Patients with diabetes mellitus are at increased risk of cardiovascular morbidity and mortality as a result of numerous pathophysiological changes, including the following:

- Epicardial coronary artery disease frequently resulting in myocardial infarction (MI)
- Microvascular disease and endothelial dysfunction causing atypical chest pain
- Cardiac remodeling with diffuse myocardial fibrosis, fatty myocardial infiltration, and diastolic dysfunction resulting in heart failure
- Peripheral vascular disease including carotid stenosis causing claudication and stroke

In addition, the workup of these patients is challenging because of the high prevalence of advanced disease, various overlapping expression of abnormalities, their rapid progression over time, their atypical presentation (eg, atypical symptoms caused by autonomous neuropathy), and the overweight frequently encountered in patients with type 2 diabetes mellitus, as well as limited exercise capacity because of peripheral vascular disease in ≈30% of patients requiring stress testing.

Various techniques are used in clinical practice and research to assess the above named pathologies, leading to a continuous improvement in understanding the natural history and relative importance of different biomarkers for prognosis and risk stratification.

Especially, the detection of epicardial coronary artery disease and its prognostic relevance has been an area of discussion given the difficulties to perform exercise testing in these patients, the overlap of significant epicardial coronary artery disease with diffuse coronary artery disease, microvascular disease, and endothelial dysfunction, and the specific difficulties the diabetic population poses on echocardiography and single photon emission computed tomography (SPECT).

Echocardiography is frequently the first-line technique in assessing patients with cardiovascular presentations because of its immediate availability. However, in the diabetic population, image quality is frequently suboptimal because of obesity, and exercise echocardiography is often impossible. The need for dobutamine as a pharmacological stressor has been shown to be an independent predictor of adverse outcome. Although dobutamine stress echocardiography allows to risk-stratify patients, it remains far from perfect, with a yearly mortality rate in patients with a negative dobutamine stress echocardiography of 4%. Echocardiography is unable to differentiate between epicardial and microvascular coronary disease and misses smaller MIs not causing significant wall motion abnormalities.

SPECT imaging is the most frequently used method to assess myocardial ischemia, especially in the United States. In patients with diabetes mellitus, SPECT has several distinct disadvantages. Its spatial resolution of ≈1 cm×1 cm does not allow detection of subendocardial ischemia. It relies on regional differences in myocardial blood flow and is thus less accurate in patients with triple vessel disease and balanced ischemia or diffuse microvascular dysfunction. The use of radioactive tracers is unfavourable in the relatively young diabetic cohort with rapid progress of disease and atypical presentations, frequently requiring repeat examinations. Obese patients tend to have lower signal in the inferolateral wall, causing false-positive findings. Finally, SPECT imaging has a low sensitivity for nontransmural MI. Despite these limitations, a recent meta-analysis of SPECT studies confirmed its ability for risk classification in diabetes mellitus. Averaged across patients with and without symptoms, a normal SPECT scan conferred a low annualized event rate for cardiac death and MI of 1.9%.5

Compared tomography plays an increasing role in assessing patients with diabetes mellitus, and there is an ongoing debate on its use in asymptomatic patients or calcium screening as a gatekeeper to ischemia testing. However, recent data from the Factor 64 study show that in diabetic patients with or without symptoms, computed tomographic angiography does not improve patient management or outcome.4

As a result of the difficulties to sufficiently work up the cardiovascular status of patients with diabetes mellitus, these patients often undergo invasive angiography frequently without therapeutic consequence.

Cardiovascular magnetic resonance (CMR) imaging has made continuous progress in assessing patients with diabetes mellitus. There is convincing data on the ability of CMR in detecting MI beyond other tests. The ICELAND MI study revealed a prevalence of 27% MI in the general population aged 67 to 93 years and 32% in patients with diabetes mellitus.5 Importantly, the number of unrecognized MIs was high in both groups (17% and 21%), demonstrating significant
underestimation of the presence of MI in patients with diabetes mellitus. Unrecognized MI had the same negative impact on prognosis than known MI, despite smaller total infarct size. Similarly, Kwong et al found a prevalence of 28% MI in diabetic patients, which was the strongest predictor of outcome during follow-up even after adjusting for diabetic-specific risk models. Turkbey et al studied 1017 patients with type 1 diabetes mellitus (741 including gadolinium contrast agent; mean age, 49 years and diabetes mellitus duration, 22 years) and found increased left ventricular mass and reduced end-diastolic volumes related to cardiovascular risk factors, HbA1c, and macroalbuminuria. In 4.3% of patients a MI was found by CMR in contrast to only 1.4% by clinical evaluation. More recently, Rijzewijk et al had found a strong association between myocardial steatosis and diastolic dysfunction in diabetic patients.

In this issue of Circulation: Cardiovascular Imaging, Heydari et al assess the utility of CMR first-pass perfusion imaging during vasodilatory stress with adenosine or regadenoson for risk classification of patients with diabetes mellitus. They examined 173 symptomatic diabetic patients with CMR and followed them up over 2.9±2.5 years. The presence of inducible myocardial ischemia, defined as at least 1 positive segment of >1 voxel thickness lasting for at least 3 heartbeats, was the strongest predictor of outcome. Patients with neither ischemia nor MI had a 0.5% yearly event rate for cardiac death or MI; those with no inducible ischemia, 1.4%; and those with inducible ischemia, 8.2%. Interestingly, the duration of diabetes mellitus did not relate to the prevalence of ischemia. The study closes an important knowledge gap. Even though previous studies assessing the accuracy of CMR perfusion imaging or its prognostic power included relatively large groups of diabetic patients, they did not specifically report their results. Although the current study does not allow directly comparing the ability of CMR for risk stratification with other imaging modalities, the results seem favorable and further advocate the use of CMR in patients with diabetes mellitus. The study has several limitations, such as its single center and retrospective nature, selection bias (only patients with an indication for CMR were included), and visual assessment of perfusion defects. It was also performed on various scanners using different stress agents (adenosine or regadenoson). Although this is suboptimal from a scientific standpoint, it supports the value of CMR perfusion imaging as a robust method, independent of the exact parameters, scanners, or protocols used.

Heydari et al touch upon an interesting area, the need for quantification. The data presented was not acquired for more advanced quantitative measures, and the extent of ischemia was only described as visually abnormal segments. Not surprisingly, the extent of perfusion abnormalities correlated with the hazard ratio for adverse events, similar to data obtained with SPECT or positron emission tomography (PET) imaging.

No analysis for the presence of microvascular disease was performed.

The value of quantitative assessment of myocardial perfusion reserve has been demonstrated in various patient groups mainly based on PET studies. Quantitative perfusion analysis overcomes the limitations of underestimating the presence of triple vessel disease in balanced ischemia, allows for an individual risk assessment supporting the decision on revascularization, and provides the information required to compare various imaging techniques in a given patient. Maybe even more important is the ability of quantitative perfusion imaging to detect microvascular dysfunction. Using Rb-82 PET, Murthy et al showed that an impaired myocardial perfusion reserve as a manifestation of microvascular dysfunction was a powerful predictor of outcome in patients with and without diabetes mellitus and remained highly significant after correction for the most important known risk factors. Importantly, patients with diabetes mellitus and a normal perfusion reserve had a similar positive outcome as those without diabetes mellitus.

Perfusion imaging is one of the many areas where CMR is becoming quantitative, and although it is by no means perfect and the required imaging and postprocessing methods are not widely available, first results show excellent correlation with microspheres in the experimental animal and demonstrate similar results to perfusion quantification by PET. CMR increasingly demonstrates its potential to assess microvascular disease. In patients after cardiac transplantation, Miller et al showed a close correlation (r=−0.55) of CMR perfusion reserve with microvascular disease as assessed by invasive hemodynamic measurements (intramyocardial resistance) or plaque burden measured by intravascular ultrasound. Ismail et al demonstrated microvascular disease in patients with hypertrophic cardiomyopathy using a pixelwise approach to exclude scarred areas. More recently, Thomson et al showed the ability of CMR perfusion imaging to detect microvascular dysfunction in women with signs and symptoms of myocardial ischemia but no obstructive coronary artery disease. They also found a strong relationship of reduced perfusion reserve with invasive coronary reactivity testing. CMR perfusion has the unique ability to combine excellent spatial with a high temporal resolution, which allows assessing the dynamics of blood flow into and within the myocardium which may be of further value in the description of epivascular and microvascular myocardial flow components.

CMR has several distinct advantages in diabetic patients. As discussed earlier, it is well suited to detect MI, and it has demonstrated high accuracy in detecting epicardial coronary artery disease while its accuracy is not reduced by balanced ischemia. It allows for assessment of microvascular disease and can measure other myocardial abnormalities frequently observed in diabetic patients, such as fatty infiltration, diastolic dysfunction, or diffuse myocardial fibrosis, as a novel strong predictor of outcome in patients with diabetes mellitus or nonischemic cardiomyopathies.

Although ionizing radiation or nephrotoxic-contrast agents do not burden the method, the use of gadolinium chelates should be restricted in patients with reduced renal function (eg, estimated glomerular filtration rate <30) because of its risk to cause nephrogenic systemic fibrosis.

Fortunately, the use of safer contrast agents, restriction of doses, and careful selection of patients have virtually eliminated the occurrence of nephrogenic systemic fibrosis.

Future research should focus on the ability of various imaging methods to provide guidance for therapy based on quantitative parameters to improve patient outcome. Clinically, the
use of CMR in diabetic patients should be considered early for risk assessment and therapeutic interventions.

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References


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