VIA MEDICA
ORIGINAL ARTICLE
Cardiology Journal
2009, Vol. 16, No. 2, pp. 121–126

ISSN 1897–5593

Adenosine-induced ST segment depression with normal perfusion

Fadi G. Hage, Jaekyeong Heo, Ami E. Iskandrian

Division of Cardiovascular Disease, Department of Medicine,
University of Alabama at Birmingham, Birmingham, Alabama, USA

Abstract

Background: *Intravenous adenosine in conjunction with myocardial perfusion imaging is commonly used for the detection of coronary artery disease and risk assessment. We have previously shown that patients with ischemic changes on the 12-lead electrocardiogram (ECG) in response to adenosine but with normal perfusion pattern have a benign outcome on short-intermediate follow-up. The long-term outcome of these patients is unknown.*

Methods: *Patients with ischemic ECG response (≥ 1 mm ST depression) to adenosine infusion but with normal perfusion on single-photon emission computed tomography (SPECT) imaging in the absence of a history of myocardial infarction or coronary revascularization were followed up for mortality, myocardial infarctions, and coronary revascularization.*

Results: *The cohort consisted of 73 patients (81% women) who were followed up for mortality for a mean of 61 ± 15 months. There were 10 deaths, and the cause of death was determined to be non-cardiac in half of those. Follow-up for the other endpoints was complete for 21 ± 10 months during which no patient had myocardial infarction and seven underwent coronary revascularization.*

Conclusions: *Patients with ischemic ECG response to intravenous adenosine administration and normal perfusion on SPECT are at low risk of cardiovascular events. The ST segment response to adenosine in this setting is likely related to non-ischemic mechanisms.* (Cardiol J 2009; 16, 2: 121–126)

Key words: adenosine, stress test, ST depression, electrocardiogram, perfusion, imaging

Editorial p. 101

Introduction

Myocardial perfusion imaging using single-photon emission computed tomography (SPECT) is widely used both for the detection of coronary artery disease and for risk assessment [1]. In the United States, more than one third of all SPECT imaging is done using coronary vasodilators, most commonly with intravenous adenosine [2]. The risk of death or myocardial infarction in patients with normal images after adenosine has been shown to be around 1% per year [3–5], slightly higher than the risk in patients with normal exercise perfusion images [6–8], which is probably related to the higher cardiovascular risk profile of this patient population. Most patients with ST segment depression noted on the electrocardiogram (ECG) after adenosine

Address for correspondence: Fadi G. Hage, MD, Zeigler Research Bldg 1024, 1530 3RD AVE S, Birmingham, AL 35294-0007, USA, tel: 205 934 2580, fax: 205 934 0424, e-mail: fadihage@uab.edu

Received: 29.09.2008 Accepted: 26.10.2008

infusion have reversible perfusion defects [9]. Although it has been suggested that patients with ischemic ECG changes during adenosine infusion but with normal perfusion on SPECT images are at increased risk [10, 11], we have previously demonstrated that this population has a benign outcome on short to intermediate follow-up [12]. We report here on the largest cohort in the literature of such patients, and show that on long-term follow-up these patients continue to be at low risk.

Methods

We studied patients with ischemic ST segment response to adenosine but with normal perfusion on SPECT imaging (Fig. 1). We previously reported the short-term outcome in a subset of these patients [12]. Patients were included if they underwent adenosine SPECT at the University of Alabama at Birmingham Nuclear Cardiology Laboratory between May 2001 and July 2003. Exclusion criteria included prior myocardial infarction, prior coronary revascularization, or the presence of left bundle branch block, non-sinus rhythm, or paced rhythm in resting ECG. Patients who were taking digitalis or had ST/T wave abnormalities that preclude the interpretation of the stress ECG response were also excluded.

Adenosine was administered intravenously at a standard infusion rate of 140 μg/kg/min for five minutes. No exercise was done during the infusion. Technetium-99m sestamibi or tetrofosmin was injected at 3 min into the adenosine infusion. The SPECT gated images were acquired with an elliptical 180° acquisition using a dual head detector (45° RAO to 45° LAO) and 8 frames per R-R cycle as previously described [12]. The perfusion images were interpreted visually without attenuation correction, and quantitative analysis (polar images) was used to supplement the visual analysis. The left ventricular ejection fraction was measured by the method of Germano et al. [13].

A standard 12-lead ECG was performed on the same day and prior to the adenosine infusion. ECG was monitored continuously during infusion and a 12-lead ECG was printed every minute. An ischemic response was defined as 1 mm or greater flat or down-sloping ST segment depression, or a 1.5 mm or greater up-sloping ST segment depression in two or more contiguous leads at 80 ms from the J point using the TP segment as the isoelectric reference in accordance with accepted guidelines [14]. The changes had to normalize after the termination of the infusion. The physician reading the ECGs was blinded to the perfusion on SPECT imaging.

Follow-up was performed for all patients by a single physician. Outcomes of interest included cardiac death, non-fatal myocardial infarction, percutaneous coronary intervention, coronary artery bypass grafting, or death from any cause. The outcomes were determined by reviewing the medical records or by telephone interviews with the patients, or if the patient was deceased, with a first degree relative. Mortality was established by conducting a search of the US Social Security Death Master File for the entire cohort on 15 February 2008.

All statistical analyses were performed using the SPSS® version 11.5 for Windows® (SPSS® Inc., Chicago, IL). Categorical data were presented as frequencies and continuous variables were presented as means ± standard deviations. The survival curve was constructed using the product-limit method (Kaplan-Meier).

The institutional review board for human research at the University of Alabama at Birmingham approved the study. There were no complications from this study.

Results

During the specified period, 73 patients satisfied the study protocol and therefore constituted the study cohort. Baseline characteristics of these patients are summarized in Table 1. The left ventricular ejection fraction by gated SPECT was 70 ± ± 11% (range 47–94).

The patients were followed up for mortality for a mean of 61 ± 15 (range 7–79) months. There were 10 deaths. The mean age of the patients at death was 71 ± 14 years. These deaths occurred at a median of 30 (range 7–60) months from the adenosine SPECT studies. The cause of death was documented to be non-cardiac in 5 of these; 4 patients died with metastatic cancers and the 5th patient was 96 years old with end-stage dementia receiving end-of-life hospice care. The cause of death in the other 5 patients was not available to us. The Kaplan-Meier curve for survival of the cohort is shown in Figure 2. Follow-up for myocardial infarction and coronary revascularization was complete for 21 ± ± 10 (range 1–38) months. During follow-up no patient had myocardial infarction. Seven patients underwent coronary revascularization; 4 had percutaneous coronary interventions (for single vessel coronary artery disease), and 3 had coronary artery bypass grafting. The coronary revascularizations were performed at a median of 2 (range 0–24) months after the adenosine SPECT. During a mean

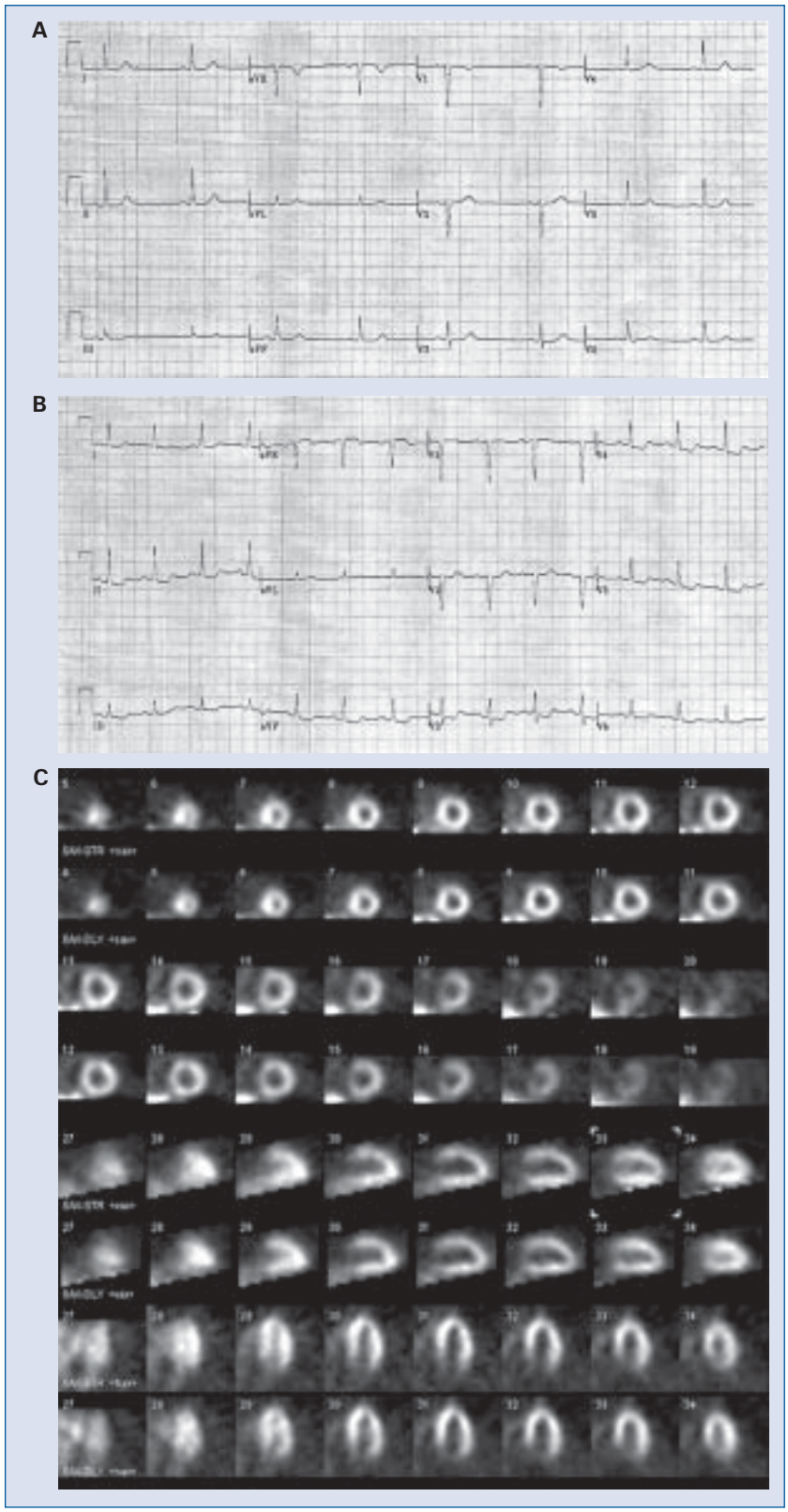

Figure 1. A stress test performed on a 48-year-old woman with renal disease who underwent screening for coronary artery disease; **A.** A 12-lead electrocardiogram at rest shows sinus rhythm with no ST depression; **B.** During adenosine infusion her electrocardiogram demonstrates 1–2 mm down-slopping ST depression in V3–V5 as well as in leads II and aVF; **C.** The adenosine (panels 1, 3, 5 and 7) and rest (remaining panels) SPECT MIBI images demonstrated normal perfusion pattern; the left ventricular ejection fraction was normal (not shown). Over the next 3 years her renal function deteriorated and she is now listed for renal transplantation.

Table 1. Baseline characteristics.

Variable	(n = 73)
Age (years)	65 ± 12
Women	60 (81%)
Diabetes mellitus	20 (27%)
Hypertension	54 (74%)
Beta-blocker therapy	18 (25%)
Calcium channel blocker therapy	25 (34%)
Nitrate therapy	6 (8%)
Prior myocardial infarction	0
Prior coronary revascularization	0
Prior stress myocardial perfusion imaging	12 (16%)
Prior coronary angiography	1 (1%)

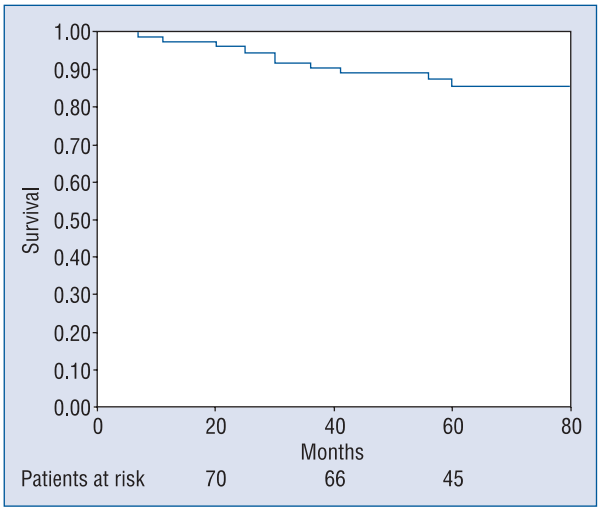

Figure 2. Kaplan-Meier curve showing the survival (from all-cause mortality) of patients with ST segment depression in response to adenosine but with normal perfusion.

follow-up of 5 years, the annual rate of all-cause mortality was 2.7% and cardiovascular mortality was 1.3% or less as the cause of death was unknown in half of the patients. On the other hand, during the mean follow-up of almost 2 years, the annual rates of myocardial infarction and coronary revascularization were 0% and 5.5%, respectively.

Discussion

The aim of this study was to determine the long-term prognosis of patients with ischemic ECG response to intravenous adenosine administration and normal perfusion on SPECT images. We report that in a cohort of 73 patients with these characteristics, the annual cardiovascular mortality during a mean follow-up of 5 years was less than 1.3%. Similarly, the annual rates of myocardial infarctions and coronary revascularization during a shorter follow-up of almost 2 years were 0% and 5.5%, respectively. This study, therefore, re-enforces our previous conclusion that this population is at low risk [12].

Most patients with ST segment depression during adenosine infusion have reversible defects and only a minority demonstrate normal perfusion on imaging [15, 16]. The ST segment depression is thought to represent myocardial ischemia secondary to coronary steal. For this to occur in the setting of normal perfusion images after adenosine administration, a 'perfectly balanced' decrease in perfusion in the coronary artery tree due to a 'perfectly balanced' symmetric distribution of stenotic coronary artery lesions has to occur. This mechanism is hypothetical, but it is widely feared in the cardiovascular community and has been notoriously labelled as 'balanced ischemia'. The high positive predictive value of ST response during adenosine infusion [9, 17–19] has raised the concern that balanced ischemia might be the reason behind the normal images, and that such patients should be considered at high-risk [10, 11]. It is well accepted now that ST segment depression during exercise stress testing does not add prognostic data to perfusion images [20]. In 2003 Abbott et al. [10] reported on 66 patients with ischemic ECG changes and normal perfusion after adenosine stress. During a follow-up period of 29 ± 12 months, 2 patients had cardiac death, 5 patients sustained non-fatal myocardial infarctions, and 9 patients underwent subsequent coronary revascularization. At the same time Klodas et al. [11] reported on 49 patients that they followed for 28 ± 20 months; in this population, the corresponding numbers are 2, 4, and 8 patients. When we examined a similar population of 65 patients from our institution with no prior myocardial infarction or coronary revascularization that we followed for 24 ± 8 months, we observed no cardiac death or myocardial infarction, while 6 patients underwent coronary revascularization [12]. Chow et al. [21] also reported on 72 patients with dipyridamole-induced ischemic ECG changes but normal perfusion using positron emission tomography. At a mean follow-up of 27 ± 13 months there were no cardiac deaths, 1 patient had non-fatal myocardial infarction, and 2 patients underwent coronary revascularization. Given that the conclusions from these studies were different, it is obvious that the rates of events do not match those seen in

patients with 3-vessel or left main coronary artery disease [22, 23] and therefore do not support the original hypothesis of balanced ischemia causing ECG changes, which was missed on perfusion imaging. This conclusion is supported by the benign outcome of these patients on long-term follow-up as shown here. Although false negative SPECT imaging with vasodilators does occur, and it should be suspected in the right clinical setting, the presence of ischemic ECG changes during stress testing does not seem to add to the prognostic power of this test. It should be noted that in the large study by Hachamovitch et al. [24], ischemic ECG changes in response to adenosine did not surface as a predictor of outcome in the overall risk prediction score after adjustments for other variables.

This ischemic ST response to adenosine, despite a normal perfusion pattern on imaging, occurs mostly in women (80–90%), as evidenced by our study and others [10–12, 21]. A similar higher preponderance of false positive ECG changes during exercise stress test in women [25, 26] suggests that there might be an intrinsic gender-related difference in the ST response to exercise as well as to vasodilation. This effect has been attributed to oestrogen [27–29]. To explore this, Henzlova et al. [30] examined the ECG response to exercise in a cohort of women with normal perfusion on SPECT imaging and found that exogenous oestrogen therapy increased the ST segment response to exercise. Several investigators have similarly suggested that oestrogen might have a digoxin-like effect on the ST segment [31–33]. It is therefore reasonable to suggest that the ST segment response to adenosine that is encountered in the setting of normal perfusion on SPECT imaging occurs probably through a non-ischemic mechanism and is more prevalent in women. The benign long-term outcome of our population lends further support to this hypothesis.

Conclusions

In conclusion, patients with ischemic ECG response to intravenous adenosine administration and normal perfusion on SPECT are at low risk of cardiovascular events, even after long-term follow-up. The ST segment response to adenosine, in this setting, is predominantly in females and is likely related to non-ischemic mechanisms.

Acknowledgements

We would like to thank Sulaf J. Mansur, MD for her critical review of the manuscript.

The authors do not report any conflict of interest regarding this work.

References

1. Klocke FJ, Baird MG, Lorell BH et al. Acc/aha/asnc guidelines for the clinical use of cardiac radionuclide imaging — executive summary: A report of the American college of cardiology/American heart association task force on practice guidelines (acc/aha/ /asnc committee to revise the 1995 guidelines for the clinical use of cardiac radionuclide imaging). Circulation, 2003; 108: 1404–1418.
2. Iskandrian AE, Verani MS. Nuclear cardiac imaging: Principles and applications. 3rd Ed. Oxford University Press, Oxford 2003.
3. Amanullah AM, Berman DS, Erel J et al. Incremental prognostic value of adenosine myocardial perfusion single-photon emission computed tomography in women with suspected coronary artery disease. Am J Cardiol, 1998; 82: 725–730.
4. Kamal AM, Fattah AA, Pancholy S et al. Prognostic value of adenosine single-photon emission computed tomographic thallium imaging in medically treated patients with angiographic evidence of coronary artery disease. J Nucl Cardiol, 1994; 1: 254–261.
5. Hachamovitch R, Berman DS, Kiat H et al. Incremental prognostic value of adenosine stress myocardial perfusion single--photon emission computed tomography and impact on subsequent management in patients with or suspected of having myocardial ischemia. Am J Cardiol, 1997; 80: 426–433.
6. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomographic technetium-99m sestamibi imaging. J Am Coll Cardiol, 1998; 32: 57–62.
7. Iskandrian AS, Hakki AH, Kane-Marsch S. Prognostic implications of exercise thallium-201 scintigraphy in patients with suspected or known coronary artery disease. Am Heart J, 1985; 110: 135–143.
8. Iskandrian AS, Hakki AH, Kane-Marsch S. Exercise thallium-201 scintigraphy in men with nondiagnostic exercise electrocardiograms. Prognostic implications. Arch Intern Med, 1986; 146: 2189–2193.
9. Marshall ES, Raichlen JS, Tighe DA, Paul JJ, Breuninger KM, Chung EK. ST-segment depression during adenosine infusion as a predictor of myocardial ischemia. Am Heart J, 1994; 127: 305–311.
10. Abbott BG, Afshar M, Berger AK, Wackers FJ. Prognostic significance of ischemic electrocardiographic changes during adenosine infusion in patients with normal myocardial perfusion imaging. J Nucl Cardiol, 2003; 10: 9–16.
11. Klodas E, Miller TD, Christian TF, Hodge DO, Gibbons RJ. Prognostic significance of ischemic electrocardiographic changes during vasodilator stress testing in patients with normal spect images. J Nucl Cardiol, 2003; 10: 4–8.
12. Hage FG, Dubovsky EV, Heo J, Iskandrian AE. Outcome of patients with adenosine-induced st-segment depression but with normal perfusion on tomographic imaging. Am J Cardiol, 2006; 98: 1009–1011.
13. Germano G, Kavanagh PB, Berman DS: An automatic approach to the analysis, quantitation and review of perfusion and function from myocardial perfusion spect images. Int J Card Imag, 1997; 13: 337–346.
14. Zipes DP, Braunwald E. Braunwald's heart disease: A textbook of cardiovascular medicine. 7th Ed. W.B. Saunders, Philadelphia, 2005.

15. Villanueva FS, Smith WH, Watson DD, Beller GA. St-segment depression during dipyridamole infusion, and its clinical, scintigraphic and hemodynamic correlates. Am J Cardiol, 1992; 69: 445–448.
16. Chambers CE, Brown KA. Dipyridamole-induced st-segment depression during thallium-201 imaging in patients with coronary artery disease: Angiographic and hemodynamic determinants. J Am Coll Cardiol, 1988; 12: 37–41.
17. Ho KT, Miller TD, Christian TF, Hodge DO, Gibbons RJ. Prediction of severe coronary artery disease and long-term outcome in patients undergoing vasodilator spect. J Nucl Cardiol, 2001; 8: 438–444.
18. Iskandrian AS, Heo J, Lemlek J et al. Identification of high-risk patients with left main and three-vessel coronary artery disease by adenosine-single photon emission computed tomographic thallium imaging. Am Heart J, 1993; 125: 1130–1135.
19. Lette J, Bertrand C, Gossard D et al. Long-term risk stratification with dipyridamole imaging. Am Heart J, 1995; 129: 880–886.
20. Gibbons RJ, Hodge DO, Berman DS et al. Long-term outcome of patients with intermediate-risk exercise electrocardiograms who do not have myocardial perfusion defects on radionuclide imaging. Circulation, 1999; 100: 2140–2145.
21. Chow BJ, Wong JW, Yoshinaga K et al. Prognostic significance of dipyridamole-induced st depression in patients with normal 82rb pet myocardial perfusion imaging. J Nucl Med, 2005; 46: 1095–1101.
22. Caracciolo EA, Davis KB, Sopko G et al. Comparison of surgical and medical group survival in patients with left main equivalent coronary artery disease. Long-term CASE experience. Circulation, 1995; 91: 2335–2344.
23. Caracciolo EA, Davis KB, Sopko G et al. Comparison of surgical and medical group survival in patients with left main coronary artery disease. Long-term CASE experience. Circulation, 1995; 91: 2325–2334.
24. Hachamovitch R, Hayes SW, Friedman JD, Cohen I, Berman DS. A prognostic score for prediction of cardiac mortality risk after adenosine stress myocardial perfusion scintigraphy. J Am Coll Cardiol, 2005; 45: 722–729.
25. Kwok Y, Kim C, Grady D, Segal M, Redberg R. Meta-analysis of exercise testing to detect coronary artery disease in women. Am J Cardiol, 1999; 83: 660–666.
26. Morise AP, Beto R. The specificity of exercise electrocardiography in women grouped by estrogen status. Int J Cardiol, 1997; 60: 55–65.
27. Bokhari S, Bergmann SR. The effect of estrogen compared to estrogen plus progesterone on the exercise electrocardiogram. J Am Coll Cardiol, 2002; 40: 1092–1096.
28. Morise AP, Dalal JN, Duval RD. Frequency of oral estrogen replacement therapy in women with normal and abnormal exercise electrocardiograms and normal coronary arteries by angiogram. Am J Cardiol, 1993; 72: 1197–1199.
29. Rovang KS, Arouni AJ, Mohiuddin SM, Tejani A, Hilleman DE. Effect of estrogen on exercise electrocardiograms in healthy postmenopausal women. Am J Cardiol, 2000; 86: 477–479.
30. Henzlova MJ, Croft LB, Diamond JA. Effect of hormone replacement therapy on the electrocardiographic response to exercise. J Nucl Cardiol, 2002; 9: 385–387.
31. Hlatky MA, Pryor DB, Harrell FE, Jr., Califf RM, Mark DB, Rosati RA. Factors affecting sensitivity and specificity of exercise electrocardiography. Multivariable analysis. Am J Med, 1984; 77: 64–71.
32. Morise AP, Dalal JN, Duval RD. Value of a simple measure of estrogen status for improving the diagnosis of coronary artery disease in women. Am J Med, 1993; 94: 491–496.
33. Rosano GM, Sarrel PM, Poole-Wilson PA, Collins P. Beneficial effect of oestrogen on exercise-induced myocardial ischaemia in women with coronary artery disease. Lancet, 1993; 342: 133–136.