Functional testing for the detection of restenosis after percutaneous transluminal coronary angioplasty: a meta-analysis

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Authors' objectives
To pool the results from studies of functional testing to detect restenosis after percutaneous transluminal coronary angioplasty (PTCA).

Searching
MEDLINE was searched from 1975 to 2000 for articles in the English language. The key terms used were 'PTCA', 'angioplasty', 'detection', 'restenosis', 'functional testing', 'exercise testing', 'sestamibi', 'thallium' and 'echocardiography'. Selected references from the articles identified were examined. Abstracts were not included in the review.

Study selection
Study designs of evaluations included in the review
The study design was not specified in the inclusion criteria. Studies in which functional test results and angiogram results were read independently were included. The report suggests that the decision to limit inclusion with regard to the timing of the diagnostic test would have excluded retrospective observational studies in favour of prospective studies, in which all patients had the test in a restricted time period.

Specific interventions included in the review
Studies of post-PTCA functional testing, by exercise treadmill testing (ETT) alone, stress nuclear imaging or stress echocardiographic imaging, were eligible for inclusion if they performed the functional test at 6 months post-PTCA. Due to the small number of studies of stress echocardiography, these were included if a follow-up functional test was performed in the first 3 to 12 months post-PTCA. Stress echocardiographic studies that used pharmacological stress agents were included, but other tests conducted with pharmacological stress agents were excluded. The definition of restenosis was not restricted by the inclusion criteria; in the included studies, it ranged from a greater than 50% to a greater than 75% narrowing of the coronary artery diameter.

Reference standard test against which the new test was compared
Coronary angiogram at 6 months. Studies that used quantitative or semiquantitative methods to evaluate the angiograms, i.e. to estimate the diameter of restenosed vessels, were included.

Participants included in the review
Studies of patients who had undergone successful PTCA were eligible for inclusion. Studies of symptomatic and asymptomatic patients, and patients with single or multi-vessel disease, were included. Studies in populations with prior positive stress tests, or angiographically demonstrated restenosis before undergoing a stress test, were excluded.

Outcomes assessed in the review
Studies that reported the sensitivity and specificity, or provided data to calculate these parameters, were included.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the relevance of each study without being blinded to the authorship or study results. Any disagreements were resolved by discussion.

Assessment of study quality
No systematic assessment of validity was undertaken. Inclusion was restricted to studies in which the functional test results and angiogram results were read independently.
Data extraction
Two reviewers independently extracted the data, and any disagreements were resolved by discussion. The data extracted included: type of imaging, population (symptomatic or asymptomatic), the number of vessels (single or multi-vessel disease), the number of participants, the proportion with restenosis, sensitivity and specificity.

Methods of synthesis
How were the studies combined?
The weighted pooled estimates of sensitivity and specificity were calculated using a random-effects model. The pooled estimates with 95% confidence intervals (CIs) were calculated for two definitions of restenosis: a coronary artery diameter narrowing of greater than 50% or a coronary artery diameter narrowing of greater than 70 or 75%.

The impact of stenting on the predictive value of the tests was examined using Bayes' Theorem (see Other Publications of Related Interest). In the theoretical model, a restenosis rate of 10% was estimated for asymptomatic patients stented for single-vessel disease, and a rate of 50% or greater was estimated for asymptomatic non-stented patients with multi-vessel PTCA. The pooled sensitivities and specificities calculated for the definition of restenosis as a coronary artery diameter narrowing of greater than 50% were used to generate positive and negative predictive values (PPVs and NPVs, respectively). The pre-test probability of restenosis was varied between 10% (low) and 50% (high) in the model. The positive and negative likelihood ratios (LRs) were also calculated from the pooled sensitivities and specificities.

How were differences between studies investigated?
Studies of each test were analysed separately in two groups, according to the definition used for restenosis. A random-effects model was used to pool the data because of heterogeneity between the studies. However, the impact of heterogeneity on the findings was not explored further.

Results of the review
Thirteen studies were included. These involved ETT (n=1,003), exercise nuclear imaging (n=398) and stress echocardiography (n=308).

The pooled sensitivity of ETT, when restenosis was defined as a coronary artery diameter narrowing of greater than 50% (n=527), was 46% (95% CI: 33, 58) and the specificity was 77% (95% CI: 67, 86). The values were 50% (95% CI: 30, 70) and 84% (95% CI: 77, 92), respectively, when restenosis was defined as a coronary artery diameter narrowing of greater than 70% (n=667). Based on studies where restenosis was defined as a coronary artery diameter narrowing of greater than 50%, the positive LR was 1.94 and the negative LR was 0.71. The values were 3.18 and 0.59, respectively, when restenosis was defined as a coronary artery diameter narrowing of greater than 70% (n=667). Assuming a restenosis rate of 30%, the test was associated with a false positive rate of 54% and a false negative rate of 23%.

For nuclear imaging, the sensitivity was 87% (95% CI: 74, 100) and the specificity was 78% (95% CI: 74, 81) when restenosis was defined as a coronary artery diameter narrowing of greater than 50% (n=262). The values were 94% (95% CI: 80, 100) and 89% (95% CI: 79, 100), respectively, when restenosis was defined as a coronary artery diameter narrowing of greater than 70% (n=136). Based on studies where restenosis was defined as a coronary artery diameter narrowing of greater than 50%, the positive LR was 3.93 and the negative LR was 0.16. The values were 8.74 and 0.07, respectively, when restenosis was defined as a coronary artery diameter narrowing of greater than 70% (n=136). Assuming a restenosis rate of 30%, the test was associated with a false positive rate of 36% and a false negative rate of 7%.

For echocardiographic imaging, the sensitivity was 63% (95% CI: 15, 100) and the specificity was 87% (95% CI: 72, 100) when restenosis was defined as a coronary artery diameter narrowing of greater than 50% (n=183). The values were 73% (95% CI: 65, 80) and 90% (95% CI: 85, 95), respectively, when restenosis was defined as a coronary artery diameter narrowing of greater than 70% (n=125). Based on studies where restenosis was defined as a coronary artery diameter narrowing of greater than 50%, the positive LR was 4.94 and the negative was LR 0.43. The values were 7.27 and 0.30, respectively, when restenosis was defined as a coronary artery diameter narrowing of greater than 70%.
(n=125). Assuming a restenosis rate of 30%, the test was associated with a false positive rate of 32% and a false negative rate of 15%.

Using a theoretical model in which the pre-test probability of restenosis was varied from 10% (low risk) to 50% (high risk), ETT alone was not a reliable test for detecting restenosis, even in a high risk non-stented population (PPV 67%, NPV 59%). On the other hand, both stress nuclear imaging and stress echocardiography were more reliable in the high-risk population (PPV greater than 80%, NPV at least 70%). However, the PPV decreased and the NPV increased as the pre-test probability declined. The largest difference was in the false positive rate of stress nuclear imaging, which increased from 37% (PPV 63) to 77% (PPV 23) as the restenosis rates declined from 30 to 10%.

Authors' conclusions
ETT alone is poorly diagnostic of post-PTCA restenosis. Stress nuclear and stress echocardiographic imaging perform better, but their predictive values are highly dependent on the pre-test probability of restenosis.

CRD commentary
The review question was clearly stated in the objectives. The inclusion and exclusion criteria, however, appear to have been determined after the content of the identified papers was known. It is unclear whether the inclusion criteria were modified before or during the study selection process. The reviewers were not blinded to the citations or to the results of the studies, therefore, the determination of the inclusion criteria and selection of eligible studies were potentially open to bias. Furthermore, wider inclusion criteria were used for studies of echocardiography for the simple reason that fewer studies were found. The search for studies was very limited and it is likely that relevant studies were missed. In addition, among the studies included there is a real possibility of language and publication bias.

The validity of the design and conduct of the included studies was not assessed systematically. Consequently, the reader is unable to judge how biases in the primary studies might have influenced the findings of the review. The included studies were presented in tabular format, showing some of the differences between the study populations and the tests used. The authors discussed their findings in the context of these differences. The methods used for the analysis were described well and some of their limitations were discussed.

The authors' conclusions need to be interpreted with care because the review methodology was of insufficient rigour to ensure reliable results.

Implications of the review for practice and research
Practice: The authors state that the value of routine post-PTCA functional testing is declining because restenosis rates are decreasing, and the practice of routine testing should, therefore, be reassessed. However, a negative functional test result in any of the three tests for a patient with a low pre-test probability of restenosis may be clinically useful because of the high negative predictive value of the tests.

Research: The authors state the need for a randomised trial of all three tests (ETT, stress nuclear imaging and stress echocardiographic imaging) in a single group of patients undergoing coronary angiographic examination at 6 months.

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Other publications of related interest
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