Noninvasive Diagnosis and Prognosis Assessment in Chronic Coronary Artery Disease

Stress Testing With and Without Imaging Perspective

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Over the past 30 years, there have been great advances in cardiovascular imaging and treatment. Early in this period, new techniques were usually investigated on a limited research basis before widespread adoption. This research helped to develop evidence to define proper application in clinical practice. Sometimes, this evidence did not support the initial promising reports. Pulmonary blood volume measurements, regional ejection fraction images, digital subtraction angiography, stress echocardiography using transesophageal pacing, pacemaker therapy for hypertrophic cardiomyopathy, laser coronary angiography, and aortic valvuloplasty were all appropriately tested on a limited scale and abandoned. 

In the past 15 years, declining Medicare reimbursements have contributed to a “make it up on volume/grow the business” mentality in medicine that often embraces a broader application of new technology before it has been adequately studied to establish its correct role. Many observers have commented that clinical practice often now “runs ahead of” guidelines. Should this pattern continue with respect to newer technology, eg, computed tomographic (CT) angiography, for the diagnostic and prognostic assessment of chronic coronary artery disease (CAD)? To answer this question, the reader must understand the current health-care crisis, the overwhelming evidence supporting the current use of stress imaging with or without imaging, and the limited evidence for CT angiography.

The Current Health-Care Crisis

The need for fundamental health-care reform is increasingly recognized. For the past 2 years, all the major presidential candidates have defined positions on health-care reform. A prominent 2-page advertisement in the Sunday New York Times signed by 10 past political leaders, including a former chairman of the Federal Reserve Board, summarized it well:

“Mounting healthcare costs...threaten American competitiveness, and, if they remain unchecked, could even bankrupt the country. ...The prognosis for our nation’s health is beyond unacceptable—it is inconsistent with America’s long-standing tradition of stewardship.”

Figure 1 shows why the current system is not sustainable. Private health insurance premiums are now 320% of what they were in 1991; this increase is more than twice the increase in the consumer price index during the same time. The striking increase in private health insurance premiums is at least in part attributable to cost-shifting, as Medicare reimbursement has failed to keep pace with inflation. Although the 2008 Medicare legislation was hailed as a great victory by many, because it eliminated the planned 10% cut...
in physician fees, the small increase in 2009 physician fees will again not keep up with general inflation, so the long-term gap between the Medicare physician reimbursement and inflation will widen.

Imaging procedures are part of the problem. Stress imaging (stress nuclear imaging and stress echocardiography) in Medicare patients increased at an annual rate of 6% per year between 1993 and 2001, far in excess of the increases in catheterization, revascularization, or acute myocardial infarction (Figure 2). The increases have been even greater for noncardiac imaging. Computed tomography, MRI, and positron emission tomography increased 4-fold for Medicare patients between 1995 and 2005 (Figure 3), an annual increase of 16% per year. Relatively few of these procedures were cardiac, because CT coronary angiography was in its infancy during this decade.

These increases in imaging have been under scrutiny in Congress. The Deficit Reduction Act of 2005 reduced Medicare reimbursement for the technical component of imaging. The 2008 Medicare legislation included a provision for an imaging appropriateness demonstration project in 2010, and a requirement that all imaging laboratories reimbursed by Medicare be accredited by 2012. The American College of Cardiology recognized these growing concerns several years ago and initiated efforts to develop appropriateness criteria.

Unfortunately, the crisis in health-care costs is about to get much worse. Beginning in 2011, when the first member of the “baby boom” generation turns 65, the U.S. population will age rapidly (Figure 4). The number of Americans older than 65 years (and therefore eligible for Medicare) will increase by 5.1 million between 2000 and 2010, by 14.4 million between 2010 and 2020, and by 16.8 million during the following decade. The number of Americans older than 65 years will double between 2000 and 2030. If current spending trends continue, the Congressional Budget Office projects that the entire federal budget will be devoted to Medicare and federal spending on Medicaid by 2040. The impact of health-care costs on state spending is just as worrisome. Retiree health-care benefits promised by the states constitute an enormous unfunded future liability, which now exceeds 381 billion dollars. In 2006, 3 states—New York, California, and Illinois—had unfunded liabilities of greater than 48 billion dollars each. As of 2006, the available state reserves for this purpose covered only 3% of the future liability.

Almost all health-care reform proposals advocate improved efficiency and value in health-care spending and seek to better align medical care with evidence-based guidelines. In the sections that follow, I will seek to convince the reader...
that the existing paradigm of stress testing with or without imaging is an integral part of existing clinical practice guidelines and supported by very robust evidence. In contrast, CT angiography is a very promising technology with far less evidence. Further research is needed before widespread clinical adoption should proceed.

**Existing Clinical Practice Guidelines**

The clinical management of patients with chronic coronary artery disease is carefully outlined in the Guidelines of American College of Cardiology (ACC)/American Heart Association (AHA)/American College of Physicians/ASIM for the Management of Patients with Chronic Stable Angina, which were first published in 1999,9,10 and subsequently updated in 2002.11,12 A revision of these ACC/AHA guidelines is currently under way and will hopefully be published next year. These guidelines were conceived under the direction of ACC/AHA Task Force on Clinical Practice Guidelines, using rigorous methodology that has been previously detailed in *Circulation* and available on both the ACC and AHA Web sites. The stable angina guidelines include 3 flow diagrams that delineate the entire process of clinical management (the European Society of Cardiology guidelines on stable angina make similar recommendations). The first

![Figure 4](http://circimaging.ahajournals.org/)

**Figure 4.** Histogram showing the number of Americans older than 65 years in the year 2000, and the projected number by decade from 2010 to 2040. The number of elderly Americans will increase dramatically in the next 2 decades because of the retirement of the baby boom generation. Based on data from the U.S. Census Bureau (no permission needed).

![Figure 5](http://circimaging.ahajournals.org/)

**Figure 5.** Flow diagram showing the use of stress testing (with or without imaging) and coronary angiography for the purposes of diagnosis and risk stratification in patients with stable angina. See text for discussion. Reproduced with permission from Ref. 9.
Table 1. High-Risk (>3% Annual Mortality Rate) Findings on Noninvasive Testing

<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe resting left ventricular dysfunction (LVEF &lt;35%)</td>
</tr>
<tr>
<td>2</td>
<td>High-risk treadmill score (score ≥ −11)</td>
</tr>
<tr>
<td>3</td>
<td>Severe exercise left ventricular dysfunction (exercise LVEF &lt;35%)</td>
</tr>
<tr>
<td>4</td>
<td>Stress-induced larger perfusion defect (particularly if anterior)</td>
</tr>
<tr>
<td>5</td>
<td>Stress-induced multiple perfusion defects of moderate size</td>
</tr>
<tr>
<td>6</td>
<td>Large, fixed perfusion defect with LV dilation or increased lung uptake</td>
</tr>
<tr>
<td>7</td>
<td>Stress-induced moderate perfusion defect with LV dilation or increased lung uptake</td>
</tr>
<tr>
<td>8</td>
<td>Echocardiographic wall motion abnormality (involving greater than two segments developing at a low dose of dobutamine (≤10 mg/kg/min) or at a low heart rate (&lt;120 beats/min)</td>
</tr>
<tr>
<td>9</td>
<td>Stress echocardiographic evidence of extensive ischemia</td>
</tr>
</tbody>
</table>

Modified from Reference 9. Reproduced with permission.

Table 2. Summary of Published Evidence of Stress Testing With or Without Imaging for the Diagnosis of CAD

<table>
<thead>
<tr>
<th>Modality</th>
<th>No. of Studies</th>
<th>Total Patients</th>
<th>Table No.</th>
<th>Guideline (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ECG</td>
<td>147</td>
<td>24,047</td>
<td>Table 7</td>
<td>Exercise Testing (21)</td>
</tr>
<tr>
<td>Exercise SPECT</td>
<td>32</td>
<td>4480</td>
<td>Table 5</td>
<td>Radionuclide Imaging (22)</td>
</tr>
<tr>
<td>Vasodilator SPECT</td>
<td>16</td>
<td>2492</td>
<td>Table 6</td>
<td>Radionuclide Imaging (22)</td>
</tr>
<tr>
<td>Exercise Echo</td>
<td>33</td>
<td>3480</td>
<td>Table 7</td>
<td>Echocardiography (23)</td>
</tr>
<tr>
<td>Dobutamine Echo</td>
<td>36</td>
<td>3280</td>
<td>Table 8</td>
<td>Echocardiography (23)</td>
</tr>
</tbody>
</table>

Supporting Evidence

There is a very robust evidence base to support the recommendations in existing clinical practice guidelines for stress testing with or without imaging.

The proper application of diagnostic testing in chronic coronary disease itself is an enormous topic. Interested readers are referred to the chronic stable angina guidelines for a comprehensive discussion. Bayes’ theorem argues strongly that diagnostic testing is best performed in patients with an intermediate pretest probability. In patients with a low or a high pretest probability, diagnostic testing has less incremental value. However, noninvasive testing may be valuable in patients with a high pretest probability for the purpose of risk stratification. Almost the entire literature on noninvasive diagnostic testing is subject to the effect of posttest referral bias, a complex topic that is carefully described in the chronic stable angina guidelines.

Various ACC/AHA guidelines tabulate the multiple published studies on the diagnostic use of exercise ECG testing, exercise single photon emission computed tomography (SPECT) myocardial perfusion imaging, and exercise echocardiography. Table 2 provides a simple summary of these evidence tables, which include many studies (and many thousands of patients) validating the use of stress testing with or without imaging for diagnostic purposes. Additional diagnostic studies in recent years suggest that the objective evidence of a large area of ischemia for a Class I-A recommendation for percutaneous intervention in stable coronary disease. The 2005 ACC/AHA/Society of Coronary Angiography and Intervention Guidelines indicate that percutaneous coronary intervention is a Class II-A (level of evidence B) indication in patients who are asymptomatic or have Canadian Cardiovascular Class I or II angina and that “the vessels…must subtend a moderate to large area of viable myocardium or be associated with a moderate or severe degree of ischemia on noninvasive testing.” Thus, the demonstration of ischemia is a well-established requirement for the clinical management of patients with chronic CAD.
have generally been modest in size and scope, as the literature was already relatively mature.

The evidence for stress testing with or without imaging is equally robust with respect to prognosis or risk stratification. The older literature on the use of treadmill exercise testing is summarized in Table 3. More recent literature has focused on the Duke treadmill score. As indicated in the stable angina guidelines, this score was first developed in a retrospective study on an inpatient population, then applied prospectively on an outpatient population, and subsequently confirmed in multiple other studies from different institutions using the same methodology and the same definitions for risk groups (high risk; intermediate risk; and low risk). As shown in Table 4, more than 60,000 patients have now been included in studies that have usually had greater than 4 years of follow-up.

The evidence supporting the prognostic value of stress myocardial perfusion SPECT imaging in the evaluation of chronic CAD is equally strong (Table 5). The study cohorts are generally large, and the total number of patients studied is more than 19,000. The average follow-up in most studies was at least 1 year and as long as 6 years. These studies have consistently shown a significant relative risk associated with abnormal studies and a very high negative predictive value for normal studies.

Similar evidence is available for stress echocardiography (Table 6). The study cohorts are again generally large, and the total number of subjects studied is more than 5000. The average follow-up ranges from 8 months to 41 months. Similar to SPECT, an ischemic stress echocardiogram is associated with a high rate of subsequent cardiac events, and a normal stress echocardiogram has a very low annual event rate.

The clinical utility of this approach is most obvious for patients who are found to be at low risk by stress testing with or without imaging. For patients with low-risk Duke treadmill scores, the 4-year hard cardiac event rate has been consistently less than 1%. Similarly, for both stress SPECT imaging and stress echocardiography, normal studies have generally been associated with a hard annual cardiac event rate of less than 1%. As indicated in the stable angina guidelines, the available data from randomized trials suggests that this low rate of cardiac events cannot be improved by revascularization. These patients can be safely treated initially with medical therapy and only investigated further if their symptoms cannot be controlled.

This strategy was supported by the results of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial, the largest randomized trial of patients with chronic CAD. A strategy of optimal medical

### Table 3. Prognostic Studies of Exercise Testing Before Development of the Duke Treadmill Score

<table>
<thead>
<tr>
<th>Study</th>
<th>Years of Enrollment</th>
<th>n</th>
<th>Length of Follow-up (y)</th>
<th>Independent Prognostic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CASS (24)</td>
<td>1974–1979</td>
<td>4083</td>
<td>5</td>
<td>1. CHF; 2. TM stage; 3. Exercise-induced ST depression</td>
</tr>
<tr>
<td>Long Beach VA (25)</td>
<td>1984–1990</td>
<td>2546</td>
<td>5</td>
<td>1. CHF/digoxin use; 2. METs; 3. Max SBP; 4. Exercise-induced ST depression</td>
</tr>
<tr>
<td>Italian CNR (26)</td>
<td>1976–1979</td>
<td>1083</td>
<td>5.5</td>
<td>1. Q wave; 2. Prior MI; 3. Effort ischemia; 4. Exercise capacity</td>
</tr>
<tr>
<td>Belgium (27)</td>
<td>1978–1985</td>
<td>470</td>
<td>5</td>
<td>1. Age; 2. Score of maximum HR, ST Depression, angina, watts, ST slope</td>
</tr>
<tr>
<td>German (28)</td>
<td>1975–1978</td>
<td>1238</td>
<td>4.5</td>
<td>1. Exercise tolerance (watts); 2. Maximum HR</td>
</tr>
</tbody>
</table>

CASS indicates Coronary Artery Surgery Study; CHF, congestive heart failure; TM, treadmill; VA, Veterans Administration; METs, metabolic equivalents; Max, maximum; SBP, systolic blood pressure; CNR, Consiglio Nazionale Ricerche; MI, myocardial infarction; and HR, heart rate.

therapy plus revascularization was not associated with improved outcomes compared with a strategy of optimal medical therapy in 2287 patients. Thus, revascularization could be safely deferred until the patient’s symptoms had proven refractory to medical therapy, when they would then be considered for revascularization to improve their symptomatic status.

The nuclear substudy of the COURAGE trial, subsequently published by Shaw et al.,70 confirmed the importance of the quantitative noninvasive assessment of perfusion on serial stress SPECT imaging in a subset of 314 patients from the COURAGE trial. Stress-induced ischemia measured quantitatively by a core laboratory was more likely to be improved by a strategy of optimal medical therapy plus revascularization compared with a strategy of optimal medical therapy. Moreover, patients who had improvement in quantitative ischemia, regardless of whether it was achieved by optimal medical therapy plus revascularization or by optimal medical therapy alone, had fewer subsequent hard events (death or nonfatal myocardial infarction), but the difference was not significant after adjustment for baseline differences.

Another potential advantage of stress testing with or without imaging is the demonstration of ischemia in patients without obstructive CAD. Recent evidence, particularly from the Women’s Ischemic Syndrome Evaluation study, a multicenter study sponsored by the National Heart, Lung, and Blood Institute,71,72 has demonstrated that many women without obstructive CAD continue to have symptoms and a poor quality of life.73,74 Many of these women have evidence of stress-induced ischemia, which is likely related to microvascular dysfunction.75 More recently, such patients have also been shown to have an adverse prognosis.76

### Table 4. Selected Studies of the Duke Treadmill Score (DTS) in Large, Broadly Defined Patient Populations With Known or Suspected Chronic CAD

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Location</th>
<th>n</th>
<th>Stress test</th>
<th>Mean Follow-up</th>
<th>Hard End Points</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mark (30)</td>
<td>Duke</td>
<td>2842</td>
<td>TMET</td>
<td>5.0</td>
<td>CD</td>
<td>Original retrospective study defining DTS</td>
</tr>
<tr>
<td>Mark (18)</td>
<td>Duke</td>
<td>613</td>
<td>TMET</td>
<td>4.0</td>
<td>CD</td>
<td>Prospective, outpatients, DTS better than clinical, defined risk thresholds</td>
</tr>
<tr>
<td>Alexander (31)</td>
<td>Duke</td>
<td>976 w</td>
<td>TMET</td>
<td>2.0</td>
<td>CD</td>
<td>Women have a lower risk than men for a given score, but DTS still predicts CD</td>
</tr>
<tr>
<td>Kwok (32)</td>
<td>Mayo</td>
<td>906</td>
<td>SPECT</td>
<td>7.0</td>
<td>D/CD/MI</td>
<td>DTS predicts all HE in patients with ST-T abn. on resting ECG</td>
</tr>
<tr>
<td>Marwick (33)</td>
<td>Cleveland</td>
<td>5375</td>
<td>Echo</td>
<td>5.5</td>
<td>D</td>
<td>DTS incremental to clinical/clinical and echo</td>
</tr>
<tr>
<td>Morise (34)</td>
<td>WV</td>
<td>4640</td>
<td>TMET</td>
<td>2.8</td>
<td>D</td>
<td>DTS of modest value; gender-specific scores better</td>
</tr>
<tr>
<td>Liao (35)</td>
<td>Duke</td>
<td>997</td>
<td>SPECT</td>
<td>4.1 med</td>
<td>D/CD/MI</td>
<td>DTS incremental to EF for D/CD, but not MI</td>
</tr>
<tr>
<td>Lauer (36)</td>
<td>Cleveland</td>
<td>33,268 (d)</td>
<td>TMET</td>
<td>6.2 med</td>
<td>D</td>
<td>DTS significant with C-index=0.73 multivariable nomogram improved C-index to 0.83</td>
</tr>
<tr>
<td>Rafie (37)</td>
<td>Palo Alto VA</td>
<td>1,959</td>
<td>TMET</td>
<td>5.4</td>
<td>CD</td>
<td>DTS significant with C-index 0.76; age adjustment improved C-index to 0.80</td>
</tr>
<tr>
<td>Peteiro (38)</td>
<td>A. Coruna Spain</td>
<td>1,647</td>
<td>Echo</td>
<td>2.5</td>
<td>CD/MI</td>
<td>DTS incremental to clinical/clinical+echo</td>
</tr>
</tbody>
</table>

TMET indicates treadmill exercise test; Echo, exercise echocardiogram; SPECT, exercise SPECT study; D, death; CD, cardiac death; MI, nonfatal myocardial infarction; HE, hard events; w, women; m, men; d, derivation set; v, validation set; C-index, concordance index; abn, abnormalities; med, median.
Limited Evidence for CT Coronary Angiography

Compared with the wealth of diagnostic and prognostic information for stress testing with or without imaging, CT coronary angiography has a fairly limited evidence base. The technology in this area has rapidly evolved. Early studies performed with 4-slice or 16-slice CT scanners are no longer relevant, as the latest generation 64-slice CT scanners have demonstrably better results when compared with invasive coronary angiography. Although multiple studies have now shown that 64-slice CT coronary angiography has a close relationship to invasive coronary angiography, these studies have by necessity focused on patients who were referred for invasive coronary angiography. Such patients are more likely to have a higher prevalence of coronary artery disease, as well as high-risk findings on other noninvasive tests, compared with the patient cohorts (consisting primarily of intermediate-likelihood patients) that are most appropriate for noninvasive assessment. There is only very limited published data regarding the subsequent outcomes of patients studied with CT angiography.

Only a few studies that have compared the results of 64-slice CT coronary angiography with SPECT myocardial perfusion imaging using a standardized approach. Figure 7 shows 4 representative studies from the most recent literature, which include only 324 total patients. Three of these studies come from leading European centers; the remaining study comes from Japan. These studies have demonstrated a consistently high negative predictive value for CT coronary angiography, i.e., a coronary angiogram that does not demonstrate obstructive disease is generally associated with a negative SPECT myocardial perfusion image. However, the negative predictive value is not 100%. Although it can be argued that this finding might reflect false-positive myocardial perfusion images, it is also possible that some of these patients had true stress-induced ischemia in the absence of obstructive disease, as described above. An anatomic approach using CT coronary angiography would therefore misclassify such patients as normal.

These 4 studies have additional limitations. Only a minority of the subjects (27% to 45%) were women. Although intermediate-risk patients were common (75% to 86%), 2 of the 4 studies included patients with known coronary artery
disease and a majority of the patients were referred to invasive angiography in 3 of the studies, suggesting that this was a more selected higher-risk group than the intermediate-likelihood and intermediate-risk patients who are most suitable for noninvasive risk assessment. Two of the 4 studies did not report body mass index. In the other 2 studies, the mean body mass index was 24 and 26, suggesting that obese patients were underrepresented in these cohorts compared with current clinical practice. Patients with atrial fibrillation were excluded in 3 of the 4 studies. Renal insufficiency is only mentioned as an exclusion in 1 of the 4 studies but presumably was an exclusion in all 4 cohorts. Thus, the spectrum of patients reported in these 4 studies is not representative of the broad population of the intermediate-risk patients who are most suitable for noninvasive assess-

<table>
<thead>
<tr>
<th>Author (ref)</th>
<th>Year</th>
<th>Stress</th>
<th>Total No. of Pts</th>
<th>Average Follow-Up, Months</th>
<th>Events</th>
<th>Ischemia</th>
<th>No Ischemia</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Picano (52)</td>
<td>1989</td>
<td>DIP†</td>
<td>539</td>
<td>36</td>
<td>D, MI</td>
<td>23.0</td>
<td>0.7</td>
<td>—</td>
</tr>
<tr>
<td>Sawada (53)</td>
<td>1990</td>
<td>NL TME</td>
<td>148</td>
<td>28.4</td>
<td>D, MI</td>
<td>—</td>
<td>—</td>
<td>0.6</td>
</tr>
<tr>
<td>Mazeika (54)</td>
<td>1993</td>
<td>DSE†</td>
<td>51</td>
<td>24</td>
<td>D, MI, UA</td>
<td>16</td>
<td>38</td>
<td>—</td>
</tr>
<tr>
<td>Krivokapick (55)</td>
<td>1993</td>
<td>DSE†</td>
<td>360</td>
<td>~12</td>
<td>D, MI</td>
<td>10.8</td>
<td>3.1</td>
<td>—</td>
</tr>
<tr>
<td>Afridi (56)</td>
<td>1994</td>
<td>DSE†</td>
<td>77</td>
<td>10</td>
<td>D, MI</td>
<td>48</td>
<td>8.9</td>
<td>3</td>
</tr>
<tr>
<td>Poldermans (57)</td>
<td>1994</td>
<td>DSE†</td>
<td>430</td>
<td>17</td>
<td>D, MI</td>
<td>6.6</td>
<td>3.4</td>
<td>—</td>
</tr>
<tr>
<td>Coletta (58)</td>
<td>1994</td>
<td>DIP†</td>
<td>268</td>
<td>16</td>
<td>D, MI</td>
<td>17.9</td>
<td>1.4</td>
<td>—</td>
</tr>
<tr>
<td>Kamaran (59)</td>
<td>1995</td>
<td>DSE†</td>
<td>210</td>
<td>8</td>
<td>D, MI</td>
<td>69</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Williams (60)</td>
<td>1996</td>
<td>DSE†</td>
<td>108</td>
<td>16</td>
<td>D, MI, Re</td>
<td>32.6</td>
<td>7.3</td>
<td>—</td>
</tr>
<tr>
<td>Anthopoulos (61)</td>
<td>1996</td>
<td>DSE†</td>
<td>120</td>
<td>14</td>
<td>D, MI</td>
<td>13.6</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Marcovitz (62)</td>
<td>1996</td>
<td>DSE†</td>
<td>291</td>
<td>15</td>
<td>D, MI</td>
<td>12.8</td>
<td>8.2</td>
<td>1.1</td>
</tr>
<tr>
<td>Hepler (63)</td>
<td>1997</td>
<td>TME†</td>
<td>508 w</td>
<td>41</td>
<td>D, MI, Re</td>
<td>9.2</td>
<td>1.3</td>
<td>—</td>
</tr>
<tr>
<td>McCully (64)</td>
<td>1998</td>
<td>NL TME</td>
<td>1325</td>
<td>23</td>
<td>D, MI</td>
<td>—</td>
<td>—</td>
<td>0.5</td>
</tr>
<tr>
<td>Chua (65)</td>
<td>1998</td>
<td>DSE†</td>
<td>860</td>
<td>24</td>
<td>D, MI</td>
<td>6.9</td>
<td>6.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Cortigiani (66)</td>
<td>1998</td>
<td>DSE or DIP†</td>
<td>456 w</td>
<td>32</td>
<td>D, MI</td>
<td>2.9</td>
<td>0.3</td>
<td>—</td>
</tr>
<tr>
<td>Davar (67)</td>
<td>1999</td>
<td>NL DSE</td>
<td>72 w</td>
<td>13</td>
<td>D, MI</td>
<td>—</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>5823</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

†New wall motion abnormality considered “positive” for inducible ischemia.
DIP indicates dipyridamole stress echocardiography; DSE, dobutamine stress echocardiography; NL, series with follow-up restricted to patients with normal studies; TME, treadmill stress echocardiography. Other abbreviations as in Table 5.
Modified from Ref. 23. Reproduced with permission.

Figure 6. Coronary flow response measured by Doppler echocardiography over the left anterior descending (LAD) in patients with cardiac Syndrome X (CSX) compared to control subjects. The CSX patients are divided into 2 groups based on the presence (+) or absence (−) of an ischemic response on dobutamine stress MRI (CMR). Reproduced with permission from Ref. 76.

Figure 7. Positive predictive value (PPV) and negative predictive value (NPV) for 4 representative series78–82 from the recent literature comparing 64-slice computed tomography coronary angiography with a standardized protocol for myocardial perfusion imaging. Modified with permission from Dorbala et al. Myocardial perfusion imaging and multidetector computed tomographic coronary angiography: appropriate for all patients with suspected coronary artery disease? J Am Coll Cardiol. 2006;48:564.
We do not know how CT angiography compares to SPECT imaging (or exercise ECG testing or exercise echocardiography) in such patients. Furthermore, the positive predictive value in these 4 studies ranged from 40% to 65%. This limited positive predictive value presumably reflects the assessment of some stenoses of intermediate severity, which might not be physiologically significant. However, several of these studies reported limited positive predictive value for more severe stenoses. Sato et al,81 (Figure 8) reported that only 54% of stenoses judged to be 70% to 80% had reversible defects by SPECT. Gaemperli et al,82 reported that the probability of SPECT ischemia was 25% for lesions of 80% diameter stenosis, and 50% for lesions of 95% stenosis (Figure 9). Thus, the significant anatomic lesions seen in these studies were often not physiologically significant. These patients would also potentially be misclassified by an anatomic approach.

These somewhat surprising results may reflect the known limitation of CT coronary angiography for the assessment of stenosis severity. Figure 10 shows results reported by Leber et al in 2005 using 64-slice CT.83 The correlation coefficient comparing the stenosis by CT coronary angiography and the stenosis by quantitative invasive coronary angiography was only 0.54. More importantly, many stenoses were judged to be 0% by one approach and 20% to 70% by the other approach. Although a more recent study84 did not find examples of such extreme discordance, the correlation coefficient between stenosis severity assessed by CT angiography and stenosis severity assessed by invasive coronary angiography was still only 0.53.

**Potential Concerns Regarding an Anatomic Approach**

During a recent visit to a major academic center in a major American city, I observed a percutaneous coronary intervention procedure in a middle-aged man with a 40% to 50% right coronary stenoses. The patient had no significant disease in the left circumflex or left anterior descending coronary artery. This patient had undergone CT coronary angiography at the suggestion of his internist because of a positive family history. He had no history of any exertional symptoms, had never had a stress test to demonstrate ischemia, and had never actually seen a cardiologist in consultation before he was directly referred by his internist for coronary intervention. When I questioned the wisdom of this approach, I was told that “if we don’t do this procedure, we will anger the referring physician, and he will find someone else in the city willing to do it.” I learned that this patient example was not an isolated one, because this particular laboratory had already seen 3 similar patients within the preceding month. Although this anecdote is not supported by any systematic data, it does demonstrate a potential abuse associated with CT coronary angiography. Noncardiologists may overreact to the presence of moderate stenoses and institute patient referrals to interventional cardiologists, who may then respond to the oculo-

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**Figure 8.** The prevalence of reversible perfusion defects on stress SPECT imaging in coronary territories supplied by vessels with varying stenosis demonstrated on computed tomography coronary angiography (CTA). The percent stenosis and the number of vessels are shown for each group. The probability values compare each group with the 200 patients who had 0% to 60% stenosis by CTA. Reproduced with permission from Ref. 81.

**Figure 9.** The predicted probability of ischemia on stress SPECT imaging from logistic regression analysis (equation shown) for a given coronary artery diameter stenosis, as assessed by quantitative invasive coronary angiography (QCA) or CT coronary angiography (CTA). Reproduced with permission from Ref. 82.

**Figure 10.** Relationship between the diameter of coronary stenosis assessed by 64-slice computed tomography (CT) and the diameter stenosis assessed by quantitative invasive coronary angiography (QCA). The regression equation is shown. The correlation coefficient was 0.54. Note the substantial number of stenoses that were 0% by one modality and not 0% by the other modality. Reproduced with permission from Ref. 83.
stenotic reflex and perform procedures of questionable benefit. Recent literature has also questioned the population radiation exposure that may occur with widespread use of CT coronary angiography. A widely publicized study used Monte Carlo simulation to estimate radiation doses and then used these doses to estimate the lifetime attributable risk of cancer for different organs. The lifetime risk clearly varied with age and gender and was greatest in young women. Although recent technical advances can substantially reduce the radiation exposure associated with CT angiography, these important measures may not be applied uniformly in practice. Depending on the specific radioisotope used, stress SPECT imaging may be associated with a similar estimated radiation dose.

An anatomic approach may possibly reduce the likelihood of appropriate medical care of the patient. Patients who are found to have normal or near-normal CT coronary angiograms may be less likely to modify their lifestyle and risk factors, and their physicians may be less likely to carefully follow them in this regard. The available outpatient data from the Minnesota Community Measurement Project, the only systematic population-based data of its kind in the country, shows disappointing results for the control of hypertension, hyperlipidemia, and diabetes. The COURAGE trial has demonstrated that optimal medical therapy can be delivered in a consistent fashion. The demonstration of normal or minimally abnormal coronary arteries on CT angiography may reduce the interest of the patient and his or her physician in appropriate lifestyle and risk factor modification.

Conclusions

The use of stress testing with or without imaging in the noninvasive diagnosis and prognostic assessment of chronic CAD is well established. Its important role is emphasized in existing clinical practice guidelines and supported by an extensive evidence base. CT coronary angiography is a very promising technique. The technical advances in this field within the past few years are truly astounding. However, much more research is needed before this technique can be applied on a widespread basis in clinical practice. In the meantime, the preferred approach should continue to be stress testing with or without imaging. Hopefully, future studies will provide more evidence to support the role of CT angiography in appropriate patients and demonstrate that its benefit justifies the required additional investment in personnel, training, and equipment.

Disclosures

R.J.G. has a research grant from King Pharmaceuticals for core laboratory studies regarding part of the development program for an adenosine agonist. R.J.G. also has served as a consultant to Cardiovascular Clinical Studies for the WOMEN study.

References


Response to Gibbons

James K. Min, MD; Leslee J. Shaw, PhD

We read with great interest the viewpoints of Dr. Gibbons on “Stress Testing With and Without Imaging Perspective.” In short, we agree with his assessment that the evidence supporting the use of stress testing is robust both for diagnostic and prognostic assessment of individuals with suspected coronary artery disease (CAD). Nevertheless, we also believe that the evidence for coronary computed tomographic angiography (CCTA) supports its use as an anatomic imaging strategy that is both clinically as well as cost efficient.

Although the paradigm of initial functional ischemia testing is good, it is far from perfect. Rates of “normal” invasive coronary angiograms, even in individuals exhibiting abnormal stress tests, remain excessively high. Indeed, the entirety of available evidence to date suggests that for patients without known CAD, CCTA is clinically as effective as ischemia coronary angiography with multi-slice computed tomography and myocardial perfusion imaging. J Am Coll Cardiol. 2006;48:2508–2514.


Furthermore, CCTA is superior to other noninvasive tests for diagnosis nonobstructive CAD and permits comprehensive coronary atherosclerosis assessment in a manner not possible by routine ischemia testing. Identification of individuals with less severe forms of atherosclerosis permits more aggressive risk factor modification and medical treatment at an earlier stage.

In these individuals without obstructive CAD by CCTA, the near-, intermediate-, and long-term prognosis is excellent. On the basis of available evidence to date, the use of CCTA permits prognostic risk assessment in a manner that is at least as robust as myocardial perfusion testing and permits more subtle distinction for individuals with milder forms of CAD. Furthermore, the warranty period of a normal CCTA persists for more than 6 years, which is longer than the 2 years that has been demonstrated for a normal myocardial perfusion scan. Thus, as the evidence for CCTA continues to grow, we believe that a CCTA-first strategy can and will be successful. Use of this paradigm, based upon previous data, would suggest a low rate of additional necessary downstream testing that is both clinically efficient as well as cost efficient.
Noninvasive Diagnosis and Prognosis Assessment in Chronic Coronary Artery Disease: Stress Testing With and Without Imaging Perspective
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