

Screening for asymptomatic coronary artery disease in type 2 diabetes mellitus



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Diabetes mellitus is a known independent risk factor for coronary artery disease (CAD) and other macrovascular complications, including stroke and peripheral vascular disease. Cardiovascular disease is a major cause of morbidity and mortality in people with type 2 diabetes. People with type 2 diabetes are disproportionately affected with cardiovascular disease compared with those without diabetes.¹ The Framingham study established that rates of myocardial infarction (MI), angina and sudden death were two times higher in people with diabetes than in those without diabetes.² Furthermore, the prognosis in patients with diabetes and confirmed MI is worse than in non-diabetic patients with CAD.³ The mortality rate after MI has also shown to be doubled in diabetic patients with CAD.⁴ Diabetes is now classified as a CAD equivalent, which means that the risk of subsequent cardiac events in asymptomatic patients with diabetes is equivalent to that in a patient with known CAD but no history of diabetes.⁵

The association between diabetes and CAD has been suggested to be stronger in women than in men.⁶ Diabetes removes the normal premenopausal gender-related differences in the prevalence of CAD. For individuals aged between 50 and 59 years, diabetes is a greater CAD risk factor in women. Women with diabetes are also more likely to die after MI than women without diabetes or men with or without diabetes.⁷ Diabetes may induce a more unfavourable cardiovascular risk profile among women.⁶

Morbidity and mortality of CAD in type 2 diabetes

The long-term survival rate after acute MI in people with type 2 diabetes is lower than in people with no diabetes and CAD. The 5-year survival rate for diabetic patients after the first coronary event is 38%, dropping to 25% for those with subsequent events, as opposed to corresponding figures in non-diabetics of 75% and 50%, respectively.⁸ The relative risk for fatal CAD associated with diabetes is 50% higher in women than in men. This may be explained by a more adverse cardiovascular risk profile in women with diabetes and CAD, viz. more severe hypertension

and a more unfavourable risk factor profile, combined with possible disparities in treatment, i.e. men with diabetes and CVD are more likely to receive aspirin, statins or antihypertensive drugs.⁶

Mechanisms for excess cardiovascular risk in diabetes

The excess risk for CAD in people with diabetes is due in part to an increased prevalence of established risk factors, namely hypertension, obesity, dyslipidaemia and a family history of premature cardiovascular disease.⁹ These 'traditional' risk factors do not fully explain the excess risk for CAD associated with diabetes. The excess vascular risk in people with diabetes may be explained by certain non-traditional risk factors, including insulin resistance, endothelial dysfunction, impaired fibrinolysis, inflammation, microalbuminuria and vascular wall abnormalities.⁹

Clinical presentation of CAD in diabetes

Type 2 diabetes usually presents with CAD in the 5th or 6th decade of life, or later. Diabetes may be diagnosed in a person at the time of presentation with angina, MI or heart failure. When compared with non-diabetic subjects, people with diabetes tend to have more premature occurrence of CAD; they have more extensive disease at the time of diagnosis, and MI is usually more extensive and severe.¹⁰

Typical symptoms of cardiac disease, i.e. angina, are common in people with type 2 diabetes.¹¹

Atypical symptoms, which include dyspnoea, fatigue and gastrointestinal symptoms, are also common presentations.¹¹

Silent myocardial ischaemia in people with diabetes

Myocardial ischaemia may be asymptomatic, i.e. people with type 2 diabetes may have silent ischaemia, and is frequently in the advanced

stage when it becomes clinically manifest.¹² Silent myocardial ischaemia (SMI) has a reported prevalence ranging from 10% to 20% in diabetic populations versus 1 - 4% in non-diabetic populations.¹³ SMI has no single definition: it includes patients without clinical symptoms of ischaemia but with a resting ECG that indicates a previous infarction or angina pectoris; it includes patients with atypical clinical symptoms; and some authors restrict the diagnosis of SMI to patients without any symptoms and with positive functional testing or angiographically documented CAD.¹³

Screening for CAD in diabetes

Because of the increased prevalence of clinical and asymptomatic CAD in people with diabetes, as well as the worse prognosis, early identification of CAD in these patients is of paramount importance.^{14,15}

Evaluation of the diabetic patient with CAD involves both risk assessment and imaging techniques.¹⁵ The risk assessment involves clinical and biochemical evaluation of risk factors for CAD.¹⁶

Imaging techniques to visualise the coronary arteries can be invasive or non-invasive. Direct visualisation of coronary arteries by angiography may be preferred to non-invasive imaging, because patients with diabetes frequently have diffuse multivessel CAD.¹⁰ Currently, conventional angiography is performed to evaluate the presence and extent of CAD. However, this is an invasive approach, associated with a minimal but definite risk of complications,¹⁷ and non-invasive imaging techniques capable of screening for CAD or capable of direct visualisation of the coronary arteries may be preferred.

Cardiodiagnostic non-invasive imaging techniques that are used for screening for CAD in people with diabetes include:

- Exercise tolerance testing (ETT)^{18,19}
- Myocardial perfusion imaging (MPI)^{11,20,21}
- Stress echocardiography^{22,23}
- Single photon emission computer tomography (SPECT)-MPI²⁰
- Electron beam computed tomography (EBCT)²⁴
- Magnetic resonance angiography (MRA)²⁵
- Multislice computed tomography (MSCT).^{17,25}

Extracardiac non-invasive imaging technique for screening for CAD in people with diabetes includes determination of the ankle-brachial blood pressure index (ABI)²⁶ and carotid intima media thickness.²⁷⁻²⁹

Given the elevated risk of cardiovascular events and the relatively high prevalence of SMI in diabetes, screening asymptomatic diabetic patients for CAD is an appealing concept. By enabling early treatment,

screening for SMI could lower the death rate from CAD in diabetic subjects. However, many factors argue against implementing a broad-based screening programme. Foremost is the lack of any published data demonstrating that a prospectively applied screening programme improves outcome in asymptomatic diabetic patients.⁸ There is no consensus concerning screening methods and interpretation of findings, so the cost effectiveness of screening is poor.

It is uncertain which asymptomatic diabetic patients should be screened and evaluated for SMI – screening all patients is not practical. In February 1998, the American Diabetes Association (ADA) published a consensus statement on the diagnosis of CAD in people with diabetes. It was recommended that asymptomatic diabetic patients with ≥ 2 risk factors for CAD be screened for CAD. It was stated that those asymptomatic patients with ≤ 1 risk factor do not require cardiac testing.²¹

According to the American Diabetes Association (ADA) Consensus Development Conference for Diagnosis of CHD in diabetes,³⁰ stress testing should be performed in individuals with diabetes who meet any of the following criteria:

- Typical or atypical cardiac symptoms
- Resting ECG suggestive of ischaemia or infarction
- Peripheral or carotid arterial occlusive disease
- Sedentary, age >35 years planning vigorous exercise programme
- 2 or more risk factors in addition to diabetes:
 - total cholesterol >6.2 mmol/l, low-density lipoprotein cholesterol >4.14 mmol/l, or high-density lipoprotein cholesterol <0.90 mmol/l
 - blood pressure >140/90 mmHg
 - smoking
 - family history of premature CAD
 - positive test for microalbuminuria.

There is lack of agreement about the type of stress test that is optimal in the evaluation of the underlying CAD.

In a cross-sectional study of 206 patients with type 2 diabetes, using coronary angiography as the gold standard for detecting CAD, the prevalence of CAD was 29%.¹⁹ The accuracy of exercise ECG testing, which was used as the screening test, was 79%, with a 'false-negative rate' of 18%. In patients who are unable to perform an exercise ECG and in those with a high chance of being 'false negative', alternative screening tests should therefore be performed.

Stress radionuclide MPI is used widely to evaluate patients with known or suspected CAD.¹² It detects decreased coronary flow reserve during exercise or pharmacological vasodilation. With technetium-

99m sestamibi imaging¹¹ the ejection fraction can be assessed and a myocardial scar visualised. Stress MPI allows quantification of perfusion abnormality, and patients can be stratified prognostically.^{11,20} The greater the myocardial perfusion abnormality, the greater the likelihood of future cardiac events.²¹ On the other hand, a normal stress MPI is associated with an excellent outcome and a cardiac event rate of <1% per year.

SPECT-MPI may have a similar prognostic value in patients with diabetes.³¹ Stress MPI with gated SPECT provides information on perfusion and function, including wall motion, ejection fraction and myocardial viability. Stress MPI may become a valuable test for better stratifying the risk of CAD in patients with diabetes.

Giri *et al.*²⁰ evaluated 4 755 patients (929 with diabetes) with symptoms of CAD, who had stress MPI with thallium-201 or technetium-99m sestamibi imaging. These patients were prospectively followed up for a mean of 2.5 years (\pm significant deviation (SD) 1.5 years) for subsequent occurrences of cardiac death, MI and revascularisation. Abnormal stress MPI was an independent predictor of cardiac death, MI and revascularisation in patients with and without diabetes. Diabetic people with ischaemic defects had an increased number of cardiac events, with the highest MI rates (17.1%) observed with three-vessel ischaemia.

A literature review of >12 000 patients with normal stress MPI using technetium-99m sestamibi imaging found an annual cardiac event rate (death, MI) of 0.6%, compared with 7.4% in patients with abnormal studies.³² The study by Giri *et al.*²⁰ confirms the low cardiac event rates associated with a normal stress MPI. Survival during the first 2 years of follow-up was identical in patients with a normal stress MPI result, irrespective of their diabetic status. However, cardiac event rates increased after 2 years in patients with diabetes but not in those without. This may be explained by the rapid progression of cardiac disease in patients with diabetes.³³ It must therefore be noted that stress MPI might be less predictive over longer periods of time in patients with diabetes, because of the more rapid progression of disease in this group. The other limitation of stress MPI is that there may be inter-observer variability in the interpretation of MPI results, which may affect clinical outcome.²⁰

A promising new imaging technique for the non-invasive detection of CAD is MSCT. This technique has been reported to be useful in the detection of coronary artery stenosis, with sensitivities and specificities ranging from 72% to 95% and 75 - 99%, respectively.¹⁷ Combined assessment of left ventricular function and the coronary artery status with MSCT may allow optimal non-invasive evaluation of patients with diabetes and CAD.

Schuij *et al.* performed MSCT in 30 patients with diabetes who were scheduled to undergo conventional angiogram.¹⁷ MSCT was shown to have a sensitivity and specificity of 95% in detecting coronary artery stenosis of >50%. MSCT may therefore allow identification of high-risk patients.

To date, the Detection of Ischaemia in Asymptomatic Diabetics (DIAD)³¹ study is the only study that is evaluating the value of non-invasive testing in truly asymptomatic patients with diabetes. In this study, 1 123 patients with type 2 diabetes, 50 - 75 years of age, with no known or suspected CAD, were randomly assigned to stress testing and 5-year clinical follow-up, or to follow-up only. Of 522 patients randomised to stress testing with SPECT-MPI, 113 (22%) had silent ischaemia. The findings suggest that 1 in 5 asymptomatic patients with type 2 diabetes aged 50 - 75 years have SMI, and this may justify screening by non-invasive tests such as MPI. In 2007, all patients will have had at least 5 years of follow-up evaluation. This should allow for defining the relationship between abnormal perfusion imaging and cardiac events in asymptomatic patients with diabetes.

Conclusion

There is a clear need for evidence-based guidelines for the early detection of CAD in people with type 2 diabetes. It is hoped that the DIAD study will define a population of patients with diabetes mellitus and a relatively high prevalence of CAD in whom MPI screening will be both efficacious and cost-effective. To guide clinical practice, what is required is a prospective angiographic analysis of the type 2 diabetes patient population in relation to clinical risk factors and additional clinical tests. A positive screening test suggests the need for angiography; although one could justify considering angiography in all those with type 2 diabetes and two additional risk factors, given that a quarter may have significant disease.

1. Haffner SM. Coronary heart disease in patients with diabetes. *N Engl J Med* 2000; 342: 1040-1042.
2. Fox CS, Coady S, Sorlie PD. Trends in cardiovascular complications of diabetes. *JAMA* 2004; 292: 2495-2499.
3. Gu K, Cowiwe C, Hams MI. Diabetes and decline in heart disease mortality in US adults. *JAMA* 1999; 281: 1291-1297.
4. Sozzi FB, Elhedy A, Roelant JR, *et al.* Prognostic value of dobutamine stress echocardiography in patients with diabetes. *Diabetes Care* 2003; 26: 1074-1078.
5. Executive Summary of the Third Report of the National Cholesterol Education Programme (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486-2497.
6. Huxley R, Bavzi F, Woodward M. Excess risk of fatal CHD associated with diabetes in men and women: meta analysis of 37 prospective cohort studies. *BMJ* 2006; 332: 73-78.
7. Kaseta J, Skafar D, Ram JL, Jacober SJ, Sowers JR. Cardiovascular disease in diabetic women. *J Clin Endocrinol Metab* 1999; 84: 1835-1838.
8. Miller TD, Redberg RF, Wackers FJ. Screening asymptomatic diabetic patients for coronary artery disease: why not? *J Am Coll Cardiol* 2006; 48(4): 761-764.
9. Fonseca V, De Souza C, Asnani S, Jialal I. Nontraditional risk factors for cardiovascular disease in diabetes. *Endocr Rev* 2004; 5: 153-175.
10. Chiariello M, Indolfi C. Silent myocardial ischaemia in patients with diabetes mellitus. *Circulation* 1996; 93: 2089-2091.
11. Consensus development conference of the diagnosis of coronary heart disease in people with diabetes, 10 - 14 February 1998, Miami, Fla. *Diabetes Care* 1998; 21 (9): 1551-1559.
12. Bari Investigators: Influence of diabetes on 5 year mortality and morbidity in a

- randomised trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularisation Investigation (BARI). *Circulation* 1997; 96: 1761-1769.
13. Janand-Delenne B, Savin B, Habib G, Bory M, Vague P, Lassaman-Vague V. Silent myocardial ischaemia in patients with diabetes. Who to screen. *Diabetes Care* 1999; 22: 1396-1400.
 14. Tabibiazar R, Edelman SV. Silent ischaemia in people with diabetes. A condition that must be heard. *Clinical Diabetes* 2003; 21(1): 5-9.
 15. Grundy SM, Howard B, Smith S Jr, Eckel R, Redberg R, Bonow RO. Prevention conference VI: Diabetes and cardiovascular disease. *Circulation* 2002; 105: 2231-2239.
 16. Grundy SM, Benjamin JJ, Burke GL. Diabetes and cardiovascular disease. A statement for health care professionals from the American Heart Association. *Circulation* 1999; 100: 1134-1146.
 17. Schuijff FJD, Bax JJ, Jukema TW. Non-invasive angiography using multislice computer tomography in patients with type 2 diabetes. *Diabetes Care* 2004; 27: 2905-2910.
 18. Inzucchi SE. Non-invasive assessment of the diabetic patient for coronary artery disease. *Diabetes Care* 2001; 24(9): 1519-1521.
 19. Bacci S, Vilella M, Vilella A. Screening of silent myocardial in type 2 diabetic patients with additional atherogenic risk factors: applicability and accuracy of the exercise stress test. *Eur J Endocrinol* 2002; 147: 649-654.
 20. Giri S, Shaw LJ, Murthy DR. Impact of diabetes on the risk stratification using stress single-photon emission computed tomography myocardial perfusion imaging in patients with symptoms suggestive of coronary artery disease. *Circulation* 2002; 105: 32-50.
 21. Wackers FJT, Zaret BL. Detection of myocardial ischaemia in patients with diabetes mellitus. *Circulation* 2002; 105: 5-7.
 22. Bigi R, Desideri A, Cortigiani L, Bax JJ, Celegon L, Fiorentini C. Stress echocardiography for risk stratification of diabetic patients with known or suspected cardiovascular disease. *Diabetes Care* 2001; 24: 1602-1607.
 23. Marwick TH, Case C, Sawada S, Vasey C. Use of stress echocardiography to predict mortality in patients with diabetes and known or suspected coronary artery disease. *Diabetes Care* 2002; 25: 1042-1048.
 24. Hosoi M, Sato T, Yamagami K. Impact of diabetes on coronary stenosis and coronary artery calcification detected by Electron Beam Computed Tomography in symptomatic patients. *Diabetes Care* 2002; 25: 696-701.
 25. De Feyter PJ, Nieman K. New coronary imaging techniques: what to expect? *Heart* 2002; 87: 195-197.
 26. Lehman ED, Riley WA, Clarkson P, Gosling RG. Non-invasive assessment of cardiovascular disease in diabetes mellitus *Lancet* 1997; 350: suppl, 14-19.
 27. Taniwaki H, Kawagishi T, Emoto M. Correlation between the intima media thickness of the carotid artery and aortic pulse wave velocity in patients with type 2 diabetes vessel wall properties in type 2 diabetes. *Diabetes Care* 1999; 22: 1851-1857.
 28. Bonora E, Tessari R, Micciolo R. Intimal medial thickness of the carotid artery in non diabetic and NIDDM patients and relation with insulin resistance. *Diabetes Care* 200: 627-631.
 29. O' Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid artery intima 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.
 30. ADA consensus development conference for diagnosis of coronary heart disease in diabetes. *Diabetes Care* 1998; 21: 1551-1559.
 31. Wackers FJT, Young LH, Inzucchi SE. Detection of silent myocardial ischaemia in asymptomatic diabetic subjects. The DIAD study. *Diabetes Care* 2004; 24: 1954-1961.
 32. Iskander S, Iskandrian AE. Risk assessment using single-photon emission computed tomography technetium-99 m sestamibi imaging. *J Am Coll Cardiol* 1998; 32: 57-62.
 33. Nesto RW, Phillips RT, Kett KG. Angina and exertional myocardial ischaemia in diabetic and non-diabetic patients: assessment by exercise thallium scintigraphy. *Ann Intern Med* 1988; 108:170-175.

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