

# Dual-Imaging Stress Echocardiography for Prognostic Assessment of High-Risk Asymptomatic Patients with Diabetes Mellitus

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**Background:** In patients with diabetes, the utility of diagnostic screening cardiac tests in subjects without clinical coronary artery disease remains controversial. The aim of this study was to assess the prognostic meaning of dual-imaging stress echocardiography (conventional wall motion analysis and Doppler-derived coronary flow velocity reserve [CFVR] of the left anterior descending coronary artery) in high-risk asymptomatic individuals with diabetes.

**Methods:** This was a prospective analysis of 230 asymptomatic patients with diabetes (128 men; mean age,  $66 \pm 9$  years) with no clinical evidence of coronary artery disease, no Q waves or deep negative waves on the electrocardiogram, and no wall motion abnormalities on resting echocardiography. Of these subjects, 147 (64%) had target organ damage and 83 (36%) had two or more associated cardiovascular risk factors. All patients underwent dipyridamole stress echocardiography with CFVR assessment of the left anterior descending coronary artery by transthoracic Doppler, and test results were entered into a database at the time of testing for a clinical and outcome follow-up (mean,  $4.6 \pm 2.7$  years).

**Results:** Inducible ischemia and reduced CFVR ( $\leq 2$ ) were detected in six and 52 patients, respectively. A total of 54 subjects (23%) had abnormal test results (ischemia or reduced CFVR). During follow-up, 39 major adverse cardiac events (MACEs) occurred: 22 hard events (18 deaths and four nonfatal myocardial infarctions) and 17 coronary revascularizations. The yearly incidence rates of hard events and MACEs in the entire study population were 2.1% and 3.6%, respectively. Abnormal test results were the only multivariate indicator of both hard events (hazard ratio, 3.69; 95% CI, 1.54–8.80) and MACEs (hazard ratio, 6.12; 95% CI, 3.22–11.62).

**Conclusions:** Abnormal test results were obtained in one of four cases and were a strong and independent predictor of future hard events and MACEs. (*J Am Soc Echocardiogr* 2016; ■:■-■.)

**Keywords:** Dipyridamole stress echocardiography, Coronary flow velocity reserve, Transthoracic Doppler, Diabetes, Screening, Asymptomatic

Diabetes mellitus is responsible for 21% of all deaths in the United States,<sup>1</sup> and coronary artery disease (CAD) is the leading cause of morbidity and mortality in patients with diabetes.<sup>2</sup> Because the cardiac event rate in patients with diabetes with no histories of CAD is similar to that in patients without diabetes with CAD,<sup>3,4</sup> individuals with diabetes should be managed as risk-equivalent CAD patients.<sup>5</sup> Of note, asymptomatic individuals with diabetes without clinical CAD have an increased prevalence of coronary atherosclerosis

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Financial support for the present study was received through institutional funding from CNR, Institute of Clinical Physiology, Pisa, Italy.

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0894-7317/\$36.00

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<http://dx.doi.org/10.1016/j.echo.2016.10.003>

compared with patients without diabetes,<sup>6</sup> as well as a high incidence of death, myocardial infarction, and need for coronary revascularization over follow-up periods ranging from 3 to 10 years.<sup>7-10</sup> In the past, screening with specialized testing was proposed in subjects with diabetes with two or more associated cardiovascular risk factors,<sup>11</sup> aiming at a change in clinical management on the basis of test results that could improve outcomes.<sup>12</sup> However, prospective studies using myocardial perfusion imaging provided conflicting results in high-risk asymptomatic patients with diabetes.<sup>13,14</sup> In fact, the Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial reported a very low cardiac event rate that was not reduced by screening for myocardial ischemia.<sup>13</sup> Conversely, the Basel Asymptomatic High-Risk Diabetics' Outcome Trial (BARDOT) documented effective prognostication by test results with, respectively, 3 and 7 times greater frequency of cardiac events and progression of disease at 2-year follow-up in patients with inducible myocardial ischemia.<sup>14</sup> The uncertainty regarding the clinical utility of test screening can be summarized by the inconsistent recommendations proposed by scientific societies: whereas the American Diabetes Association currently does not recommend routine screening,<sup>15</sup> the European Society of

## Abbreviations

**BARDOT** = Asymptomatic High-Risk Diabetics' Outcome Trial**CAD** = Coronary artery disease**CFVR** = Coronary flow velocity reserve**DIAD** = Detection of Ischemia in Asymptomatic Diabetics**LAD** = Left anterior descending coronary artery**MACE** = Major adverse cardiac event

Cardiology's guidelines on diabetes attribute a class IIb recommendation to the screening of patients with diabetes at particularly high risk, such as those with peripheral artery disease, high coronary artery calcium scores, or proteinuria, emphasizing, however, the need to better define the characteristics of subjects to be screened.<sup>16</sup>

Dual-imaging stress echocardiography, combining conventional wall motion analysis with two-dimensional echocardiography and coronary flow velocity reserve (CFVR) with pulsed

antagonists ( $n = 11$ ), or both medications ( $n = 5$ ) (Table 1). Phylline-containing drugs and beverages were discontinued  $\geq 24$  hours before testing. All patients gave written informed consent when they underwent stress echocardiography. When patients signed the informed consent document, they also authorized physicians to use their clinical data. Stress echocardiographic data were collected and analyzed by stress echocardiographers not involved in patient care. Test results were available to referring physicians, and indication for coronary revascularization was determined on the basis of several factors, of which test result was only one. Echocardiographers performing stress imaging were not involved in management and decision making for these patients.

## Definitions

Arterial hypertension,<sup>22</sup> hyperlipidemia,<sup>5</sup> overweight or obesity,<sup>23</sup> family history of premature CAD,<sup>24</sup> and smoking habit were taken as associated cardiovascular risk factors and defined according to standard definitions. Peripheral artery disease was assessed using Doppler ultrasound and/or arteriography, and carotid artery disease was defined using Doppler techniques. Microalbuminuria was a level of albumin ranging from 30 to 299 mg in a 24-hour urine collection, while macroalbuminuria was a urinary albumin excretion of  $\geq 300$  mg/24 h.<sup>15</sup> Diabetic retinopathy was defined according to the criteria of the Early Treatment of Diabetic Retinopathy Study.<sup>25</sup> Nerve conduction test and electromyography were adopted for refining the diagnosis of peripheral neuropathy.

## Stress Echocardiography

Transthoracic stress echocardiographic studies were performed using a commercially available ultrasound machine (iE33 [Philips Medical Systems, Andover, MA] and Vivid 7 [GE Healthcare, Little Chalfont, United Kingdom]) equipped with multifrequency phased-array sector scan probes (S3–S8) and with second-harmonic technology. Two-dimensional echocardiography and 12-lead electrocardiographic monitoring were performed in combination with high-dose dipyridamole (up to 0.84 mg over 6 min).<sup>13</sup> Echocardiographic images were semiquantitatively assessed using a 17-segment, four-point scale model of the left ventricle.<sup>26</sup> A wall motion score index was derived by dividing the sum of individual segment scores by the number of interpretable segments. Ischemia was defined as stress-induced wall motion abnormality. CFVR was assessed during the standard stress echocardiographic examination by an intermittent imaging of both wall motion and LAD flow.<sup>17</sup> Coronary flow in the mid-distal portion of the LAD was searched in the low parasternal long-axis section under the guidance of color Doppler flow mapping.<sup>17</sup> All studies were digitally stored to simplify offline review and measurement. Coronary flow parameters were analyzed offline using the built-in calculation package of the ultrasound unit. Flow velocities were measured at least twice for each study: at baseline and at peak stress (before aminophylline injection). At each time point, three optimal profiles of peak diastolic Doppler flow velocities were measured, and the results were averaged. CFVR was defined as the ratio between hyperemic peak and basal peak diastolic coronary flow velocities. A value of CFVR  $\leq 2$  was considered reduced.<sup>18</sup> The test result was considered normal in the case of no ischemia and CFVR  $> 2$  and abnormal in the case of ischemia and/or CFVR  $\leq 2$ . All investigators from contributing centers passed quality control criteria for regional wall motion and

Doppler flow measurement of the mid-distal left anterior descending coronary artery (LAD), is the recommended technique during vasodilator stress echocardiography,<sup>17</sup> having demonstrated feasibility  $> 90\%$ <sup>18</sup> and the ability to improve the diagnostic<sup>19</sup> and prognostic<sup>20</sup> value of standard stress echocardiography. Of interest, in patients with diabetes with no stress-induced ischemia, reduced CFVR of the LAD was found to be a strong predictor of death or myocardial infarction in both an unselected sample<sup>18</sup> and patients with chest pain and angiographically normal or near normal coronary arteries.<sup>21</sup>

The aim of this prospective, observational study was to assess the prognostic implications of dual-imaging stress echocardiography in high-risk asymptomatic subjects with diabetes with no clinical evidence of CAD.

## METHODS

## Patients

This was a prospective analysis of 230 asymptomatic patients (128 men; mean age,  $66 \pm 9$  years) with diabetes mellitus<sup>15</sup> lasting  $13 \pm 10$  years who underwent dipyridamole stress echocardiography with CFVR assessment of the LAD by transthoracic Doppler from January 2007 to December 2012 at two Italian cardiology institutions (in Lucca and Cesena). Inclusion criteria were (1) no history of chest pain, dyspnea, or syncope; (2) no history of CAD (i.e., acute coronary syndrome, coronary revascularization, and/or angiographic evidence of  $\geq 50\%$  diameter coronary stenosis); (3) target organ damage, as defined by macrovascular disease (peripheral or carotid artery disease) or microvascular disease (albuminuria, retinopathy, or peripheral neuropathy), or the presence of two or more associated cardiovascular risk factors; (4) no pathologic Q waves or deep negative waves on the electrocardiogram; (5) no wall motion abnormalities on resting echocardiography; (6) no significant valvular or congenital heart disease; (7) no prognostically relevant noncardiac diseases (cancer, end-stage renal or liver disease, or severe obstructive pulmonary disease); and (8) adequate acoustic window for imaging of the left ventricle (for two-dimensional echocardiography) and LAD flow Doppler (for CFVR assessment). Follow-up information was available for all patients. Therapy was discontinued 72 hours before the test in 40 of 76 patients who were taking  $\beta$ -blockers and 24 hours before the test in 37 of 53 patients who were taking calcium antagonists. Accordingly, 47 individuals (20%) were evaluated under  $\beta$ -blockers ( $n = 31$ ), calcium

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