

## The Nuclear Utility in the Community (NUC) Study: Technetium<sup>99m</sup> Based Myocardial Perfusion Imaging Predicts Outcome in the Community Outpatient Setting

Gregory S Thomas MD, MPH,<sup>1,2</sup> Michael I Miyamoto MD, MS,<sup>1,3</sup> A Peter Morello III ScB,<sup>1,4</sup> Haresh Majmundar CNMT,<sup>1</sup> Jennifer J Thomas BA,<sup>1,5</sup> Christine Sampson,<sup>1</sup> Joshua T Ondatje BS,<sup>1</sup> Melyssa M Payne BS,<sup>1</sup> Lisa A Ryals CNMT,<sup>1</sup> Daniel B Kramer BA,<sup>6</sup> Rory Hachamovitch MD, MS,<sup>7</sup> Leslee J Shaw PhD<sup>8</sup>

<sup>1</sup> Mission Internal Medical Group

<sup>2</sup> University of California, Irvine

<sup>3</sup> University of California, San Diego

<sup>4</sup> Brown University

<sup>5</sup> Yale University

<sup>6</sup> Harvard Medical School

<sup>7</sup> University of Southern California

<sup>8</sup> Atlanta Cardiovascular Research Institute

### ABSTRACT

**Background.** While the prognostic value of myocardial perfusion imaging (MPI) has been well validated in academic centres, the feasibility of extending this data to community-based MPI remains uncertain. Additionally, while <sup>99m</sup>Tc-based radioisotopes have become the predominant tracers used for MPI in the United States (US), often performed with pharmacologic stress, most prognostic studies have reported on patients undergoing thallium<sup>201</sup> studies performed with exercise stress. This study was carried out to evaluate the prognostic value of community-based MPI and to assess the incremental value of individual elements of <sup>99m</sup>Tc SPECT.

**Methods.** We prospectively followed 1,612 consecutive patients undergoing stress <sup>99m</sup>Tc-based SPECT in a US outpatient community laboratory who experienced 71 hard events (cardiac death or nonfatal MI) over 24±7 months. Mean age was 65±12 years and 612 women were included. Patients were censored from further follow-up at the time of revascularisation.

**Results.** Patients whose scans were normal incurred an annualised event rate of 0.4%, compared to 2.3% for those with abnormal scans (p<0.0001). Subset analysis demonstrated comparable risk stratification for women and men and those referred for pharmacologic and exercise stress. After adjusting for pre-test variables, multivariable Cox regression analysis found the most potent independent components of MPI to be, in decreasing order of importance, transient ischaemic dilation, extent of reversibility, post-stress ejection fraction, extent and severity of the stress perfusion defect, and the overall test result (normal or abnormal). Each 1% decrement of ejection fraction (EF) predicted a 3% increase in risk (p=0.0009). Post-MPI angiography and revascularisation increased commensurate with the extent and severity of the MPI result including decreasing post-stress EF.

**Conclusion.** A normal myocardial perfusion study predicts extraordinarily low 2-year risk. A study that is abnormal should not be regarded as simply abnormal; its components allow further independent predictive power. Based on the Nuclear Utility in the Community study, perfusion imaging is portable and transferable to the outpatient community setting in the US and, by implication, worldwide.

*Keywords:* adenosine, prognosis, radioisotopes, scintigraphy, women

### INTRODUCTION

Myocardial perfusion imaging (MPI) plays a critical role in the evaluation of patients with suspected or known coronary artery disease (CAD) in the US. MPI has

attained Class I or II indications in the evaluation of patients with suspected CAD, stable angina, acute coronary syndrome, myocardial infarction (MI), following revascularisation and prior to high risk

noncardiac surgery.<sup>1</sup> Initially only a diagnostic test, over the last decade MPI now provides essential prognostic information and has become integrated into mainstream cardiology care. For example, in our outpatient laboratory, 53% of patients undergoing testing have known CAD while 47% are undergoing MPI for diagnostic purposes.

Between 1992 and 2001, MPI use increased almost fourfold in the United States (US) with 7.8 million studies performed in 2001.<sup>2,3</sup> In 2003, an estimated 1 in 15 Americans aged 40 or above underwent MPI. Traditionally, hospitals performed the majority of MPI, but today outpatient imaging in the physician office drives much of the growth of MPI in the US. Between 1992 and 2003, the percentage of all scans performed in the office setting increased from 13 to 40%.<sup>2,3</sup> While the prognostic value of MPI in academic hospital-based centres has been well documented, only scant evidence suggests that similar prognostic information can be obtained in the community.<sup>4,5,6</sup>

Concomitantly, the availability of technetium-based perfusion agents and expanded computer processing power has facilitated the increasing use of gated single photon emission tomography (SPECT).<sup>7</sup> Between 1996 and 2002, the percentage of perfusion scans in which ejection fraction (EF) was obtained in the US Medicare population increased from 10 to 92%.<sup>8</sup> However, few studies have evaluated the prognostic value of EF obtained by gated SPECT as well as other non-perfusion characteristics such as transient ischaemic dilation or resting left ventricle size when assessed by these new <sup>99m</sup>Tc labelled agents. As well, while few studies have evaluated the prognostic value of pharmacologic stress, pharmacologic stress constituted 43% of all stress MPI studies in 2003.<sup>3</sup> Thus, the aims of the Nuclear Utility in the Community (NUC) study were threefold:

1. to evaluate the prognostic value of exercise and pharmacologic MPI in the community setting
2. to determine the components of <sup>99m</sup>Tc-sestamibi MPI that best predict outcome, and
3. to evaluate the post-test utilisation of cardiac catheterisation and revascularisation following MPI performed in this non-academic setting.

The original publication of the NUC study was published in 2004.<sup>9</sup>

## METHODS

### *Study Population*

The study population consisted of 1,612 patients who underwent 1,782 <sup>99m</sup>Tc-sestamibi stress gated SPECT imaging studies between August 1997 and March 1999 in the outpatient nuclear cardiology laboratory of the Mission Internal Medical Group in Mission Viejo, California. Follow-up was obtained in 99.81% of patients at a mean of  $24 \pm 7$  months, ranging from a minimum of 13 to a maximum of 36 months. Over the study period, 252 (16%) underwent percutaneous coronary intervention (PCI), and 105 (7%) underwent coronary artery bypass grafting (CABG). As revascularisation was expected to alter natural history, patients were censored from further follow-up at the time of revascularisation.

### *Stress and SPECT Protocols*

Exercise was the method of stress in 63% of patients, adenosine in 34%, and dobutamine in 3%. Among patients undergoing adenosine stress, 66% underwent simultaneous low-level treadmill exercise during a 6-minute adenosine infusion of 140mcg/kg/min (termed "Adenoex"), as previously described.<sup>10</sup> Simultaneous treadmill exercise was not performed if the patient was judged by the supervising physician to be physically unable to walk for 6 minutes or if his/her resting electrocardiogram demonstrated left bundle branch block or right ventricular pacing. SPECT imaging, image interpretation and grading of severity were performed as previously described.<sup>1</sup> One of 2 nuclear cardiologists certified by the Certification Board of Nuclear Cardiology (GST, MIM) interpreted each study and included an overall 5-point global score of normal, probably normal, equivocal, probably abnormal, or abnormal. A scan was defined to be abnormal if either perfusion, left ventricular function, or left ventricular size was abnormal. Expected abnormal septal motion secondary to bundle branch block, ventricular pacing, or following cardiac surgery was regarded as normal. For the purposes of the prognostic component of this investigation, scans interpreted as normal, probably normal, or equivocal were grouped as normal. Those scored as abnormal or probably abnormal were grouped as abnormal. Only in evaluating the use of post-test coronary angiography and revascularisation was the 5-point scoring system retained.

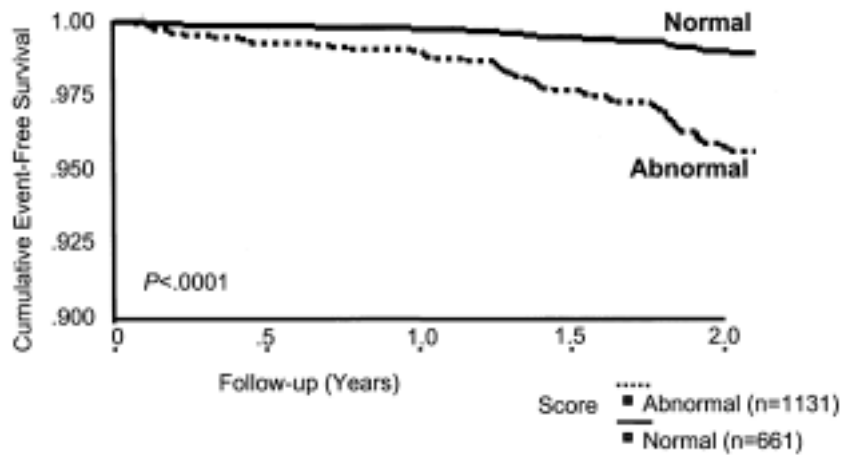


Fig. 1. Event-free survival by global score.\*

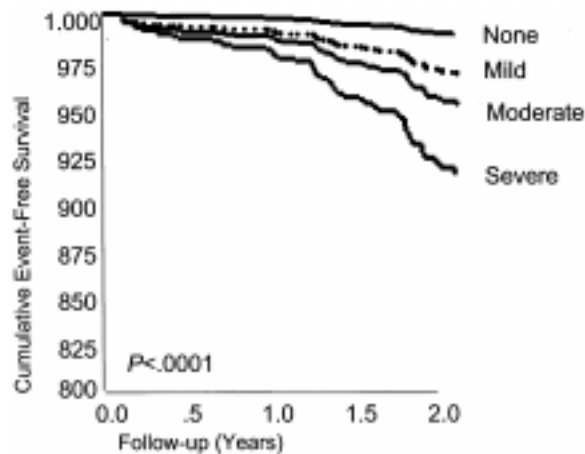


Fig. 2. Event-free survival by extent and severity.\*

**RESULTS**

**Risk Stratification**

Among patients with normal and abnormal scans, 2-year event-free survival was 99.2% and 95.4%, respectively ( $p < 0.0001$ ) (Fig. 1). Of the events that occurred in patients with normal scans, all were nonfatal MI.

The extent and severity of the stress defect enabled further stratification (Fig. 2). Patients with extent and severity scores of none, mild, moderate and severe experienced 2-year event-free survival rates of 99.0%, 97.0%, 95.3%, and 91.7%, respectively ( $p < 0.0001$ ). Similarly, event-free survival based on the degree of reversibility was 98.6%, 96.0%, and 91.3% for those

with none-mild, moderate, and severe reversibility, respectively ( $p < 0.0001$ ).

The stratification observed based on the degree of transient ischaemic dilation (TID) is shown in Figures 3a and 3b. Two-year event-free survival for all patients with no, mild and moderate-severe TID was 97.0%, 93.8%, and 88.0%, respectively ( $p < 0.0001$ ). For only those undergoing dual isotope imaging, the respective 2-year event-free survival was 99.0%, 95% and 92.5% ( $p < 0.0001$ ).

Post-stress EF was also highly predictive of outcome as shown in this survival curve bracketed by its confidence limits (Fig. 4). Event-free survival was directly related to post-stress EF, such that event-free survival decreased from 99.0 to 87.0% with a decreasing post-stress EF of 70 to 20% ( $p < 0.0001$ ).

Integrating function and perfusion, overall event-free survival for patients with an EF above or below 40%,

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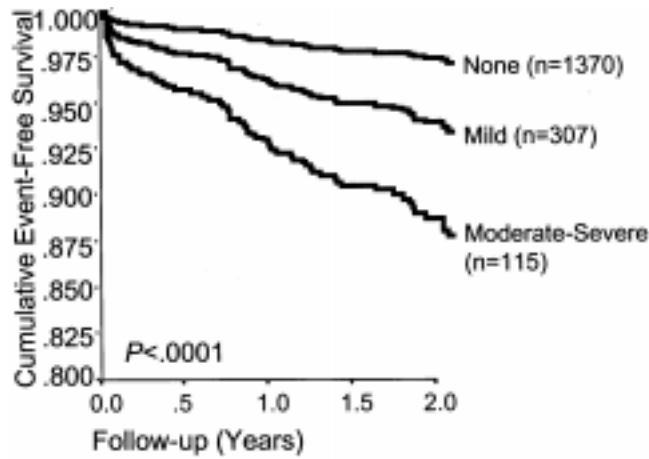


Fig. 3a. Event-free survival by TID during 2-day Tc99m and dual isotope studies.\*

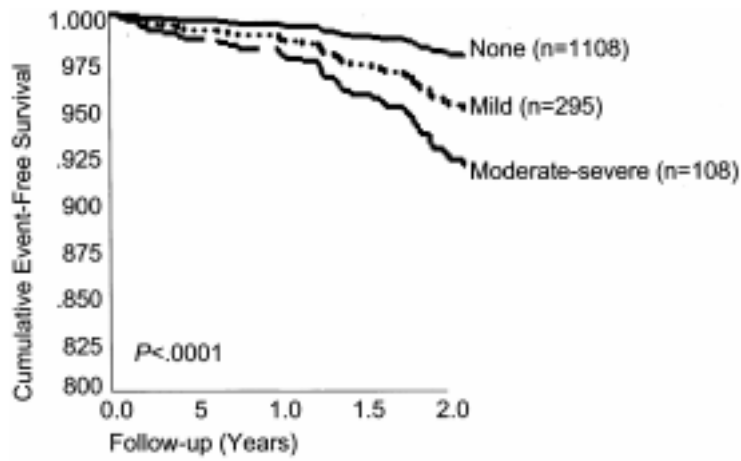


Fig. 3b. Event-free survival by TID during dual isotope SPECT.\*

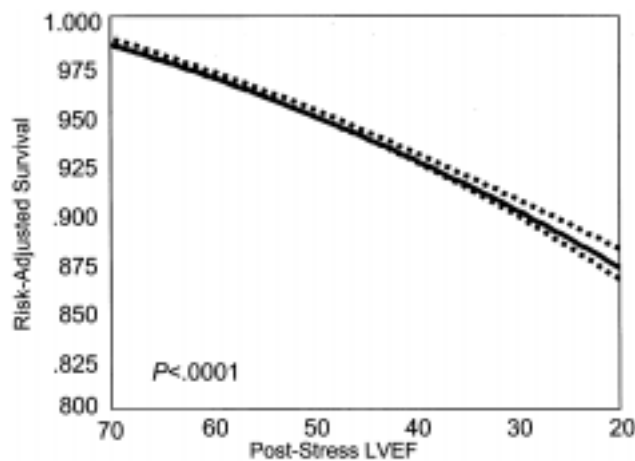


Fig. 4. Risk-adjusted event-free survival by post-stress EF.\*

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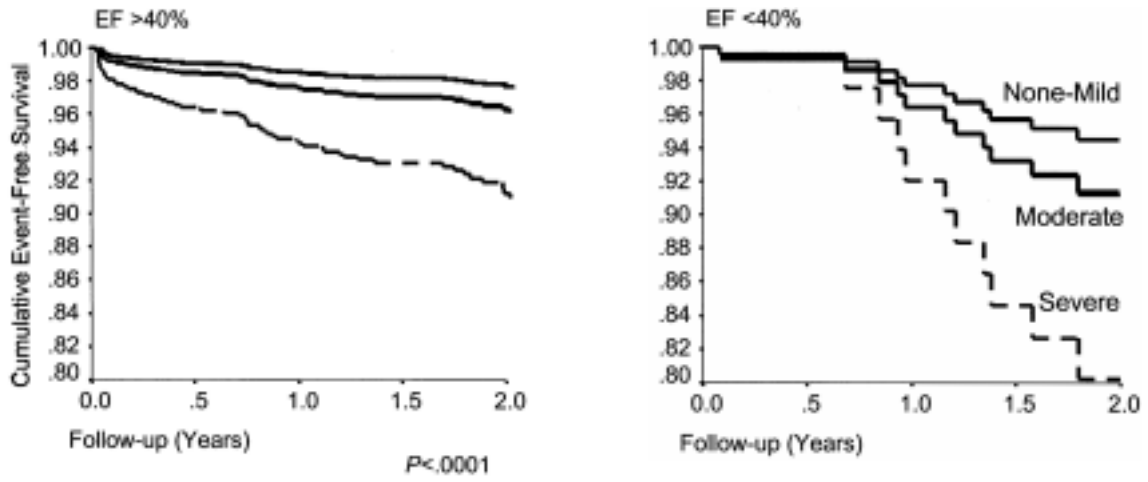


Fig. 5. Event-free survival based on reversibility relative to EF.\*

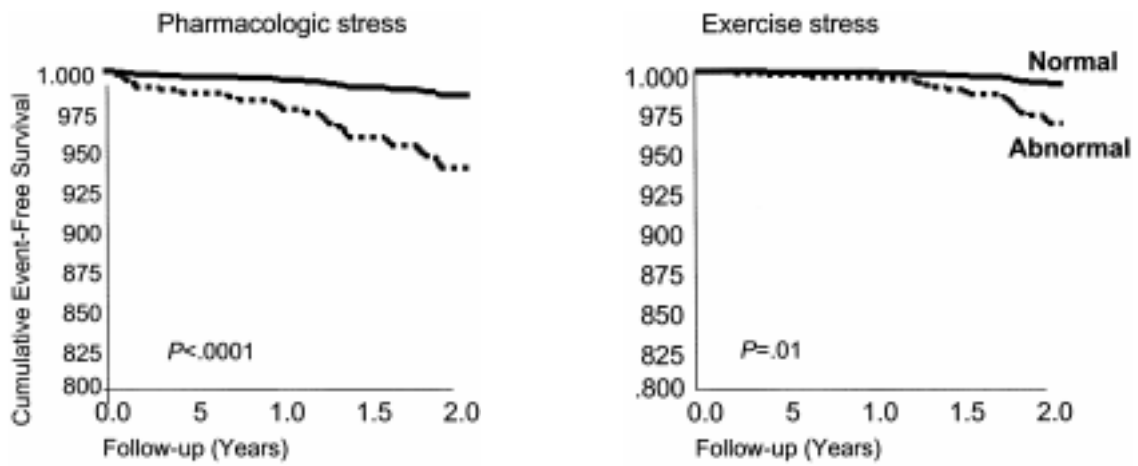


Fig. 6. Event-free survival by stress type.

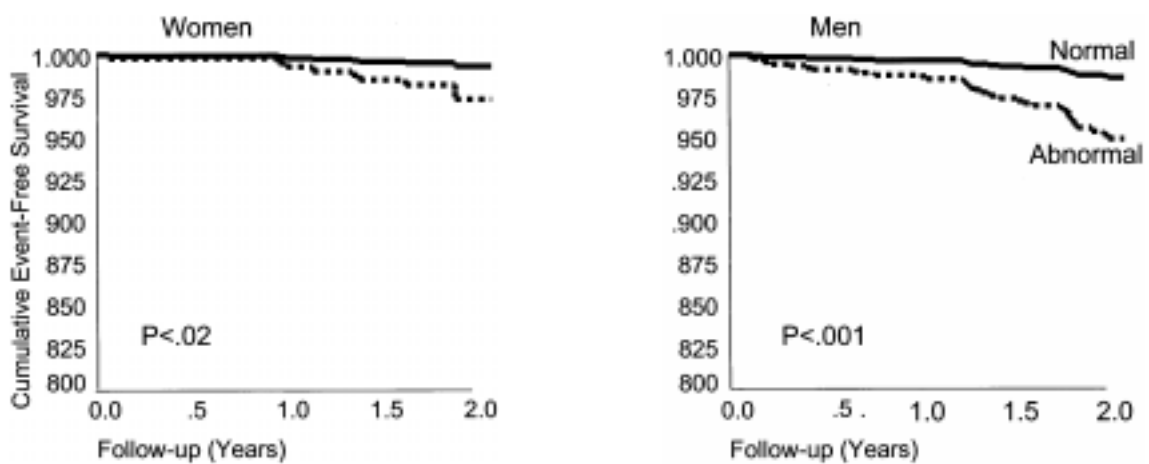


Fig. 7. Event-free survival by gender.

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with and without inducible ischaemia, is shown in Figure 5. For those whose EF was >40%, the 2-year event-free survival rate worsened from 97.8 to 92.0% as the degree of ischaemia increased. For those patients with an EF <40%, survival worsened from 94.2 to 80.4% with increasing ischaemia. Ischaemia predicted outcome in each EF decile from >50% down to <20% ( $p<0.0001$ ).

### ***Cox Multivariable Regression Model***

After adjusting for age, gender, resting ECG, prior known CAD, cigarette smoking, hypertension, hypercholesterolemia, diabetes, and family history of CAD, the most important independent prognostic variables were, in order of importance, TID, extent of reversibility, post-stress EF, extent and severity of the stress perfusion defect, and the global score (Table 1). For TID, the relative risk increased 3.3-fold for patients with moderate to severe TID and 1.6-fold for patients with mild TID ( $p=0.0002$ ). For post-stress EF, each 1% decrement in EF represented a 3% increase in risk ( $p=0.0009$ ).

### ***Subset Analysis***

Figure 6 demonstrates the stratification observed based on the type of stress, either pharmacologic (adenosine in 548 and dobutamine in 48) or exercise in 1016.

Figure 7 demonstrates stratification in men and women. Women represented 612 members of the cohort and had an average age of  $66\pm 11$  compared to  $64\pm 12$  years for men. While women experienced lower annualised event rates than men, they were well stratified by MPI. Women with normal and abnormal SPECT scans had event rates of 0.4% and 1.8%, respectively ( $p<0.0001$ ); for men the respective rates were 0.6% and 3.6% ( $p<0.0001$ ).

### ***Post-test Use of Cardiac Catheterisation and Coronary Revascularisation***

During the study period, 499 patients (31%) underwent coronary angiography. The frequency of angiography based on the global score is represented in Figure 8. Catheterisation was rarely performed in patients with normal scans: 2% at 90 days and 3% at the end of 2 years ( $p<0.0001$ ).

Catheterisation increased with increasing ischaemia, with 47% of those with a severe reversibility score undergoing angiography within 90 days and 67% within 2 years ( $p<0.0001$ ). Revascularisation also increased with increasing ischaemia (Fig. 9). Among patients with normal scans, PCI was performed in only 0.3% during

Table 1. Multivariable Cox Models – Risk-adjusted\*.

|                   | Relative Risk | 95% CI   |          | P value |
|-------------------|---------------|----------|----------|---------|
|                   |               | Lower CI | Upper CI |         |
| TID               | 1.63          | 1.2      | 2.21     | .002    |
| Reversibility     | 1.58          | 1.16     | 2.15     | .003    |
| Post-stress EF    | 0.97          | 0.96     | 0.99     | .009    |
| Extent & Severity | 1.37          | 1.03     | 1.82     | .03     |
| Global Score      | 2.49          | 1.90     | 3.26     | .03     |

\* Controlling for age, gender, rest ECG, Hx CAD, smoking, chol, DM, Family Hx CAD

the first 90 days and 1.0% by the end of 2 years ( $p<0.0001$ ). CABG was performed in 0.4% and 0.7% over the same time intervals ( $p<0.001$ ). The highest rates of PCI (37% at 2 years) and CABG (14.0% at 2 years) occurred in patients with a severe reversibility score ( $p<0.001$ ).

As seen with reversibility, catheterisation, PCI, and CABG increased with increasing extent and severity of the stress defect and with decreasing post-stress EF ( $p<0.0001$ ).<sup>9</sup> (Data not shown)

## **DISCUSSION**

MPI, as demonstrated in this cohort of 1,612 patients, is a powerful predictor of risk of cardiac death and MI. Patients with normal scans had a remarkably low event rate, lower than the expected annual MI or cardiac death rate of approximately 1% per year in a US aged matched population. Of those with abnormal studies, multiple elements of MPI provide incremental prognostic information after multivariable adjustment for clinical factors. In descending rank order, these include TID, defect reversibility, post-stress EF, extent and severity of the defect at stress and the global score. These elements determine the degree of abnormality that can then be used to determine the need for catheterisation and potential intervention to alter this risk. As demonstrated in the NUC study, clinicians' use of post-MPI angiography, PCI and CABG increased commensurate with the prognostic risk assessed by MPI.

The incremental value of MPI extends consistently across multiple subgroups, including those referred for pharmacologic and exercise testing, women, and men. The prognostic power of perfusion imaging performed in the community as assessed in this study compares favourably to those obtained in academic centres.<sup>4,6</sup> Thus, perfusion imaging is a mature technique,

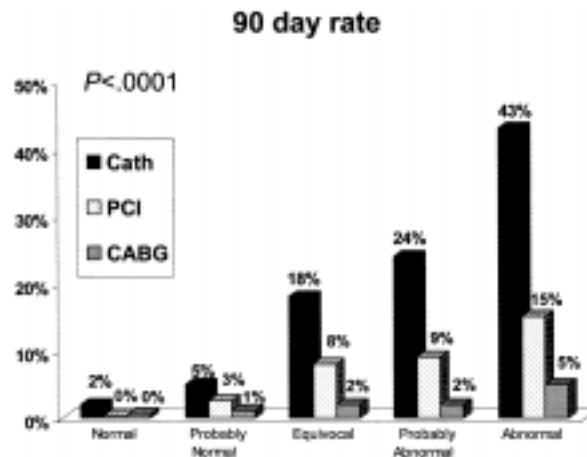


Fig. 8. The relationship between global score and percutaneous coronary intervention and coronary artery bypass surgery.\*

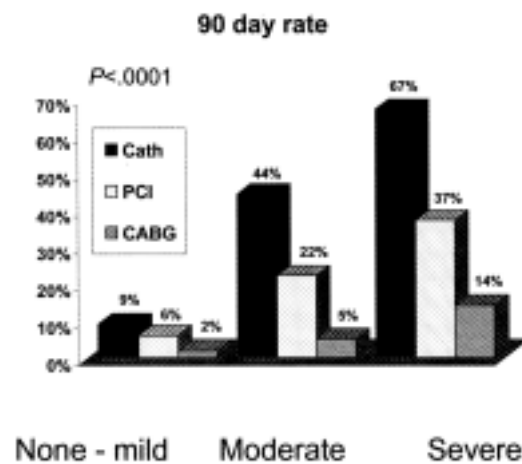


Fig. 9. The relationship between reversibility and percutaneous coronary intervention and coronary artery bypass surgery.\*

evidence-based, portable and transferable to a community setting in the US and, by implication, to communities throughout the world.

Challenges do exist, however, to the successful use of MPI in the community setting. Strategies to meet these challenges include careful adherence to the procedural guidelines of the American Society of Nuclear Cardiology (ASNC) and the practice guidelines of ASNC/American College of Cardiology/American Heart Association; laboratory accreditation and certification of the physician by the Certification Board of Nuclear Cardiology, the ASNC Report Card and most importantly, an emphasis on quality in all aspects of MPI.<sup>11</sup>

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The NUC study focused on newer elements of MPI other than just perfusion. These included gated SPECT imaging and the use of the dual isotope technique. The demonstration in the NUC study that EF obtained by gated SPECT provides incremental prognostic information confirms the earlier observations of Sharir *et al.*<sup>12,13</sup> Following the original publication of the NUC study, Travin *et al.* also found EF to provide incremental prognostic power.<sup>14</sup> In regards to the dual isotope technique, TID had not been known to provide incremental prognostic information with dual isotope imaging until demonstrated in the NUC study. In their study, Travin *et al.* also recently demonstrated that post-stress wall motion evaluation, in the form of a wall motion score, added incremental prognostic information. A comprehensive meta-analysis of gated MPI was recently reported by Shaw and Iskandrian.<sup>15</sup>

Following publication of the NUC study, Hachamovitch *et al.* compared the impact of

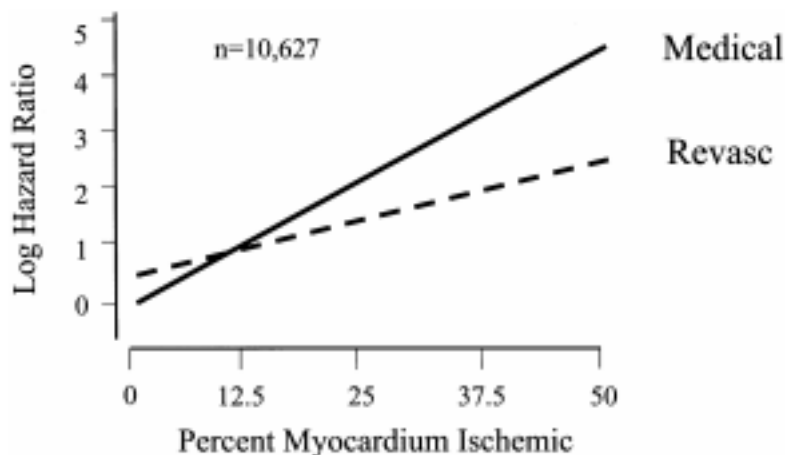


Fig. 10. Cardiac death based on revascularisation versus medical treatment, risk-adjusted.\*

revascularisation in a non-randomised study of 10,627 patients following perfusion imaging.<sup>16</sup> The risk adjusted cardiac death rates in those undergoing revascularisation and medical therapy are compared in Figure 10. Hachamovitch observed that in those patients with more than 10% of their myocardium found to be ischaemic on MPI, those who underwent revascularisation experienced 50% fewer events than those who were treated medically. While the NUC study was performed prior to the report of Hachamovitch *et al*, clinicians reacted to perfusion studies in a manner consistent with the results of Hachamovitch, infrequently performing catheterisation and revascularisation in patients with a mild amount of ischaemia and increasingly doing so as the degree of reversibility increased.

### EMERGING TECHNOLOGIES

Non-invasive imaging will continue to improve. Cardiac MRI (CMR) is a rapidly evolving technique with the potential to assess perfusion and thus infer coronary stenosis. Its greater spatial resolution than MPI raises the potential for greater diagnostic accuracy while the lack of ionising radiation raises the potential for greater patient safety. Sixteen-slice, and 64-slice, CT cameras, with their potential to image the coronary arteries with increasing accuracy, will become widely available in the US. The value of each of these and future technologies will be judged against the robust prognostic power of MPI with its incremental prognostic elements of perfusion gated SPECT EF, wall motion and TID. In

\* Adapted and reprinted from Hachamovitch *et al*, Comparison of the short-term survival benefit associated with revascularization compared with medical therapy in patients with no prior coronary artery disease undergoing stress myocardial perfusion single photon emission computed tomography. *Circulation* 2003; 107:2900-7.

addition, as demonstrated in the NUC study, the predictive power of MPI can be duplicated in the community sector. The convergence of these emerging technologies, with the assessment of anatomy (by multislice cardiac CT) incorporated with perfusion assessment (MPI or CMR) has intriguing potential. These techniques can be combined in a single device as “fusion” or “coupled” using 2 different devices which are actually overlaid on one another by software or cognitively by the imager and/or clinician.

### CONCLUSION

Using all its components, extent, severity and reversibility of perfusion defects, gated SPECT EF, wall motion and the presence or absence of TID, MPI is a powerful predictor of clinical risk and can be used as a reliable gauge to determine the need to change the predicted clinical course by angiography and revascularisation.

### ACKNOWLEDGEMENTS

We would like to thank the staff and physicians of the Cardiology Division and Imaging Unit of the Mission Internal Medical Group for their expert work, dedication and spirit.

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