Pharmacologic Stress Testing

Update in Cardiac Imaging

Stress SPECT/PET vs. Stress Echo in Patients with Suspected or Known CAD

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Disclosures

Speaker’s Bureau:

• Astellas
Pharmacologic Stress Testing

Ischemic Cascade

Taqueti, Progress in CV Diseases, 2015: 644-653
### Multimodality AUC

<table>
<thead>
<tr>
<th>Indication Text</th>
<th>Exercise ECG</th>
<th>Stress RNI</th>
<th>Stress Echo</th>
<th>Stress CMR</th>
<th>Calcium Scoring</th>
<th>CCTA</th>
<th>Invasive Coronary Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Low pre-test probability of CAD</td>
<td>A</td>
<td>R</td>
<td>M</td>
<td>R</td>
<td>R</td>
<td>R</td>
<td>R</td>
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<tr>
<td>Low pre-test probability of CAD</td>
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<td>ECG interpretable AND able to exercise</td>
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<tr>
<td>2. Low pre-test probability of CAD</td>
<td>A</td>
<td>A</td>
<td>M</td>
<td>R</td>
<td>M</td>
<td>R</td>
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<tr>
<td>3. Intermediate pre-test probability of CAD</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>M</td>
<td>R</td>
<td>M</td>
<td>R</td>
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<tr>
<td>5. High pre-test probability of CAD</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>R</td>
<td>M</td>
<td>A</td>
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</tr>
</tbody>
</table>

Table 1.1: Symptomatic

Refer to pages 16 and 17 for relevant definitions, in particular Table A and text for age, sex, symptom presentation, and risk factors relevant to each pre-test probability category.

Appropriate Use Key: A = Appropriate; M = May Be Appropriate; R = Rarely Appropriate.

A = Appropriate; CAD = coronary artery disease; CCTA = coronary computed tomography angiography; CMR = cardiac magnetic resonance; ECG = electrocardiogram; Echo = echocardiography; M = May Be Appropriate; R = Rarely Appropriate; RNI = radionuclide imaging.
Pharmacologic Stress Testing

Sensitivity/Specificity – Echo and SPECT

Table 3. Sensitivity and Specificity of Noninvasive Tests for the Detection of Coronary Artery Disease

<table>
<thead>
<tr>
<th>Diagnostic Test</th>
<th>Sensitivity (Range)*</th>
<th>Specificity (Range)*</th>
<th>Studies</th>
<th>Patients</th>
<th>Patients with Coronary Disease</th>
<th>Sensitivity for Left Main or Three-Vessel Disease</th>
<th>Studies</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planar thallium imaging</td>
<td>0.79 (0.70–0.94)</td>
<td>0.73 (0.43–0.97)</td>
<td>6</td>
<td>510</td>
<td>66</td>
<td>0.93</td>
<td>2</td>
<td>72</td>
</tr>
<tr>
<td>Single-photon emission computed tomography</td>
<td>0.88 (0.73–0.98)</td>
<td>0.77 (0.53–0.96)</td>
<td>8</td>
<td>628</td>
<td>70</td>
<td>0.98</td>
<td>3</td>
<td>92</td>
</tr>
<tr>
<td>Echocardiography†</td>
<td>0.76 (0.40–1.00)</td>
<td>0.88 (0.80–0.95)</td>
<td>10</td>
<td>1174</td>
<td>64</td>
<td>0.94</td>
<td>4</td>
<td>115</td>
</tr>
<tr>
<td>Positron emission tomography</td>
<td>0.91 (0.69–1.00)</td>
<td>0.82 (0.73–0.88)</td>
<td>3</td>
<td>206</td>
<td>68</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exercise electrocardiography‡</td>
<td>0.68</td>
<td>0.77</td>
<td>132</td>
<td>24 074</td>
<td>66</td>
<td>0.86</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>

Pharmacologic Stress Testing

Prognostic Value of Normal Exercise MPI and Ex Echo

<table>
<thead>
<tr>
<th>Exercise Imaging Modality and Events</th>
<th>n</th>
<th>Mean Follow-Up (Months)</th>
<th>Mean Age (yrs)</th>
<th>Women (%)</th>
<th>Summary Event Rate After a Negative Test (%) (95% CI)</th>
<th>Negative Predictive Value (%) (95% CI)</th>
<th>Annualized Event Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI and cardiac death</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPI</td>
<td>8,008</td>
<td>36</td>
<td>54</td>
<td>34</td>
<td>1.21 (0.98-1.48)</td>
<td>98.8 (98.5-99.0)</td>
<td>0.45</td>
</tr>
<tr>
<td>Thallium</td>
<td>868</td>
<td>45</td>
<td>57</td>
<td>32</td>
<td>3.11 (2.05-4.53)</td>
<td>96.9 (95.5-97.9)</td>
<td>0.70</td>
</tr>
<tr>
<td>Sestamibi</td>
<td>1,802</td>
<td>32</td>
<td>58</td>
<td>35</td>
<td>1.28 (0.81-1.92)</td>
<td>98.7 (98.1-99.2)</td>
<td>0.34</td>
</tr>
<tr>
<td>Thallium/ sestamibi</td>
<td>4,938</td>
<td>23</td>
<td>61</td>
<td>39</td>
<td>0.83 (0.60-1.13)</td>
<td>99.2 (98.9-99.4)</td>
<td>0.45</td>
</tr>
<tr>
<td>Tetrofosmin</td>
<td>400</td>
<td>43</td>
<td>57</td>
<td>28</td>
<td>1.5 (0.55-3.26)</td>
<td>98.5 (96.8-99.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>Echo</td>
<td>3,021</td>
<td>33</td>
<td>56</td>
<td>46</td>
<td>1.56 (1.14-2.07)</td>
<td>98.4 (97.9-98.9)</td>
<td>0.54</td>
</tr>
<tr>
<td>Revascularization and unstable angina</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MPI</td>
<td>1,756</td>
<td>36</td>
<td>52</td>
<td>36</td>
<td>3.42 (2.61-4.40)</td>
<td>96.6 (95.6-97.4)</td>
<td>1.25</td>
</tr>
<tr>
<td>Echo</td>
<td>380</td>
<td>32</td>
<td>54</td>
<td>45</td>
<td>2.63 (1.26-4.84)</td>
<td>97.4 (95.2-98.7)</td>
<td>0.95</td>
</tr>
</tbody>
</table>

Echo = echocardiography; MPI = myocardial perfusion imaging; other abbreviations as in Table 1.
Pharmacologic Stress Testing

Submaximal Normal Stress Echo

JACC 2012;60:1393–401
Pharmacologic Stress Testing

EVINCI Study

- Prospective European centers
- Prevalence of CAD: 29%

Neglia, Circ CVI, 2015
Pharmacologic Stress Testing

EVINCI Study

Prospective European centers

Prevalence of CAD: 29%

Figure 3. Sensitivity and specificity of noninvasive imaging techniques.

Neglia, Circ CVI, 2015
Pharmacologic Stress Testing

Nuc MPI vs Stress Echo in the PreOp Evaluation of Pts for Kidney Tx

113 kidney transplant candidates

Type of stress test

- 53 SMPI
  - Yes
  - 53 Dx
  - No
  - 0 Non-Dx

- 60 SE
  - Yes
  - 48 Dx
  - No
  - 12 Non-Dx

Diagnostic quality

Ischemia on imaging

Further testing

- 8 Positive
- 45 Negative
- 3 Positive
- 45 Negative
- 1 SMPI+ 2 Angio-

- 8 Angio+
- 1 Angio-
- 2 Angio-
- 3 Angio-
- 3 Angio+

- 2 FP
- 3 FN
**Pharmacologic Stress Testing**

**Equivocal Stress Echo -> Request Stress Nuclear?**

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**Table 2.1. Sequential or Follow-Up Testing (<90 Days): Uncertain Prior Results**

<table>
<thead>
<tr>
<th>Indication text</th>
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<th>Stress RNI</th>
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<th>CCTA</th>
<th>Invasive Coronary Angiography</th>
</tr>
</thead>
<tbody>
<tr>
<td>30. Prior exercise ECG test</td>
<td>R</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>R</td>
<td>A</td>
<td>M</td>
</tr>
<tr>
<td>31. Prior stress imaging study (assumes not repeat of same type of stress imaging)</td>
<td>R</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>R</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>32. Prior CCTA</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>33. Coronary stenosis or anatomic abnormality of unclear significance found on cardiac CCTA</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td></td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>34. Coronary stenosis or anatomic abnormality of unclear significance on previous coronary angiography</td>
<td>M</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>R</td>
<td>R</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2.1 Table Footnotes:**

- Appropriate Use Key: A = Appropriate; M = May Be Appropriate; R = Rarely Appropriate.
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Pharmacologic Stress Testing

Importance of Anatomical Info

Subclinical atherosclerosis

56% of Normal Stress MPS have Moderate to Extensive CAC

JACC, 2004;44:923-30
Pharmacologic Stress Testing

Importance of Anatomical Info

Subclinical atherosclerosis

Table 3
CAC score determined risk classifications and treatment recommendations in the 5–20% ASCVD risk group.

<table>
<thead>
<tr>
<th>Score</th>
<th>Risk</th>
<th>Treatment Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>very low</td>
<td>statin not recommended(^a)</td>
</tr>
<tr>
<td>1–99</td>
<td>mildly Increased</td>
<td>moderate intensity statin if &lt; 75th%</td>
</tr>
<tr>
<td>100–299</td>
<td>moderately increased</td>
<td>moderate to high intensity if &gt; 75th%</td>
</tr>
<tr>
<td>&gt;300</td>
<td>moderate to severely increased</td>
<td>moderate to high intensity statin + ASA 81mg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>high intensity statin + ASA 81mg</td>
</tr>
</tbody>
</table>

\(^a\) Excluding familial hypercholesterolemia.

- New treatment guidelines based on CAC score
- Big advantage for PET-CT and SPECT-CT!
  - Dedicated CCS
  - CAC can be visually assessed from the low dose CT AC scan
    (Einstein, JACC 2010;56:1914–21)

Pharmacologic Stress Testing

Annualized cardiac mortality by ischemia% and MFR

Myocardial Flow Reserve

Circulation, 2011;124:2215-2224
Annualized cardiac mortality by ischemia% and MFR

Myocardial Flow Reserve

Big Advantage for PET MPI!
Pharmacologic Stress Testing

Imaging Protocols (Radiation Dosimetry)
Pharmacologic Stress Testing

Stress Imaging Protocols ($^{201}$Tl)

A

Stress $^{201}$Tl

- $^{201}$Tl
  - 2.5-3.5 mCi

Stress Imaging Protocol:

1. STRESS SPECT
2. REDIST SPECT
3. LATE REDIST SPECT

Dosage:
- 201Tl: 2.5–3.5 mCi
- 99mTc: 20–30 mCi

Exposure:
- 11–15 mSv

B

Dual-isotope rest $^{201}$Tl/stress $^{99mTc}$

- $^{201}$Tl
  - 2.5-3.5 mCi

- $^{99mTc}$
  - 20-30 mCi

Stress Imaging Protocol:

1. REST $^{201}$Tl SPECT
2. STRESS $^{99mTc}$ SPECT
3. STRESS $^{99mTc}$ SPECT
4. REDIST $^{201}$Tl SPECT

Dosage:
- 201Tl: 2.5–3.5 mCi
- 99mTc: 20–30 mCi

Exposure:
- 17–24 mSv
Stress Imaging Protocols ($^{201}\text{Tl}$)

$^{201}\text{Tl}$ Protocols should be avoided (higher radiation dosimetry than $^{99m}\text{Tc}$ protocols)
Stress Imaging Protocols ($^{99m}$Tc)

- **Pharmacologic Stress Testing**

**A**

- Same-day low dose rest/high dose stress (Rest First)

- $^{99m}$Tc 5-12 mCi

- 1 HR

- REST SPECT

- 1-4 HR

- STRESS SPECT

- 15-60 MIN

- 5-13 mSv
Pharmacologic Stress Testing

Stress Imaging Protocols ($^{99mTc}$)

**A**
- Same-day low dose rest/high dose stress (Rest First)
- $^{99mTc}$ 5-12 mCi
- 1 HR
- REST SPECT
- 1-4 HR
- STRESS SPECT
- 15-60 MIN
- 5-13 mSv

**B**
- Same-day low dose stress/high dose rest (Stress First)
- $^{99mTc}$ 5-12 mCi
- 15-60 MIN
- STRESS SPECT
- 1-4 HR
- REST SPECT
- 1 HR
- 5-13 mSv

* Attenuation correction or imaging in multiple positions is recommended
Pharmacologic Stress Testing

Stress Imaging Protocols ($^{99mTc}$)

A

Same-day low dose rest/high dose stress (Rest First)

$^{99mTc}$ 5-12 mCi

REST SPECT

1 HR

B

Low dose stress only

$^{99mTc}$ 5-12 mCi

STRESS SPECT*

15-60 MIN

$^{99mTc}$ 15-36 mCi

STRESS SPECT

1-4 HR

15-60 MIN

5-13 mSv

1-4 mSv

Stress only if stress images are normal, 75-85% dose reduction to stress lab staff (Hyun, ASNC 2014)

* Attenuation correction or imaging in multiple positions is recommended
Pharmacologic Stress Testing

Stress Imaging Protocols ($^{99m}Tc$)

**Morbid obesity (350-500 lbs)**

**A**
- Two-day high dose rest/high dose stress (Rest First)
- $^{99m}Tc$ 30 mCi
- 1 HR REST SPECT
- 24 HR STRESS SPECT
- 15-60 MIN $^{99m}Tc$ 30 mCi
- 17 mSv

**B**
- Two-day high dose stress/high dose rest (Stress First)
- $^{99m}Tc$ 30 mCi
- 15-60 MIN STRESS SPECT
- 24 HR $^{99m}Tc$ 30 mCi
- 1 HR REST SPECT
- 17 mSv

* Attenuation correction or imaging in multiple positions is recommended
Pharmacologic Stress Testing

Stress Imaging Protocols ($^{99mTc}$)

Morbid obesity (350-500 lbs)

A

Two-day high dose rest/high dose stress (Rest First)

$^{99mTc}$ 30 mCi

REST SPECT

1 HR

$^{99mTc}$ 30 mCi

STRESS SPECT

24 HR

17 mSv

B

Stress only (high dose stress)

$^{99mTc}$ 30 mCi

STRESS SPECT*

15-60 MIN

8 mSv

Stress only if stress images are normal, 75-85% dose reduction to stress lab staff (Hyun, ASNC 2014)

* Attenuation correction or imaging in multiple positions is recommended
### Stress Imaging Protocols ($^{99m}$Tc and $^{201}$Tl)

#### Radiation Dosimetry

<table>
<thead>
<tr>
<th>Protocol</th>
<th>Dose (mSv)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same-day $^{99m}$Tc – Rest/Stress</td>
<td>5-13</td>
</tr>
<tr>
<td>Same-day $^{99m}$Tc - Stress/Rest</td>
<td>5-13</td>
</tr>
<tr>
<td>Low Dose $^{99m}$Tc Stress only</td>
<td>1-4</td>
</tr>
<tr>
<td>Two-day $^{99m}$Tc - Rest/Stress</td>
<td>17</td>
</tr>
<tr>
<td>Two-day $^{99m}$Tc - Stress/Rest</td>
<td>17</td>
</tr>
<tr>
<td>High Dose $^{99m}$Tc Stress only</td>
<td>8</td>
</tr>
<tr>
<td>Stress $^{201}$Tl</td>
<td>11-15</td>
</tr>
<tr>
<td>Dual-isotope rest $^{201}$Tl/stress $^{99m}$Tc</td>
<td>17-24</td>
</tr>
<tr>
<td>Rest Rb/Stress Rb PET</td>
<td>2-3</td>
</tr>
</tbody>
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Pharmacologic Stress Testing

Stress Imaging Protocols ($^{99m}\text{Tc}$ and $^{201}\text{Tl}$)

### Radiation Dosimetry

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<td>1-4</td>
</tr>
<tr>
<td>Two-day $^{99m}\text{Tc}$ - Rest/Stress</td>
<td>17</td>
</tr>
<tr>
<td>Two-day $^{99m}\text{Tc}$ - Stress/Rest</td>
<td>17</td>
</tr>
<tr>
<td>High Dose $^{99m}\text{Tc}$ Stress only</td>
<td>8</td>
</tr>
<tr>
<td>Stress $^{201}\text{Tl}$</td>
<td>11-15</td>
</tr>
<tr>
<td>Dual-isotope rest $^{201}\text{Tl}$/stress $^{99m}\text{Tc}$</td>
<td>17-24</td>
</tr>
<tr>
<td>Rest/Stress Rb PET</td>
<td>2-3</td>
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Stress Imaging Protocols ($^{99mTc}$ and $^{201Tl}$)

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<th>Protocol</th>
<th>Dose (mSv)</th>
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</thead>
<tbody>
<tr>
<td>Same-day $^{99mTc}$ - Rest/Stress</td>
<td>5-13</td>
</tr>
<tr>
<td>Same-day $^{99mTc}$ - Stress/Rest</td>
<td>5-8</td>
</tr>
<tr>
<td>Low Dose $^{99mTc}$ Stress only</td>
<td>1-2</td>
</tr>
<tr>
<td>Two-day $^{99mTc}$ - Rest/Stress</td>
<td>17</td>
</tr>
<tr>
<td>Two-day $^{99mTc}$ - Stress/Rest</td>
<td>17</td>
</tr>
<tr>
<td>High Dose $^{99mTc}$ Stress only</td>
<td>8</td>
</tr>
<tr>
<td>Stress $^{201Tl}$</td>
<td>11-15</td>
</tr>
<tr>
<td>Dual-isotope rest $^{201Tl}$/stress $^{99mTc}$</td>
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<td>Rest/Stress Rb PET</td>
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Pharmacologic Stress Testing

Protocols:
Pharmacologic Stress Testing
Pharmacologic Stress Testing

Stress Nuclear Pearls

- **Exercise stress → Symptom limited!**
  - ▼ 85% of MPHR is not indication to inject and stop
  - ▼ Underestimates ischemia and exercise capacity
  - ▼ ICANL applications – 40% of labs use 85% MPHR as primary endpoint

- ▼ 50-60% of pts presenting for pharm stress are able to undergo exercise stress adequately
Pharmacologic Stress Testing

Caffeine

Regadenoson

For patients receiving caffeine prior to the 2\textsuperscript{nd} regadenoson MPS study, the number of reversible defects identified was reduced by approximately 60%.

For patients with $\geq 3$ reversible segments, 21/23 (91%) had fewer reversible segments after receiving caffeine.

**Pharmacologic Stress Testing**

### Effect of Antianginals on Vasodilator Stress

<table>
<thead>
<tr>
<th>Vessel Sens.</th>
<th>Off Meds</th>
<th>On Meds</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>93%</td>
<td>64%</td>
</tr>
<tr>
<td>LCx</td>
<td>79%</td>
<td>50%</td>
</tr>
<tr>
<td>RCA</td>
<td>100%</td>
<td>73%</td>
</tr>
<tr>
<td>Overall</td>
<td>92%</td>
<td>62%</td>
</tr>
</tbody>
</table>

❤ CONCLUSION: Antianginal drugs before vasodilator stress reduce the extent/severity of perfusion defects, resulting in underestimation of CAD

Sharir, JACC 1998;31:1540-6
Pharmacologic Stress Testing

Survival by Exercise Duration

Rozanski, JNC 2010;17:999-1008
Pharmacologic Stress Testing

Universal Stress Protocol

Exercise + Regadenoson Protocol
(< 85% MPHR, no ischemic symptoms/ECG changes)

Inject isotope

Exercise stress — Slow walk

Regadenoson 0.4 mg IV over 10 sec,
5 cc saline flush IV

SPECT

15 min (if slow walk)
60 min (if no walk)
Pharmacologic Stress Testing

ASNC Imaging Guidelines


Exercise
Adenosine
Regadenoson
Dipyridamole
Dobutamine

ASNC Guidelines:  http://www.asnc.org/guidelines

ASNC Practice Points - Pharmacologic and Exercise Stress:
  http://www.asnc.org/guidelines
Pharmacologic Stress Testing

Thank you!
Rebuttal Slides
Pharmacologic Stress Testing

Best Practices (Minimizing Rad Dose)

ASNC Goal (2010): By 2014, 50% of SPECT and PET MPI studies ≤ 9 mSv.

1. Use stress/rest protocols instead of rest/stress protocols. Use stress only if stress is normal.
2. Use weight-based dosing
3. Use recommended radiopharmaceutical doses
4. Avoid $^{201}$Tl and dual-isotope (rest $^{201}$Tl/stress $^{99}$mTc) protocols
5. PET MPI, if available
6. Newer solid-state systems and/or novel software
7. Use AUC – avoid inappropriate testing

Pharmacologic Stress Testing

Most helpful result

1. Normal Exercise TM ECG
2. Normal Exercise Echo
3. Normal Exercise MPI SPECT
   Rest and stress perfusion normal by Quant
4. Normal rest/stress Rb PET
   Rest and stress perfusion normal by Quant
   Normal absolute rest and stress flows. Normal MFR.
   No coronary calcification on AC CT scan
Pharmacologic Stress Testing

Most helpful result

1. Normal Exercise TM ECG
2. Normal Exercise Echo
3. Normal Exercise MPI SPECT
   - Rest and stress perfusion normal by Quant
4. Normal rest/stress Rb PET
   - Rest and stress perfusion normal by Quant
   - Normal absolute rest and stress flows. Normal MFR.
   - No coronary calcification on AC CT scan

→ Don’t need to recommend statin
Pharmacologic Stress Testing

Most helpful result

1. Normal Exercise TM ECG
2. Normal Exercise Echo
3. Normal Exercise MPI SPECT
   Rest and stress perfusion normal by Quant
4. Normal rest/stress Rb PET
   Rest and stress perfusion normal by Quant
   Normal absolute rest and stress flows. Normal MFR.
   Extensive coronary calcification on AC CT scan
Pharmacologic Stress Testing

Most helpful result

1. Normal Exercise TM ECG
2. Normal Exercise Echo
3. Normal Exercise MPI SPECT
   Rest and stress perfusion normal by Quant
4. Normal rest/stress Rb PET
   Rest and stress perfusion normal by Quant
   Normal absolute rest and stress flows. Normal MFR.
   Extensive coronary calcification on AC CT scan
   → Recommend high intensity statin and aspirin 81 mg
   → Knowing CAC extent very helpful to interpreting physician
Pharmacologic Stress Testing

Bridging gap with PET/CT and SPECT/CT

Normal ETT/SE/MPI $\rightarrow$ Add **CCS**
(if $>0$, Rx with statin;
Many pts will have moderate to extensive CAC)
Pharmacologic Stress Testing

Bridging gap with PET/CT and SPECT/CT

Normal ETT/SE/MPI → Add CCS (if >0, Rx with statin; Many pts will have moderate to extensive CAC)

Borderline SE/MPI or Abnormal ETT → CCTA (very high NPV), instead of another functional study which won’t get pt to low LK by Bayesian analysis
Pharmacologic Stress Testing

Thank you!