Cardiac CT: A review of its role in stratifying risk and early detection of silent CAD

Ajay Yerramasu, Shreenidhi Venuraju, Avijit Lahiri

Diabetes is a major cause of mortality and morbidity and is expected to affect an estimated 333 million people worldwide by 2025 (International Diabetes Federation, 2007). Cardiovascular disease contributes to approximately 70 % of all deaths among people with diabetes (Gu et al, 1998). Coronary artery disease (CAD) is often asymptomatic and is associated with worse prognosis in these individuals (Donnan et al, 2002). Hence, it is important to identify CAD at the earliest stage so that aggressive preventive measures can be instituted in a cost-effective manner. Clinically derived risk stratification strategies such as Framingham and UKPDS risk scores are easier to apply but have significant limitations (Guzder et al, 2005; Coleman et al, 2007). Calcification occurs in the atherosclerotic plaque and represents the 'tomb stone' of the macrophages involved in the inflammatory process in the atherosclerotic plaque (Stary, 2001). The small amount of calcium deposit in the coronary artery plaque can be detected by ultra-fast computerised tomography (CT) imaging. Coronary artery calcium (CAC) imaging is an established and sensitive marker of the atherosclerotic burden and offers independent and incremental prognostic information when added to the Framingham risk score (Greenland et al, 2004). CAC imaging in people with diabetes promises to be a cost-effective method for early detection of silent CAD (Raggi et al, 2004).

Article points

1. Cardiovascular disease contributes to approximately 70 % of all deaths among people with diabetes.

2. Coronary calcium imaging is a sensitive marker for atherosclerotic burden and can be used for early coronary artery disease risk stratification in asymptomatic people with diabetes.

Key words

- Coronary calcium
- Coronary artery calcium
- Coronary artery disease
- Risk stratification
- Osteoprotegerin

The heart is a difficult organ to image owing to its constant motion and the superimposed respiratory motion. The advent of electron beam computed tomography (EBCT) has improved the temporal speed of the CT scanners, allowing us to image the beating heart. EBCT allows identification and quantification of coronary calcium in a rapid, non-invasive and accurate manner. The complete procedure takes fewer than 10 minutes, making it convenient for patients and ideal for screening purposes. The scan is non-enhanced and there is no need for any potentially harmful contrast agents. The radiation dose is small compared with other diagnostic procedures such as coronary angiography (Becker et al, 1999). The extent of calcification is expressed as Agatston units (AUs). The Agatston score can be used to categorise the

Ajay Yerramasu is a Cardiology Research Registrar, Shreenidhi Venuraju is a Cardiology Research Registrar and Avijit Lahiri is a Consultant Cardiologist. All are based at Wellington Cardiac Imaging & Research Centre, London.
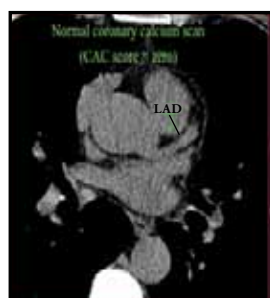
Figure 1. A: Normal coronary calcium scan.

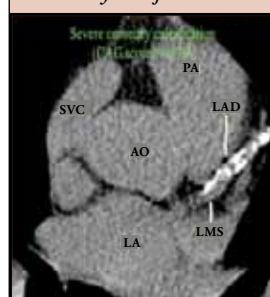*Figure 1. B: Mild coronary calcification.*

Figure 1. C: Severe coronary calcification.

Figure 1. A: EBCT scan showing no evidence of coronary calcification, (CAC = 0AU); B: EBCT scan showing mild calcification of left anterior descending (LAD) coronary artery, total CAC = 46AU; C: EBCT scan showing extensive calcification of LAD coronary artery, total CAC = 1178AU (LA: Left Atrium, AO: Aorta, SVC: Superior vena cava, PA: Pulmonary artery, LMS: Left Main Stem.

severity of coronary calcification as minimal (<10), mild (11–100), moderate (101–400), severe (401–1000) or extensive (>1000; *Figure 1*). Calcium scores tend to be higher in males than females and increase with age; hence, age- and sex-adjusted scores have been shown to be better risk predictors than absolute scores (Raggi et al, 2000).

Multidetector Spiral CT scanners (MSCTs) were introduced in 1998 and are gradually replacing the more expensive EBCT scanners. MSCT utilises multiple parallel detector rows to allow rapid simultaneous acquisition of multiple slices. Besides coronary calcium imaging, the improved spatial resolution makes them ideal for non-invasive CT coronary angiography. CAC scores obtained by MDCT scanners are comparable to those obtained by EBCT scanners (Stanford et al, 2004).

Prognostic value of coronary artery calcium

Calcification in the coronary arteries was believed to be a sign of stable disease; however, this has been proven to be untrue by several large-scale trials (Shaw et al, 2003; Greenland et al, 2004; Arad et al, 2005; Budoff et al, 2007; *Table 1*). CAC is not only a sensitive marker for coronary atherosclerosis but it also accurately quantifies the overall coronary atherosclerotic burden (Sangiorgi et al, 1998). CAC correlates positively with other established risk factors such as age, family history of coronary heart disease (CHD), serum lipids, Framingham risk score and carotid intima media thickness (CMT). It offers independent and incremental information over and above the conventional risk factors. In a large observational study, Budoff and colleagues followed a cohort of over 25 000 people for a mean period of 6.8 years; they established that CAC was an independent predictor of mortality in a multivariate model corrected for age, gender, ethnicity and conventional risk factors (Budoff et al, 2007); compared with individuals with zero CAC score, those with a score >1000 AU have a 12.5-fold increase in all-cause mortality.

Is there a role for CAC in screening for CAD?

A large number of trials have shown that nearly 70 % of people with acute myocardial infarction have no evidence of significant coronary artery stenosis, suggesting that 'plaque rupture' of the vulnerable plaque is the main cause of acute coronary syndromes (Ambrose et al, 1988; Giroud et al, 1992; Falk et al, 1995). Thus, detection of the 'total atherosclerotic burden' by coronary calcium imaging increases the power of detecting the vulnerable individual.

A number of strategies have been developed and validated for risk assessment, such as the Framingham and UKPDS risk scores. These strategies take into account the traditional risk factors such as the individual's age, gender, ethnicity, BMI, waist–hip ratio, smoking status, diabetes, lipid profile and family history. Using these criteria, people can be divided into a low-risk group with a <10 % risk of CAD mortality over 10 years and a high-risk group with a >20 % 10-year risk (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). However, a significant number of people will fall into an intermediate risk category with 10–20 % 10-year CAD risk. These individuals need additional risk assessment to ensure they receive appropriate primary prevention measures. In view of its excellent sensitivity for sub-clinical atherosclerosis, CAC imaging may be particularly helpful in this intermediate-risk group. Patients with 0–10 AU scores may be reassured and spared from undergoing further investigations as well as life-long statin and aspirin treatments. The negative predictive value of CAC imaging is equally robust. Four major trials have shown that a CAC score of 0–10 Au is associated with a very low risk of mortality (Shaw et al, 2003; Greenland et al, 2004; Arad et al, 2005; Budoff et al, 2007).

Lack of adherence is a significant problem in people with diabetes and hyperlipidaemia, particularly those who are asymptomatic (Cramer, 2004; Wens et al, 2005). The visual impact of coronary calcium may increase people's awareness of their disease and thus improve their adherence to advice on lifestyle changes and medication (Alm-Roijer et al, 2004). However, the initial study by O'Malley and colleagues failed to demonstrate significant improvement in modifiable risk factors 1 year after coronary calcium scanning (O'Malley et al, 2003). There is, therefore, a need to perform more studies to test this concept.

Coronary calcium imaging in diabetes

In people with diabetes CAC imaging has been found to be particularly useful. People with diabetes with coronary calcification have a worse prognosis compared with non-diabetic subjects with the same extent of coronary calcification (Wong et al, 2005; *Figure 2*). One of the important clinical goals faced by every physician managing people with diabetes is to accurately identify the CAD risk of the individual and address it appropriately. The guidelines from the National Cholesterol Education Program (NCEP) Adult Treatment Panel III recommend that diabetes should be considered as a 'CHD equivalent' in estimating the risk of CAD, which means that people

Table 1. Prognostic value of coronary artery calcium (CAC) as shown by different large scale studies.

Author (year)	N	Duration of follow up	No. of hard events	Patient characteristics and average age	Risk of increased CAC scores compared with a CAC score of zero	
Budoff et al (2007)	25 253	6.8 ± 3 years	510 deaths	Asymptomatic individuals referred for screening; 56 ± 11 years	CAC score 11–100 10–299 300–399 400–699 700–1000 >1000	Relative risk of death 2.2 4.5 6.4 9.2 10.4 12.5
Anand et al (2006)	510	2.2 years	20 cardiac events (2 CHD deaths, 9 non-fatal MIs)	People with asymptomatic type 2 diabetes; 53 ± 8 years	CAC score 101–400 401–1000 >1000	Relative risk of events 10.1 40.6 58
Arad et al (2005) (St Francis Heart Study)	4903	4.3 years	40 non-fatal MI coronary death	Asymptomatic, apparently healthy men and women aged 50 to 70 years	For CAC of 100–399 AU, relative risk of death or non-fatal MI = 10.4	
Greenland et al (2004)	1312	7 years	16 CHD deaths, 84 non-fatal MI s	Asymptomatic individuals >45 years with at least one coronary risk factor, diabetic patients were excluded; 65.7 years	For CAC > 300 AU, Hazard ratio of a CHD death or nonfatal MI was 3.9	
Shaw et al (2003)	10 377	5 years	249 deaths	Asymptomatic individuals referred for screening; 53 ± 0.1 years	CAC Score 11–100 101–400 401–1000 >1000	Relative risk of death 1.64 1.74 2.54 4.03
Park et al (2002) (South Bay Heart Watch study)	967	6.4 ± 1.3 years	50 CHD deaths/ non-fatal MIs	Non-diabetic subjects with CRP <10; 66 ± 8 years	Compared with low CAC tertile (<3.7 AU), in high tertile of CAC (>142.1 AU), relative risk of CHD death or non-fatal MI = 4.9 ± 6.1 (depending CRP levels)	
Arad et al (1996)	1173	19 months	1 death, 7 non-fatal MIs	Asymptomatic individuals referred for screening	For CAC >680; odds ratio = 20	

Acronyms – CAC: coronary artery calcium; CHD: coronary heart disease; MI: myocardial infarction; CRP: C-reactive protein.

with diabetes with no history of CHD carry the same risk of coronary events as people with established CHD, which is more than 20 % over 10 years (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cho-lesterol in Adults, 2001). Thus, all people with diabetes should be considered for intensive risk-reduction treatments with reduction of LDL to target and below, along with appropriate lifestyle changes. However, such a blanket approach, while effective in reducing the overall number of events in the population as a whole, might not be ideal in addressing the risk of an individual. In fact, studies incorporating the CAC imaging have shown that perhaps not all people with diabetes are the same in terms of their cardiovascular risk. In the presence of low CAC scores, the risk of coronary events is low, regardless of the presence or absence of diabetes. A study by Raggi et al showed that people with diabetes with no detectable coronary calcium have excellent 5-year survival that was not significantly different from people without diabetes (98.8 % versus 99.4 %, respectively; *P* = 0.49; Raggi et al, 2004; *Figure 2*). On the other hand, those with severe coronary calcification are much more likely to

have asymptomatic myocardial perfusion abnormalities and face an exponentially higher risk of coronary events.

Although CT imaging can detect coronary artery calcium in people with asymptomatic diabetes, it cannot estimate the additional risk of silent myocardial ischaemia or high-risk coronary artery obstructive disease. Myocardial perfusion imaging (MPI) is an established non-invasive technique that identifies high-risk individuals, as suggested by NICE guidelines (NICE, 2003). Recently, data from the Detection of Ischemia in Asymptomatic Diabetics trial showed evidence of silent ischaemia using MPI, but this may not be cost effective given the large number of people with diabetes (Wackers et al, 2004). Anand and colleagues, in a recent prospective trial in the UK, combined CAC imaging and MPI in 510 asymptomatic people with uncomplicated type 2 diabetes (Anand et al, 2006). CAC was present (>10 AU) in 46 % of individuals, with 26 % having moderate-to-high CAC scores (>400 AU). Of note, none of the participants with CAC <10 AU were found to have myocardial perfusion abnormalities, nearly a

Page points

1. Studies incorporating the CAC imaging have shown that perhaps not all people with diabetes are the same in terms of their cardiovascular risk. In the presence of low CAC scores, the risk of coronary events is low, regardless of the presence or absence of diabetes.

2. Although CT imaging can detect coronary artery calcium in people with asymptomatic diabetes, it cannot estimate the additional risk of silent myocardial ischaemia or high-risk coronary artery obstructive disease.

third of people with CAC >100 AU were found to have myocardial perfusion abnormalities. Over a median follow-up period of 2.2 years, 20 cardiac events were noted in people with CAC >10 AU, and no events were noted in those with CAC <10 AU (*Figure 3*). In the DIAD trial, more than one in five people were shown to have evidence of myocardial ischaemia, yet the conventional risk factors could identify only a small fraction of these people (Wackers et al, 2004). CAC imaging helps to select the subset of individuals most likely to have asymptomatic perfusion abnormalities and who are at high risk of coronary events. MPI added incremental value when added to CAC imaging for predicting cardiac events, while CAC score was superior to UKPDS and Framingham scores in predicting cardiac events.

Although CAC is a sensitive marker of the overall atherosclerotic burden, it is not specific for haemodynamically significant coronary artery stenosis. On the contrary, MPI is aimed at detecting haemodynamically significant coronary artery stenosis, but provides no information about the non-stenotic lesions. In view of this, the prognostic information provided by CAC and MPI is independent and complementary (*Figure 4*). Thus, Ramakrishna and colleagues showed that the 10-year mortality in people with both a severe CAC score and high-risk MPI was 42 %, compared with 27 % and 31 % for people with only severe CAC score and only high-risk MPS, respectively (Ramakrishna et al, 2007).

Progression of coronary atherosclerosis

Owing to the non-invasive nature and relative low cost of the CT scan, progression of CAD can be measured easily with either EBCT or MSCT techniques. Studies have shown that the progression of CAC on serial evaluation is associated with an increased risk of coronary events. In a retrospective analysis, people with rapid progression of CAC were shown to be at greater risk of acute coronary events during a follow-up period of 2.2 ± 1.3 years (Raggi et al, 2003). Raggi and colleagues showed that people with diabetes with no coronary calcium on the baseline scan were more likely to develop CAC on the subsequent scans, compared with controls without diabetes (42 % versus 25 %; $P = 0.046$). Diabetes and hypertension were shown to be the best predictors of CAC progression, with odds ratios of 3.1 and 1.9, respectively (Raggi et al, 2005). Recent evidence from Anand and colleagues who measured CAC at baseline and at a median of 1.8 years, suggests that baseline CAC severity and sub-optimal glycaemic control are strong predictors of CAC progression in people with type 2 diabetes (Anand et al, 2007).

Progression of CAC and therapeutic trials

Although early small retrospective trials suggested reduction in CAC progression with HMG co-A reductase inhibitors (Callister et al, 1998), recent trials have been disappointing. A prospective study of 10 mg versus 80 mg atorvastatin with 1-year follow-up EBCT scan (Schmermund et al, 2006). There was no significant difference between the two groups; however, people at entry were already on HMG CoA reductase inhibitors and a treatment period of 1 year was probably insufficient. High-risk groups such as those with hyperlipidaemia should be targeted for therapeutic trials. In view of the fact that people with diabetes were shown to have disease progression, which was related to lack of diabetes control as measured by HbA_{1c}, aggressive management of diabetes may slow disease progression.

The role of biomarkers and combined imaging technique

While CAC imaging is a safe, non-invasive test, its availability is limited, thereby triggering the search to identify simple blood markers that detect atherosclerotic cascade. Several potential markers have been investigated for this purpose and osteoprotegerin (OPG) appears to be a promising candidate. Anand and colleagues prospectively evaluated the relationship between OPG, coronary calcification and short-term cardiovascular risk in asymptomatic people with uncomplicated type 2 diabetes and with no prior history of CAD (Anand et al, 2006). OPG levels showed a positive correlation with cardiovascular risk factors (waist–hip ratio, age and systolic blood pressure), duration of diabetes, microvascular disease (retinopathy and peripheral neuropathy), UKPDS and Framingham risk scores, as well CAC scores. In contrast, vascular inflammatory markers such as high sensitivity-C-reactive protein and interleukin-6 predicted neither CAC scores nor short-term cardiovascular events. Over a median follow up of 18 months, OPG and CAC remained strong predictors of coronary events. Mean OPG levels were significantly higher in people with cardiovascular events than in those without (32 versus 6.8; $P < 0.0001$). In the multivariate model, CAC score was the only independent predictor of short-term cardiovascular risk. CAC scores and plasma OPG levels were found to be better predictors than the clinically derived UKPDS and Framingham risk scores. Thus, combining novel biomarkers and CT imaging may achieve improved identification of high-risk individuals who can then be targeted for aggressive management or further investigations. The role of OPG in predicting long-

Potential role of CAC imaging in the primary care

There has been considerable emphasis regarding the aggressive management of people with diabetes in the community (Griffin, 2001; Kassianos, 2005; Patient plus, 2008); hence, the primary care physicians play a significant role in their management. Despite aggressive risk management of people with diabetes, the cardiac event and death rates continue to be extremely high. Thus, the value of coronary calcium imaging in this subset would be to 'select out' those high-risk individuals with high calcium scores for further investigations or interventions.

Availability of coronary calcium imaging

Coronary calcium imaging was previously carried out with very expensive CT equipment (electron beam CT scanners) and there were only three such scanners in the UK (all in London); thus, the test was not widely available to the NHS patients. However, the less expensive and versatile multidetector CT scanners have multiple uses and are widely available in NHS hospitals. These scanners are capable of coronary calcium measurements. Therefore, with proper training and propagation of knowledge, the coronary calcium scan can become widely available and the cost could be reduced substantially (from the current cost of £550–£400 to about £150 per scan, depending on the volume of scanning).

Conclusion

Several recent studies have proved CAC imaging to be a robust technique for CAD risk stratification. It is especially helpful in people with asymptomatic diabetes with no known history of CAD. The evolving role of cardiac CT in evaluating high-risk individuals should be incorporated into clinical protocols. The advantage of cardiac CT is the clear delineation between the low- and high-risk individuals at a relatively low cost. ■

Donnan PT et al (2002) *Diabetes Medicine* **19**: 448–55
Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001) *JAMA* **285**: 2486–97
Falk E, Shah PK, Fuster V (1995) Coronary plaque disruption. *Circulation* **92**: 657–71
Giroud D et al (1992) *American Journal of Cardiology* **69**: 729–32
Greenland P et al (2004) *JAMA* **291**: 210–5
Griffin SJ (2001) *BMJ* **323**: 946–7
Gu K et al (1998) *Diabetes Care* **21**: 1138–45
Guzder RN et al (2005) *Diabetic Medicine* **22**: 554–62
International Diabetes Federation (2007) *Diabetes e-Atlas*. Available at: http://www.eatlas.idf.org/ (accessed 18.03.2008)
Kassianos G (2005) *International Journal of Clinical Practice* **59**: 1123–5
Kiechl S et al (2004) *Circulation* **109**: 2175–80
NICE (2003) *Myocardial perfusion scintigraphy for the diagnosis and management of angina and myocardial infarction: Technology Appraisal 73*. Available at: http://www.nice.org.uk/nicemedia/pdf/TA073guidance.pdf (accessed 18.03.2008)
O'Malley PG et al (2003) *JAMA* **289**: 2215–23
Park R et al (2002) *Circulation* **106**: 2073–7
Patient plus (2008) *Managing Diabetes In General Practice*. Available at: http://www.patient.co.uk/showdoc/40002297/ (accessed 18.03.2008)
Raggi P et al (2000) *Circulation* **101**: 850–5
Raggi P et al (2003) *American Journal of Cardiology* **92**: 827–9
Raggi P et al (2004) *Journal of the American College of Cardiology* **43**: 1663–9
Raggi P et al (2005) *Hypertension* **46**: 238–43
Ramakrishna G et al (2007) *American Heart Journal* **153**: 807–14
Sangiorgi G et al (1998) *Journal of the American College of Cardiology* **31**: 126–33
Schmermund A et al (2006) *Circulation* **113**: 427–37
Shaw LJ et al (2003) *Radiology* **228**: 826–33
Stanford W et al (2004) *Radiology* **230**: 397–402
Stary HC (2001) *American Journal of Cardiology* **88**: 16E–19E
Wackers FJ et al (2004) *Diabetes Care* **27**: 1954–61
Wens J et al (2005) *BMC Family Practice* **6**: 20
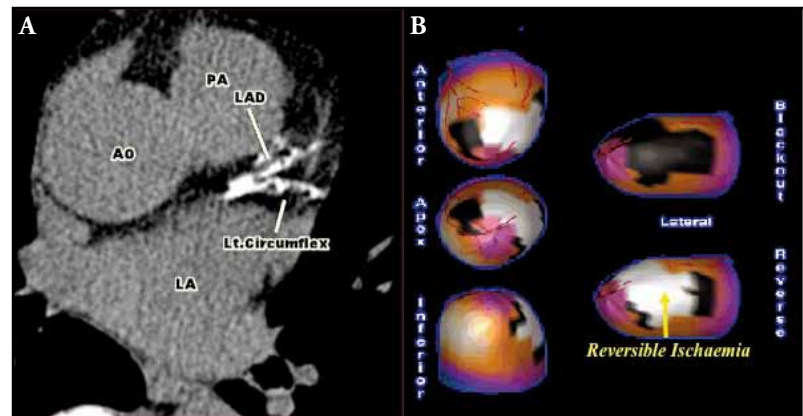Wong ND et al (2005) *Diabetes Care* **28**: 1445–50

Figure 3. A: EBCT of 67 year old asymptomatic diabetic patient with hypertension and high cholesterol, showing extensive calcification of left anterior descending and left circumflex arteries. Right coronary artery (not shown here) was also calcified. CAC score was 2866 Au. B: Myocardial perfusion imaging using Tc – 99m sestamibi gated SPECT (3 D View) showing extensive 'silent' reversible ischaemia (in white) in the lateral wall.

Alm-Roijer C et al (2004) *European Journal of Cardiovascular Nursing* **3**: 321–30
Ambrose JA et al (1988) *Journal of the American College of Cardiology* **12**: 56–62
Anand DV et al (2006) *European Heart Journal* **27**: 713–21
Anand D et al (2007) *Heart* **93**: A62
Arad Y et al (1996) *Circulation* **93**: 1951–3
Arad Y et al (2005) *Journal of the American College of Cardiology* **46**: 158–65
Becker C et al (1999) *Rofo* **170**: 99–104
Budoff MJ, Shaw LJ, Liu ST et al (2007) Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. *Journal of the American College of Cardiology* **49**: 1860–70
Callister TQ et al (1998) *New England Journal of Medicine* **339**: 1972–8
Coleman RL et al (2007) *Diabetes Care* **30**: 1292–3
Cramer JA (2004) *Diabetes Care* **27**: 1218–24