



# Assessment of coronary artery disease in patients with (a)symptomatic diabetes

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**This editorial refers to 'Risk stratification in uncomplicated type 2 diabetes: prospective evaluation of the combined use of coronary artery calcium imaging and selective myocardial perfusion scintigraphy' by D.V. Anand *et al.*, doi:10.1093/eurheartj/ehi808**

The prevalence of diabetes mellitus has increased exponentially over the past years, with 200 million people currently having diabetes. It is estimated that the prevalence worldwide will exceed 360 million patients in 2030. The majority of these patients will have type 2 diabetes.

There is a close relationship between type 2 diabetes and the development of coronary artery disease. In addition, patients with type 2 diabetes have a two to four fold higher risk of a cardiovascular event when compared with non-diabetic patients.<sup>2</sup> Moreover, the progression of coronary artery disease appears faster when compared with non-diabetic patients.

In the landmark study by Haffner *et al.*,<sup>1</sup> the 7-year incidence of myocardial infarction was assessed in 1373 non-diabetic individuals and compared with the incidence in 1059 patients with type 2 diabetes. In non-diabetic individuals, the 7-year incidence rates of myocardial infarction were 3.5 and 18.8% in individuals without and with previous infarction, respectively. In diabetic individuals, these figures were 20.2 and 45.0%, respectively. These observations indicated that diabetic patients without previous myocardial infarction have a high risk for myocardial infarction, as high as the risk of re-infarction in a non-diabetic individual with previous myocardial infarction. In addition, cardiovascular death is the most common cause of mortality in patients with type 2 diabetes. Morrish *et al.*<sup>2</sup> evaluated the mortality rates in diabetic patients from 10 centres (including 4713 patients), revealing a mortality rate of 52% of cardiovascular disease in patients with type 2 diabetes.

Indeed, recent guidelines for the management of patients with diabetes emphasize the importance of modification of risk factors for cardiovascular disease, and vice versa, guidelines for management of patients with coronary artery

disease recognize diabetes as one of the most important risk factors for cardiovascular disease.

The current guidelines for management of patients with diabetes recognizes the need for detection of coronary artery disease, and non-invasive testing is recommended in symptomatic patients with type 2 diabetes.<sup>3</sup> At present, various non-invasive techniques are available, including exercise-electrocardiography (ECG), nuclear imaging, and stress echocardiography. All these techniques aim at detection of myocardial ischaemia as surrogate of coronary artery disease. In general, exercise-ECG may not be ideal due to the lower accuracy for assessment of ischaemia and the inability of a substantial amount of patients with diabetes to perform an exercise test. The lower accuracy of exercise-ECG may be, in part, related to the ischaemic cascade, in which ECG abnormalities occur late in the cascade. The combination of imaging and stress testing may thus be preferred for assessment of myocardial ischaemia. Imaging allows visualization of induction of perfusion (using nuclear imaging) or systolic wall motion (mainly echocardiography, but magnetic resonance imaging can also be used) abnormalities, both sensitive markers of ischaemia. In addition, the imaging studies can be performed in combination with pharmacological stress rather than physical exercise when needed. Both nuclear myocardial perfusion imaging and stress echocardiography have been demonstrated to have a high accuracy for the detection of coronary artery disease in patients with type 2 diabetes. In addition, extensive abnormalities on these non-invasive imaging tests have been predictive for future cardiovascular events. Alternatively, a normal study was associated with an excellent prognosis, with annual event rates >2%. In non-diabetic patients, the low event rate in the presence of a normal study is maintained over years, but in diabetic patients, the so-called warranty period of a normal study is limited to 2–3 years, indicating the rapid progression of coronary artery disease in these patients. For example, Elhendy *et al.*<sup>4</sup> demonstrated that the event rate in diabetic patients with a normal exercise echocardiogram increased from 0% in the first year to 1.8% at 3-year and 7.6% at 5-year follow-up.

For asymptomatic diabetic patients, the guidelines are less clear. The American Diabetes Association<sup>5</sup> has proposed that diabetic patients with an abnormal resting ECG, evidence of peripheral vascular disease, or two or more risk factors should be evaluated for occult coronary artery disease. However, whether all asymptomatic diabetic

The opinions expressed in this article are not necessarily those of the Editors of the *European Heart Journal* or of the European Society of Cardiology.

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patients should be screened for coronary artery disease remains a matter of debate.<sup>6</sup> Still, the available data reveal a high incidence of patients with silent ischaemia among the asymptomatic patients with type 2 diabetes. For example, in the Detection of Silent Myocardial Ischemia in Asymptomatic Diabetics (DIAD) study,<sup>7</sup> 22% of patients exhibited evidence of silent myocardial ischaemia on nuclear myocardial perfusion imaging. Of interest, 41% of all abnormal SPECT studies occurred in the patients with less than two risk factors. Moreover, multivariate analysis demonstrated that only autonomic dysfunction was predictive of an abnormal SPECT study. The precise incidence of silent ischaemia is not clear; Rajagopalan *et al.*<sup>8</sup> recently reported that 58% of asymptomatic patients with type 2 diabetes had an abnormal SPECT study, whereas Zellweger *et al.*<sup>9</sup> noted that 42% of asymptomatic diabetic patients had an abnormal SPECT study. However, these observations demonstrate that silent ischaemia is common among patients with type 2 diabetes, and screening may be indicated. Whether SPECT imaging should be the first line test, however, is still unclear.

Anand *et al.*<sup>10</sup> propose an interesting algorithm for screening of patients with type 2 diabetes for coronary artery disease. The authors evaluated 510 asymptomatic patients with type 2 diabetes using electron beam computed tomography (EBCT). This imaging technique allows visualization of atherosclerosis (coronary artery calcium) rather than ischaemia, and may thus permit identification of coronary artery disease in an early stage. Nuclear myocardial perfusion imaging was performed in patients with a calcium score >100. Agatston units, i.e. 127 (25%) underwent gated exercise sestamibi SPECT. For comparison, 53 randomly selected patients with a calcium score ≤100 also underwent SPECT. None of the patients with calcium score ≤10 had abnormalities on SPECT. The incidence of abnormal SPECT studies increased in parallel to the calcium score, from 18.4% in patients with calcium score between 11 and 100 to 71.4% in patients with a calcium score >1000. These observations suggest that sequential use of EBCT and SPECT may optimize screening of asymptomatic diabetic patients, and EBCT may be used as gatekeeper for SPECT. This proposal is further strengthened by the prognostic data also provided in the study by Anand *et al.*<sup>10</sup> During a mean follow-up of 18 ± 5 months, no events occurred in the patients with a calcium score ≤10, whereas the majority (82%) of events occurred in patients with a calcium score >400. Importantly, on multivariate analysis, the calcium score and the extent of SPECT perfusion abnormalities were the only predictors of future events. On the basis of this stepwise approach, patients with atherosclerosis on EBCT but without ischaemia may be referred for risk factor modification, aggressive medical therapy, and careful monitoring. Conversely, patients with atherosclerosis and

ischaemia may be referred for invasive coronary angiography with intervention if required.

In conclusion, the number of patients with diabetes type 2 will increase dramatically over the next few years. For adequate risk stratification, assessment of coronary artery disease may be indicated. Management guidelines suggest non-invasive imaging techniques such as nuclear myocardial perfusion imaging and stress echocardiography for the detection of coronary artery disease in patients with symptoms of coronary artery disease. In asymptomatic patients, screening for coronary artery disease is less established. Although a substantial amount of patients may have silent ischaemia, not all patients may benefit from imaging to detect ischaemia. A stepwise screening, with assessment of atherosclerosis by EBCT, followed by SPECT if needed, may allow optimal risk stratification of asymptomatic diabetes.

**Conflict of interest:** none declared.

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