# *Multifunction CardioGram – MCG*

## *A Computational Electrophysiological Tool for the Detection of Myocardial Ischemia Caused by Anatomically Significant Coronary Artery Disease*

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**Presentation to the MEDCAC**

# *Disclosures – John E. Strobeck, MD, PhD*

- ***I have no conflicts of interest or financial disclosures to report.***

## Agenda

- **State of the Art for Coronary Artery Disease (CAD) Detection**
- **Unmet Medical Needs for Non-Invasive Diagnosis of Anatomically Significant Coronary Artery Disease**
- **Direct Trial Comparison of MCG to Single Photon Emission Computed Tomography (SPECT) Myocardial Perfusion Imaging (MPI)**
- **MEDCAC Questions**
- **Evidence-based Clinical Use of MCG in the Non-Invasive Diagnosis of Coronary Artery Disease.**

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Low Diagnostic Yield of Elective Coronary Angiography

Manesh R. Patel, M.D., Eric D. Peterson, M.D., M.P.H., David Dai, M.S., J. Matthew Brennan, M.D., Rita F. Redberg, M.D., H. Vernon Anderson, M.D., Ralph G. Brindis, M.D., and Pamela S. Douglas, M.D.

NEJM March 2010;362:886-95

# *The Patel Study Design*

- Retrospective study group included 400,000 patients without known coronary artery disease undergoing elective coronary catheterization. Women represented 47.3% of group.

- Patients with acute coronary syndromes, acute MI, cardiogenic shock, those that required emergent or urgent catheterization, and those known to have CAD were excluded from analysis.

- Relevant coronary stenosis was defined as 70% stenosis of a major epicardial artery or 50% stenosis of the left main

- Note: The study group included a cohort of patients that are similar, if not identical to the patients who were studied in all the trial of MCG.
- *Data Source: American College of Cardiology National Data Registry from 363 Hospitals; Reporting period Jan 2004 –April 2008*

# *The Patel Study Results:*

- Only 38% of patients had relevant coronary stenosis; 23% had intermediate blockage; and 39% were reported to have normal exams *(< 20% blockage)*

- Of the female cohort, 33% had relevant coronary stenosis; 55.4% had "normal" exams

- 84% of the 400,000 patients in the study group tested positive on sequential noninvasive testing (i.e. EKG, exercise or pharmacological stress with radionuclide or ECHO Imaging, or CTA), yet only 41% actually had obstructive disease. Of the remaining 16% who either had normal noninvasive test results or did not undergo pre-testing at all, 35% had obstructive disease on coronary angiography.

# *The Patel Study – More Results*

| Female Population Statistics ( P < 0.001) | | |
|---|---|---|
| **Total Cohort** | **Obstructive CAD** | **Non-obstructive CAD** |
| **47.3%** | **33.9%** | **55.4%** |

| Median Age ( P < 0.001) | | |
|---|---|---|
| **Total Cohort** | **Obstructive CAD** | **Non-obstructive CAD** |
| **61** | **66** | **58** |

| **Clinical Presentations (%)** ( P < 0.001) | | | |
|---|---|---|---|
| | **Total Cohort** | **Obstructive CAD** | **Non-obstructive CAD** |
| **Asymptomatic** | **30%** | **31.5%** | **29.1%** |
| **Atypical Symptoms** | **36.8%** | **24.6%** | **44.2%** |
| **Stable Angina** | **33.2%** | **43.9%** | **26.7%** |

# *The Patel Study – Even More Results*

| Framingham Risk Score (%) Distribution ($p < 0.001$) | | | |
|---|---|---|---|
| | **Low** | **Intermediate** | **High** |
| **Total Population** | **29.2%** | **55%** | **15.8%** |
| **Obstructive CAD** | **13.5%** | **59.4%** | **27.1%** |
| **Nonobstructive CAD** | **38.6%** | **52.4%** | **13.5%** |

| Various Clinical Model's Pretest Predictability (C-Statistic) (CI = 95%) | | | | |
|---|---|---|---|---|
| | Overall | Low | Intermediate | High |
| Framingham risk score only | **0.67** | **NA** | **NA** | **NA** |
| Clinical risk factors added | **0.74** | **0.72** | **0.66** | **0.61** |
| Symptoms added | **0.76** | **0.75** | **0.69** | **0.65** |
| Results of Noninvasive testing added | **0.76** | **0.76** | **0.70** | **0.66** |

# *The Patel Study Conclusions*

- There were limitations to the study – however, the authors concluded:
- “Finally, although a positive non-invasive test was associated with the presence of obstructive coronary artery disease, the addition of information obtained from non-invasive tests had a limited effect on the model’s predictive ability over and above the effect achieved from the addition of clinical risk factors and symptoms.”
- “Our data support ongoing efforts to improve overall strategies for patient selection, including, but not limited to improving the quality of non-invasive testing in order to determine the optimal decision-making algorithm for the evaluation of suspected obstructive coronary artery disease.”

# *Non-Invasive Diagnosis of CAD – Limitations of SPECT*

- SPECT Myocardial Perfusion Imaging (MPI)
  - high cost of test
  - study quality technician, site, and equipment dependent
  - relatively long acquisition protocols
  - poor spatial resolution, limited detection of subendocardial perfusion defects
  - roll-off of tracer uptake at higher myocardial blood flows reducing sensitivity in detecting mild-to-moderate stenoses.
  - ECG-gating difficult in presence of arrhythmia
  - motion artifacts related to patient and respiratory motion
  - scatter and partial volume artifacts in the inferior wall related to gut and biliary uptake of tracer
  - variable attenuation artifacts resulting from breast, chest wall, or subdiaphragmatic attenuation
  - only relative perfusion is assessed with SPECT MPI, thus it has reduced sensitivity for detecting left main disease, 3-vessel disease, or obstruction(s) with collaterals if there is balanced ischemia

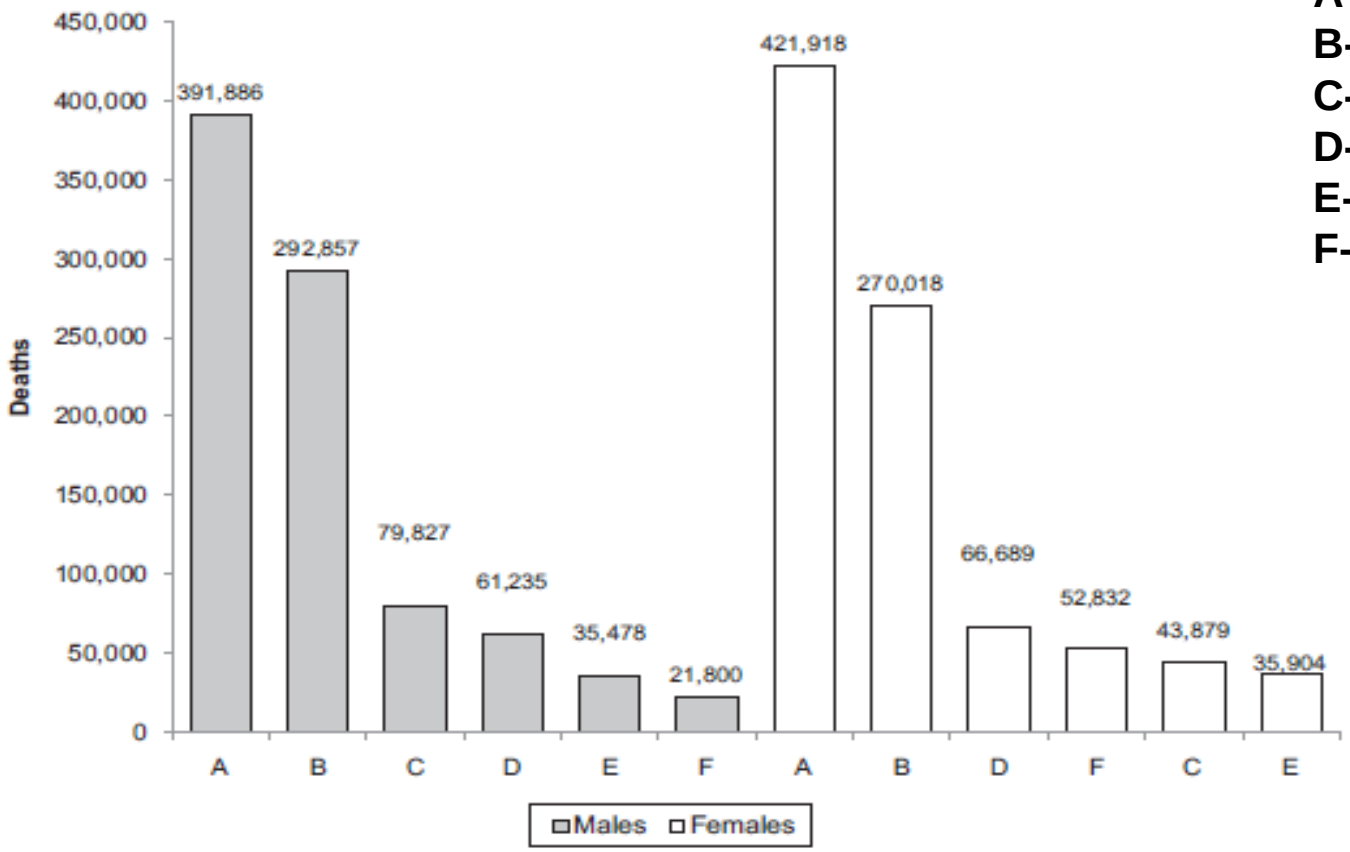
# *Non-Invasive Diagnosis of CAD – Limitations of SPECT*

- An analysis of 32 studies including 4480 patients with known or suspected CAD demonstrated mean sensitivity and specificity of 87% and 73%, respectively, for exercise myocardial SPECT for detecting a >50% stenosis. (Specificity range = 23% - 88%)
- An analysis of 16 studies of patients with known or suspected CAD including 2492 patients demonstrated sensitivity and specificity of 89% and 75%, respectively, for vasodilator stress with dipyridamole or adenosine for the detection of a >50% stenosis.
- In both of these analyses, the prevalence of CAD was high (>75%) in the population studied.
- Sensitivity and Specificity would be expected to fall with lower risk (prevalence) patients or with definition of CAD as >70% stenosis.

*(Klocke, FJ Circulation 108:1404-1418, 2003)*

APRIL 28, 2003
www.time.com AOL Keyword: TIME
IRAQ: INSIDE THE OCCUPATION / THE SEARCH FOR SADDAM
TIME
WOMEN & HEART DISEASE
Is your biggest worry breast cancer? Think again. ONE OUT OF THREE women will die of heart disease. What you can do to protect yourself

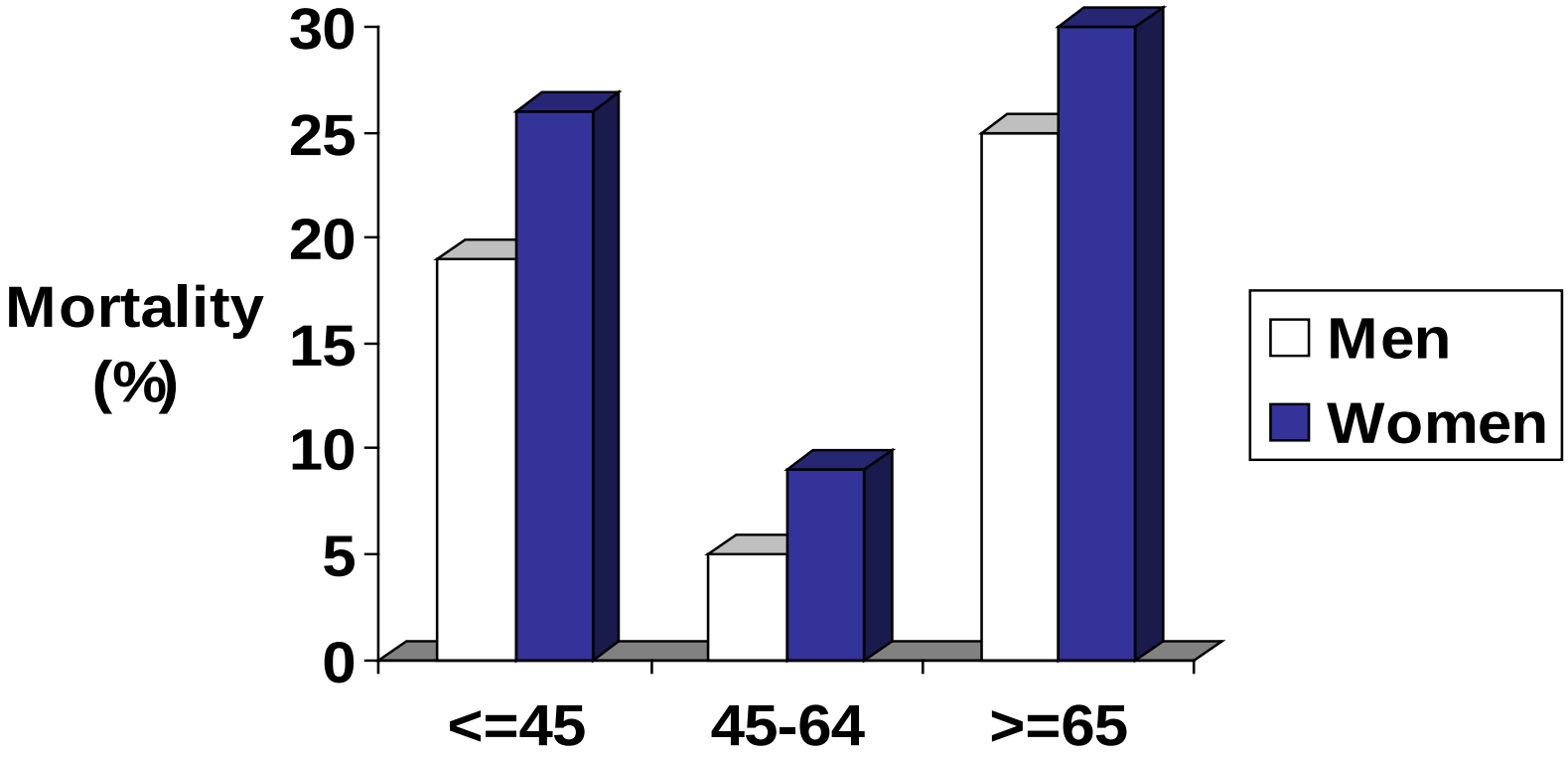
# *Cardiovascular Deaths in Women*




**A- CVD**
**B-Cancer**
**C-Accidents**
**D-Pulmonary**
**E-Diabetes**
**F-Alzheimers**

Heart Disease and Stroke statistics 2011 Update Circ e18-209

# *Mortality within 1st year after 1st MI*




Heart Disease and Stroke statistics 2011 Update Circ e18-209

# *US Women with CAD Face Greater Challenges than Men*

- Evidence has confirmed substantial delays in healthcare seeking behavior, less intensive resource utilization patterns, and longer times to diagnosis for women as compared to men. Of the 1.1 million hospitalizations for acute myocardial infarctions each year, more men are admitted regardless of age group (721,000 in men vs. 410,000 women).

- Sudden cardiac death is often the first manifestation of coronary artery disease in a high proportion of women (52%) (42% for men).

- Under-recognition and under-diagnosis of CAD is a major contributing factor to the consistently higher mortality rates seen in women. Evidence-based practice program reports from the Agency for Healthcare Research and Quality continue to find a paucity of women enrolled in cardiovascular diagnostic research trials.

- Urgently needed: A well-designed and effective diagnostic strategy in women at risk for coronary heart disease because up to 50% of initial cardiac events are fatal.

# A Paired-Comparision of the MultiFunction CardioGramsm (MCG) and Sestamibi SPECT Myocardial Perfusion Imaging (MPI) to Quantitative Coronary Angiography for the Detection of Relevant Coronary Artery Stenosis (>70%) - A Single-Center Study of 116 Consecutive Patients Referred for Coronary Angiography.

Strobeck, et al. Accepted for Publication in the *International Journal of Medical Science*, October 2011.

## *Protocol for the MCG vs. Nuclear Stress Imaging Paired- Comparison Trial*

- Single-Center prospective study enrolling 165 consecutive symptomatic patients with known or suspected coronary disease and/or valvular heart disease who agreed to undergo both MCG testing and stress MPI with sestamibi and a cardiac catheterization if stress MPI was abnormal, suggestive of ischemia, and/or if significant valvular disease was present, or if persistent chest pain was present with a normal stress MPI.
- Studies were all performed in an ICANL Certified Nuclear Laboratory maintained with rigid quality control.
- Community, non-academic setting typical of an average cardiology practice.
- MCG severity score of $< 4.0$ was used to indicate the absence of relevant coronary stenosis. Severity score $\geq 4.0$ indicated presence of stenosis.
- Use of 4 as the cut point was determined pre-study – based on previously published data.
- Patients with normal or equivocal stress MPI and insignificant valvular heart disease were not recommended for cardiac catheterization unless they demonstrated a persistent pattern of chest pain.

## *Protocol for the MCG vs. Nuclear Stress Imaging Paired-Comparison Trial – Cont'd*

- 49 Patients were excluded from analysis because of normal stress MPI and no evidence of valvular heart disease. 4/49 had MCG Scores of ≥ 4.0, or 8% of the normal MPI group of 49.

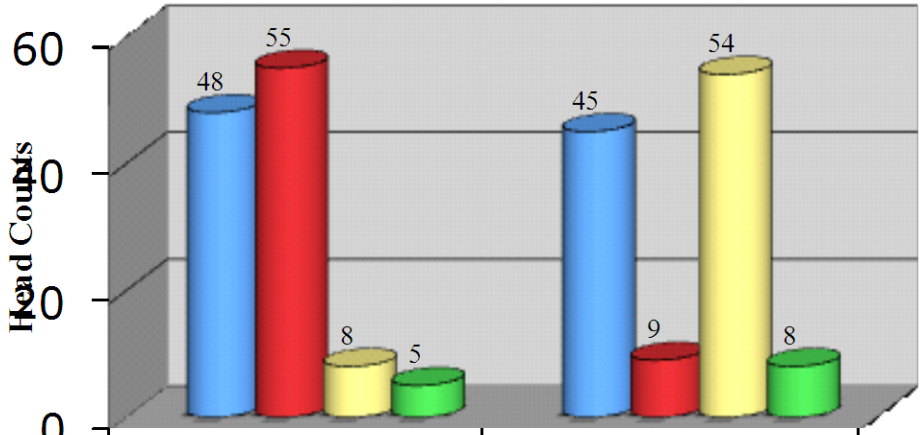
- 116 Patients with abnormal stress MPI, and/or significant valvular heart disease (8/116), or persistent chest pain with normal stress MPI (4/116) were included in the analysis.

- Standard nuclear stress test criteria for defining the presence or absence of myocardial ischemia were applied and all patients whose tests were indicative of coronary ischemia underwent coronary angiography to evaluate for critical stenosis. Standard echocardiographic criteria were used to define significant aortic or mitral valvular disease.

- Relevant stenosis was defined as: coronary stenosis >70% in one or more major epicardial vessels or bypass grafts or >50% in the left main. (Same as Patel study)

# *MCG vs. Nuclear Stress Imaging Paired Comparison Trial:*
## *The Overall Trial Results*

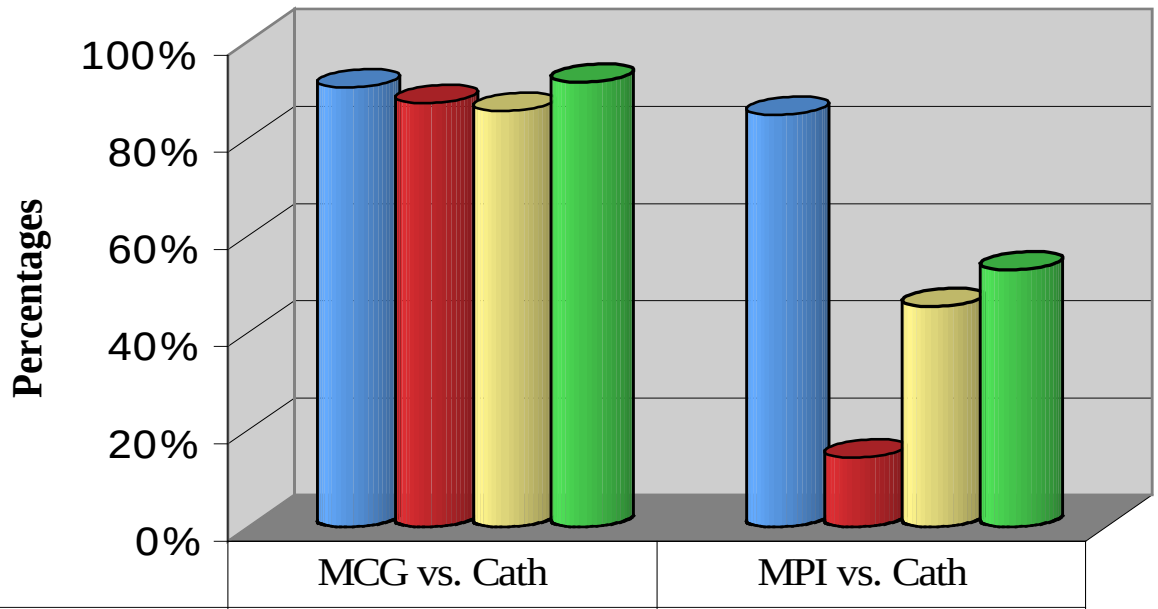
**MCG/Cath vs. MPI/Cath**




| | MCG vs. Cath | Nuclear vs. Cath |
|---|---|---|
| TP | 48 | 45 |
| TN | 55 | 9 |
| FP | 8 | 54 |
| FN | 5 | 8 |

**MCG vs. MPI**

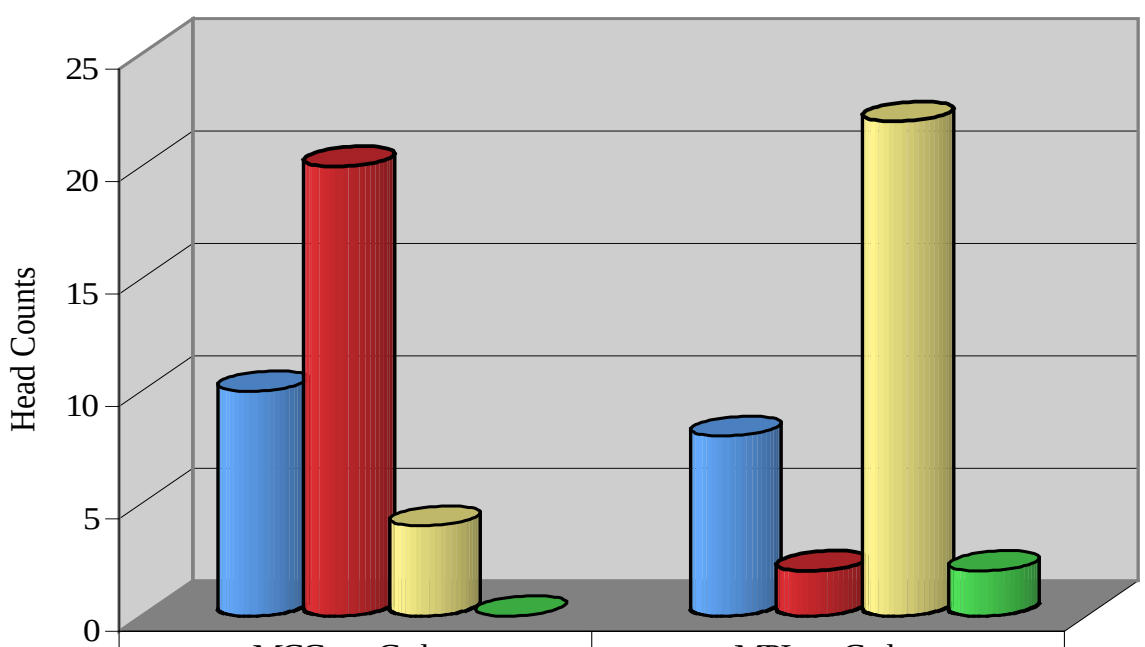
# *MCG vs. Nuclear Stress Imaging Paired Comparison Trial:*
## *The Overall Trial Results*




| | MCG vs. Cath | MPI vs. Cath |
|---|---|---|
| Sensitivity | 91% | 85% |
| Specificity | 87% | 14% |
| PPV | 86% | 45% |
| NPV | 92% | 53% |

**MCG vs. MPI**

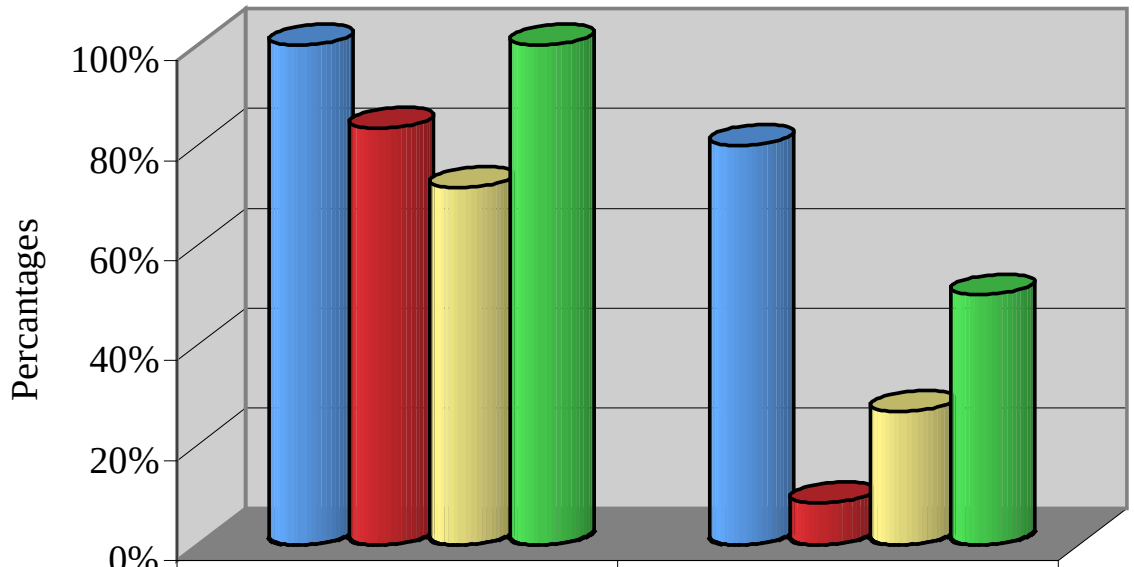
# *MCG vs. Nuclear Stress Imaging Paired Comparison Trial:*
## *Females Cohort Results*




| | MCG vs. Cath | MPI vs. Cath |
|---|---|---|
| TP | 10 | 8 |
| TN | 20 | 2 |
| FP | 4 | 22 |
| FN | 0 | 2 |

# *MCG vs. Nuclear Stress Imaging Paired Comparison Trial:*
## *Female Cohort Results*

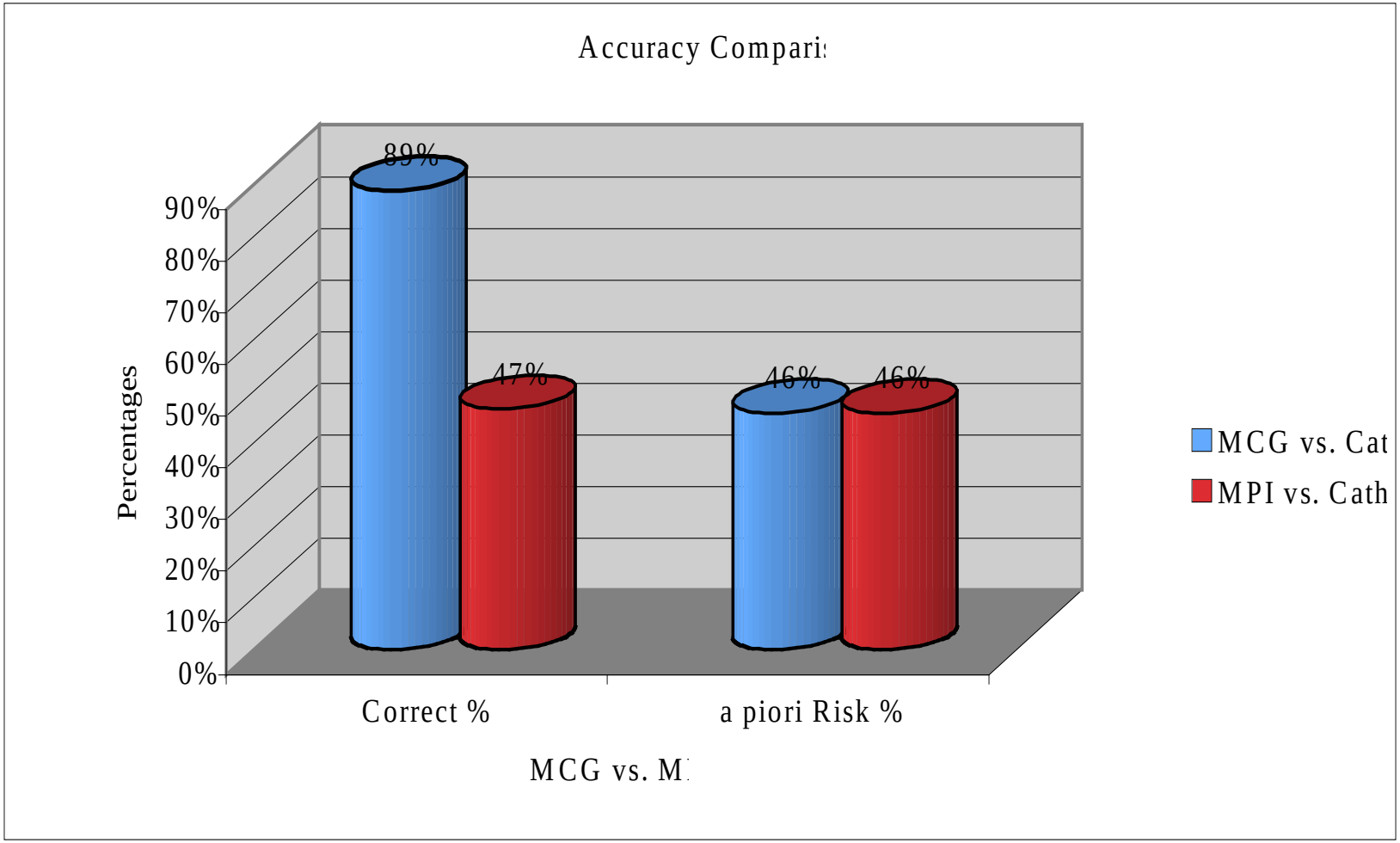
**MCG/Cath vs. MPI/Cath for Females**



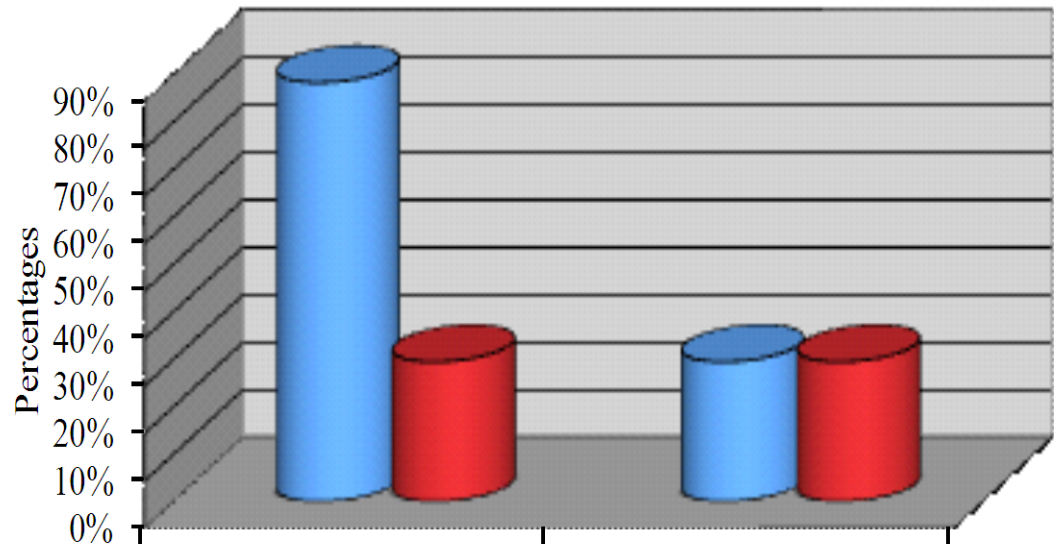

| | MCG vs. Cath | MPI vs. Cath |
|---|---|---|
| Sensitivity | 100% | 80% |
| Specificity | 83% | 8% |
| PPV | 71% | 27% |
| NPV | 100% | 50% |

**MCG/Cath vs. MPI/Cath**

# *MCG vs. Nuclear Stress Imaging Paired Comparison Trial: Overall Trial Results*



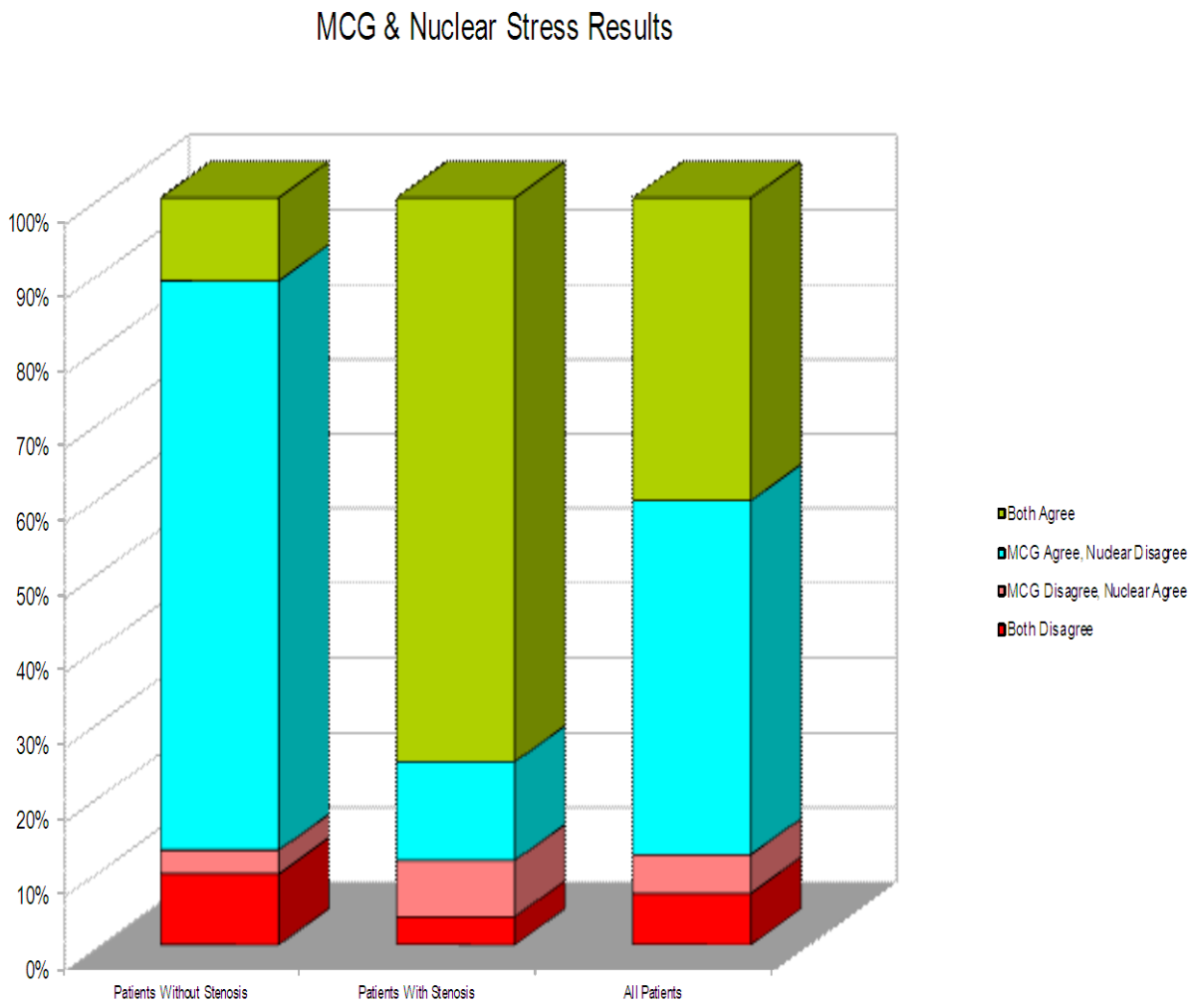
# *MCG vs. Nuclear Stress Imaging Paired Comparison Trial: Female Trial Results*




| | Correct % | a piori Risk % |
|---|---|---|
| MCG vs. Cath | 88% | 29% |
| MPI vs. Cath | 29% | 29% |

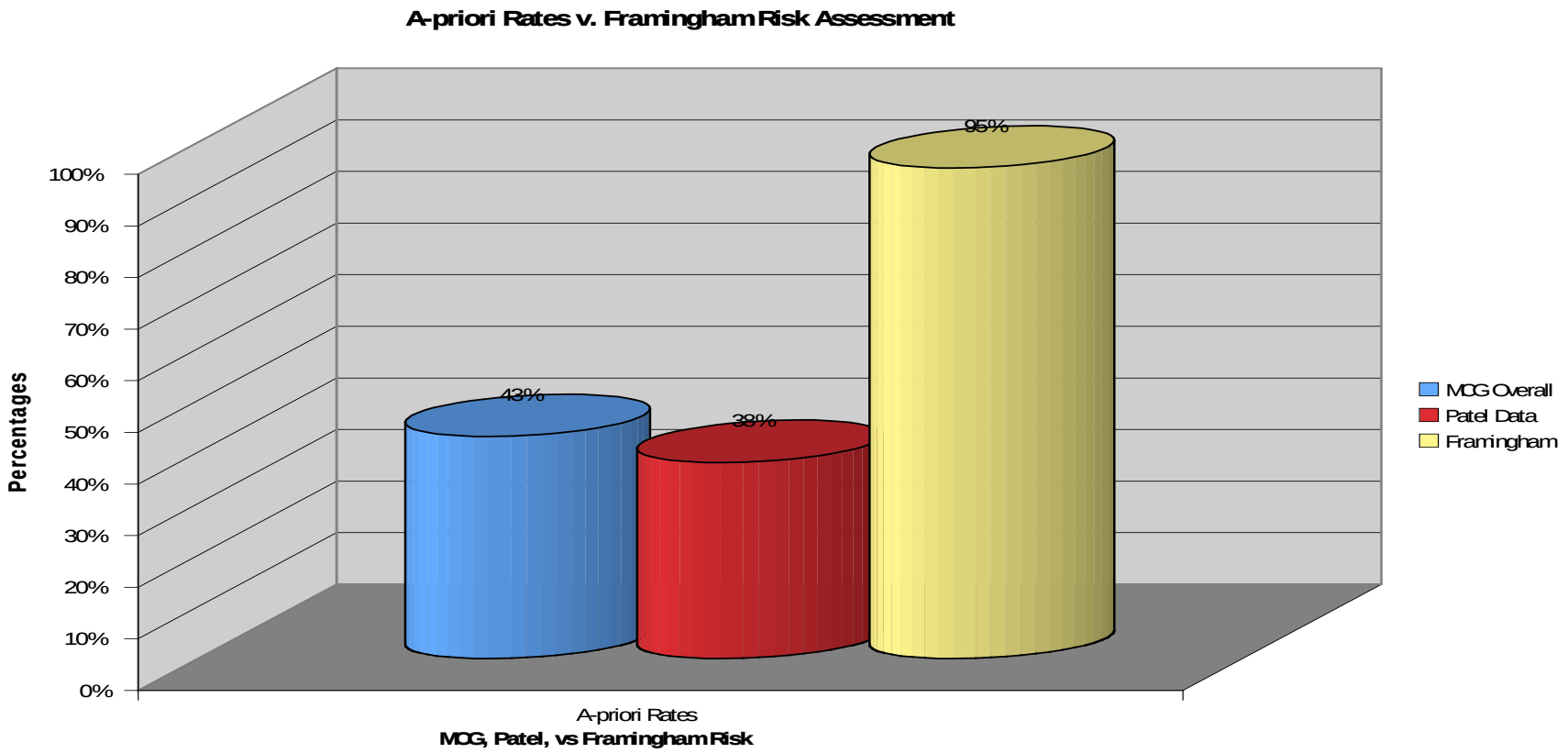
MCG vs. MPI

# *MCG vs. Nuclear Stress Imaging Paired Comparison Trial: Accuracy in patients with or without Critical CAD*



# *Real Critical CAD Detection Rate by Coronary Angiography*

***All patients destined to receive coronary angiogram belong to the intermediate risk group with >10 and <90% risk of CAD, <u>not</u> the high risk groups with ≥ 90% risk.***
***This has profound relevancy to the Patel Study.***



## *In My View, The Data on MCG Supports Positive MEDCAC Votes on the Following Questions:*

1. How confident are you that there is adequate evidence to determine whether or not SAECG technologies are able to reliably and accurately detect:
   b. patients with signs and symptoms suggestive of ACS with or without chest pain
2. If the result of Question 1 is at least intermediate (mean vote ≥ 2.5) in any of the conditions noted, how confident are you that ECG based signal analysis technologies are able to reliably and accurately detect:
   b. patients with signs/symptoms suggestive of ACS with or without chest pain
3. How confident are you that there is adequate evidence to determine whether or not the incremental information obtained from SAECG technologies beyond that provided by the standard 12 lead ECG, improves physician decision making in the management of :
   b. patients with signs/symptoms suggestive of ACS with or without chest pain
4. If the result of Question 3 is at least intermediate (mean vote ≥ 2.5), how confident are you that the incremental information obtained from SAECG technologies beyond that provided by the standard 12 lead ECG, improves physician decision making in the management of:
   b. patients with signs/symptoms suggestive of ACS with or without chest pain.

## *In My View, The Data on MCG Supports Positive MEDCAC Votes on the Following Questions:*

5. How confident are you that there is adequate evidence to determine whether or not the incremental information obtained from SAECG technologies beyond that provided by the standard 12 lead ECG, can eliminate the need (at the level of an individual patient) for
   c. invasive test of cardiac anatomy/functioning (i.e. coronary angiography)
6. If the result of Question 5 is at least intermediate (mean vote $\geq 2.5$), how confident are you that the incremental information obtained from SAECG technologies beyond that provided by the standard 12 lead ECG, can eliminate the need (at the level of an individual patient) for
   c. invasive test of cardiac anatomy/functioning (i.e. coronary angiography)
10. How confident are you that these conclusions are generalizable to:
    - The Medicare patient population?
    - Community based settings?

## *MEDCAC Questions Requiring Further Discussion:*

7. How confident are you that there is adequate evidence to determine whether or not the use of SAECG technologies significantly improves patient health outcomes?

8. If the result of Question 7 is at least intermediate (mean vote ≥ 2.5), how confident are you that the use of SAECG technologies significantly improves patient health outcomes?

## *Existing Data Supports the Following Regarding the MCG:*

- MCG is a non-invasive, minimal risk test that is indicated to detect the presence of relevant coronary stenosis in patients at intermediate risk of CAD who are being considered for coronary angiography.

- MCG provides immediate, accurate, objective assessment of anatomically significant CAD/Ischemia in symptomatic patients with known or suspected coronary disease, at intermediate pre-test risk levels of CAD, at all ages, particularly in women and those over 65 yr.

- Accuracy of MCG severity score is independent of the resting EKG morphology or the presence of arrhythmia or a paced rhythm.

- MCG provides comparable sensitivity as well as better specificity, negative predictive value and overall accuracy as compared to standard stress MPI testing to indicate the presence of relevant coronary stenosis.

- Should improve the selection of patients for coronary angiography and reduce the number of normal coronary angiograms.