



**Systematic Review of
Coronary Computed Tomographic
Angiography (CCTA):**

Preliminary Findings

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**Dan Ollendorf, MPH, ARM
Chief Review Officer**

**Michelle Kuba, MPH
Senior Technology Analyst**

Systematic Review Framework

- Key questions:
 - What is the impact of CCTA on clinical outcomes
 - Potential benefits
 - ? More accurate than other non-invasive tests
 - ? Avoid need for invasive angiography in many patients
 - Potential harms
 - Radiation dose
 - Contrast reactions
 - ? Incidental findings
 - What is the diagnostic accuracy of CCTA?

Review Scope

- CCTA use in:
 - Emergency Dept. triage of acute chest pain of unknown origin to diagnose acute coronary syndromes (ACS) and/or coronary artery disease (CAD)
 - Outpatient presentation with stable chest pain and low-to-intermediate CAD risk to diagnose CAD
- CCTA technology:
 - 64-slice or better precision
 - Newer, dual-source scanners included in review
 - Reports between 2005 (introduction of 64-slice CCTA) and present evaluated

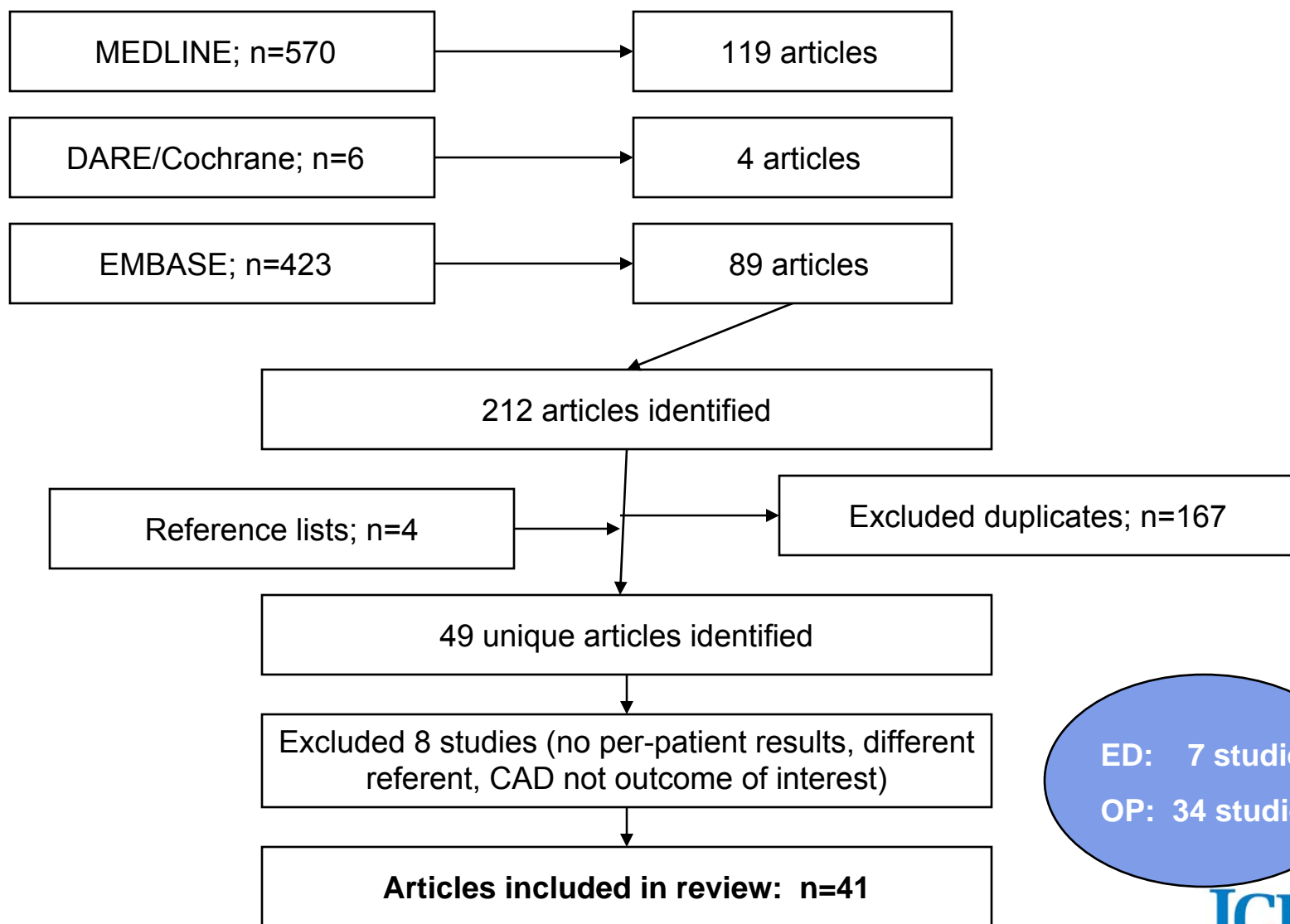
Major Exclusions

- Diagnosis confirmation:
 - Receipt of invasive coronary angiography (ICA) by nonrandom sample of subjects and/or inability to identify true negatives in sample
- CCTA:
 - Data not reported on per-patient basis:
 - Per-vessel and/or per-segment only

Important Considerations

- Most studies in sample involved higher-risk populations (including some with known CAD)
 - Studies that focused on low-to-intermediate populations or provided stratified findings highlighted
 - Meta-analysis findings compared between studies that did and did not include patients with known CAD
- Relatively few studies account for patients with non-evaluative tests
 - Patients typically excluded from analyses
 - Primary meta-analysis conducted using conservative assumption:
 - All patients with non-diagnostic results (3.2% in our sample) considered false-positives

Literature Search Results



ED: 7 studies
OP: 34 studies

Description of Included Studies

- All published studies conducted in single centers
- In outpatient studies, accuracy tested most often by conducting CCTA in patients already scheduled for ICA:
 - 26 of 34 outpatient studies
 - In other studies, CCTA used in diagnosis of patients with suspected CAD:
 - ICA used in all patients or as dictated by CCTA results
- Underlying CAD prevalence varied considerably:
 - Mean (SD): 59.0% (20.9%)
 - Range: 18.2%-91.0%

Description of Included Studies

- ED
 - 7 studies met criteria (N=594)
 - Age range: 46-58 years
 - Men/women: 346/248
 - 1 RCT, others single-center case series
 - Most used clinical diagnosis algorithm for confirmation
- Outpatient
 - 34 studies met criteria (N=3,349)
 - Age range: 46-69 years
 - Men/women: 2,114/1,235
 - Most used ICA alone or in combination as referent

Evidence Table: Studies of CCTA Prognostic Ability

Table 1. Studies examining prognostic ability of 64-slice or better CCTA based on clinical follow-up.

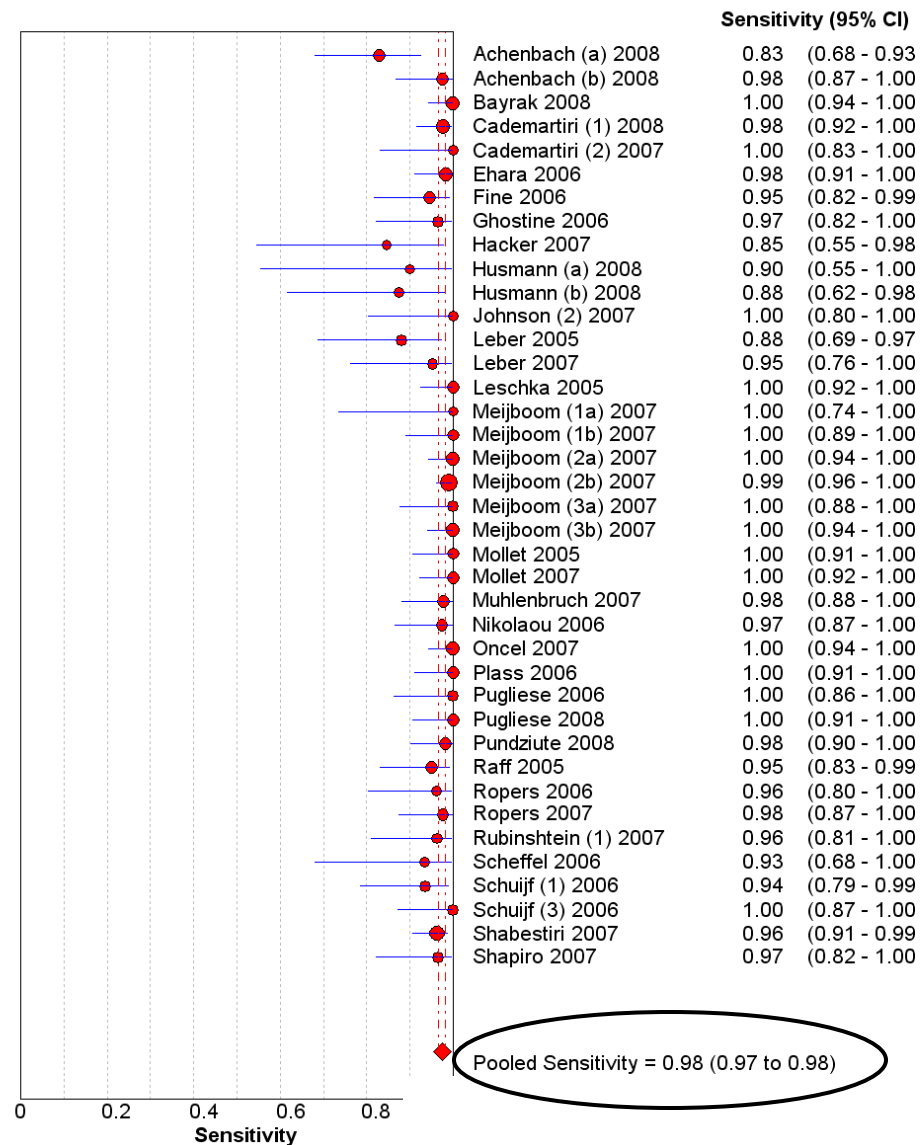
| Author | Year | Study Type | Setting | Sample Size | Age (Mean, SD) | % Male | CAD Risk | Follow-Up | Diagnosis Method | Major Findings |
|-------------|------|-------------------------|---------|-------------|----------------|--------|--------------|------------------|---|--|
| Goldstein | 2007 | RCT | ED | 99 | 48 (11) | 43% | Very low | 6 months | ICA, repeat testing (MACE) | CCTA correctly and definitively diagnosed 94 of 99 (95%) |
| Hoffmann | 2006 | Single-center (MA) | ED | 103 | 54 (12) | 60% | Low | Mean: 5.2 months | Record review (index visit only, ACS) | Sensitivity 100% for ACS, specificity 82% |
| Hollander | 2007 | Single-center (PA) | ED | 54 | 46.5 (8.5) | 46% | Low | 30 days | Survey, record review (cardiac death/acute MI) | No events recorded; CAD confirmed in 4 of 6 CCTA-positive patients |
| Johnson | 2007 | Single-center (Germany) | ED | 55 | 67 (10) | 64% | N/A | ≥5 months | Record review, repeat enzymes (obstructive CAD) | CCTA correctly and definitively diagnosed 51 of 55 (93%) |
| Pundziute | 2007 | Single-center (Holland) | OP | 100 | 59 (12) | 73% | Intermediate | Mean: 16 months | Record review, clinic visits, survey (MACE) | 1-yr event rate 0% in CCTA (-) patients; 30% in CCTA (+) |
| Rubinshtein | 2007 | Single-center (Israel) | ED | 58 | 56 (10) | 64% | Intermediate | 15 months | Telephone survey (MACE) | Event-based sensitivity 92%, specificity 76% |
| Savino | 2006 | Single-center (SC) | ED | 23 | 56 (13) | 61% | N/A | ED visit only | Record review | All moderate/severe stenoses on CCTA confirmed by ICA |

CAD: coronary artery disease; RCT: randomized controlled trial; MACE: major adverse cardiovascular event; CCTA: coronary computed tomographic angiography; OP: outpatient; ACS: acute coronary syndromes; MI: myocardial infarction; ICA: invasive coronary angiography; ED: emergency department

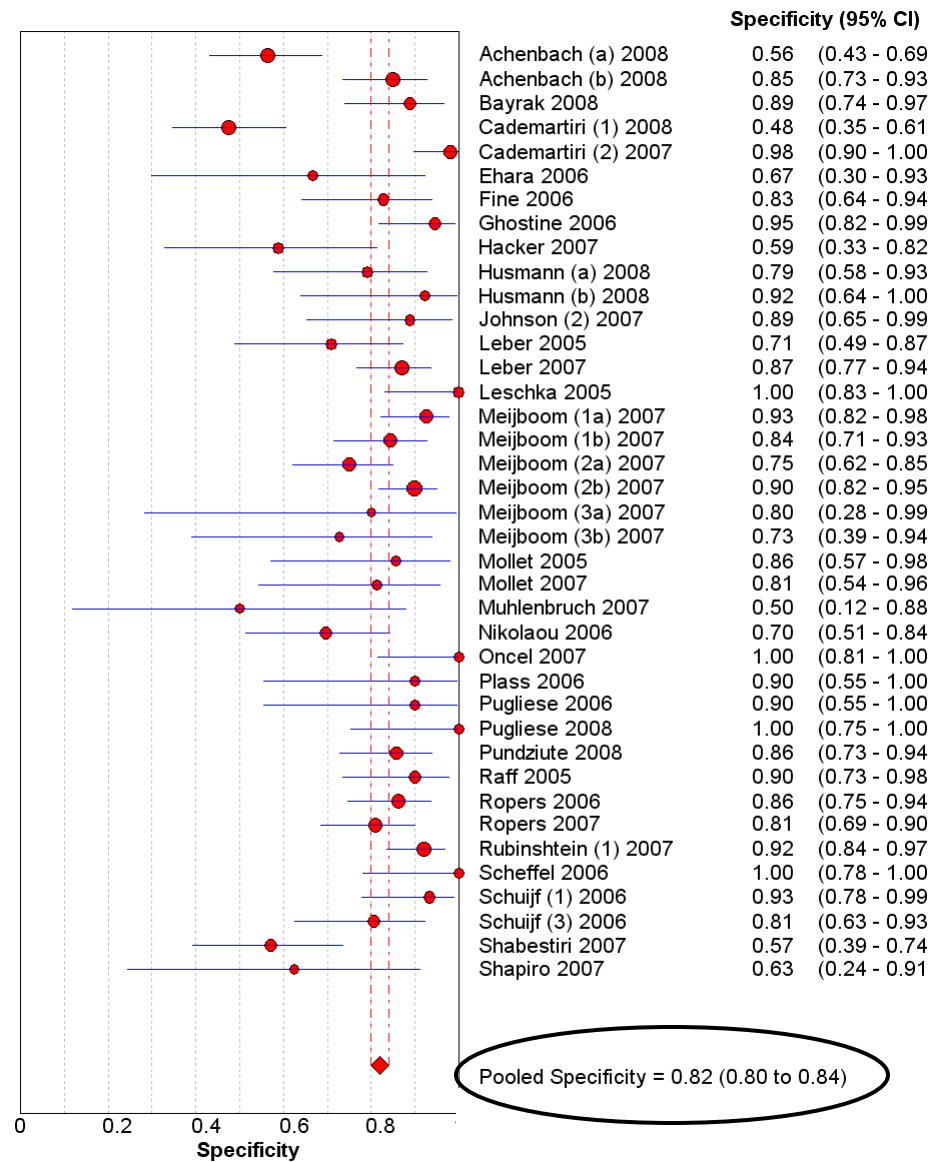
Meta-Analysis: Diagnostic Accuracy

- Meta-analysis indicated for deriving pooled test accuracy estimates:
 - Study design and analysis of accuracy relatively standardized
 - Between-study heterogeneity and inconsistency within reasonable ranges
 - Studies using ICA as referent (33 OP, 1 ED) included
- Random-effects models specified for sensitivity and specificity, positive and negative likelihood ratios:
 - Appropriate choice when other factors expected to influence study outcome (e.g., CAD prevalence)

Meta-Analysis Results: Sensitivity



Meta-Analysis Results: Specificity



Pooled Positive LR: 5.34 (95% CI: 4.12, 6.93)
 Pooled Negative LR: 0.05 (95% CI: 0.03, 0.07)

Harms: Radiation Dose

- Effective dose reported in 17 studies (3 ED, 14 OP):
 - Overall range: 4.6 – 21.4 mSv
 - Lowest rates reported for studies using dual-source scanners (Johnson 2007, Leber 2007)
- 6 studies reported separate doses for men and women:
 - Men: 7.45-15.2 mSv (mean: 12.4)
 - Women: 10.24-21.4 mSv (mean: 14.2)
- Similar range reported in other studies (5-32 mSv); mean of 16 mSv in recent literature review*

Harms: Radiation Dose

| Radiation exposure scenario | Approximate effective dose (mSv) |
|---|----------------------------------|
| Chest x ray | 0.02 |
| Round-trip flight, New York-Seattle | 0.06 |
| Low-dose CT colonography | 0.5 |
| Head CT | 2.0 |
| Single-screening mammogram (breast dose) | 3.0 |
| Annual background dose caused by natural radiation | 3.0/yr |
| CCTA (lower reported range) | 2.0-8.0 |
| Invasive coronary angiography | 5.0-7.0 |
| Adult abdominal CT scan | 10.0 |
| Single photon emission computed tomography (SPECT) | 9.0-13.0 |
| CCTA (higher reported range) | 12.0-14.0 |
| Typical dose to A-bomb survivor at 2.3 km distance from ground zero Hiroshima | 13.0 |
| Annual radiation worker annual exposure limit | 20.0/yr |
| Annual exposure on international space station | 170/yr |

Harms: Radiation Dose

- Recent study* concluded non-negligible lifetime cancer risk attributable to 1 CCTA:
 - 0.22% and 0.08% in women/men aged 60 years
 - Use of tube current modulation estimated to reduce risks to 0.14% and 0.05% respectively
- Estimates still open to substantial debate:
 - No reliable long-term outcome data
 - Speculation on risk function:
 - ? Linear or non-linear association
 - ? Presence of dose threshold? ? Competing risks

Harms: Contrast Reactions

- Risk of serious reactions to contrast media very low:
 - Severe reaction: 0.001-0.003%
 - Death: <0.001%
- Effects on serum creatinine not generally associated with severe or permanent renal injury
- CCTA studies do not report rates of contrast reaction:
 - Very low perceived risk; exclusion of patients with known contrast allergy or compromised renal status

Harms: Incidental Findings

- Reported rate of major findings from 64-slice CCTA ranges between 10-15%:
 - Large pulmonary nodules only one type of finding
 - Bladder mass, aortic aneurysm, pulmonary emboli and infection, hepatic angiomas other examples
- Incidental findings with other CAD diagnostic tests not unheard of:
 - Example: 1.2% in patients receiving SPECT
- Little data or consensus on follow-up requirements or long-term outcome from these findings

Summary

- Published literature on 64-slice CCTA expanded rapidly 2005-2008
 - Relatively few studies evaluate impact on “hard” patient outcomes
 - Most studies involved populations w/high CAD prevalence
- CCTA diagnostic accuracy appears to be high
 - Major utility = ruling out obstructive CAD
 - Appears to add value as prognostic tool
- Rate of non-diagnostic findings an important consideration:
 - Inclusion of such patients = lower PPV
- Very limited evidence/conjecture on long-term effects of radiation dose and f/u requirements from incidental findings

Key Questions/Next Steps

- Are there studies that you would suggest highlighting or de-emphasizing in our analyses?
- Are there studies not included in these analyses you would recommend we consider?

Appendix: Detailed Findings

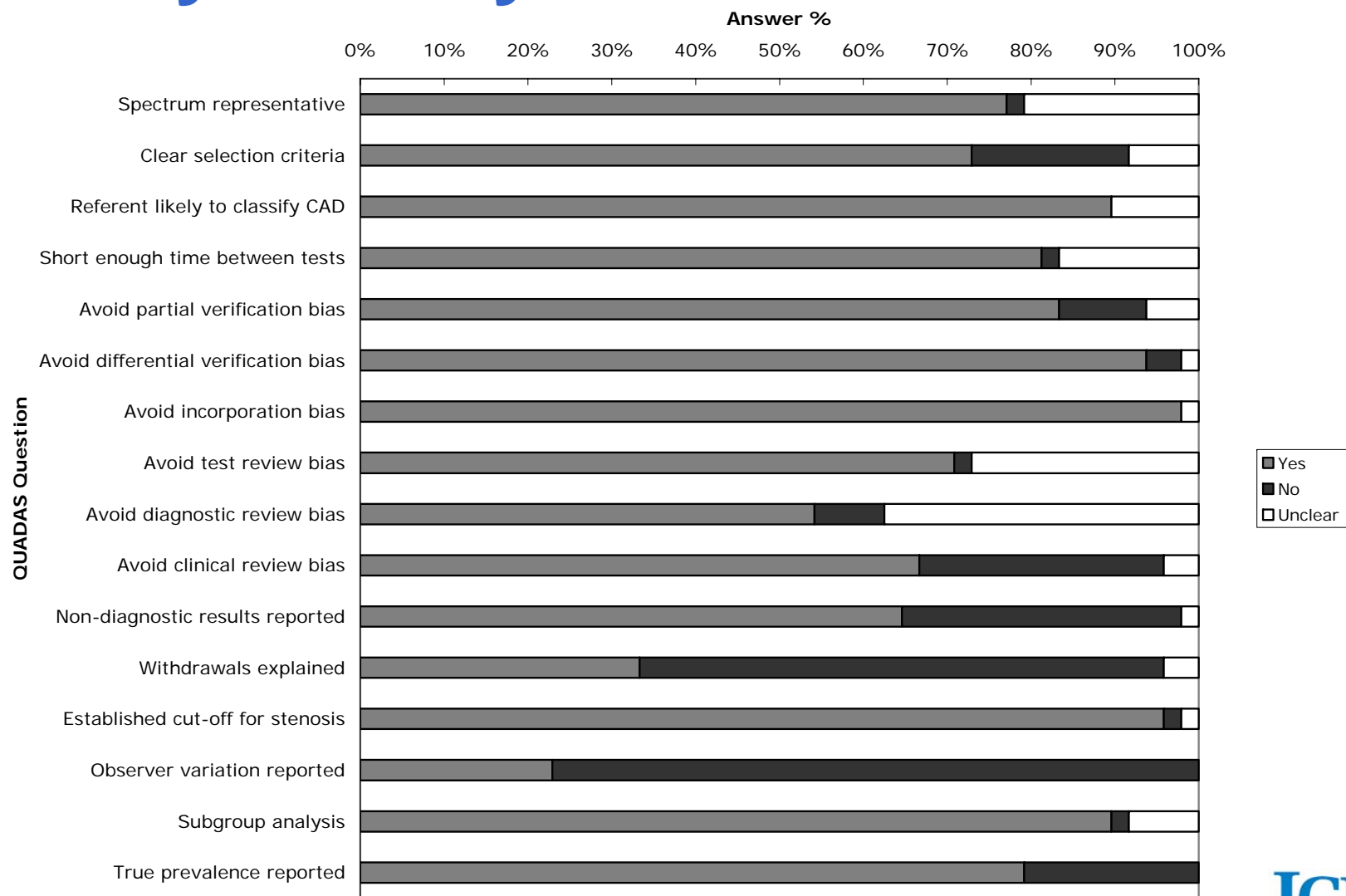
Highlighted Studies

| Author | Setting | Relevance | Key Findings |
|-------------------|------------|---------------------------------------|---|
| Goldstein 2007 | ED | RCT of CCTA vs. standard triage care | Accuracy similar between arms; CCTA had lower resource use/costs |
| Husmann 2008 | Outpatient | Stratified by CAD risk | Sensitivity/NPV unaffected by risk level; PPV improved w/higher risk |
| Meijboom 2007 (1) | Outpatient | Stratified by CAD pretest probability | Essentially identical to Husmann |
| Meijboom 2007 (2) | Outpatient | Stratified by gender | Sensitivity/NPV unaffected by gender; Specificity/PPV better in men |
| Pundziute 2008 | Outpatient | Stratified by gender | No differences by gender in any accuracy measure |
| Pundziute 2007 | Outpatient | Event-based study | 1-year cardiac event rate for CCTA (-) = 0%; 30% for CCTA (+) |
| Mollett 2007 | Outpatient | Typical practice diagnostic pathway | Good sensitivity/NPV for CCTA alone improved when added to stress EKG |

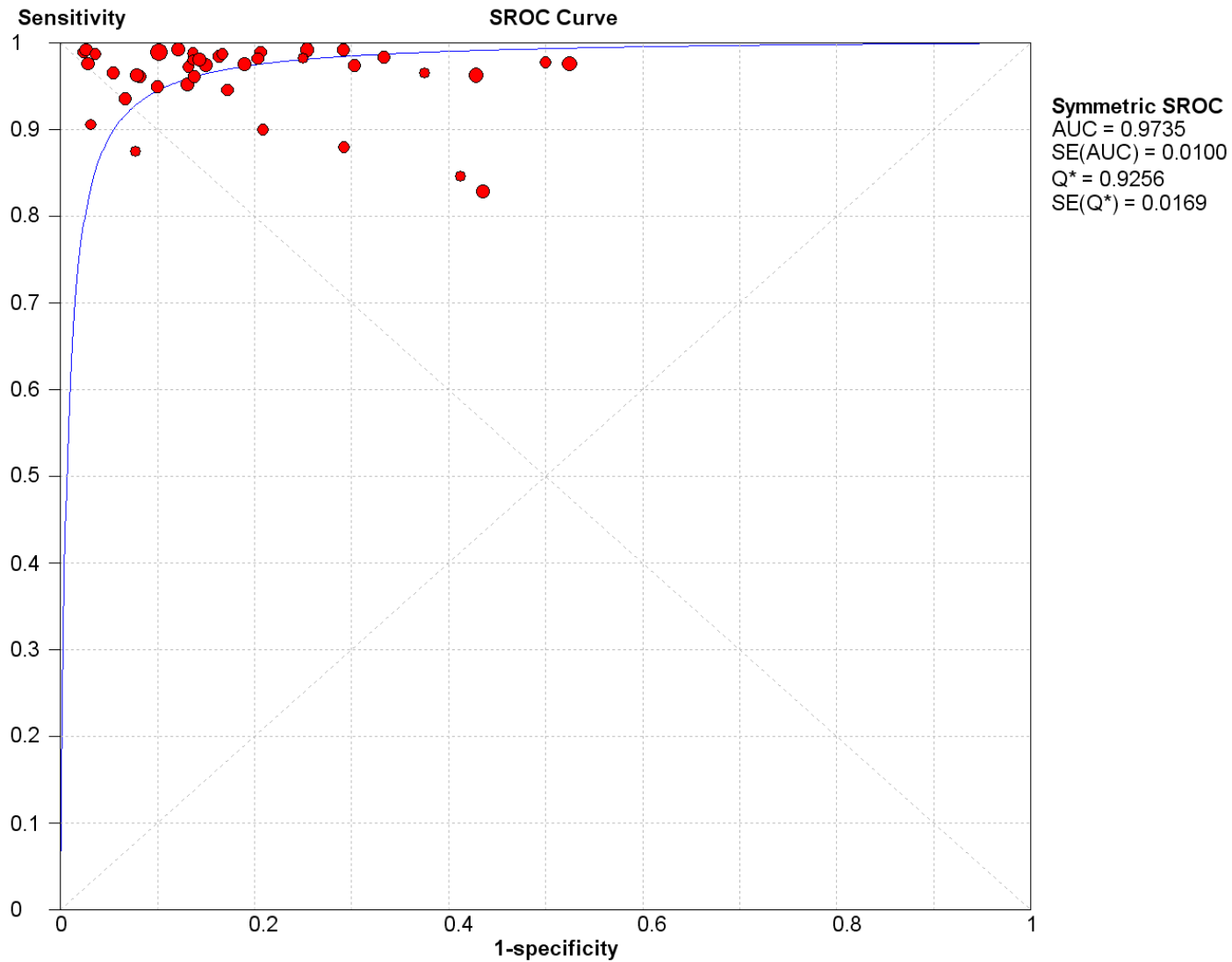
Evidence Quality

- QUADAS (internal validity rating tool) used to rate studies:
 - 12 of 14 core elements retained, 4 new elements added (consistent with systematic review by Mowatt et al.):
 - Use of standardized % cutoff to define stenosis
 - Reported data on inter-observer variation
 - Data stratified for highlighted subgroups
 - Reported or derived true disease prevalence
 - 9 studies rated as “good”, 30 rated as “fair”:
 - Major issues with studies around lack of data on patient withdrawals, inter-observer variation, blinded ICA review, nondiagnostic results, and availability of clinical data

Study Quality Overview



Meta Analysis: SROC Curve



Diagnostic Accuracy: No Known Prior CAD

Summary Sensitivity

| Study | Sen | [95% Conf. Interval.] | TP/(TP+FN) | TN/(TN+FP) |
|----------------------|--------------|-----------------------|------------|------------|
| --- | | | | |
| Cademartiri 2008 | 0.976 | 0.917 - 0.997 | 82/84 | 29/50 |
| Cademartiri 2007 | 1.000 | 0.832 - 1.000 | 20/20 | 51/52 |
| Ghostine 2006 | 0.966 | 0.822 - 0.999 | 28/29 | 35/37 |
| Achenbach (b) 2008 | 0.975 | 0.868 - 0.999 | 39/40 | 51/57 |
| Achenbach (a) 2008 | 0.829 | 0.679 - 0.928 | 34/41 | 35/44 |
| Husmann (b) 2008 | 0.875 | 0.617 - 0.984 | 14/16 | 12/13 |
| Husmann (a) 2008 | 0.900 | 0.555 - 0.997 | 9/10 | 19/24 |
| Leber 2007 | 0.952 | 0.762 - 0.999 | 20/21 | 60/67 |
| Leschka 2005 | 1.000 | 0.925 - 1.000 | 47/47 | 20/20 |
| Meijboom (1a) 2007 | 1.000 | 0.735 - 1.000 | 12/12 | 50/54 |
| Meijboom (1b) 2007 | 1.000 | 0.891 - 1.000 | 32/32 | 43/51 |
| Mollet 2007 | 1.000 | 0.923 - 1.000 | 46/46 | 13/15 |
| Mollet 2005 | 1.000 | 0.907 - 1.000 | 38/38 | 12/13 |
| Muhlenbruch 2007 | 0.978 | 0.882 - 0.999 | 44/45 | 3/6 |
| Oncel 2007 | 1.000 | 0.942 - 1.000 | 62/62 | 18/18 |
| Plass 2006 | 1.000 | 0.912 - 1.000 | 40/40 | 9/10 |
| Raff 2005 | 0.950 | 0.831 - 0.994 | 38/40 | 27/30 |
| Scheffel 2006 | 0.933 | 0.681 - 0.998 | 14/15 | 15/15 |
| Pugliese 2008 | 1.000 | 0.907 - 1.000 | 38/38 | 13/13 |
| Ropers 2006 | 0.962 | 0.804 - 0.999 | 25/26 | 50/55 |
| Ropers 2007 | 0.975 | 0.868 - 0.999 | 39/40 | 47/57 |
| Rubinshtein (1) 2007 | 0.963 | 0.810 - 0.999 | 26/27 | 70/73 |
| Schuijf (2) 2006 | 1.000 | 0.872 - 1.000 | 27/27 | 25/31 |
| Shabestiri 2007 | 0.963 | 0.908 - 0.990 | 104/108 | 20/30 |
| --- | | | | |
| Pooled Sen | 0.971 | 0.958 - 0.981 | | |
| --- | | | | |

Diagnostic Accuracy: No Known Prior CAD (cont'd)

Summary Specificity

| Study | Spe | [95% Conf. Interval.] | TP/(TP+FN) | TN/(TN+FP) |
|----------------------|--------------|-----------------------|------------|------------|
| --- | | | | |
| Cademartiri 2008 | 0.580 | 0.432 - 0.718 | 82/84 | 29/50 |
| Cademartiri 2007 | 0.981 | 0.897 - 1.000 | 20/20 | 51/52 |
| Ghostine 2006 | 0.946 | 0.818 - 0.993 | 28/29 | 35/37 |
| Achenbach (b) 2008 | 0.895 | 0.785 - 0.960 | 39/40 | 51/57 |
| Achenbach (a) 2008 | 0.795 | 0.647 - 0.902 | 34/41 | 35/44 |
| Husmann (b) 2008 | 0.923 | 0.640 - 0.998 | 14/16 | 12/13 |
| Husmann (a) 2008 | 0.792 | 0.578 - 0.929 | 9/10 | 19/24 |
| Leber 2007 | 0.896 | 0.797 - 0.957 | 20/21 | 60/67 |
| Leschka 2005 | 1.000 | 0.832 - 1.000 | 47/47 | 20/20 |
| Meijboom (1a) 2007 | 0.926 | 0.821 - 0.979 | 12/12 | 50/54 |
| Meijboom (1b) 2007 | 0.843 | 0.714 - 0.930 | 32/32 | 43/51 |
| Mollet 2007 | 0.867 | 0.595 - 0.983 | 46/46 | 13/15 |
| Mollet 2005 | 0.923 | 0.640 - 0.998 | 38/38 | 12/13 |
| Muhlenbruch 2007 | 0.500 | 0.118 - 0.882 | 44/45 | 3/6 |
| Oncel 2007 | 1.000 | 0.815 - 1.000 | 62/62 | 18/18 |
| Plass 2006 | 0.900 | 0.555 - 0.997 | 40/40 | 9/10 |
| Raff 2005 | 0.900 | 0.735 - 0.979 | 38/40 | 27/30 |
| Scheffel 2006 | 1.000 | 0.782 - 1.000 | 14/15 | 15/15 |
| Pugliese 2008 | 1.000 | 0.753 - 1.000 | 38/38 | 13/13 |
| Ropers 2006 | 0.909 | 0.800 - 0.970 | 25/26 | 50/55 |
| Ropers 2007 | 0.825 | 0.701 - 0.913 | 39/40 | 47/57 |
| Rubinshtein (1) 2007 | 0.959 | 0.885 - 0.991 | 26/27 | 70/73 |
| Schuijf (2) 2006 | 0.806 | 0.625 - 0.925 | 27/27 | 25/31 |
| Shabestiri 2007 | 0.667 | 0.472 - 0.827 | 104/108 | 20/30 |
| --- | | | | |
| Pooled Spe | 0.871 | 0.846 - 0.893 | | |
| --- | | | | |

Diagnostic Accuracy: Known Prior CAD

Summary Sensitivity

| Study | Sen | [95% Conf. Interval.] | TP/(TP+FN) | TN/(TN+FP) |
|--------------------|--------------|-----------------------|------------|------------|
| ---- | | | | |
| Ehara 2006 | 0.983 | 0.911 - 1.000 | 59/60 | 6/7 |
| Fine 2006 | 0.946 | 0.818 - 0.993 | 35/37 | 24/25 |
| Bayrak 2008 | 1.000 | 0.944 - 1.000 | 64/64 | 32/36 |
| Hacker 2007 | 0.846 | 0.546 - 0.981 | 11/13 | 10/17 |
| Johnson (2) 2007 | 1.000 | 0.805 - 1.000 | 17/17 | 16/18 |
| Leber 2005 | 0.880 | 0.688 - 0.975 | 22/25 | 17/20 |
| Meijboom (2a) 2007 | 1.000 | 0.943 - 1.000 | 63/63 | 45/60 |
| Meijboom (2b) 2007 | 0.989 | 0.962 - 0.999 | 188/190 | 80/89 |
| Nikolaou 2006 | 0.974 | 0.865 - 0.999 | 38/39 | 23/29 |
| Pugliese 2006 | 1.000 | 0.863 - 1.000 | 25/25 | 9/10 |
| Pundziute 2008 | 0.981 | 0.901 - 1.000 | 53/54 | 42/46 |
| Schuijf (1) 2006 | 0.935 | 0.786 - 0.992 | 29/31 | 28/29 |
| Shapiro 2007 | 0.963 | 0.810 - 0.999 | 26/27 | 5/5 |
| ---- | | | | |
| Pooled Sen | 0.977 | 0.962 - 0.987 | | |
| ---- | | | | |

Diagnostic Accuracy: Known Prior CAD (cont'd)

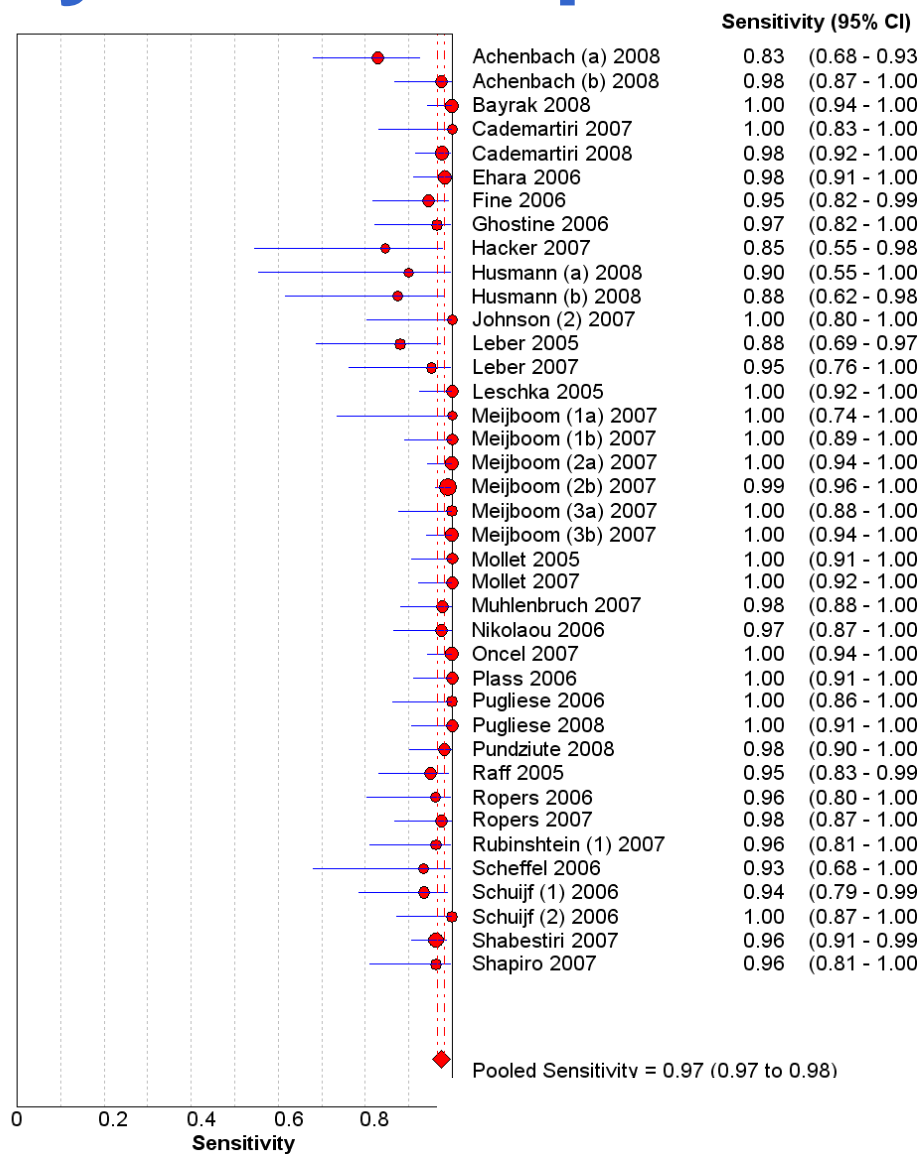
Summary Specificity

| Study | Spe | [95% Conf. Interval.] | | TP/(TP+FN) | TN/(TN+FP) |
|--------------------|--------------|-----------------------|----------------|------------|------------|
| --- | | | | | |
| Ehara 2006 | 0.857 | 0.421 | - 0.996 | 59/60 | 6/7 |
| Fine 2006 | 0.960 | 0.796 | - 0.999 | 35/37 | 24/25 |
| Bayrak 2008 | 0.889 | 0.739 | - 0.969 | 64/64 | 32/36 |
| Hacker 2007 | 0.588 | 0.329 | - 0.816 | 11/13 | 10/17 |
| Johnson (2) 2007 | 0.889 | 0.653 | - 0.986 | 17/17 | 16/18 |
| Leber 2005 | 0.850 | 0.621 | - 0.968 | 22/25 | 17/20 |
| Meijboom (2a) 2007 | 0.750 | 0.621 | - 0.853 | 63/63 | 45/60 |
| Meijboom (2b) 2007 | 0.899 | 0.817 | - 0.953 | 188/190 | 80/89 |
| Nikolaou 2006 | 0.793 | 0.603 | - 0.920 | 38/39 | 23/29 |
| Pugliese 2006 | 0.900 | 0.555 | - 0.997 | 25/25 | 9/10 |
| Pundziute 2008 | 0.913 | 0.792 | - 0.976 | 53/54 | 42/46 |
| Schuijf (1) 2006 | 0.966 | 0.822 | - 0.999 | 29/31 | 28/29 |
| Shapiro 2007 | 1.000 | 0.478 | - 1.000 | 26/27 | 5/5 |
| --- | | | | | |
| Pooled Spe | 0.862 | 0.824 | - 0.895 | | |
| --- | | | | | |

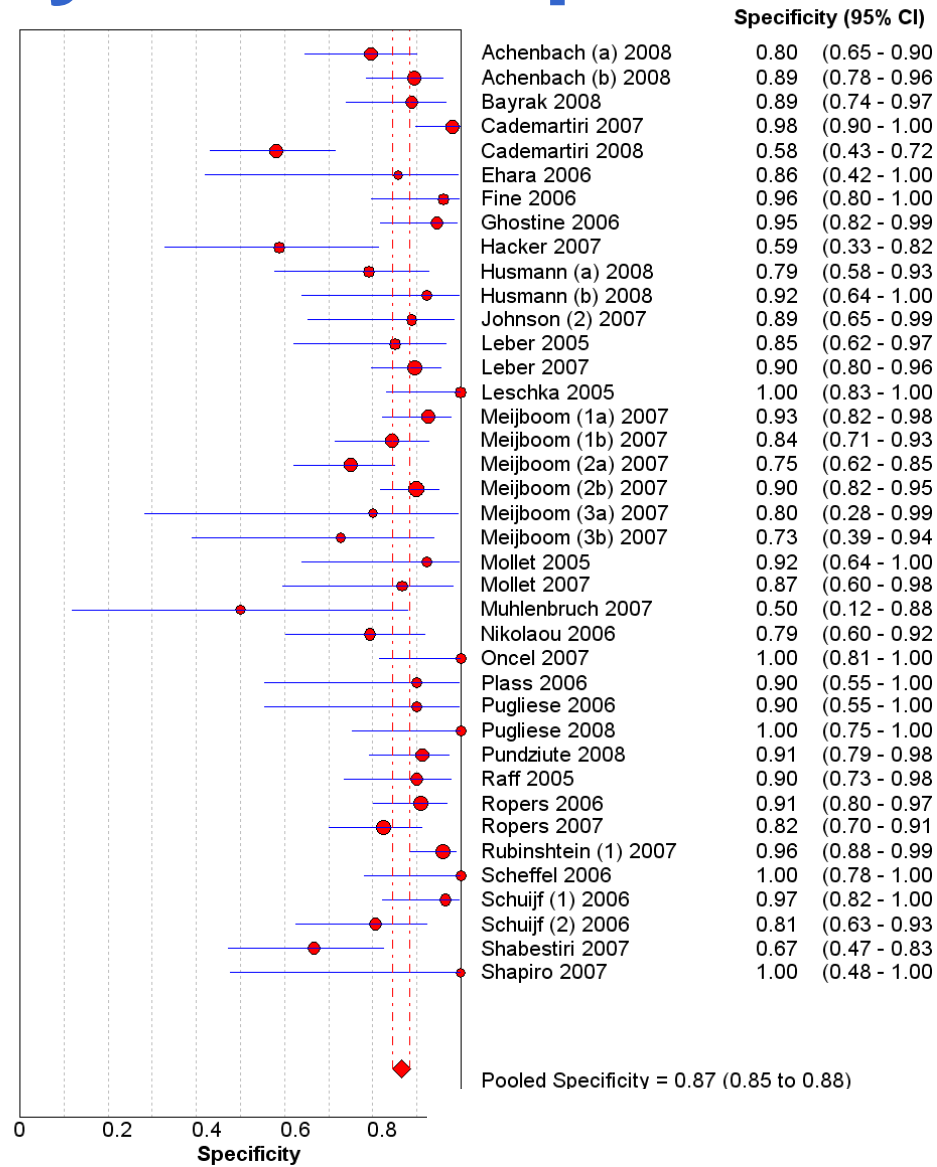
Alternative Analyses

- Pooled results (outpatient studies) using “as reported” framework:
 - Analyses conducted using data as reported—patients with nondiagnostic results *excluded* from analysis
 - Approach results in higher specificity/PLR, sensitivity/NLR essentially unchanged:
 - Specificity 87% vs. 82% in primary analyses
 - PLR 6.62 vs. 5.34

Sensitivity: “As Reported” Analysis



Specificity: “As Reported” Analysis



SROC Curve: “As Reported” Analysis

