (mg/dL)		143.3 (85.9)	142.7 (86.1)	144.6 (86.7)
LDL/HDL ratio		2.4 (1.1)	2.5 (1.1)	2.2 (0.9)

Treatment: Statin		47 (38%)	25 (29%)	22 (57%)
Others		9 (7%)	7 (8%)	2 (5%)
Use of aspirin	122	33 (27%)	23 (27%)	10 (26%)
Creatinine (mg/dL)	120	1.04 (0.60)	1.08 (0.60)	0.94 (0.60)
Estimated GFR (mL/min/1.73 m^2)	120	62.1 (22.0)	63.3 (20.4)	59.7 (25.4)
< 45		28 (23%)	17 (20%)	11 (28%)
< 30		10 (8%)	5 (6%)	5 (13%)
Use of hemodialysis	2	2 (1%)	2 (2%)	0 (0%)
Albuminuria (mg/day or mg/g of creatinine)	117			
< 30		32 (27%)	16 (20%)	16 (45%)
30-299		40 (34%)	28 (34%)	12 (33%)
≥ 300		45 (39%)	37 (46%)	8 (22%)
Renal dysfunction††	122	25 (20%)	17 (20%)	8 (21%)
Brain natriuretic peptide (pg/mL)	113	37.2 (26.1-48.2)	19.4 (7.5-47.5)	24.8 (11-39.8)
Rest ECG				
Any abnormal findings	122	27 (22%)	19 (22%)	8 (21%)
CVRR (%)	102	2.94 (1.81-4.52)	2.68 (1.79-4.24)	3.45 (1.83-4.91)

Ischemic findings on exercise stress ECG	64	25 (39%)	15 (36%)	10 (43%)
Cardio thoracic ratio on chest x-ray (%)	113	48.0 (4.4)	47.6 (4.5)	48.9 (4.0)
ABI	122	1.07 (0.17)	1.06 (0.18)	1.09 (0.17)
baPWV (cm/sec)	108	2012.2 (377.3)	1940.5 (300.3)	2168.3 (474.8)
PAD	122	21 (17%)	17 (20%)	4 (10%)
Echocardiography‡‡				
Ejection fraction (%)	108	67.3 (8.6)	66.4 (9.5)	69.4 (6.0)
Septal + posterior wall thickness (mm)	108	21.2 (3.4)	21.3 (3.4)	20.9 (3.4)
> 25		10 (9%)	6 (8%)	4 (11%)
E/A ratio	107	0.76 (0.21)	0.77 (0.17)	0.75 (0.28)
DT (msec)	107	236.4 (59.1)	232.6 (60.5)	244.6 (56.0)
E/E' ratio	96	11.3 (3.4)	11.0 (2.86)	12.1 (4.35)
Abnormal wall motion	108	6 (5%)	6 (8%)	0 (0%)
Ultrasound of carotid artery	81			
Maximum carotid IMT (mm)		1.78 (1.07)	1.97 (1.13)	1.39 (0.86)
≥ 1.1		53 (67%)	41 (77%)	12 (46%)
CAC scores (Agatston units)	83	216.8 (52.0-602.7)	300.4 (65.6-1201.2)	110.9 (0-275.8)

* Data are number, number (%), mean (SD), or median (IQR). To convert the values for cholesterol and triglycerides to millimoles

per liter (mmol/L), multiply by 0.02586 and 0.01129, respectively. PDR = proliferative diabetic retinopathy, ARB = angiotensin II receptor blockers, ACE-I = angiotensin converting enzyme inhibitors, CCB = Calcium channel blockers, LDL = low-density lipoprotein, HDL = high-density lipoprotein, GFR = glomerular filtration rate, ECG = electrocardiogram, CVRR = coefficients of variance of RR intervals, ABI = ankle-brachial index, baPWV = brachial-ankle pulse wave velocity, PAD = peripheral arterial disease, DT = deceleration time, IMT = intima-media thickness, CAC = coronary artery calcium.

† Body-mass index was calculated as the weight in kilograms divided by the square of height in meters.

‡ Brinkman index was daily cigarette number multiplied by smoking years.

§ Cerebrovascular disease was defined as stroke or transient ischemic attack.

¶ Oral agents for the treatment of diabetes included metformin, sulfonylureas, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors.

‖ Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medication.

** Dyslipidemia was defined as LDL ≥ 140 mg/dL, HDL < 40 mg/dL, or the use of lipid-lowering drug.

†† Renal dysfunction was defined as the estimated GFR < 30 mL/min/1.73 m^2 or the estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria which was ≥ 30 mg/day or ≥ 30 mg/g of creatinine.

‡‡ E/A ratio was the ratio of the peak Doppler velocities of early to late diastolic flow in the mitral inflow. E/E' ratio was the ratio of the peak Doppler velocities of early in the mitral inflow to the early diastolic velocity at the septal mitral annulus.

Table 2 Analyses of Clinical Variables for Asymptomatic CHD

	Univariate Analysis		
Variable	Asymptomatic CHD (+)	Asymptomatic CHD (-)	P value
	59 (53%)	53 (47%)	
Men‡	51 (86%)	26 (49%)	< 0.001
Age (y.o.)	62.4 (8.8)	65.3 (7.7)	0.07
Weight (kg)	65.3 (12.9)	64.7 (12.7)	0.79
Body-mass index (kg/m^2)	24.0 (3.4)	25.3 (4.6)	0.08
Waist (cm)	90.0 (11.4)	91.1 (11.9)	0.60
Current smoker†	26 (44%)	10 (18%)	0.004
Brinkman index‡	660 (0-1110)	0 (0-600)	< 0.001
History of cerebrovascular disease	22 (37%)	21 (39%)	0.80
Duration of diabetes (years)	16.7 (10.5)	14.9 (10.0)	0.34
Age at the time of diabetes diagnosis (y.o.)*	46.7 (12.2)	51.4 (11.9)	0.04
Any diabetic retinopathy	46 (78%)	42 (79%)	0.86
PDR or after photocoagulation	36 (61%)	34 (64%)	0.73
A1C (%)	7.3 (1.5)	7.4 (1.6)	0.76
Use of insulin	33 (55%)	21 (39%)	0.08
Hypertension	46 (78%)	40 (75%)	0.75
Dyslipidemia	45 (76%)	39 (73%)	0.74
Total cholesterol (mg/dL)	192.8 (38.4)	196.0 (39.5)	0.67
LDL cholesterol (mg/dL)	113.0 (36.6)	120.0 (38.5)	0.33

HDL cholesterol (mg/dL)	50.7 (13.7)	53.5 (15.7)	0.32
Triglyceride (mg/dL)	151.5 (89.0)	136.6 (82.3)	0.36
LDL/HDL ratio	2.4 (1.0)	2.4 (1.0)	0.85
Use of statin	21 (35%)	22 (41%)	0.52
Use of aspirin	16 (27%)	15 (28%)	0.88
Creatinine (mg/dL)	1.03 (0.60)	0.87 (0.35)	0.09
GFR (mL/min/1.73 m^2)	63.9 (20.7)	65.2 (20.0)	0.74
< 45	13 (22%)	9 (17%)	0.50
< 30	2 (3%)	3 (5%)	0.56
Albuminuria ≥ 30 (mg/day or mg/g of creatinine)	43 (76%)	32 (62%)	0.11
Brain natriuretic peptide (pg/mL)	20.7 (7.6-35.4)	17.4 (9.5-42.9)	0.99
Rest ECG			
Abnormal findings	12 (20%)	12 (22%)	0.76
CVRR (%)	2.99 (2.04-4.25)	2.49 (1.67-5.11)	0.56
Ischemic findings on exercise stress ECG	12 (41%)	10 (35%)	0.66
Cardio thoracic ratio on chest x-ray (%)	47.3 (4.4)	48.8 (4.1)	0.08
ABI	1.06 (0.20)	1.06 (0.15)	0.98
baPWV (cm/sec)	1955.3 (306.4)	2067.4 (448.7)	0.14
PAD	12 (22%)	8 (16%)	0.42
Echocardiography			

Ejection fraction (%)*	65.6 (9.1)	69.0 (8.0)	0.04
Septal wall + posterior wall thickness (mm)	20.8 (3.7)	21.2 (3.0)	0.55
E/A ratio*	0.81 (0.16)	0.71 (0.24)	0.02
DT (msec)	225.7 (58.2)	247.5 (61.9)	0.07
E/E' ratio	10.8 (3.3)	11.8 (3.2)	0.15
Abnormal wall motion	4 (7%)	2 (4%)	0.47
Ultrasound of carotid artery			
Maximum carotid IMT (mm)†	2.11 (1.30)	1.41 (0.70)	0.005
≥ 1.1	28 (75%)	20 (55%)	0.07
CAC scores (Agatston units)†	349.8 (99.6-1229.1)	133.2 (0.0-359.0)	0.003

Multivariate Analysis

Variable	Odds Ratio	95% Confidence interval	P value
Men‡	6.18	2.30 to 16.64	<0.001
Age (y.o.)	0.94	0.89 to 1.00	0.07
Body-mass index ≥25	0.49	0.20 to 1.23	0.13
Current smoking	2.05	0.75 to 5.54	0.15
Hypertension	1.26	0.45 to 3.50	0.65
Dyslipidemia	2.16	0.77 to 6.05	0.14

Data are number (%), mean (SD), median (IQR), odds ratio, or 95% CI. *P value < 0.05. †P value < 0.01. ‡P value < 0.001. To convert the values for cholesterol and triglycerides to millimoles per liter (mmol/L), multiply by 0.02586 and 0.01129, respectively.

CHD = coronary heart disease, PDR = proliferative diabetic retinopathy, ARB = angiotensin II receptor blockers, ACE-I =

angiotensin converting enzyme inhibitors, CCB = Calcium channel blockers, LDL = low-density lipoprotein, HDL = high-density lipoprotein, GFR = glomerular filtration rate, ECG = electrocardiogram, CVRR = coefficients of variance of RR intervals, ABI = ankle-brachial index, baPWV = brachial-ankle pulse wave velocity, PAD = peripheral arterial disease, DT = the deceleration time, IMT = intima-media thickness, CAC = coronary artery calcium.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Asymptomatic coronary heart disease in type 2 diabetic patients with vascular complications: a cross-sectional study

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TITLE

Asymptomatic coronary heart disease in type 2 diabetic patients with vascular complications: a cross-sectional study

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Key words

Diabetes, asymptomatic coronary heart disease, microvascular disease, macrovascular disease, vascular complications.

Word count

2934 words

ABSTRACT

Background

Recent studies have suggested that microvascular and macrovascular diseases are associated with coronary events.

Objective

To test the hypothesis that asymptomatic coronary heart disease (CHD) may be present in many diabetic patients with vascular complications.

Design

From April 2009 to August 2010, we conducted a cross-sectional study to assess the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications at a national diabetes center in Japan. Eligibility criteria included type 2 diabetic patients with no known CHD and one or more of the following four criteria: 1) proliferative diabetic retinopathy or after photocoagulation; 2) estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or an estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria; 3) peripheral arterial disease; and 4) cerebrovascular disease. Each patient underwent a stress singlephoton emission computed tomography (SPECT); patients with myocardial perfusion abnormalities then underwent

coronary angiography.

Results

A total of 1008 patients with type 2 diabetes were screened, and 122 eligible patients consented to participate. Stress SPECT revealed myocardial perfusion abnormalities in 96 (79%) patients. Of the 112 patients who completed the study protocol, 59 (53%) had asymptomatic CHD with ≥ 50% diameter stenosis. Additionally, 35 (31%) patients had multivessel disease or left main disease, and 42 (38%) had a coronary artery with ≥ 75% diameter stenosis. In the multivariate logistic-regression analysis to identify coronary risk factors associated with asymptomatic CHD, the only significant predictor was a male sex (odds ratio, 6.18; 95% confidence interval, 2.30 to 16.64; $P < 0.001$).

Conclusions

Asymptomatic CHD with ≥ 50% diameter stenosis and myocardial perfusion abnormalities was detected in more than half of the type 2 diabetic patients with vascular complications.

ARTICLE SUMMERY

Article focus

・Many past studies have reported that some diabetic patients have asymptomatic CHD.

・No definite markers for effectively identifying the presence of asymptomatic CHD in diabetic patients presently exist.

・In recent studies, microvascular and macrovascular diseases were associated with the subsequent coronary events.

Key Messages

・Asymptomatic CHD with ≥ 75% diameter stenosis and myocardial perfusion abnormalities was detected in around 40% of the type 2 diabetic patients with vascular complications.

・Traditional coronary risk factors might not be effective in screening for asymptomatic CHD among type 2 diabetic patients.

Strengths and limitations of this study

・This study is the report that many type 2 diabetic patients with vascular complications have asymptomatic CHD with multivessel disease and severe stenosis in addition to myocardial ischemia on stress SPECT.

- We demonstrated that type 2 diabetic patients with advanced microvascular or macrovascular diseases had a far greater prevalence of myocardial perfusion abnormalities and asymptomatic CHDs, compared with previous data.

- This study was performed at a single center and was limited to a specific geographical area.

INTRODUCTION

Diabetes is a risk factor of coronary heart disease (CHD) which is a leading cause of mortality.[1] Many studies have revealed that some diabetic patients may have asymptomatic CHD, and a retrospective study and a small randomized trial suggested a possible benefit from CHD screening.[2, 3] In a large randomized controlled trial, however, routine screening for asymptomatic CHD among type 2 diabetic patients was of no benefit to the cardiac outcome.[4] In addition, traditional coronary risk factors such as hypertension and dyslipidemia were not associated with silent ischemia and asymptomatic CHD.[5, 6] Therefore, aggressive routine screening for asymptomatic CHD among all diabetic patients with or without these risk factors is not recommended at present. No definite markers for effectively identifying the presence of asymptomatic CHD in diabetic patients presently exist, and further investigations are needed.

In recent studies, microvascular and macrovascular diseases were associated with the subsequent coronary events. Diabetic retinopathy was associated with the onset of CHD and cardiovascular disease.[7-10] Patients with proliferative diabetic retinopathy (PDR) and after photocoagulation had a particularly high risk of cardiovascular disease.[11] An independent association was also observed between renal dysfunction and cardiovascular events,[12-16] and the risk of cardiovascular disease was increased when proteinuria developed.[17, 18] Moreover, many studies suggested that macrovascular diseases such as peripheral arterial disease (PAD) and

cerebrovascular disease were strongly associated with CHD.[19-24]

Thus, we hypothesized that asymptomatic CHD may be present in many type 2 diabetic patients with vascular complications such as advanced diabetic retinopathy, renal dysfunction, PAD, or cerebrovascular disease, although each complication is regarded as etiologically nonidentical from others, especially between micro- and macrovascular complications for which hyperglycemia and hypercholesterolemia play an important role, respectively.[10, 24] The aim of this study was to assess the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications and no known CHD.

METHODS

Study Design and Participants

From April 2009 to August 2010, we conducted a cross-sectional study, and patients were enrolled at the National Center for Global Health and Medicine in Tokyo, Japan. The institutional review boards approved this study, and all the patients provided their written informed consent. Eligibility criteria included type 2 diabetic patients without suggestive symptoms of CHD between the ages of 40 and 75 years. Additionally, all the patients had one or more of the following four criteria: 1) PDR or after photocoagulation; 2) renal dysfunction; 3) PAD; and 4) cerebrovascular disease. An ophthalmologist diagnosed the PDR or after photocoagulation. Renal dysfunction was defined as an estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or an estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria, corresponding to ≥ 30 mg/day or ≥ 30 mg/g of creatinine. The estimated GFR was calculated using the following formula,[25] as recommended by the Japanese Society of Nephrology: estimated GFR (mL/min/1.73 m^2) = $194 \times Cre^{-1.094} \times Age^{-0.287}$ (× 0.739 if patient is a woman). PAD was defined as an ankle-brachial index (ABI) < 0.9, confirmed peripheral artery stenosis based on radiological images, or after surgical treatment. Cerebrovascular disease was defined as stroke or transient ischemic attack. The exclusion criteria included 1) known CHD or suspected CHD; 2) the presence of antibodies to glutamic acid decarboxylase; 3) acute kidney

injury; and 4) a very poor prognosis and inappropriate conditions for testing. The inclusion criteria and exclusion criteria were confirmed using clinical records, laboratory data, questionnaires, and questioning by the physician.

Diagnostic Approach and Evaluation of Outcomes

Stress singlephoton emission computed tomography (SPECT) has a high negative predictive value to rule-out CHD and does not require the use of contrast medium. To avoid unnecessary tests, we first performed stress SPECT in all the patients who met the study criteria; patients who exhibited myocardial perfusion abnormalities then underwent conventional coronary angiography (CAG), 64-slice multidetector-row computed tomography (MDCT) coronary angiography, or both examinations. We referred to the conventional CAG findings when the patients underwent both imaging procedures. The left main coronary artery, the left anterior descending coronary artery, the left circumflex coronary artery, and the right coronary artery were each assessed using the American Heart Association classification.[26] We diagnosed asymptomatic CHD when a coronary artery with ≥ 50% diameter stenosis was confirmed using coronary angiography.[19] The primary end point of this study was the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications.

Stress SPECT

Electrocardiogram (ECG)-gated stress SPECT imaging was performed in all the patients using a dual-headed gamma camera (E.cam; Siemens, Munich, Germany). Patients underwent exercise stress (n = 75) according to the Bruce protocol. Exercise testing was terminated when the patients achieved a heart rate of 85% or more of the predicted maximal heart rate, a sufficient blood pressure response (such as a systolic blood pressure ≥ 250 mmHg), a feeling that further exercise was impossible, or significant severe ischemic changes on an ECG recording. Patients who were unable to perform the exercise (n = 47) underwent a pharmacologic stress test comprised of a 6-minute adenosine infusion protocol, as recommended by The Japanese Society of Nuclear Cardiology. Technetium-99m tetrofosmin SPECT imaging was performed using a 1-day protocol in 108 patients, and thallium-201 was used in 14 patients. Two experienced doctors of nuclear cardiology independently evaluated the images without knowing the details of the clinical information. We diagnosed myocardial perfusion abnormalities when one or more of the doctors pointed out the presence of abnormal myocardial perfusion on the stress SPECT images. For the image analysis, quantitative gated SPECT data were also used. Ischemia was diagnosed when one or more of the doctors pointed out a reversible defect. On the other hand, a scar was diagnosed when the defect was not reversible.

Conventional CAG

When patients had severe coronary calcifications with coronary artery calcium (CAC) scores ≥ 400 Agatston units, an irregular heart rhythm, advanced renal dysfunction, or severe stenosis on MDCT coronary angiography, we aggressively conducted conventional CAG to assess the coronary arteries. Conventional CAG images were interpreted by two experienced cardiologists blinded to the detailed patient characteristics in a usual clinical setting.

64-slice MDCT

In the absence of contraindications, the patients who had myocardial perfusion abnormalities underwent MDCT tests to determine their CAC scores followed by coronary angiography. The imaging was performed using 64-slice MDCT with a slice thickness of 0.5 mm (Aquilion64; Toshiba Medical Systems, Otawara, Japan). If necessary and tolerated, oral beta-blockers (metoprolol 40 mg to 100 mg) were provided before the scan to achieve a heart rate < 60 beats/min. We performed a nonenhanced prospective electrocardiographically gated scan to measure the CAC scores, which were calculated using the Agatston method[27]. The MDCT coronary angiography was performed using 64 × 0.5 mm collimation and retrospective electrocardiographic gating. MDCT images were interpreted by an experienced cardiologist in cooperation with radiologists who were unaware of the detailed clinical backgrounds in a usual

clinical setting. All the coronary arteries and side branches with a luminal diameter ≥ 2.0 mm were assessed.

Other Measurements

The rest and exercise stress ECG tests were assessed by a trained cardiologist who had no knowledge of the clinical findings of the patients. We diagnosed an abnormality on the rest ECG findings if ST segment abnormalities, T wave abnormalities, an abnormal Q wave, or a complete left bundle branch block were observed; ischemia was diagnosed on an exercise stress ECG if the exercise induced any ischemic changes.

We measured the ABI to evaluate PAD and the brachial-ankle pulse wave velocity (baPWV) to assess the presence of arteriosclerosis in the peripheral arteries (Form PWV/ABI; Colin Company, Komaki, Japan).[28] The lowest ABI and the highest baPWV for the left and right sides were used in subsequent analyses.

To estimate cardiac function such as the ejection fraction and the wall motion, we conducted an echocardiography examination (Aplio 80; Toshiba Medical Systems, Otawara, Japan). The examinations were performed by a trained ultrasonographer and cardiologist who had no knowledge of the patients' clinical information. Doppler echocardiography was also performed to assess the peak Doppler velocities of the early (E) and late diastolic flows (A), the

deceleration time (DT), and the E/A ratio for the mitral inflow. Moreover, tissue Doppler imaging of the mitral annulus was measured from the apical 4-chamber view. A sample volume was placed at the septal mitral annulus and the early (E') diastolic velocity was measured. We analyzed the E/E' ratio to assess the cardiac function.[29]

The carotid intima-media thickness (IMT) was evaluated using high-resolution B-mode ultrasound with a 10-MHz linear transducer (Aplio XG; Toshiba Medical Systems, Otawara, Japan).[30] A trained ultrasonographer and a doctor or a skilled doctor alone who were unaware of the patient' characteristics assessed the maximum carotid IMT. The maximum carotid IMT was defined as the thickest IMT for the left and right sides from the common carotid artery to the internal carotid artery.

Statistical Methods

Data are presented as the number (%), mean with standard deviation (SD), and median with lower and upper ends of the interquartile range (IQR). Continuous variables were compared using t tests and Wilcoxon rank sum tests. Categorical variables were compared using chi-square tests. A multivariate logistic-regression analysis of coronary risk factors, such as age, sex, overweight or obesity, current smoking habit, hypertension, and dyslipidemia, was performed to identify coronary risk factors associated with asymptomatic CHD. P values < 0.05

according to a two sided test were considered statistically significant for all the tests. All analyses were performed using Stata software, version 11.1 (Stata Corp, College Station, Texas).

RESULTS

A total of 1008 patients with type 2 diabetes between the ages of 40 and 75 years were screened, and 219 met the inclusion criteria for this study. Of the 206 eligible patients without any exclusion criteria, 122 consented to participate (Figure 1). The clinical characteristics of this study population are presented in Table 1. The mean age was 64.1 ± 8.3 years, and 84 (68%) were men, and the mean A1C was 7.7 ± 1.5 %. The numbers of patients with PDR or after photocoagulation, renal dysfunction, PAD, and cerebrovascular disease were 76 (62%), 25 (20%), 21 (17%), and 46 (37%), respectively.

Of the 122 patients, 96 (79%) had myocardial perfusion abnormalities on stress SPECT: 70 (58%) had ischemia and 26 (21%) had scar. Of the 96 patients with myocardial perfusion abnormalities, 42 underwent conventional CAG, 83 underwent MDCT coronary angiography, and 39 underwent both examinations. Ten patients did not undergo either MDCT coronary angiography or CAG and were excluded from the analysis to determine the prevalence of asymptomatic CHD. Of the 112 patients who completed the study protocol, 59 (53%) had asymptomatic CHD (Figure 2A). Thus, more than half of the patients who met any one of the four inclusion criteria for vascular complications had asymptomatic CHD (Figure 2B). The prevalences of asymptomatic CHD among the patients who met only one criteria and among the patients who met more than one of the four inclusion criteria for vascular complications were not significantly different (P = 0.50). The prevalence of asymptomatic CHD in patients with

myocardial perfusion abnormalities on stress SPECT are shown in Figure 2C. The prevalences of asymptomatic CHD among patients with ischemia and among those with scar were not significantly different. The CAC scores for the patients with and for those without asymptomatic CHD were significantly different (Figure 2D).

The majority of patients with asymptomatic CHD had multivessel disease. 59 Patients with asymptomatic CHD had 1.8 ± 0.8 vessels with ≥ 50% diameter stenosis: 24 (41%) patients had one-vessel disease, 22 (37%) had two-vessel disease, and 13 (22%) had three-vessel disease or left main disease. The maximum percent diameter stenosis in patients with asymptomatic CHD is also assessed. 42 (71%) Patients had ≥ 75% diameter stenosis and 24 (41%) had ≥ 90% diameter stenosis. The analyses of the clinical variables among the patients with and those without asymptomatic CHD are shown in Table 2. Men, a current smoking habit, age at the time of diabetes diagnosis, the ejection fraction, the E/A ratio, the maximum carotid IMT, and the CAC scores differed significantly between the two groups in a univariate analysis. However, abnormal findings on the rest ECG, ischemic findings on the exercise stress ECG, and abnormal wall motion on echocardiography were not significantly different. When a multivariate logistic-regression analysis was performed to identify coronary risk factors independently associated with asymptomatic CHD, the only significant predictor was a male sex (odds ratio, 6.18; 95% confidence interval, 2.30 to 16.64; $P < 0.001$). The result was similar when the

duration of diabetes was added to the multivariate analysis.

DISCUSSION

This study reports that many type 2 diabetic patients with vascular complications have asymptomatic CHD with multivessel disease and severe stenosis in addition to myocardial ischemia on stress SPECT. Moreover, asymptomatic CHD was detected in more than half of the patients who met any one of the four inclusion criteria for vascular complications. Many past studies have reported that some diabetic patients have asymptomatic CHD. However, under which conditions the diabetic patients were most likely to have asymptomatic CHD was unclear. We demonstrated that type 2 diabetic patients with advanced microvascular or macrovascular diseases had a far greater prevalence of myocardial perfusion abnormalities and asymptomatic CHDs, compared with previous data.[5, 6] Because the diabetic complications had progressed, the patients might have had severe autonomic denervation of the heart, accounting for their asymptomatic presentation.[31] The statistical analysis revealed that asymptomatic CHD was more common among men than among women. However, other coronary risk factors were not associated with asymptomatic CHD. These results may be similar to those of previous studies.[5,

[6] Thus, traditional coronary risk factors might not be effective in screening for asymptomatic CHD among type 2 diabetic patients. Unfortunately, we could not sufficiently examine the CAC score (n=83) and the maximum IMT (n=81) in 122 patients and thus could not include these parameters as covariates in the multivariate analysis. Further research will be required to identify possibly useful markers such as the ejection fraction, E/A ratio, maximum carotid IMT, and CAC scores.

Importantly, some patients without significant coronary stenosis exhibited abnormal findings, such as ischemia on stress ECG, abnormal wall motion on echocardiography, or myocardial perfusion abnormalities on stress SPECT. Although these facts might suggest the possibility of false-positive results, coronary microvascular dysfunction may be responsible for cardiac disorders because the patients had many coronary microvascular risk factors, such as diabetes, cigarette smoking, dyslipidemia, and hypertension.[32, 33] Further investigation is needed for coronary microvascular dysfunction.

Our study had several limitations. Firstly, this study was performed at a single center and was limited to a specific geographical area. Thus, large-scale studies at multiple centers throughout the world will be necessary to confirm these results. However, we believe that this is an extremely important study that may lead to numerous future trials and that may have a large influence on diabetic management. Secondly, we did not perform further tests in patients with

normal myocardial perfusion on stress SPECT. Therefore, some patients with normal myocardial perfusion might have had asymptomatic CHD. However, stress SPECT has a very high sensitivity for CHD and affects the decisions regarding future treatment.[34] Consequently, this diagnostic approach may enable unnecessary angiography to be effectively avoided. Thirdly, the coronary arteries in some of the patients were evaluated using MDCT coronary angiography alone. In large-scale studies, a high rate of agreement between MDCT coronary angiography and conventional CAG has been confirmed.[35] Furthermore, conventional CAG was performed in most of the severe calcification cases with CAC scores ≥400 Agatston units, which could be problematic for MDCT coronary angiography.[36] The median CAC scores in the 44 patients who underwent MDCT coronary angiography alone was 149.0 (14.1-383.4) Agatston units. Thus, we assumed that the diagnosis of CHD was accurate. Fourthly, our approach based on image information representing anatomic rather than functional aspects possibly misses some of the ischemic changes of CHD and this may explain the lack between vasculopathy and asymptomatic CHD observed in our current survey. Lastly, we had only 21 subjects with PAD and that may be because of the relatively low prevalence of isolated PAD (e.g., PAD without CHD) in the Japanese population, and, in fact, a paper from Japan reported that around half of the patients with PAD in their study also had CHD.[37] The high mean PWV values possibly reflected advanced arteriosclerosis of the subjects. In addition, it should be mentioned that the

renal function did not worsen in any of the patients after coronary angiography and MDCT in this series of observations.

In conclusion, this study revealed that asymptomatic CHD with myocardial perfusion abnormalities was detected in more than half of the type 2 diabetic patients with vascular complications. A relationship between CHD and sudden cardiac death has been revealed,[38] and we expect that the results of this study may contribute greatly to reducing myocardial infarction and sudden cardiac death among type 2 diabetic patients. However, the best approach to treating asymptomatic CHD remains unknown. Therefore, randomized controlled trials are needed to determine the optimal management.

Contributors: TT conceived the study. TT, MH and MN designed the protocol. MH, MM and KK evaluated the SPECT images. MKa and MH evaluated the coronary angiography images. TT, HK, YT, MKi, HN and RYH contributed to the data collection and the preparation. TT and TS analyzed all the data. All the authors contributed to the interpretation of the results and approved the final version.

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Data sharing: No additional data available.

References

1.Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;**339**:229-34.

2.Sorajja P, Chareonthaitawee P, Rajagopalan N, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. *Circulation*. 2005;**112**:I311-6.

3.Faglia E, Manuela M, Antonella Q, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *Am Heart J*. 2005;**149**:e1-6.

4.Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA*. 2009;**301**:1547-55.

5.Wackers FJ, Young LH, Inzucchi SE, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*. 2004;**27**:1954-61.

6.Scognamiglio R, Negut C, Ramondo A, et al. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol*. 2006;**47**:65-71.

7.Rajala U, Pajunpaa H, Koskela P, et al. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. *Diabetes Care*. 2000;**23**:957-61.

8.Chew EY, Ferris FL, 3rd, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. *Ophthalmology*. 2003;**110**:1683-9.

9.van Hecke MV, Dekker JM, Stehouwer CD, et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. *Diabetes Care*. 2005;**28**:1383-9.

10.Cheung N, Wang JJ, Klein R, et al. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2007;**30**:1742-6.

11.Targher G, Bertolini L, Zenari L, et al. Diabetic retinopathy is associated with an increased

incidence of cardiovascular events in Type 2 diabetic patients. *Diabet Med*. 2008;**25**:45-50.

12. Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;**63**:225-32.

13. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;**351**:1296-305.

14. Patel UD, Young EW, Ojo AO, et al. CKD progression and mortality among older patients with diabetes. *Am J Kidney Dis*. 2005;**46**:406-14.

15. Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol*. 2006;**17**:2034-47.

16. Sukhija R, Aronow WS, Kakar P, et al. Relation of microalbuminuria and coronary artery disease in patients with and without diabetes mellitus. *Am J Cardiol*. 2006;**98**:279-81.

17. Tonelli M, Jose P, Curhan G, et al. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ*. 2006;**332**:1426.

18. Hallan S, Astor B, Romundstad S, et al. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study. *Arch Intern Med*. 2007;**167**:2490-6.

19.Janand-Delenne B, Savin B, Habib G, et al. Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care*. 1999;**22**:1396-400.

20.Cosson E, Guimfack M, Paries J, et al. Are silent coronary stenoses predictable in diabetic patients and predictive of cardiovascular events? *Diabetes Metab*. 2003;**29**:470-6.

21.Nesto RW, Watson FS, Kowalchuk GJ, et al. Silent myocardial ischemia and infarction in diabetics with peripheral vascular disease: assessment by dipyridamole thallium-201 scintigraphy. *Am Heart J*. 1990;**120**:1073-7.

22.Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol*. 2005;**25**:1463-9.

23.Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbidity and mortality implications. *Circulation*. 2006;**114**:688-99.

24.Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;**295**:180-9.

25.Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;**53**:982-92.

26.Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery

Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;**51**:5-40.

27. Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;**15**:827-32.

28. Koji Y, Tomiyama H, Ichihashi H, et al. Comparison of ankle-brachial pressure index and pulse wave velocity as markers of the presence of coronary artery disease in subjects with a high risk of atherosclerotic cardiovascular disease. *Am J Cardiol*. 2004;**94**:868-72.

29. Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation*. 2000;**102**:1788-94.

30. O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. *N Engl J Med*. 1999;**340**:14-22.

31. Niakan E, Harati Y, Rolak LA, et al. Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy. *Arch Intern Med*. 1986;**146**:2229-30.

32. Nitenberg A, Valensi P, Sachs R, et al. Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. *Diabetes*. 1993;**42**:1017-25.

33.Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;**356**:830-40.

34.Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;**107**:2900-7.

35.Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;**359**:2324-36.

36.Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*. 2008;**52**:1724-32.

37.Iwashima Y, Horio T, Suzuki Y, et al. Adiponectin and inflammatory markers in peripheral arterial occlusive disease. *Atherosclerosis*. 2006;**188**:384-90.

38.Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;**104**:2158-63.

Figure legends

Figure 1. Flowchart of Study Participants.

Figure 2. Prevalence of Myocardial Perfusion Abnormalities and Asymptomatic CHD (A). Prevalence of Asymptomatic CHD for Each of the Vascular Complications (B). Prevalence of Asymptomatic CHD in Patients with Ischemia or Scar (C). CAC Scores in Patients With or Without Asymptomatic CHD (D).

CHD = coronary heart disease, CAC = coronary artery calcium, PDR = proliferative diabetic retinopathy, GFR = glomerular filtration rate, and PAD = peripheral arterial disease.

Table 1 Characteristics of Study Population*

	N	All	Men	Women
		122	84 (69%)	38 (31%)
Age (y.o.)	122	64.1 (8.3)	63.9 (8.3)	64.6 (8.5)
Weight (kg)	122	64.6 (12.4)	66.7 (12.1)	60.1 (12.2)
Body-mass index (kg/m^2)†	122	24.5 (4.0)	24.3 (3.7)	25.1 (4.5)
Waist (cm)	112	90.3 (11.2)	89.8 (10.7)	91.5 (12.5)
Smoking	122			
Non		47 (39%)	16 (18%)	31 (82%)
Former		37 (30%)	34 (41%)	3 (8%)
Current		38 (31%)	34 (41%)	4 (10%)
History of cerebrovascular disease§	122	46 (37%)	32 (38%)	14 (36%)
Duration of diabetes (years)	122	16.0 (10.2)	16.5 (9.8)	15.2 (11.1)
Age at the time of diabetes diagnosis (y.o.)	122	49.0 (12.2)	48.4 (11.8)	50.4 (13.1)
Any diabetic retinopathy	122	97 (79%)	67 (79%)	30 (79%)
PDR or after photocoagulation	122	76 (62%)	50 (59%)	26 (68%)
A1C (%)	122	7.7 (1.5)	7.8 (1.7)	7.5 (1.2)
Treatment for diabetes	122			
Diet		7 (6%)	7 (8%)	0 (0%)

Oral agents			59 (48%)	37 (44%)	22 (58%)
Insulin			15 (12%)	13 (16%)	2 (5%)
Insulin + Oral agents¶			41 (34%)	21 (32%)	14 (37%)
Hypertension‖		122	95 (77%)	66 (78%)	29 (76%)
Treatment:	ARB/ACE-I		88 (72%)	61 (72%)	27 (71%)
	CCB		55 (45%)	37 (44%)	18 (47%)
	Diuretics		16 (13%)	9 (10%)	7 (18%)
	Others		4 (3%)	3 (3%)	1 (2%)
Dyslipidemia**		122	90 (73%)	60 (71%)	30 (79%)
Total cholesterol (mg/dL)			192.7 (39.0)	194.7 (42.4)	188.3 (30.9)
LDL cholesterol (mg/dL)			115.6 (40.5)	119.6 (43.8)	106.5 (30.4)
HDL cholesterol (mg/dL)			52.4 (14.8)	51.1 (13.5)	55.3 (17.2)
Triglyceride (mg/dL)			143.3 (85.9)	142.7 (86.1)	144.6 (86.7)
LDL/HDL ratio			2.4 (1.1)	2.5 (1.1)	2.2 (0.9)
Treatment:	Statin		47 (38%)	25 (29%)	22 (57%)
	Others		9 (7%)	7 (8%)	2 (5%)
Use of aspirin		122	33 (27%)	23 (27%)	10 (26%)
Creatinine (mg/dL)		120	1.04 (0.60)	1.08 (0.60)	0.94 (0.60)

Estimated GFR (mL/min/1.73 m^2)	120	62.1 (22.0)	63.3 (20.4)	59.7 (25.4)
< 45		28 (23%)	17 (20%)	11 (28%)
< 30		10 (8%)	5 (6%)	5 (13%)
Use of hemodialysis	2	2 (1%)	2 (2%)	0 (0%)
Albuminuria (mg/day or mg/g of creatinine)	117			
< 30		32 (27%)	16 (20%)	16 (45%)
30-299		40 (34%)	28 (34%)	12 (33%)
≥ 300		45 (39%)	37 (46%)	8 (22%)
Renal dysfunction††	122	25 (20%)	17 (20%)	8 (21%)
Brain natriuretic peptide (pg/mL)	113	37.2 (26.1-48.2)	19.4 (7.5-47.5)	24.8 (11-39.8)
Rest ECG				
Any abnormal findings	122	27 (22%)	19 (22%)	8 (21%)
Abnormal Q wave changes		3 (2%)	2 (2%)	1 (2%)
Ischemic findings on exercise stress ECG	64	25 (39%)	15 (36%)	10 (43%)
Cardio thoracic ratio on chest x-ray (%)	113	48.0 (4.4)	47.6 (4.5)	48.9 (4.0)
ABI	122	1.07 (0.17)	1.06 (0.18)	1.09 (0.17)
baPWV (cm/sec)	108	2012.2 (377.3)	1940.5 (300.3)	2168.3 (474.8)
PAD	122	21 (17%)	17 (20%)	4 (10%)

Echocardiography‡‡				
Ejection fraction (%)	108	67.3 (8.6)	66.4 (9.5)	69.4 (6.0)
Septal + posterior wall thickness (mm)	108	21.2 (3.4)	21.3 (3.4)	20.9 (3.4)
> 25		10 (9%)	6 (8%)	4 (11%)
E/A ratio	107	0.76 (0.21)	0.77 (0.17)	0.75 (0.28)
DT (msec)	107	236.4 (59.1)	232.6 (60.5)	244.6 (56.0)
E/E' ratio	96	11.3 (3.4)	11.0 (2.86)	12.1 (4.35)
Abnormal wall motion	108	6 (5%)	6 (8%)	0 (0%)
Ultrasound of carotid artery	81			
Maximum carotid IMT (mm)		1.78 (1.07)	1.97 (1.13)	1.39 (0.86)
≥ 1.1		53 (67%)	41 (77%)	12 (46%)
CAC scores (Agatston units)	83	216.8 (52.0-602.7)	300.4 (65.6-1201.2)	110.9 (0-275.8)

* Data are number, number (%), mean (SD), or median (IQR). To convert the values for cholesterol and triglycerides to millimoles per liter (mmol/L), multiply by 0.02586 and 0.01129, respectively. PDR = proliferative diabetic retinopathy, ARB = angiotensin II receptor blockers, ACE-I = angiotensin converting enzyme inhibitors, CCB = Calcium channel blockers, LDL = low-density lipoprotein, HDL = high-density lipoprotein, GFR = glomerular filtration rate, ECG = electrocardiogram, ABI = ankle-brachial index, baPWV = brachial-ankle pulse wave velocity, PAD = peripheral arterial disease, DT = deceleration time, IMT = intima-media thickness, CAC = coronary artery

calcium.

† Body-mass index was calculated as the weight in kilograms divided by the square of height in meters.

§ Cerebrovascular disease was defined as stroke or transient ischemic attack.

¶ Oral agents for the treatment of diabetes included metformin, sulfonylureas, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors.

‖ Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medication.

** Dyslipidemia was defined as LDL ≥ 140 mg/dL, HDL < 40 mg/dL, or the use of lipid-lowering drug.

†† Renal dysfunction was defined as the estimated GFR < 30 mL/min/1.73 m^2 or the estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria which was ≥ 30 mg/day or ≥ 30 mg/g of creatinine.

‡‡ E/A ratio was the ratio of the peak Doppler velocities of early to late diastolic flow in the mitral inflow. E/E' ratio was the ratio of the peak Doppler velocities of early in the mitral inflow to the early diastolic velocity at the septal mitral annulus.

Table 2 Analyses of Clinical Variables for Asymptomatic CHD

Univariate Analysis

Variable	Asymptomatic CHD (+)	Asymptomatic CHD (-)	P value
	59 (53%)	53 (47%)	
Men	51 (86%)	26 (49%)	< 0.001
Age (y.o.)	62.4 (8.8)	65.3 (7.7)	0.07
Weight (kg)	65.3 (12.9)	64.7 (12.7)	0.79
Body-mass index (kg/m^2)	24.0 (3.4)	25.3 (4.6)	0.08
Waist (cm)	90.0 (11.4)	91.1 (11.9)	0.60
Current smoker	26 (44%)	10 (18%)	0.004
History of cerebrovascular disease	22 (37%)	21 (39%)	0.80
Duration of diabetes (years)	16.7 (10.5)	14.9 (10.0)	0.34
Age at the time of diabetes diagnosis (y.o.)	46.7 (12.2)	51.4 (11.9)	0.04
Any diabetic retinopathy	46 (78%)	42 (79%)	0.86
PDR or after photocoagulation	36 (61%)	34 (64%)	0.73
A1C (%)	7.3 (1.5)	7.4 (1.6)	0.76
Use of insulin	33 (55%)	21 (39%)	0.08
Hypertension	46 (78%)	40 (75%)	0.75
Dyslipidemia	45 (76%)	39 (73%)	0.74

Total cholesterol (mg/dL)	192.8 (38.4)	196.0 (39.5)	0.67
LDL cholesterol (mg/dL)	113.0 (36.6)	120.0 (38.5)	0.33
HDL cholesterol (mg/dL)	50.7 (13.7)	53.5 (15.7)	0.32
Triglyceride (mg/dL)	151.5 (89.0)	136.6 (82.3)	0.36
LDL/HDL ratio	2.4 (1.0)	2.4 (1.0)	0.85
Use of statin	21 (35%)	22 (41%)	0.52
Use of aspirin	16 (27%)	15 (28%)	0.88
Creatinine (mg/dL)	1.03 (0.60)	0.87 (0.35)	0.09
GFR (mL/min/1.73 m^2)	63.9 (20.7)	65.2 (20.0)	0.74
< 45	13 (22%)	9 (17%)	0.50
< 30	2 (3%)	3 (5%)	0.56
Albuminuria ≥ 30 (mg/day or mg/g of creatinine)	43 (76%)	32 (62%)	0.11
Brain natriuretic peptide (pg/mL)	20.7 (7.6-35.4)	17.4 (9.5-42.9)	0.99
Rest ECG			
Ischemic findings on exercise stress ECG	12 (41%)	10 (35%)	0.66
Cardio thoracic ratio on chest x-ray (%)	47.3 (4.4)	48.8 (4.1)	0.08
ABI	1.06 (0.20)	1.06 (0.15)	0.98
baPWV (cm/sec)	1955.3 (306.4)	2067.4 (448.7)	0.14

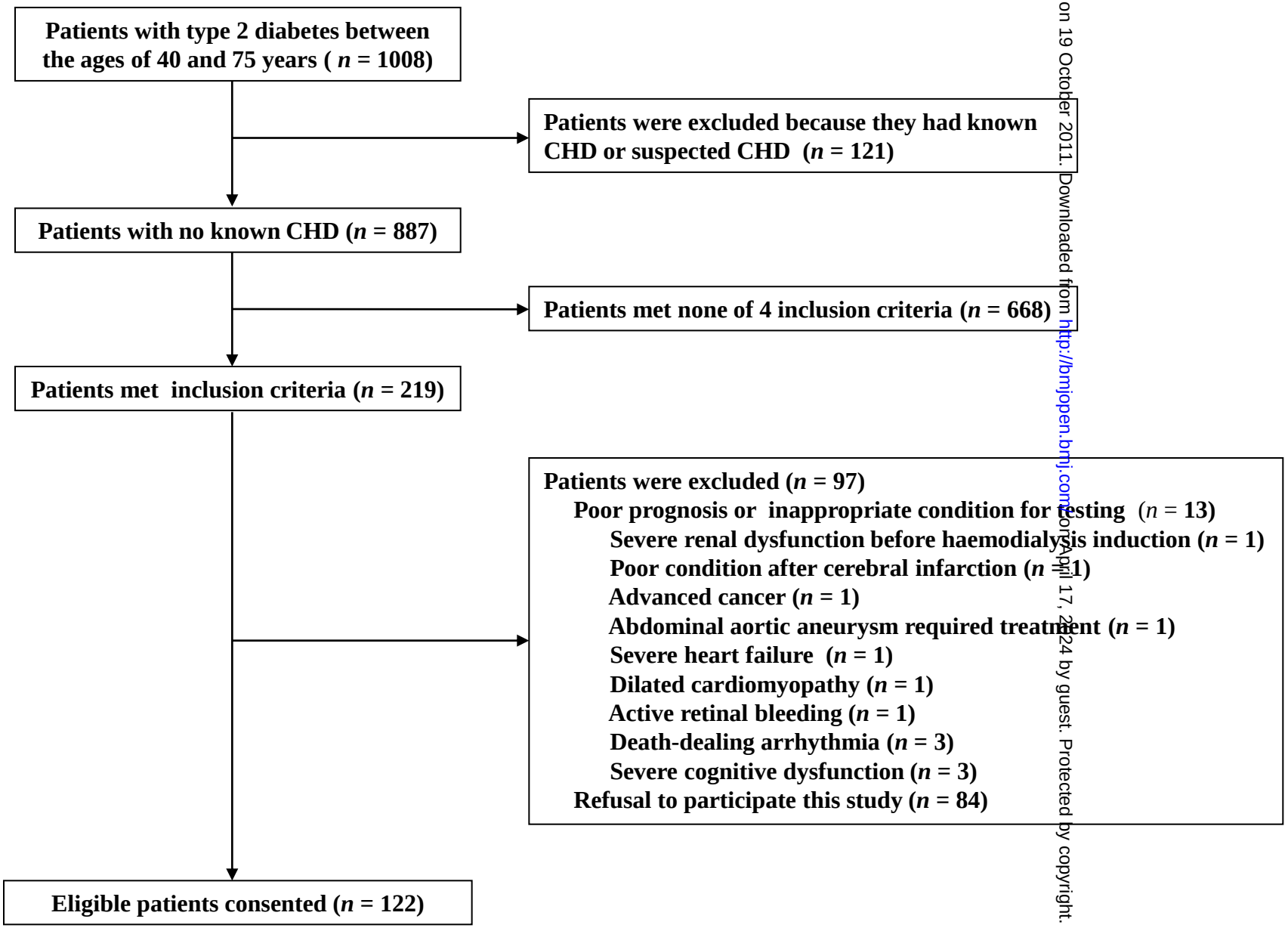
PAD	12 (22%)	8 (16%)	0.42
Echocardiography			
Ejection fraction (%)	65.6 (9.1)	69.0 (8.0)	0.04
Septal wall + posterior wall thickness (mm)	20.8 (3.7)	21.2 (3.0)	0.55
E/A ratio	0.81 (0.16)	0.71 (0.24)	0.02
DT (msec)	225.7 (58.2)	247.5 (61.9)	0.07
E/E' ratio	10.8 (3.3)	11.8 (3.2)	0.15
Abnormal wall motion	4 (7%)	2 (4%)	0.47
Ultrasound of carotid artery			
Maximum carotid IMT (mm)	2.11 (1.30)	1.41 (0.70)	0.005
≥ 1.1	28 (75%)	20 (55%)	0.07
CAC scores (Agatston units)	349.8 (99.6-1229.1)	133.2 (0.0-359.0)	0.003

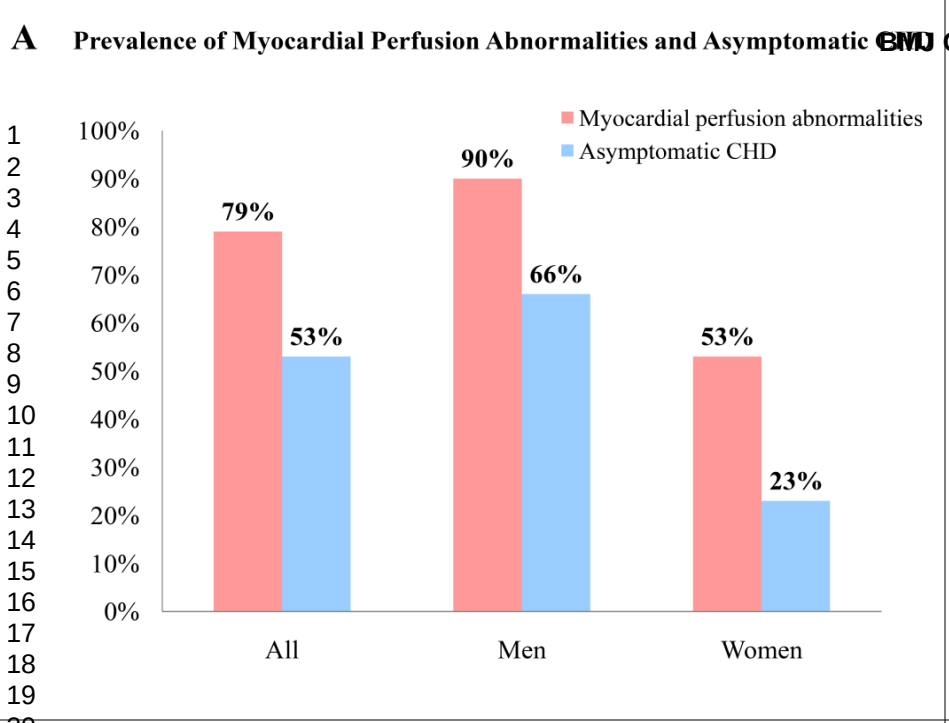
Multivariate Analysis

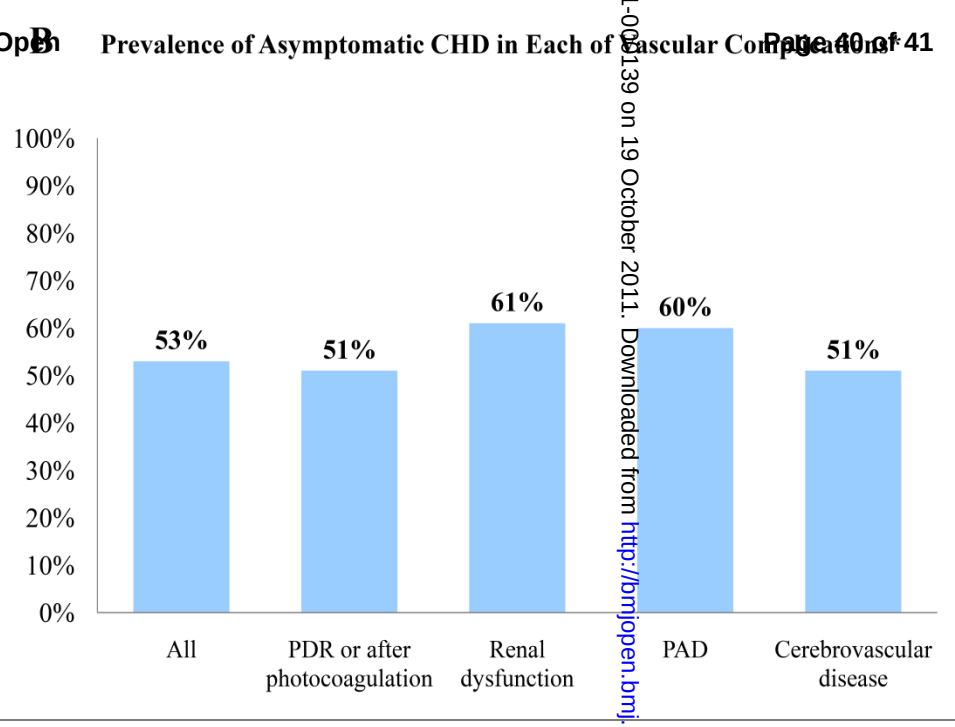
Variable	Odds Ratio	95% Confidence interval	P value
Men	6.18	2.30 to 16.64	<0.001
Age (y.o.)	0.94	0.89 to 1.00	0.07
Body-mass index ≥25	0.49	0.20 to 1.23	0.13

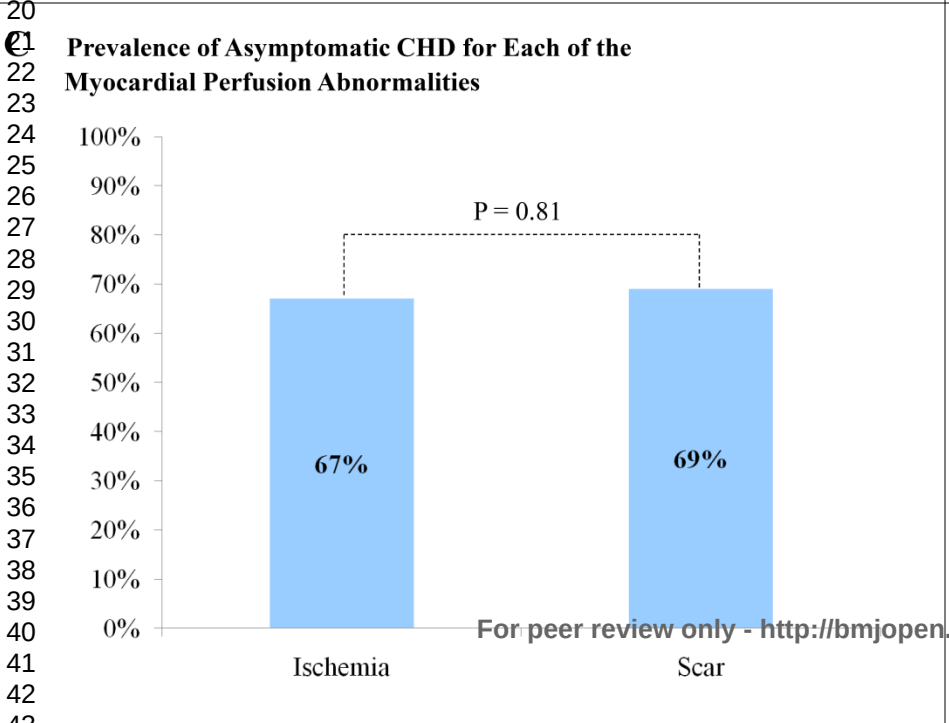
Current smoking	2.05	0.75 to 5.54	0.15
Hypertension	1.26	0.45 to 3.50	0.65
Dyslipidemia	2.16	0.77 to 6.05	0.14

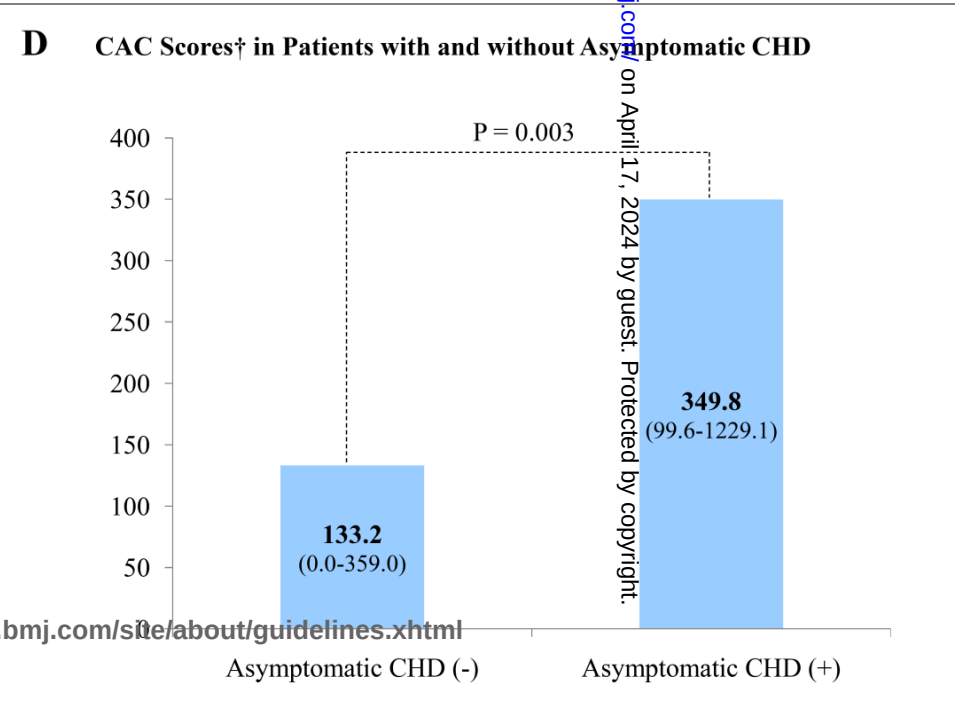
Data are number (%), mean (SD), median (IQR), odds ratio, or 95% CI. To convert the values for cholesterol and triglycerides to millimoles per liter (mmol/L), multiply by 0.02586 and 0.01129, respectively. CHD = coronary heart disease, PDR = proliferative diabetic retinopathy, ARB = angiotensin II receptor blockers, ACE-I = angiotensin converting enzyme inhibitors, CCB = Calcium channel blockers, LDL = low-density lipoprotein, HDL = high-density lipoprotein, GFR = glomerular filtration rate, ECG = electrocardiogram, ABI = ankle-brachial index, baPWV = brachial-ankle pulse wave velocity, PAD = peripheral arterial disease, DT = the deceleration time, IMT = intima-media thickness, CAC = coronary artery calcium.











STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Asymptomatic coronary heart disease in type 2 diabetic patients with vascular complications: a cross-sectional study

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Note: The following files were submitted by the author for peer review, but cannot be converted to PDF. You must view these files (e.g. movies) online.
BMJ Open. Figure 2

TITLE

Asymptomatic coronary heart disease in type 2 diabetic patients with vascular complications: a cross-sectional study

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Key words

Diabetes, asymptomatic coronary heart disease, microvascular disease, macrovascular disease, vascular complications.

Word count

2934 words

ABSTRACT

Background

Recent studies have suggested that microvascular and macrovascular diseases are associated with coronary events.

Objective

To test the hypothesis that asymptomatic coronary heart disease (CHD) may be present in many diabetic patients with vascular complications.

Design

From April 2009 to August 2010, we conducted a cross-sectional study to assess the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications at a national diabetes center in Japan. Eligibility criteria included type 2 diabetic patients with no known CHD and one or more of the following four criteria: 1) proliferative diabetic retinopathy or after photocoagulation; 2) estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or an estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria; 3) peripheral arterial disease; and 4) cerebrovascular disease. Each patient underwent a stress singlephoton emission computed tomography (SPECT); patients with myocardial perfusion abnormalities then underwent

coronary angiography.

Results

A total of 1008 patients with type 2 diabetes were screened, and 122 eligible patients consented to participate. Stress SPECT revealed myocardial perfusion abnormalities in 96 (79%) patients. Of the 112 patients who completed the study protocol, 59 (53%) had asymptomatic CHD with ≥ 50% diameter stenosis. Additionally, 35 (31%) patients had multivessel disease or left main disease, and 42 (38%) had a coronary artery with ≥ 75% diameter stenosis. In the multivariate logistic-regression analysis to identify coronary risk factors associated with asymptomatic CHD, the only significant predictor was a male sex (odds ratio, 6.18; 95% confidence interval, 2.30 to 16.64; $P < 0.001$).

Conclusions

Asymptomatic CHD with ≥ 50% diameter stenosis and myocardial perfusion abnormalities was detected in more than half of the type 2 diabetic patients with vascular complications.

ARTICLE SUMMERY

Article focus

・Many past studies have reported that some diabetic patients have asymptomatic CHD.

・No definite markers for effectively identifying the presence of asymptomatic CHD in diabetic patients presently exist.

・In recent studies, microvascular and macrovascular diseases were associated with the subsequent coronary events.

Key Messages

・Asymptomatic CHD with ≥ 75% diameter stenosis and myocardial perfusion abnormalities was detected in around 40% of the type 2 diabetic patients with vascular complications.

・Traditional coronary risk factors might not be effective in screening for asymptomatic CHD among type 2 diabetic patients.

Strengths and limitations of this study

・This study is the report that many type 2 diabetic patients with vascular complications have asymptomatic CHD with multivessel disease and severe stenosis in addition to myocardial ischemia on stress SPECT.

・We demonstrated that type 2 diabetic patients with advanced microvascular or macrovascular diseases had a far greater prevalence of myocardial perfusion abnormalities and asymptomatic CHDs, compared with previous data.

・This study was performed at a single center and was limited to a specific geographical area.

INTRODUCTION

Diabetes is a risk factor of coronary heart disease (CHD) which is a leading cause of mortality.[1] Many studies have revealed that some diabetic patients may have asymptomatic CHD, and a retrospective study and a small randomized trial suggested a possible benefit from CHD screening.[2, 3] In a large randomized controlled trial, however, routine screening for asymptomatic CHD among type 2 diabetic patients was of no benefit to the cardiac outcome.[4] In addition, traditional coronary risk factors such as hypertension and dyslipidemia were not associated with silent ischemia and asymptomatic CHD.[5, 6] Therefore, aggressive routine screening for asymptomatic CHD among all diabetic patients with or without these risk factors is not recommended at present. No definite markers for effectively identifying the presence of asymptomatic CHD in diabetic patients presently exist, and further investigations are needed.

In recent studies, microvascular and macrovascular diseases were associated with the subsequent coronary events. Diabetic retinopathy was associated with the onset of CHD and cardiovascular disease.[7-10] Patients with proliferative diabetic retinopathy (PDR) and after photocoagulation had a particularly high risk of cardiovascular disease.[11] An independent association was also observed between renal dysfunction and cardiovascular events,[12-16] and the risk of cardiovascular disease was increased when proteinuria developed.[17, 18] Moreover, many studies suggested that macrovascular diseases such as peripheral arterial disease (PAD) and

cerebrovascular disease were strongly associated with CHD.[19-24]

Thus, we hypothesized that asymptomatic CHD may be present in many type 2 diabetic patients with vascular complications such as advanced diabetic retinopathy, renal dysfunction, PAD, or cerebrovascular disease, although each complication is regarded as etiologically nonidentical from others, especially between micro- and macrovascular complications for which hyperglycemia and hypercholesterolemia play an important role, respectively.[10, 24] The aim of this study was to assess the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications and no known CHD.

METHODS

Study Design and Participants

From April 2009 to August 2010, we conducted a cross-sectional study, and patients were enrolled at the National Center for Global Health and Medicine in Tokyo, Japan. The institutional review boards approved this study, and all the patients provided their written informed consent. Eligibility criteria included type 2 diabetic patients without suggestive symptoms of CHD between the ages of 40 and 75 years. Additionally, all the patients had one or more of the following four criteria: 1) PDR or after photocoagulation; 2) renal dysfunction; 3) PAD; and 4) cerebrovascular disease. An ophthalmologist diagnosed the PDR or after photocoagulation. Renal dysfunction was defined as an estimated glomerular filtration rate (GFR) < 30 mL/min/1.73 m^2 or an estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria, corresponding to ≥ 30 mg/day or ≥ 30 mg/g of creatinine. The estimated GFR was calculated using the following formula,[25] as recommended by the Japanese Society of Nephrology: estimated GFR (mL/min/1.73 m^2) = 194 × $Cre^{-1.094}$ × $Age^{-0.287}$ (× 0.739 if patient is a woman). PAD was defined as an ankle-brachial index (ABI) < 0.9, confirmed peripheral artery stenosis based on radiological images, or after surgical treatment. Cerebrovascular disease was defined as stroke or transient ischemic attack. The exclusion criteria included 1) known CHD or suspected CHD; 2) the presence of antibodies to glutamic acid decarboxylase; 3) acute kidney

injury; and 4) a very poor prognosis and inappropriate conditions for testing. The inclusion criteria and exclusion criteria were confirmed using clinical records, laboratory data, questionnaires, and questioning by the physician.

Diagnostic Approach and Evaluation of Outcomes

Stress singlephoton emission computed tomography (SPECT) has a high negative predictive value to rule-out CHD and does not require the use of contrast medium. To avoid unnecessary tests, we first performed stress SPECT in all the patients who met the study criteria; patients who exhibited myocardial perfusion abnormalities then underwent conventional coronary angiography (CAG), 64-slice multidetector-row computed tomography (MDCT) coronary angiography, or both examinations. We referred to the conventional CAG findings when the patients underwent both imaging procedures. The left main coronary artery, the left anterior descending coronary artery, the left circumflex coronary artery, and the right coronary artery were each assessed using the American Heart Association classification.[26] We diagnosed asymptomatic CHD when a coronary artery with ≥ 50% diameter stenosis was confirmed using coronary angiography.[19] The primary end point of this study was the prevalence of asymptomatic CHD among type 2 diabetic patients with vascular complications.

Stress SPECT

Electrocardiogram (ECG)-gated stress SPECT imaging was performed in all the patients using a dual-headed gamma camera (E.cam; Siemens, Munich, Germany). Patients underwent exercise stress (n = 75) according to the Bruce protocol. Exercise testing was terminated when the patients achieved a heart rate of 85% or more of the predicted maximal heart rate, a sufficient blood pressure response (such as a systolic blood pressure ≥ 250 mmHg), a feeling that further exercise was impossible, or significant severe ischemic changes on an ECG recording. Patients who were unable to perform the exercise (n = 47) underwent a pharmacologic stress test comprised of a 6-minute adenosine infusion protocol, as recommended by The Japanese Society of Nuclear Cardiology. Technetium-99m tetrofosmin SPECT imaging was performed using a 1-day protocol in 108 patients, and thallium-201 was used in 14 patients. Two experienced doctors of nuclear cardiology independently evaluated the images without knowing the details of the clinical information. We diagnosed myocardial perfusion abnormalities when one or more of the doctors pointed out the presence of abnormal myocardial perfusion on the stress SPECT images. For the image analysis, quantitative gated SPECT data were also used. Prior to interpreting the images, the data were reviewed for artifacts. A 20-segment model was used for reference and the images were comprehensively interpreted. Ischemia was diagnosed when one or more of the doctors pointed out a reversible defect. On the other hand, a scar was diagnosed

when the defect was not reversible.

Conventional CAG

When patients had severe coronary calcifications with coronary artery calcium (CAC) scores ≥ 400 Agatston units, an irregular heart rhythm, advanced renal dysfunction, or severe stenosis on MDCT coronary angiography, we aggressively conducted conventional CAG to assess the coronary arteries. Conventional CAG images were interpreted by two experienced cardiologists blinded to the detailed patient characteristics in a usual clinical setting.

64-slice MDCT

In the absence of contraindications, the patients who had myocardial perfusion abnormalities underwent MDCT tests to determine their CAC scores followed by coronary angiography. The imaging was performed using 64-slice MDCT with a slice thickness of 0.5 mm (Aquilion64; Toshiba Medical Systems, Otawara, Japan). If necessary and tolerated, oral beta-blockers (metoprolol 40 mg to 100 mg) were provided before the scan to achieve a heart rate < 60 beats/min. We performed a nonenhanced prospective electrocardiographically gated scan to measure the CAC scores, which were calculated using the Agatston method[27]. The MDCT coronary angiography was performed using 64 × 0.5 mm collimation and retrospective

electrocardiographic gating. MDCT images were interpreted by an experienced cardiologist in cooperation with radiologists who were unaware of the detailed clinical backgrounds in a usual clinical setting. All the coronary arteries and side branches with a luminal diameter ≥ 2.0 mm were assessed.

Other Measurements

The rest and exercise stress ECG tests were assessed by a trained cardiologist who had no knowledge of the clinical findings of the patients. We diagnosed an abnormality on the rest ECG findings if ST segment abnormalities, T wave abnormalities, an abnormal Q wave, or a complete left bundle branch block were observed; ischemia was diagnosed on an exercise stress ECG if the exercise induced any ischemic changes.

We measured the ABI to evaluate PAD and the brachial-ankle pulse wave velocity (baPWV) to assess the presence of arteriosclerosis in the peripheral arteries (Form PWV/ABI; Colin Company, Komaki, Japan).[28] The lowest ABI and the highest baPWV for the left and right sides were used in subsequent analyses.

To estimate cardiac function such as the ejection fraction and the wall motion, we conducted an echocardiography examination (Aplio 80; Toshiba Medical Systems, Otawara, Japan). The examinations were performed by a trained ultrasonographer and cardiologist who had no

knowledge of the patients' clinical information. Doppler echocardiography was also performed to assess the peak Doppler velocities of the early (E) and late diastolic flows (A), the deceleration time (DT), and the E/A ratio for the mitral inflow. Moreover, tissue Doppler imaging of the mitral annulus was measured from the apical 4-chamber view. A sample volume was placed at the septal mitral annulus and the early (E') diastolic velocity was measured. We analyzed the E/E' ratio to assess the cardiac function.[29]

The carotid intima-media thickness (IMT) was evaluated using high-resolution B-mode ultrasound with a 10-MHz linear transducer (Aplio XG; Toshiba Medical Systems, Otawara, Japan).[30] A trained ultrasonographer and a doctor or a skilled doctor alone who were unaware of the patient' characteristics assessed the maximum carotid IMT. The maximum carotid IMT was defined as the thickest IMT for the left and right sides from the common carotid artery to the internal carotid artery.

Statistical Methods

Data are presented as the number (%), mean with standard deviation (SD), and median with lower and upper ends of the interquartile range (IQR). Continuous variables were compared using t tests and Wilcoxon rank sum tests. Categorical variables were compared using chi-square tests. A multivariate logistic-regression analysis of coronary risk factors, such as age,

sex, overweight or obesity, current smoking habit, hypertension, and dyslipidemia, was performed to identify coronary risk factors associated with asymptomatic CHD. P values < 0.05 according to a two sided test were considered statistically significant for all the tests. All analyses were performed using Stata software, version 11.1 (Stata Corp, College Station, Texas).

RESULTS

A total of 1008 patients with type 2 diabetes between the ages of 40 and 75 years were screened, and 219 met the inclusion criteria for this study. Of the 206 eligible patients without any exclusion criteria, 122 consented to participate (Figure 1). The clinical characteristics of this study population are presented in Table 1. The mean age was 64.1 ± 8.3 years, and 84 (68%) were men, and the mean A1C was 7.7 ± 1.5 %. The numbers of patients with PDR or after photocoagulation, renal dysfunction, PAD, and cerebrovascular disease were 76 (62%), 25 (20%), 21 (17%), and 46 (37%), respectively.

Of the 122 patients, 96 (79%) had myocardial perfusion abnormalities on stress SPECT: 70 (58%) had ischemia and 26 (21%) had scar. Of the 96 patients with myocardial perfusion abnormalities, 42 underwent conventional CAG, 83 underwent MDCT coronary angiography, and 39 underwent both examinations. Ten patients did not undergo either MDCT coronary angiography or CAG and were excluded from the analysis to determine the prevalence of asymptomatic CHD. Of the 112 patients who completed the study protocol, 59 (53%) had asymptomatic CHD (Figure 2A). Thus, more than half of the patients who met any one of the four inclusion criteria for vascular complications had asymptomatic CHD (Figure 2B). The prevalences of asymptomatic CHD among the patients who met only one criteria and among the patients who met more than one of the four inclusion criteria for vascular complications were not significantly different (P = 0.50). The prevalence of asymptomatic CHD in patients with

myocardial perfusion abnormalities on stress SPECT are shown in Figure 2C. The prevalences of asymptomatic CHD among patients with ischemia and among those with scar were not significantly different. The CAC scores for the patients with and for those without asymptomatic CHD were significantly different (Figure 2D).

The majority of patients with asymptomatic CHD had multivessel disease. 59 Patients with asymptomatic CHD had 1.8 ± 0.8 vessels with ≥ 50% diameter stenosis: 24 (41%) patients had one-vessel disease, 22 (37%) had two-vessel disease, and 13 (22%) had three-vessel disease or left main disease. The maximum percent diameter stenosis in patients with asymptomatic CHD is also assessed. 42 (71%) Patients had ≥ 75% diameter stenosis and 24 (41%) had ≥ 90% diameter stenosis. The analyses of the clinical variables among the patients with and those without asymptomatic CHD are shown in Table 2. Men, a current smoking habit, age at the time of diabetes diagnosis, the ejection fraction, the E/A ratio, the maximum carotid IMT, and the CAC scores differed significantly between the two groups in a univariate analysis. However, abnormal findings on the rest ECG, ischemic findings on the exercise stress ECG, and abnormal wall motion on echocardiography were not significantly different. When a multivariate logistic-regression analysis was performed to identify coronary risk factors independently associated with asymptomatic CHD, the only significant predictor was a male sex (odds ratio, 6.18; 95% confidence interval, 2.30 to 16.64; $P < 0.001$). The result was similar when the

duration of diabetes was added to the multivariate analysis.

DISCUSSION

This study reports that many type 2 diabetic patients with vascular complications have asymptomatic CHD with multivessel disease and severe stenosis in addition to myocardial ischemia on stress SPECT. Moreover, asymptomatic CHD was detected in more than half of the patients who met any one of the four inclusion criteria for vascular complications. The association found between asymptomatic CHD and PAD in type 2 diabetic patients was similar to the association discovered in the previous study in which myocardial scintigraphy and coronary angiography were used to examine diabetic patients for the presence of silent coronary stenosis.[20] Many past studies have reported that some diabetic patients have asymptomatic CHD. However, under which conditions the diabetic patients were most likely to have asymptomatic CHD was unclear. We demonstrated that type 2 diabetic patients with advanced microvascular or macrovascular diseases had a far greater prevalence of myocardial perfusion abnormalities and asymptomatic CHDs, compared with previous data.[5, 6] Because the diabetic complications had progressed, the patients might have had severe autonomic denervation of the heart,

accounting for their asymptomatic presentation.[31] The statistical analysis revealed that asymptomatic CHD was more common among men than among women. However, other coronary risk factors were not associated with asymptomatic CHD. These results may be similar to those of previous studies.[5, 6] Thus, traditional coronary risk factors might not be effective in screening for asymptomatic CHD among type 2 diabetic patients. We could not fully examine the CAC score (n=83) and the maximum IMT (n=81) in 122 patients. However, the results of the supplemental analyses showed that both the CAC score and maximum carotid IMT were significant predictors when each factor was separately included in the multivariate analysis (CAC scores and maximum carotid IMT values for the analyses were available for 83 subjects and 75 subjects, respectively, and the p-value was 0.034 and 0.036, respectively). Further research will be required to identify possibly useful markers such as the ejection fraction, E/A ratio, maximum carotid IMT, and CAC scores.

Importantly, some patients without significant coronary stenosis exhibited abnormal findings, such as ischemia on stress ECG, abnormal wall motion on echocardiography, or myocardial perfusion abnormalities on stress SPECT. Although these facts might suggest the possibility of false-positive results, coronary microvascular dysfunction may be responsible for cardiac disorders because the patients had many coronary microvascular risk factors, such as diabetes, cigarette smoking, dyslipidemia, and hypertension.[32, 33] Further investigation is needed for

coronary microvascular dysfunction.

Our study had several limitations. Firstly, this study was performed at a single center and was limited to a specific geographical area. Thus, large-scale studies at multiple centers throughout the world will be necessary to confirm these results. However, we believe that this is an extremely important study that may lead to numerous future trials and that may have a large influence on diabetic management. Secondly, we did not perform further tests in patients with normal myocardial perfusion on stress SPECT. Therefore, some patients with normal myocardial perfusion might have had asymptomatic CHD. However, stress SPECT has a very high sensitivity for CHD and affects the decisions regarding future treatment.[34] Consequently, this diagnostic approach may enable unnecessary angiography to be effectively avoided. Thirdly, the coronary arteries in some of the patients were evaluated using MDCT coronary angiography alone. In large-scale studies, a high rate of agreement between MDCT coronary angiography and conventional CAG has been confirmed.[35] Furthermore, conventional CAG was performed in most of the severe calcification cases with CAC scores ≥400 Agatston units, which could be problematic for MDCT coronary angiography.[36] The median CAC scores in the 44 patients who underwent MDCT coronary angiography alone was 149.0 (14.1-383.4) Agatston units. Thus, we assumed that the diagnosis of CHD was accurate. Fourthly, our approach based on image information representing anatomic rather than functional aspects possibly misses some of the

ischemic changes of CHD and this may explain the lack between vasculopathy and asymptomatic CHD observed in our current survey. Lastly, we had only 21 subjects with PAD and that may be because of the relatively low prevalence of isolated PAD (e.g., PAD without CHD) in the Japanese population, and, in fact, a paper from Japan reported that around half of the patients with PAD in their study also had CHD.[37] The high mean PWV values possibly reflected advanced arteriosclerosis of the subjects. In addition, it should be mentioned that the renal function did not worsen in any of the patients after coronary angiography and MDCT in this series of observations.

In conclusion, this study revealed that asymptomatic CHD with myocardial perfusion abnormalities was detected in more than half of the type 2 diabetic patients with vascular complications. A relationship between CHD and sudden cardiac death has been revealed,[38] and we expect that the results of this study may contribute greatly to reducing myocardial infarction and sudden cardiac death among type 2 diabetic patients. However, the best approach to treating asymptomatic CHD remains unknown. Therefore, randomized controlled trials are needed to determine the optimal management.

Contributors: TT conceived the study. TT, MH and MN designed the protocol. MH, MM and KK evaluated the SPECT images. MKa and MH evaluated the coronary angiography images.

TT, HK, YT, MKi, HN and RYH contributed to the data collection and the preparation. TT and TS analyzed all the data. All the authors contributed to the interpretation of the results and approved the final version.

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Competing interests: None declared.

Ethical approval: This study was approved by the institutional review boards by the National Center for Global Health and Medicine in Tokyo, Japan.

Data sharing: No additional data available.

References

1.Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. *N Engl J Med*. 1998;**339**:229-34.

2.Sorajja P, Chareonthaitawee P, Rajagopalan N, et al. Improved survival in asymptomatic diabetic patients with high-risk SPECT imaging treated with coronary artery bypass grafting. *Circulation*. 2005;**112**:I311-6.

3.Faglia E, Manuela M, Antonella Q, et al. Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. *Am Heart J*. 2005;**149**:e1-6.

4.Young LH, Wackers FJ, Chyun DA, et al. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. *JAMA*. 2009;**301**:1547-55.

5.Wackers FJ, Young LH, Inzucchi SE, et al. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. *Diabetes Care*. 2004;**27**:1954-61.

6.Scognamiglio R, Negut C, Ramondo A, et al. Detection of coronary artery disease in asymptomatic patients with type 2 diabetes mellitus. *J Am Coll Cardiol*. 2006;**47**:65-71.

7.Rajala U, Pajunpaa H, Koskela P, et al. High cardiovascular disease mortality in subjects with visual impairment caused by diabetic retinopathy. *Diabetes Care*. 2000;**23**:957-61.

8.Chew EY, Ferris FL, 3rd, Csaky KG, et al. The long-term effects of laser photocoagulation treatment in patients with diabetic retinopathy: the early treatment diabetic retinopathy follow-up study. *Ophthalmology*. 2003;**110**:1683-9.

9.van Hecke MV, Dekker JM, Stehouwer CD, et al. Diabetic retinopathy is associated with mortality and cardiovascular disease incidence: the EURODIAB prospective complications study. *Diabetes Care*. 2005;**28**:1383-9.

10.Cheung N, Wang JJ, Klein R, et al. Diabetic retinopathy and the risk of coronary heart disease: the Atherosclerosis Risk in Communities Study. *Diabetes Care*. 2007;**30**:1742-6.

11.Targher G, Bertolini L, Zenari L, et al. Diabetic retinopathy is associated with an increased incidence of cardiovascular events in Type 2 diabetic patients. *Diabet Med*. 2008;**25**:45-50.

12.Adler AI, Stevens RJ, Manley SE, et al. Development and progression of nephropathy in type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS 64). *Kidney Int*. 2003;**63**:225-32.

13.Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med*. 2004;**351**:1296-305.

14.Patel UD, Young EW, Ojo AO, et al. CKD progression and mortality among older patients with diabetes. *Am J Kidney Dis*. 2005;**46**:406-14.

15.Tonelli M, Wiebe N, Culleton B, et al. Chronic kidney disease and mortality risk: a systematic review. *J Am Soc Nephrol*. 2006;**17**:2034-47.

16.Sukhija R, Aronow WS, Kakar P, et al. Relation of microalbuminuria and coronary artery disease in patients with and without diabetes mellitus. *Am J Cardiol*. 2006;**98**:279-81.

17.Tonelli M, Jose P, Curhan G, et al. Proteinuria, impaired kidney function, and adverse outcomes in people with coronary disease: analysis of a previously conducted randomised trial. *BMJ*. 2006;**332**:1426.

18.Hallan S, Astor B, Romundstad S, et al. Association of kidney function and albuminuria with cardiovascular mortality in older vs younger individuals: The HUNT II Study. *Arch Intern Med*. 2007;**167**:2490-6.

19.Janand-Delenne B, Savin B, Habib G, et al. Silent myocardial ischemia in patients with diabetes: who to screen. *Diabetes Care*. 1999;**22**:1396-400.

20.Cosson E, Guimfack M, Paries J, et al. Are silent coronary stenoses predictable in diabetic patients and predictive of cardiovascular events? *Diabetes Metab*. 2003;**29**:470-6.

21.Nesto RW, Watson FS, Kowalchuk GJ, et al. Silent myocardial ischemia and infarction in diabetics with peripheral vascular disease: assessment by dipyridamole thallium-201 scintigraphy. *Am Heart J*. 1990;**120**:1073-7.

22.Doobay AV, Anand SS. Sensitivity and specificity of the ankle-brachial index to predict future cardiovascular outcomes: a systematic review. *Arterioscler Thromb Vasc Biol*. 2005;**25**:1463-9.

23.Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease: morbidity and mortality implications. *Circulation*. 2006;**114**:688-99.

24.Bhatt DL, Steg PG, Ohman EM, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. *JAMA*. 2006;**295**:180-9.

25.Matsuo S, Imai E, Horio M, et al. Revised equations for estimated GFR from serum creatinine in Japan. *Am J Kidney Dis*. 2009;**53**:982-92.

26.Austen WG, Edwards JE, Frye RL, et al. A reporting system on patients evaluated for coronary artery disease. Report of the Ad Hoc Committee for Grading of Coronary Artery Disease, Council on Cardiovascular Surgery, American Heart Association. *Circulation*. 1975;**51**:5-40.

27.Agatston AS, Janowitz WR, Hildner FJ, et al. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol*. 1990;**15**:827-32.

28.Koji Y, Tomiyama H, Ichihashi H, et al. Comparison of ankle-brachial pressure index and pulse wave velocity as markers of the presence of coronary artery disease in subjects with a high risk of atherosclerotic cardiovascular disease. *Am J Cardiol*. 2004;**94**:868-72.

29.Ommen SR, Nishimura RA, Appleton CP, et al. Clinical utility of Doppler echocardiography and tissue Doppler imaging in the estimation of left ventricular filling pressures: A comparative simultaneous Doppler-catheterization study. *Circulation*. 2000;**102**:1788-94.

30.O'Leary DH, Polak JF, Kronmal RA, et al. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study

Collaborative Research Group. *N Engl J Med*. 1999;**340**:14-22.

31. Niakan E, Harati Y, Rolak LA, et al. Silent myocardial infarction and diabetic cardiovascular autonomic neuropathy. *Arch Intern Med*. 1986;**146**:2229-30.

32. Nitenberg A, Valensi P, Sachs R, et al. Impairment of coronary vascular reserve and ACh-induced coronary vasodilation in diabetic patients with angiographically normal coronary arteries and normal left ventricular systolic function. *Diabetes*. 1993;**42**:1017-25.

33. Camici PG, Crea F. Coronary microvascular dysfunction. *N Engl J Med*. 2007;**356**:830-40.

34. Hachamovitch R, Hayes SW, Friedman JD, et al. Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation*. 2003;**107**:2900-7.

35. Miller JM, Rochitte CE, Dewey M, et al. Diagnostic performance of coronary angiography by 64-row CT. *N Engl J Med*. 2008;**359**:2324-36.

36. Budoff MJ, Dowe D, Jollis JG, et al. Diagnostic performance of 64-multidetector row coronary computed tomographic angiography for evaluation of coronary artery stenosis in individuals without known coronary artery disease: results from the prospective multicenter ACCURACY (Assessment by Coronary Computed Tomographic Angiography of Individuals Undergoing Invasive Coronary Angiography) trial. *J Am Coll Cardiol*.

2008;**52**:1724-32.

37.Iwashima Y, Horio T, Suzuki Y, et al. Adiponectin and inflammatory markers in peripheral arterial occlusive disease. *Atherosclerosis*. 2006;**188**:384-90.

38.Zheng ZJ, Croft JB, Giles WH, et al. Sudden cardiac death in the United States, 1989 to 1998. *Circulation*. 2001;**104**:2158-63.

Figure legends

Figure 1. Flowchart of Study Participants.

Figure 2. Prevalence of Myocardial Perfusion Abnormalities and Asymptomatic CHD (A). Prevalence of Asymptomatic CHD for Each of the Vascular Complications (B). Prevalence of Asymptomatic CHD in Patients with Ischemia or Scar (C). CAC Scores in Patients With or Without Asymptomatic CHD (D).

CHD = coronary heart disease, CAC = coronary artery calcium, PDR = proliferative diabetic retinopathy, GFR = glomerular filtration rate, and PAD = peripheral arterial disease.

Table 1 Characteristics of Study Population*

	N	All	Men	Women
		122	84 (69%)	38 (31%)
Age (y.o.)	122	64.1 (8.3)	63.9 (8.3)	64.6 (8.5)
Weight (kg)	122	64.6 (12.4)	66.7 (12.1)	60.1 (12.2)
Body-mass index (kg/m²)†	122	24.5 (4.0)	24.3 (3.7)	25.1 (4.5)
Waist (cm)	112	90.3 (11.2)	89.8 (10.7)	91.5 (12.5)
Smoking	122			
Non		47 (39%)	16 (18%)	31 (82%)
Former		37 (30%)	34 (41%)	3 (8%)
Current		38 (31%)	34 (41%)	4 (10%)
History of cerebrovascular disease§	122	46 (37%)	32 (38%)	14 (36%)
Duration of diabetes (years)	122	16.0 (10.2)	16.5 (9.8)	15.2 (11.1)
Age at the time of diabetes diagnosis (y.o.)	122	49.0 (12.2)	48.4 (11.8)	50.4 (13.1)
Any diabetic retinopathy	122	97 (79%)	67 (79%)	30 (79%)
PDR or after photocoagulation	122	76 (62%)	50 (59%)	26 (68%)
A1C (%)	122	7.7 (1.5)	7.8 (1.7)	7.5 (1.2)
Treatment for diabetes	122			
Diet		7 (6%)	7 (8%)	0 (0%)

Oral agents		59 (48%)	37 (44%)	22 (58%)
Insulin		15 (12%)	13 (16%)	2 (5%)
Insulin + Oral agents¶		41 (34%)	21 (32%)	14 (37%)
Hypertension‖	122	95 (77%)	66 (78%)	29 (76%)
Treatment: ARB/ACE-I		88 (72%)	61 (72%)	27 (71%)
CCB		55 (45%)	37 (44%)	18 (47%)
Diuretics		16 (13%)	9 (10%)	7 (18%)
Others		4 (3%)	3 (3%)	1 (2%)
Dyslipidemia**	122	90 (73%)	60 (71%)	30 (79%)
Total cholesterol (mg/dL)		192.7 (39.0)	194.7 (42.4)	188.3 (30.9)
LDL cholesterol (mg/dL)		115.6 (40.5)	119.6 (43.8)	106.5 (30.4)
HDL cholesterol (mg/dL)		52.4 (14.8)	51.1 (13.5)	55.3 (17.2)
Triglyceride (mg/dL)		143.3 (85.9)	142.7 (86.1)	144.6 (86.7)
LDL/HDL ratio		2.4 (1.1)	2.5 (1.1)	2.2 (0.9)
Treatment: Statin		47 (38%)	25 (29%)	22 (57%)
Others		9 (7%)	7 (8%)	2 (5%)
Use of aspirin	122	33 (27%)	23 (27%)	10 (26%)
Creatinine (mg/dL)	120	1.04 (0.60)	1.08 (0.60)	0.94 (0.60)

Estimated GFR (mL/min/1.73 m²)	120	62.1 (22.0)	63.3 (20.4)	59.7 (25.4)
< 45		28 (23%)	17 (20%)	11 (28%)
< 30		10 (8%)	5 (6%)	5 (13%)
Use of hemodialysis	2	2 (1%)	2 (2%)	0 (0%)
Albuminuria (mg/day or mg/g of creatinine)	117			
< 30		32 (27%)	16 (20%)	16 (45%)
30-299		40 (34%)	28 (34%)	12 (33%)
≥ 300		45 (39%)	37 (46%)	8 (22%)
Renal dysfunction††	122	25 (20%)	17 (20%)	8 (21%)
Brain natriuretic peptide (pg/mL)	113	37.2 (26.1-48.2)	19.4 (7.5-47.5)	24.8 (11-39.8)
Rest ECG				
Any abnormal findings	122	27 (22%)	19 (22%)	8 (21%)
Abnormal Q wave changes		3 (2%)	2 (2%)	1 (2%)
Ischemic findings on exercise stress ECG	64	25 (39%)	15 (36%)	10 (43%)
Cardio thoracic ratio on chest x-ray (%)	113	48.0 (4.4)	47.6 (4.5)	48.9 (4.0)
ABI	122	1.07 (0.17)	1.06 (0.18)	1.09 (0.17)
baPWV (cm/sec)	108	2012.2 (377.3)	1940.5 (300.3)	2168.3 (474.8)
PAD	122	21 (17%)	17 (20%)	4 (10%)

Echocardiography‡‡				
Ejection fraction (%)	108	67.3 (8.6)	66.4 (9.5)	69.4 (6.0)
Septal + posterior wall thickness (mm)	108	21.2 (3.4)	21.3 (3.4)	20.9 (3.4)
> 25		10 (9%)	6 (8%)	4 (11%)
E/A ratio	107	0.76 (0.21)	0.77 (0.17)	0.75 (0.28)
DT (msec)	107	236.4 (59.1)	232.6 (60.5)	244.6 (56.0)
E/E' ratio	96	11.3 (3.4)	11.0 (2.86)	12.1 (4.35)
Abnormal wall motion	108	6 (5%)	6 (8%)	0 (0%)
Ultrasound of carotid artery	81			
Maximum carotid IMT (mm)		1.78 (1.07)	1.97 (1.13)	1.39 (0.86)
≥ 1.1		53 (67%)	41 (77%)	12 (46%)
CAC scores (Agatston units)	83	216.8 (52.0-602.7)	300.4 (65.6-1201.2)	110.9 (0-275.8)

* Data are number, number (%), mean (SD), or median (IQR). To convert the values for cholesterol and triglycerides to millimoles per liter (mmol/L), multiply by 0.02586 and 0.01129, respectively. PDR = proliferative diabetic retinopathy, ARB = angiotensin II receptor blockers, ACE-I = angiotensin converting enzyme inhibitors, CCB = Calcium channel blockers, LDL = low-density lipoprotein, HDL = high-density lipoprotein, GFR = glomerular filtration rate, ECG = electrocardiogram, ABI = ankle-brachial index, baPWV = brachial-ankle pulse wave velocity, PAD = peripheral arterial disease, DT = deceleration time, IMT = intima-media thickness, CAC = coronary artery calcium.

† Body-mass index was calculated as the weight in kilograms divided by the square of height in meters.

§ Cerebrovascular disease was defined as stroke or transient ischemic attack.

¶ Oral agents for the treatment of diabetes included metformin, sulfonylureas, thiazolidinediones, meglitinides, and alpha-glucosidase inhibitors.

‖ Hypertension was defined as a systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or the use of antihypertensive medication.

** Dyslipidemia was defined as LDL ≥ 140 mg/dL, HDL < 40 mg/dL, or the use of lipid-lowering drug.

†† Renal dysfunction was defined as the estimated GFR < 30 mL/min/1.73 m^2 or the estimated GFR < 45 mL/min/1.73 m^2 plus albuminuria which was ≥ 30 mg/day or ≥ 30 mg/g of creatinine.

‡‡ E/A ratio was the ratio of the peak Doppler velocities of early to late diastolic flow in the mitral inflow. E/E' ratio was the ratio of the peak Doppler velocities of early in the mitral inflow to the early diastolic velocity at the septal mitral annulus.

Table 2 Analyses of Clinical Variables for Asymptomatic CHD

Univariate Analysis

Variable	Asymptomatic CHD (+)	Asymptomatic CHD (-)	P value
	59 (53%)	53 (47%)	
Men	51 (86%)	26 (49%)	< 0.001
Age (y.o.)	62.4 (8.8)	65.3 (7.7)	0.07
Weight (kg)	65.3 (12.9)	64.7 (12.7)	0.79
Body-mass index (kg/m^2)	24.0 (3.4)	25.3 (4.6)	0.08
Waist (cm)	90.0 (11.4)	91.1 (11.9)	0.60
Current smoker	26 (44%)	10 (18%)	0.004
History of cerebrovascular disease	22 (37%)	21 (39%)	0.80
Duration of diabetes (years)	16.7 (10.5)	14.9 (10.0)	0.34
Age at the time of diabetes diagnosis (y.o.)	46.7 (12.2)	51.4 (11.9)	0.04
Any diabetic retinopathy	46 (78%)	42 (79%)	0.86
PDR or after photocoagulation	36 (61%)	34 (64%)	0.73
A1C (%)	7.3 (1.5)	7.4 (1.6)	0.76
Use of insulin	33 (55%)	21 (39%)	0.08
Hypertension	46 (78%)	40 (75%)	0.75
Dyslipidemia	45 (76%)	39 (73%)	0.74

Total cholesterol (mg/dL)	192.8 (38.4)	196.0 (39.5)	0.67
LDL cholesterol (mg/dL)	113.0 (36.6)	120.0 (38.5)	0.33
HDL cholesterol (mg/dL)	50.7 (13.7)	53.5 (15.7)	0.32
Triglyceride (mg/dL)	151.5 (89.0)	136.6 (82.3)	0.36
LDL/HDL ratio	2.4 (1.0)	2.4 (1.0)	0.85
Use of statin	21 (35%)	22 (41%)	0.52
Use of aspirin	16 (27%)	15 (28%)	0.88
Creatinine (mg/dL)	1.03 (0.60)	0.87 (0.35)	0.09
GFR (mL/min/1.73 m^2)	63.9 (20.7)	65.2 (20.0)	0.74
< 45	13 (22%)	9 (17%)	0.50
< 30	2 (3%)	3 (5%)	0.56
Albuminuria ≥ 30 (mg/day or mg/g of creatinine)	43 (76%)	32 (62%)	0.11
Brain natriuretic peptide (pg/mL)	20.7 (7.6-35.4)	17.4 (9.5-42.9)	0.99
Rest ECG			
Ischemic findings on exercise stress ECG	12 (41%)	10 (35%)	0.66
Cardio thoracic ratio on chest x-ray (%)	47.3 (4.4)	48.8 (4.1)	0.08
ABI	1.06 (0.20)	1.06 (0.15)	0.98
baPWV (cm/sec)	1955.3 (306.4)	2067.4 (448.7)	0.14

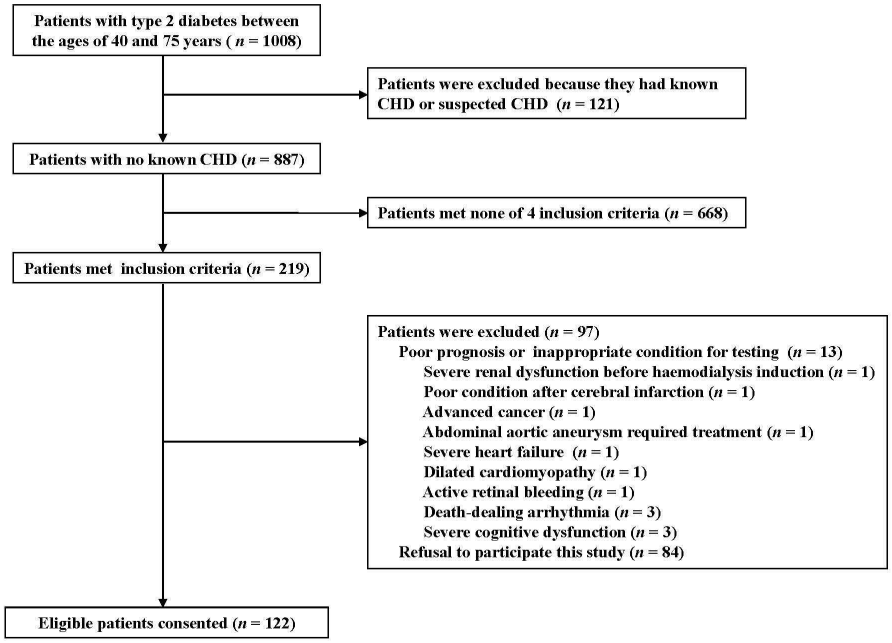
PAD	12 (22%)	8 (16%)	0.42
Echocardiography			
Ejection fraction (%)	65.6 (9.1)	69.0 (8.0)	0.04
Septal wall + posterior wall thickness (mm)	20.8 (3.7)	21.2 (3.0)	0.55
E/A ratio	0.81 (0.16)	0.71 (0.24)	0.02
DT (msec)	225.7 (58.2)	247.5 (61.9)	0.07
E/E' ratio	10.8 (3.3)	11.8 (3.2)	0.15
Abnormal wall motion	4 (7%)	2 (4%)	0.47
Ultrasound of carotid artery			
Maximum carotid IMT (mm)	2.11 (1.30)	1.41 (0.70)	0.005
≥ 1.1	28 (75%)	20 (55%)	0.07
CAC scores (Agatston units)	349.8 (99.6-1229.1)	133.2 (0.0-359.0)	0.003

Multivariate Analysis

Variable	Odds Ratio	95% Confidence interval	P value
Men	6.18	2.30 to 16.64	<0.001
Age (y.o.)	0.94	0.89 to 1.00	0.07
Body-mass index ≥25	0.49	0.20 to 1.23	0.13

Current smoking	2.05	0.75 to 5.54	0.15
Hypertension	1.26	0.45 to 3.50	0.65
Dyslipidemia	2.16	0.77 to 6.05	0.14

Data are number (%), mean (SD), median (IQR), odds ratio, or 95% CI. To convert the values for cholesterol and triglycerides to millimoles per liter (mmol/L), multiply by 0.02586 and 0.01129, respectively. CHD = coronary heart disease, PDR = proliferative diabetic retinopathy, ARB = angiotensin II receptor blockers, ACE-I = angiotensin converting enzyme inhibitors, CCB = Calcium channel blockers, LDL = low-density lipoprotein, HDL = high-density lipoprotein, GFR = glomerular filtration rate, ECG = electrocardiogram, ABI = ankle-brachial index, baPWV = brachial-ankle pulse wave velocity, PAD = peripheral arterial disease, DT = the deceleration time, IMT = intima-media thickness, CAC = coronary artery calcium.



169x127mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.