What To Do With Symptomatic Nonobstructive Coronary Artery Disease?

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"Classification is a key to knowledge and an international classification makes for comparability between items of new knowledge arising out of work in new environments."

Dr. M.K. Rajakumar, President of World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians
Definition of Syndrome X

• “patients aged <80 years with chest pain, positive exercise test for myocardial ischemia and angiographically smooth coronary arteries.” Asbury et al (Eur Heart J 2004;25:1695-701)

• “no significant coronary artery stenosis (<50% luminal narrowing)” Zachariae R et al. Eur Heart J 2004;25:1695-701
Acknowledging that mild CAD is equivalent to normal coronary arteries is an assumption that needs further investigation.

Manfrini O, Bugiardini R.
Who has atherosclerosis despite normal coronary arteries at angiography?

I believe most of us
Coronary Atherosclerosis in 262 Heart Transplant Donors with Normal Angiograms

Percent reaching 0.5 mm threshold

<table>
<thead>
<tr>
<th>Mean Donor Age (years)</th>
<th>Percent Reaching 0.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>17%</td>
</tr>
<tr>
<td>20-29</td>
<td>37%</td>
</tr>
<tr>
<td>30-39</td>
<td>60%</td>
</tr>
<tr>
<td>40-49</td>
<td>71%</td>
</tr>
<tr>
<td>&gt; 50</td>
<td>85%</td>
</tr>
</tbody>
</table>
Who has anginal pain, despite nonobstructive CAD?

The size of the population may vary, depending upon:

• the different clinical settings (SA-ACS)
• the doctors’ perception of the disease
Prevalence of Non Obstructive Coronary Artery Disease in Patients with Suspected Angina

The Coronary Artery Surgery Study (CASS)    Women's Ischemia Syndrome Evaluation (WISE) Study

Chaitman BR et al Circulation 1981;64:360-367
Sharaf BL et al Am J Cardiol 2001;87:937-41
**Frequency of Non-obstructive CAD in ACS**

<table>
<thead>
<tr>
<th>TIMI 11B</th>
<th>TIMI 16</th>
<th>TIMI 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>Time to enrollment</td>
<td>Frequency (%)</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>24 h</td>
<td>14.6%</td>
</tr>
<tr>
<td>TIMI 16</td>
<td>72 h</td>
<td>8.4%</td>
</tr>
<tr>
<td>TIMI 22</td>
<td>10 d</td>
<td>5%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TIMI 11B</th>
<th>TIMI 16</th>
<th>TIMI 22</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>Femels</td>
<td>Percentage</td>
</tr>
<tr>
<td>TIMI 11B</td>
<td>8.8%</td>
<td>26.4%</td>
</tr>
<tr>
<td>TIMI 16</td>
<td>6%</td>
<td>14.7%</td>
</tr>
<tr>
<td>TIMI 22</td>
<td>3.9%</td>
<td>8.7%</td>
</tr>
</tbody>
</table>
Non-obstructive CAD in ACS Trials: Misperception and Gender Bias.

Many patients had been catheterized before the entry into the study in OPUS TIMI 16 and PROVE IT TIMI 22 and were not enrolled if they had non obstructive coronary disease.

There is not awareness that atherosclerosis poses a serious health risk even in its mild form, especially in women.

Woman were more often excluded.
What’s the CV risk associated with chest pain despite NCA?

This question is relevant because patients’ symptoms and prognosis may be improved with drugs.
Six-year Cardiovascular Event Rates by Coronary Artery Disease (CAD) and Persistent Chest Pain (PChP)

Prognosis of Mild-CAD and Normal Angiography

Event Rates at 1 year (710 UA/NSTEMI patients)

TIMI 11B - OPUS-TIMI 16 - PROVE-IT TIMI 22

Mild-CAD + Normal

- **Death**: 0.7% (Mild-CAD), 1.1% (Normal), p=ns
- **MI**: 0.7% (Mild-CAD), 1.4% (Normal), p=ns
- **Death+MI**: 1.3% (Mild-CAD), 2.1% (Normal), p=ns
- **Revascul**: 0.8% (Mild-CAD), 3.2% (Normal), p=0.01*
- **UA**: 9.7% (Mild-CAD), 11.3% (Normal), p=ns
- **Stroke**: 0.2% (Mild-CAD), 0.4% (Normal), p=ns
- **Primary End-Point**: 11.2% (Mild-CAD), 13.5% (Normal), p=0.046*

Euro Heart Survey ACS
Mortality rates through 1-year follow-up
(Kaplan-Meier rates)

- Obstructive CAD (n=5145): 3% (30 days), 7.7% (1 year)
- Non-obstructive CAD (n=279): 0.7% (30 days), 2.1% (1 year)
### Six-month clinical outcomes in patients with mild disease

**GRACE (Global Registry of Acute Coronary Events)**

<table>
<thead>
<tr>
<th></th>
<th>Normal or mild disease</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men (n = 857)</td>
</tr>
<tr>
<td>Death</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>15 (2)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (1)</td>
</tr>
<tr>
<td>Rehospitalisation</td>
<td>113 (15)</td>
</tr>
<tr>
<td>Combined end point*</td>
<td>132 (17)</td>
</tr>
</tbody>
</table>

Day S et al. Heart 2009;95:20-26
Sex Differences in Mortality Following Acute Coronary Syndromes

- No obstructive disease
- Single-vessel disease
- 2-vessel disease
- 3-vessel disease

A convenience sample of patients pooled from 11 independent, international, randomized ACS clinical trials between 1993 and 2006. Of 136,247 patients, 38,048 (28%) were women; 102,004 (26% women) with ST-segment elevation myocardial infarction (STEMI), 14,466 (29% women) with non-STEMI (NSTEMI), and 19,777 (40% women) with unstable angina.

Berger JS et al. JAMA 2009;302:874-882
Do we have methods of risk stratification in this population?

Consistent with the notion that these patients are mainly women they often present with reduced coronary flow reserve

There are a variety of questions that are relevant to clinical decision-making

- How can vascular dysfunction be tested?
- Is vascular dysfunction a prognostic marker?

How can vascular dysfunction be tested?

- Bugiardini et al.   J Am Coll Cardiol 1993   Abnormal Tl-201 perfusion
- Reis SE et al.       J Am Coll Cardiol 1999    Abnormal coronary flow velocity
  (intracoronary adenosine/doppler)
  (MRI spectroscopy)
- Buffon et al.   Am J Physiol 2001     Abnormal lipid hydroperoxide and
  conjugated dienes production
  by MRI
Assessing the Causes of Reduced Coronary Flow Reserve

- There are a number of likely causes for impairment of coronary flow reserve in patients with nonobstructive coronary angiograms.

- Impaired coronary flow reserve does not necessarily mean endothelial vascular dysfunction, because the abnormality could reside in the endothelium independent response.

- Dysfunction of the endothelium dependent vasodilatation is strictly related to early atherogenetic process.

Relationship Between Microvascular Coronary Vasomotor Function and Acute Cardiovascular Events

**Acetylcholine**

- *p*=0.047

**Sodium Nitroprusside**

- *p*=0.106

**Adenosine**

- *p*=0.107

Halcox JP. Circulation 2002;106:653
Endothelial function predicts future development of coronary artery disease in women with chest pain and normal coronary angiogram.

Changes in coronary diameters (%)

- ACh-positive group: 100%
- ACh-negative group: 23% (Atherosclerosis) and 77% (Smooth coronary arteries)

Patients With Chest Pain

Symptoms Stable?

Yes

Myocardial Stress Evaluation (Gated Spect, MRI, or PET)

No

Normal Myocardial Stress Evaluation?

Yes

Evaluate Nonischemic Cardiac and Noncardiac Causes of Chest Pain
Consider Tricyclic Antidepressant Therapy
Cardiac Risk Factor Management

No

Coronary Angiography

Normal Angiography or Nonobstructive CAD (<50% luminal diameter reduction)?

Yes

Consider Coronary Vascular Function Study

No

Medical Management
Consider Coronary Revascularization

Normal Coronary Vascular Function Study Results?

Yes

Aggressive Medical and Symptoms Management (Aspirin, B-blockers, Statins, ACE-inhibitors, Tricyclic Antidepressant, Exercise Training)

No

Bugiardini R, Bairey Merz CN.
Baseline Characteristics According to Presence or Absence of a Primary End Point in Patients With Nonobstructive Coronary Artery Disease in the PROVE IT-TIMI 22, OPUS-TIMI 16, and TIMI 11B Trials

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patients With Primary End Point (n = 75)*</th>
<th>Patients Without a Primary End Point (n = 626)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>38.7</td>
<td>47.9</td>
<td>.13</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>58.2 (11.1)</td>
<td>57.1 (11.8)</td>
<td>.42</td>
</tr>
<tr>
<td>White race</td>
<td>84.0</td>
<td>84.7</td>
<td>.88</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>14.7</td>
<td>14.5</td>
<td>.98</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>53.3</td>
<td>45.1</td>
<td>.17</td>
</tr>
<tr>
<td>Current smoker</td>
<td>26.7</td>
<td>30.9</td>
<td>.45</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>8.0</td>
<td>9.0</td>
<td>.79</td>
</tr>
<tr>
<td>History of PAD</td>
<td>4.0</td>
<td>2.7</td>
<td>.46</td>
</tr>
<tr>
<td>Drug for management of qualifying event</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>94.2</td>
<td>96.9</td>
<td>.24</td>
</tr>
<tr>
<td>β-Blocker</td>
<td>69.6</td>
<td>63.9</td>
<td>.36</td>
</tr>
<tr>
<td>ACE-I</td>
<td>26.1</td>
<td>26.3</td>
<td>.97</td>
</tr>
<tr>
<td>Index event</td>
<td></td>
<td></td>
<td>.04</td>
</tr>
<tr>
<td>NSTE-MI</td>
<td>18.2</td>
<td>30.1</td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>81.8</td>
<td>69.9</td>
<td></td>
</tr>
<tr>
<td>TIMI risk score†</td>
<td></td>
<td></td>
<td>.003</td>
</tr>
<tr>
<td>0-2</td>
<td>50.0</td>
<td>67.0</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>50.0</td>
<td>33.0</td>
<td></td>
</tr>
<tr>
<td>Elevated cardiac markers</td>
<td>29.7</td>
<td>41.0</td>
<td>.06</td>
</tr>
<tr>
<td>ST-deviation</td>
<td>68.0</td>
<td>57.8</td>
<td>.09</td>
</tr>
</tbody>
</table>

Abbreviations: ACE-I, angiotensin converting enzyme inhibitors; ACS,
**PROGNOSTIC VALUE OF TIMI RISK SCORE IN NON-OBSTURCTIVE CAD AT 1-YEAR FOLLOW-UP**

**EVENT RATES**

<table>
<thead>
<tr>
<th>TIMI Risk Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>34.6%</td>
<td>24.5%</td>
<td>23.3%</td>
<td>9.9%</td>
<td>1.4%</td>
<td>6.3%</td>
</tr>
</tbody>
</table>

**Distribution of TIMI Risk Score**

- Age <65y, at least 3 risk factors, ST-deviation, aspirin in last 7 days, elevated markers, severe angina symptoms, prior significant stenosis.

**PRIMARY END POINT**

- TIMI Risk Score

**DEATH & AMI**

- TIMI Risk Score

*Bugiardini R et al.*

*Arc Int Med (in press)*
Remarks

• Because the event rate of patients with nonobstructive CAD in ACS is very high, physicians should classify virtually every patient admitted with a clinical diagnosis of ACS to a disease category, even if the angiographic evaluation is absolutely negative.

• We fear that the potential perplexity that this message might cause among primary care physicians is considerable, which implies further investigations in the attempt to define “internationally recognized” methods of risk stratification.

• There is interest in an immediate intensive medical intervention that might “stabilize” potentially vulnerable plaques despite the challenge of purposely designed clinical trials to prove the benefit of such an approach.
Troubling findings in normal or near normal coronary angiography

- Thousands of patients (prevalently women) are told that they have no significant heart disease following demonstration of normal or near normal coronary arteries and, often, are offered no treatment beyond reassurance.

- Physicians are puzzled still in the subset of patients at greater risk, namely those presenting with acute coronary syndrome.

- Nevertheless all clinical trials on acute coronary syndrome enroll and treat everyone with a new set of therapies, regardless of their coronary anatomy, or even if these patients did not get catheterization.

- New guidelines and recommendations are needed in the attempt to alleviate some of this confusion.

- Otherwise there is a contradiction in the logic.
Acute Coronary Syndrome

>200,000

10-20% non-obstructive

ACS with non-obstructive CAD

>20,000

11.2% event rates

Non-obstructive CAD re-hospitalized

>4,000

2% death and MI

Non-obstructive CAD death & MI
Is standard medical therapy for ACS given to all of these patients?

It should be.

All clinical trials on acute coronary syndrome enroll and treat everyone with new sets of therapies, regardless of their coronary anatomy, or even if these patients did not get catheterization.
Health care disparities in EHS-ACS between patients with and without obstructive lesions
Patients With Chest Pain

- Symptoms Stable?
  - Yes: Myocardial Stress Evaluation (Gated Spect, MRI, or PET)
    - Yes: Normal Myocardial Stress Evaluation?
      - Yes: Evaluate Nonischemic Cardiac and Noncardiac Causes of Chest Pain
        - Consider Tricyclic Antidepressant Therapy
      - No: Normal Angiography or Nonobstructive CAD (<50% luminal diameter reduction)?
        - Yes: Consider Coronary Vascular Function Study
        - No: Medical Management Consider Coronary Revascularization
  - No: Consider Coronary Angiography
    - No: Normal Coronary Vascular Function Study Results?
      - Yes: Aggressive Medical and Symptoms Management (Aspirin, B-blockers, Statins, ACE-inhibitors, Tricyclic Antidepressant, Exercise Training)
      - No: Medical Management Consider Coronary Revascularization

Chest Pain and Normal Coronary Angiograms

Diagnosis of Vascular Dysfunction

Consistent with the notion that these patients are mainly women and that women are protected against CHD, they often present with:

- Reduced Coronary Flow Reserve

A variety of questions are relevant to clinical decision-making:

- How can vascular dysfunction be tested?
- Is vascular dysfunction a prognostic marker?
Treatment of Nonobstructive CAD in ACS

Interpretation 1

- Physicians undertreat patients with nonobstructive coronary artery disease who are prevalently women.
- Nonstenotic lesions unseen by traditional angiography may cause myocardial infarction/death and justifies the use of medical intervention that might “stabilize” potentially vulnerable plaques.
- Whether the adherence to evidence-based management for acute coronary syndrome translates into better outcomes of patients without obstructive coronary artery disease is not known.
Treatment of Nonobstructive CAD in ACS

Interpretation 2#

• Physicians in clinical trials prescribe therapies that have not been fully proven in scientific studies, but they underuse traditional treatment with statins, beta-blockers and ACE inhibitors despite clear benefits of these drugs with respect to mortality rate.

• When researchers come up with a new treatment, they must prove to their colleagues and to patients that the new treatment is better or at least equal to existing treatments.

• This principle appears to be violated in patients with non-obstructive CAD.

• Otherwise there is a contradiction in the logic
Patients with non-obstructive coronary artery disease and normal angiograms: remarks

(1) Patients with rather stable symptoms or suspected angina have a prognosis that is not as benign as previously thought.

(2) Assessment of severe endothelial dysfunction may identify groups who will develop atherosclerosis and subsequent events (up to 14% at 4 year follow-up).

(3) Patients with acute coronary syndrome have a relatively poor prognosis at 1-year follow-up, with 2% rate of MI and death and 11.2% of recurrence of UA.

(4) The TIMI Risk Score could be used in clinical practice to predict the likelihood of non-obstructive CAD patients to develop future coronary events. Up to 30% of patients have a score ≥ 3-4, and have 2.8-4% of death and myocardial infarction annually.

(5) Aggressive medical treatment is warrant in non-obstructive coronary artery disease and “normal “angiograms, and especially in ACS.
• The assumption that nonobstructive coronary artery disease carries a good prognosis was not based on hard data and had not been examined in a large study until now [3-6]. The current study demonstrates that the assumption turns out to be incorrect, at least in those patients presenting with an ACS.

• Patients with NSTE-ACS and nonobstructive coronary artery disease may have a wide spectrum of risk for cardiac ischemic events, and they need methods of risk stratification.
Do we have methods of risk stratification in this population?

An effective risk stratification may bear on the decision to prescribe new antithrombotic therapies, even in this “lower” risk group, in whom the treatment benefit may be smaller.
Six-year CV event rates by CAD and PChP.

Research on normal or near normal angiography

- Since 1984, more women than men die each year from heart disease.
- Women often do not have obstructive CAD, so they experience myocardial ischemia by a pathophysiological mechanism different from that of the majority of men with obstructive CAD.
- The assumption is that part of the failure to translate in women what is generally known to be of therapeutic benefit into clinical practice could reflect a lack of information on prognosis and treatment of non-obstructive CAD and normal angiography in the usual clinical settings.
Relation between epicardial coronary cross-sectional area response to acetylcholine and risk of cardiovascular event

Prevalence of Non-obstructive CAD in ACS Trials

• Many patients had been catheterized before the entry into the study in OPUS-TIMI 16 and PROVE IT-TIMI 22 and were not enrolled if they had non-obstructive coronary disease.

• Women were more often excluded.

• There is not awareness that atherosclerosis poses a serious health risk even in its mild form, especially in women.
**Frequency of Non-obstructive CAD in TIMI 11B, TIMI 16, TIMI 22**

TIMI investigators, 2005
There is not awareness that atherosclerosis poses a serious health risk even in its mild form, especially in women.
Coronary Angiography

Normal Angiography or Non-obstructive CAD (<50% luminal diameter reduction)?

Yes
- Consider Coronary Vascular Function Study

No
- Medical Management Consider Coronary Revascularization

Consider Coronary Vascular Function Study Results?

No
- Aggressive Medical and Symptoms Management (Aspirin, B-blockers, Statins, ACE-inhibitors, Tricyclic Antidepressant, Exercise Training)

*Modified from Bugiardini R, Bairey Merz CN. JAMA. 2005;293:477*
# Myocardial Flow Reserve Index: An NHLBI WISE Study

**Risk factors**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Full population n=184</th>
<th>(I_{MFRI}) n=55</th>
<th>(A_{MFRI}) n=129</th>
</tr>
</thead>
<tbody>
<tr>
<td>Former cigarette smoker</td>
<td>31%</td>
<td>33%</td>
<td>30%</td>
</tr>
<tr>
<td>Current cigarette smoker</td>
<td>20%</td>
<td>24%</td>
<td>18%</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>65%</td>
<td>69%</td>
<td>63%</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>67%</td>
<td>75%</td>
<td>63%</td>
</tr>
<tr>
<td>History of diabetes</td>
<td>26%</td>
<td>35%</td>
<td>22%</td>
</tr>
<tr>
<td>History of dyslipidemia</td>
<td>60%</td>
<td>62%</td>
<td>59%</td>
</tr>
</tbody>
</table>

**Extent of coronary disease (≥ 70% stenosis)**

<table>
<thead>
<tr>
<th>Extent of disease</th>
<th>Full population n=184</th>
<th>(I_{MFRI}) n=55</th>
<th>(A_{MFRI}) n=129</th>
</tr>
</thead>
<tbody>
<tr>
<td>O Vessel disease</td>
<td>86%</td>
<td>78%</td>
<td>89%</td>
</tr>
<tr>
<td>1 Vessel disease</td>
<td>12%</td>
<td>20%</td>
<td>9%*</td>
</tr>
<tr>
<td>2 Vessel disease</td>
<td>2%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>3 Vessel disease</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

\(A_{MFRI}: \geq 2\) out of 12 myocardial regions had an MFRI ≥ 1.5

\[p < 0.05\] between \(A_{MFRI}\) and \(I_{MFRI}\)

Treatment of Nonobstructive CAD in ACS

The rules of thumb used by individual clinicians are personal and idiosyncratic.

Consensus exists that patients with non-obstructive lesions actually have some risk of future coronary events and should be given aspirin.
Chest Pain and a Normal Coronary Angiogram

Raffaele Bugiardini

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FREQUENCY of NON-OBSTRICTIVE CAD in TIMI 11B, TIMI 16, TIMI 22

TIMI investigators, 2005
Hazard Ratios for baseline variables of TIMI Risk Score in TIMI 11B, OPUS-TIMI16, and PROVE-IT/TIMI 22 patients with non-obstructive CAD

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &gt;65 y</td>
<td>0.70</td>
<td>0.41</td>
<td>1.20</td>
</tr>
<tr>
<td>At least 3 risk factors</td>
<td>0.96</td>
<td>0.52</td>
<td>1.81</td>
</tr>
<tr>
<td>ST-deviation</td>
<td>1.24</td>
<td>0.75</td>
<td>2.04</td>
</tr>
<tr>
<td>Use of aspirin in last 7 days</td>
<td>2.61</td>
<td>1.52</td>
<td>4.48</td>
</tr>
<tr>
<td>Elevated serum markers</td>
<td>0.83</td>
<td>0.48</td>
<td>1.40</td>
</tr>
<tr>
<td>Severe angina symptoms (&gt;2 events in last 24h)</td>
<td>1.56</td>
<td>0.95</td>
<td>2.58</td>
</tr>
</tbody>
</table>

*TIMI investigators, 2005*
TIMI Risk Score 1-year follow-up

Percent of Patients

![Bar chart showing the percent of patients for different TIMI Risk Scores.]

Event Rates

![Bar chart showing event rates for different TIMI Risk Scores.]

TIMI investigators, 2005
Prognostic Value TIMI Risk Score 1-year follow-up

Percent of Patients

Event Rates

TIMI investigators, 2005
Chest Pain With Normal Coronary Angiograms: Lessons From the WISE Trial

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Italy
Prevalence of Non Obstructive CAD among Women with Acute Coronary Syndrome

GUSTO IIb

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ach-positive</th>
<th>Ach-negative</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location favoring ischemic origin, %</td>
<td>82%</td>
<td>72%</td>
<td>ns</td>
</tr>
<tr>
<td>Duration, min</td>
<td>17.9 ± 12.3</td>
<td>28.9 ± 14</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Intensity (scale from 1 to 4)</td>
<td>2.0 ± 0.9</td>
<td>2.8 ± 1.1</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Setting in which occurs, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>36%</td>
<td>28%</td>
<td>ns</td>
</tr>
<tr>
<td>Exertional/Psychological Stress</td>
<td>41%</td>
<td>40%</td>
<td>ns</td>
</tr>
<tr>
<td>Rest and Exertional</td>
<td>23%</td>
<td>32%</td>
<td>ns</td>
</tr>
<tr>
<td>Episodes per week, n</td>
<td>7.9 ± 5.3</td>
<td>9.1 ± 5.5</td>
<td>ns</td>
</tr>
<tr>
<td>Labeled “typical” by cardiologist, %</td>
<td>64%</td>
<td>52%</td>
<td>ns</td>
</tr>
</tbody>
</table>

* 59% of patients in Ach-positive group developed angiographically visible atherosclerosis at 10 year follow-up

Women with chest pain and normal coronary arteries at angiography were first described 37 years ago. (Likoff et al NEJM 1967).

Focus of scientific attention only in the past 10 to 15 years.

Recent interest stimulated by studies which, starting in early 1990’, reported higher death rate in in specific subsets of women with non obstructive CAD as well as to report differences in vascular function. (Quyyumi AA et al. Circulation. 1992)

Tendency to disregard these women relative to their symptoms was in part due to perception of a more benign course in women.
Clinical Methods for Assessing Endothelium-Dependent Dilation

Coronary Arteries
- Epicardial Artery Diameter $\Delta$ with ACh
- CBF $\Delta$ with ACh
- Epicardial Artery Diameter $\Delta$ with Adenosine

Forearm
- Brachial Artery Diameter $\Delta$ with Arterial Occlusion
- Forearm Blood Flow with ACh
Suwaidi JA, Hamasaki S, Higano ST, Nishimura RA, Holmes DR Jr, Lerman A.
Circulation 2000;101:948-954.

- Follow-up (average 28-month) was obtained in 157 patients

- Patients had angiographically coronary artery lesions <40% lumen diameter stenosis without evidence of coronary spasm.

- Exclusion criteria included history of myocardial infarction, percutaneous coronary revascularization, CABG, unstable angina pectoris, history of variant angina

- A normal coronary endothelium-dependent function was defined as an increase in CBF of >50% in response to acetylcholine (10-4 mol/L).
Long-term Follow-up of Patients with Mild Coronary Artery Disease and Endothelial Dysfunction

% Change CBF (Ach)

% Cardiac Events

Follow-up (average 28-month) was obtained in 308 subjects undergoing cardiac catheterization for investigation of chest pain or abnormal noninvasive cardiac investigations.

Subjects who were referred for revascularization after cardiac catheterization were excluded.

Subjects with unstable angina, recent myocardial infarction (<3 months), NYHA class III to IV heart failure, or unrevascularized 3-vessel or left main disease were excluded.

Coronary endothelium-dependent function was assessed by changes in CBF and vessel diameters in response to acetylcholine (10-6 mol/L).
Relationship between endothelium-dependent coronary vascular function and cardiovascular prognosis

Acute cardiovascular events or coronary revascularization procedure

Sudden cardiac death, myocardial infarction, or stroke

—··· represents tertile with greater fall in CVR (A and C) or epicardial vasodilation (B and D) with Ach

— 2 tertiles with lesser fall in CVR (A and C) or epicardial vasoconstriction (B and D) with Ach

Halcox JPJ et al. Circulation, 2002;106:653-658
von Mering GO, Arant CB, Wessel TR, et al. (WISE).


- Follow-up (average 48-month) was obtained in 168 women undergoing cardiac catheterization for investigation of suspected myocardial ischemia.

- Coronary reactivity testing was performed in an epicardial coronary artery free of obstructive CAD (<50% diameter).

- Seventy-five percent had no or only mild epicardial coronary artery disease (CAD).

- Coronary endothelium-dependent function was assessed by changes in CBF and vessel diameters in response to acetylcholine (10^{-6} mol/L).
Follow-up (average 47-month) was obtained in 198 patients undergoing cardiac catheterization for unstable angina.

Patients with impaired left ventricular ejection fraction (<45%) as assessed by echocardiography were excluded.

Forearm blood flow (FBF) responses to acetylcholine (ACH; 10 to 50 µg/min) were measured by venous occlusion plethysmography before hospital discharge within 5 days of an episode of an ACS.
Prognostic value of systemic endothelial dysfunction in patients with acute coronary syndromes
Long-term Prognosis of Non-obstructive Coronary Artery Disease in the Setting of Acute Coronary Syndrome - PROVE IT-TIMI 22

Clinical events through follow-up (Kaplan-Meier rates)

<table>
<thead>
<tr>
<th></th>
<th>Non Obstructive CAD</th>
<th>Non Obstructive CAD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Obstructive CAD</td>
<td>Obstructive CAD</td>
</tr>
<tr>
<td></td>
<td>N=3325</td>
<td>N=178</td>
</tr>
<tr>
<td>Death - %</td>
<td>3.5</td>
<td>0.6</td>
</tr>
<tr>
<td>p-value</td>
<td>0.1048</td>
<td>0.0104</td>
</tr>
<tr>
<td>MI - %</td>
<td>7.4</td>
<td>1.2</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0040</td>
<td>0.0040</td>
</tr>
<tr>
<td>Death or MI - %</td>
<td>10.4</td>
<td>1.9</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0013</td>
<td>0.0013</td>
</tr>
<tr>
<td>Revascularization - %</td>
<td>19.6</td>
<td>4.9</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Unstable angina - %</td>
<td>4.3</td>
<td>2.4</td>
</tr>
<tr>
<td>p-value</td>
<td>0.2972</td>
<td>0.2972</td>
</tr>
<tr>
<td>Stroke - %</td>
<td>0.9</td>
<td>1.8</td>
</tr>
<tr>
<td>p-value</td>
<td>0.1920</td>
<td>0.1920</td>
</tr>
<tr>
<td>Primary endpoint* - %</td>
<td>26.8</td>
<td>9.7</td>
</tr>
<tr>
<td>p-value</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Death/MI/UA/revascularization/stroke

Bugiardini R et al. in press
STUDY POPULATION

42 women (mean age 51.6 ± 8.8)

Inclusion Criteria:
- de novo angina
- ECG ischemia during exercise stress test
- myocardial reversible perfusion defects (SPECT)
- normal angiograms.

Exclusion Criteria:
- hypercholesterolemia and/or hypertriglyceridemia
- diabetes mellitus
- valvular heart disease
- cardiomyopathy

Superoxide Dismutase Activity

Cardiac Syndrome X
Healthy Controls
Coronary Artery Disease

Placebo
Statin+ACE-I

p<0.001

Superoxide Dismutase Activity (U/ml)

Baseline
6 months

Superoxide Dismutase Activity

$p<0.001$

$\begin{align*}
\text{Cardiac Syndrome X} & \quad \text{Healthy Controls} & \quad \text{Coronary Artery Disease} \\
\text{Superoxide Dismutase Activity (U/ml)} & \quad & \\
0 & \quad & \\
100 & \quad & \\
200 & \quad & \\
300 & \quad & \\
\end{align*}$

Flow mediated dilation (%)

$\begin{align*}
\text{Superoxide Dismutase Activity (U/ml)} & \quad \text{Flow mediated dilation} \\
0 & \quad 0 \\
100 & \quad 1 \\
200 & \quad 2 \\
300 & \quad 3 \\
400 & \quad 4 \\
\end{align*}$

$(r=0.38; p=0.01)$

Sex Differences in Mortality Following Acute Coronary Syndromes

A convenience sample of patients pooled from 11 independent, international, randomized ACS clinical trials between 1993 and 2006. Of 136,247 patients, 38,048 (28%) were women; 102,004 (26% women) with ST-segment elevation myocardial infarction (STEMI), 14,466 (29% women) with non-STEMI (NSTEMI), and 19,777 (40% women) with unstable angina.

Berger JS et al. JAMA 2009;302:874-882