Diagnostic accuracy of nitroglycerine as a ‘test of treatment’ for cardiac chest pain: a systematic review

Katherine Grailey,1 Paul P Glasziou1,2

ABSTRACT
To determine the accuracy of using nitroglycerine as a ‘test of treatment’ in the diagnosis of cardiac chest pain, we undertook a systematic review of studies of diagnostic accuracy. Databases searched included PubMed, Cochrane Database, Google Scholar, Science Citation Index, EMBASE and manual searching of bibliographies of known primary and review articles. Studies were included if sublingual nitroglycerine was the index test, its effect on the patient’s pain score was recorded and the reference test was performed on at least 80% of patients. The data from the five papers were used to form 2×2 contingency tables. Five eligible studies were found, all in the acute setting (although one paper collected its data in the follow-up setting, all patients had acute presentations). The sensitivity ranged from 35% to 92% and the specificity from 12% to 63%. However, in all but one paper the Youden indices were close to zero suggesting that the response to nitroglycerine is not useful as a diagnostic test. The combined sensitivity was 0.52 (95% CI 0.48 to 0.56) and combined specificity was 0.49 (95% CI 0.46 to 0.52). The diagnostic OR from the combined studies was 1.2 (95% CI 0.97 to 1.5), which is not significantly different from 1. In the acute setting, nitroglycerine is not a reliable test of treatment for use in the diagnosis of coronary artery disease. However, further studies are needed to determine the diagnostic accuracy of nitroglycerine for recurrent exertional chest pain.

INTRODUCTION
Coronary artery disease is a huge economic burden to a stretched healthcare system and is the leading cause of death in the UK.3 The incidence of angina pectoris is 0.83 per thousand population aged 31–70 years. New cases of angina pectoris can be crudely estimated at 22 600 patients per annum.2 It is in the interests of both the patient and NHS resources to effectively identify patients who require further investigation for chest pain of a cardiac aetiology. It is crucial to prevent missed diagnoses and deaths in patients with coronary artery disease, occurrences that can lead to an increased mortality in this patient group.5

Nitroglycerine is thought to induce venous dilation and enhance pooling, thereby relieving the load on the stressed ischaemic heart. Administration of nitroglycerine has been shown to be safe, and effective in significantly reducing chest pain, although often patients will not experience complete relief of symptoms.4 Some patients presenting with oesophageal spasm find nitroglycerine relieves the acute symptom of chest pain.5 Consequently, if nitroglycerine is effective in relieving chest pains of different aetiologies, then it will not be effective as a diagnostic tool. Recent NICE guidance6 warns: ‘Do not use people’s response to glyceryl trinitrate (GTN) to make a diagnosis’, although response to GTN is included as one of the three features of typical angina.

Chest pain is a diagnostic dilemma in both the emergency department and the general practice setting, with several protocols and clinical recommendations being designed to aid the accuracy of this process.7 8 None of these systems are perfectly accurate in diagnosing coronary artery disease, with 1–4% of patients with acute coronary syndrome being sent home from accident and emergency departments.9 It is commonly believed that if a patient’s chest pain is relieved following the administration of nitroglycerine, then this chest pain is likely to be of a cardiac aetiology. Hence, response to nitroglycerine has been used as a test in the diagnosis of coronary heart disease10 and is frequently used in the emergency department when assessing patients presenting with chest pain.

This review aims to assess the usefulness of nitroglycerine as a diagnostic tool for the presence of coronary artery disease, by examining whether its effectiveness in relieving chest pain corresponds to a diagnosis made by a reference standard.

METHODS
Search strategy
Studies were identified by searching PubMed, EMBASE and Google Scholar from the beginning of each database until February 2010. A Science Citation Index forward search looked for further articles eligible for inclusion. The bibliographies of primary studies identified and of relevant review articles found through initial searches were checked for additional relevant studies.

The PubMed search strategy included terms for the index test, reference tests, the patient problem and a diagnostic filter: (1) chest pain OR angina OR myocardial infarction OR acute coronary syndrome OR myocardial ischaemia; (2) acute OR recurrent; (3) nitroglycerin OR glyceryl tri-nitrate OR GTN; (4) coronary artery disease/diagnosis; (5) angio*; (6) cardio* exam*; (7) stress echo* OR ECG; (8) #1 AND #2 AND #3 AND (#4 OR #5 OR #6 OR #7).

Study selection and data extraction
Cohort and cross-sectional studies were reviewed, initially by screening the title and abstract (by both authors) and then by reviewing the full documents. To be included in the review the studies had to be cohort studies in patients with chest pain in whom the index test—administration of sublingual nitroglycerine—was performed, and a reference test of clinical diagnosis was performed on more than 80%
### Table 1: Characteristics of participants, interventions and diagnostic outcome of patients receiving nitroglycerine for chest pain

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Diercks et al.¹¹</th>
<th>Steede et al.¹²</th>
<th>Henrikson et al.¹³</th>
<th>Stry et al.¹⁴</th>
<th>Wu et al.¹⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients</td>
<td>664 (52% male)</td>
<td>270</td>
<td>459</td>
<td>223 (47% female)</td>
<td>405 (66% male)</td>
</tr>
<tr>
<td>Mean age</td>
<td>54±12 years</td>
<td>Not stated</td>
<td>Not stated</td>
<td>60±14 years</td>
<td>61 years</td>
</tr>
<tr>
<td><strong>Presenting complaint</strong></td>
<td>Active chest pain during medical evaluation</td>
<td>Active chest pain, admitted with an uncertain diagnosis</td>
<td>Documented chest pain during medical evaluation; admitted with a diagnosis of ‘rule out MI or ‘chest pain’</td>
<td>Presented with ongoing chest pain</td>
<td>Presented with chest pain &gt;1 month; no history of MI, coronary angiography/ angioplasty or CABG.</td>
</tr>
<tr>
<td><strong>Setting</strong></td>
<td>Emergency department in a urban tertiary care centre</td>
<td>Emergency department of an academic tertiary care centre</td>
<td>Emergency department of an urban community teaching hospital</td>
<td>Emergency department of an academic teaching hospital</td>
<td>Outpatients department of an academic tertiary care centre</td>
</tr>
<tr>
<td><strong>Intervention</strong></td>
<td>Sublingual nitroglycerine</td>
<td>Sublingual nitroglycerine 400 µg given every 5 min up to three doses</td>
<td>0.4 µg sublingual nitroglycerine or 0.4 µg spray nitroglycerine</td>
<td>Nitroglycerine administered within 10 min of presentation</td>
<td>Sublingual nitroglycerine. Dose and type not stated/paper.</td>
</tr>
<tr>
<td>Evaluation of pain</td>
<td>11-point numeric scale within 10 min of nitroglycerine</td>
<td>10-point numeric scale; time frame between nitroglycerine and record not stated</td>
<td>Patient self-reported pain within 5 min of first dose of nitroglycerine</td>
<td>Patients reported pain on a numeric scale of 1-10, before and within 10 min of nitroglycerine</td>
<td>Patients reported relief by nitroglycerine as part of a chest pain questionnaire.</td>
</tr>
<tr>
<td>Categorisation of response</td>
<td>No, minimal, moderate or significant/complete reduction</td>
<td>Positive if reduction ≥3 points on/complete resolution</td>
<td>Positive if ≥50% in chest pain</td>
<td>Positive if reduction in pain ≥2 units, no reduction in pain</td>
<td>Relief—yes or no</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td>MI, ACS, cardiac catheterisation showing &gt;70% stenosis or positive provocation test</td>
<td>MI, ACS, CAD on angiogram with &gt;70% stenosis, positive exercise tolerance test (diagnosis by attending physician)</td>
<td>MI, ACS, abnormal stress test, CAD on angiogram &gt;50% stenosis in left main coronary artery or &gt;70% in other coronary arteries, (diagnosis by staff cardiologist)</td>
<td>CAD on angiogram (by cardiologist) Stenosis &gt;50% of the luminal diameter in &gt;1 major branch.</td>
<td></td>
</tr>
<tr>
<td>Prevalence of cardiac chest pain</td>
<td>122 (18%)</td>
<td>83 (31%)</td>
<td>141 (34%)</td>
<td>74 (33%)</td>
<td>244 (60%)</td>
</tr>
<tr>
<td>Reference standard for AMI</td>
<td>Elevation of the cardiac injury marker troponin I above diagnostic threshold (&gt;2.0 ng/ml)</td>
<td>Troponin level</td>
<td>Not distinguished from active CAD</td>
<td>Raised cardiac enzymes</td>
<td>Not distinguished from cardiac chest pain</td>
</tr>
<tr>
<td>AMI of CHD (%)</td>
<td>68/122 (56%)</td>
<td>35/83 (42%)</td>
<td>91/141 (69%)</td>
<td>32/74 (43%)</td>
<td>0/244 (0%)</td>
</tr>
</tbody>
</table>

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CAD, coronary artery disease; CHD, coronary heart disease; MI, myocardial infarction.
The literature search identified 153 potential studies from which five eligible primary cohort studies were found. There were three prospective observational cohort studies and one retrospective observational cohort study. One further primary retrospective study was found through a forward citation search. However, this study did not report a forward citation search. There is some variability in the methodological quality of the index test, although with different methods of elimination for the index test, measured using different methods of eliminating the index test, there was at least 80% verification of the reference standard. The three prospective studies demonstrated the nature of the reference standard. The remaining five studies met all the inclusion criteria and included in total included 1978 patients, all presenting to the emergency department of large hospitals with a complaint of chest pain and admitted with an uncertain diagnosis. None of the studies examined the use of nitroglycerine in recurrent chest pain and admitted with an uncertain diagnosis. None of the studies examined the use of nitroglycerine in recurrent chest pain; the diagnosis was acute chest pain and those with recurrent chest pain; the diagnosis was provided.

There is some variability in the methodological quality of the index test, although with different methods of administration for the index test, which is an important element not reported. The study by Henrikson et al. was the strongest elements reported. The study by Henrikson et al. has the strongest elements reported. The study by Henrikson et al. demonstrated the largest difference in the methodological quality of the index test, due to the nature of the index test, which was clear in the methodological quality of the index test, due to the nature of the index test.

The retrospective review has the poorest methodological quality, due to a lack of reported follow-up. The paper by Wu et al. also demonstrated the largest difference in the methodological quality of the index test, due to the nature of the index test, which was clear in the methodological quality of the index test, due to the nature of the index test.

### Table 2: Design, methods and results of the five eligible studies

<table>
<thead>
<tr>
<th>Study design</th>
<th>DIERSKIS et al.</th>
<th>STEELE et al.</th>
<th>HENRIKSEN et al.</th>
<th>SHRY et al.</th>
<th>WU et al.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruitment</td>
<td>Prospective observational cohort</td>
<td>Prospective observational cohort</td>
<td>Prospective observational cohort</td>
<td>Retrospective case note review</td>
<td>Retrospective observational cohort</td>
</tr>
<tr>
<td>Index test</td>
<td>Index test applied to all patients regardless of initial pain score</td>
<td>The index test was not applied to those with an obvious diagnosis of myocardial ischaemia or those who could not quantify their pain</td>
<td>Patient recruitment was consecutive, helping to minimise bias</td>
<td>Paper does not state whether patients were consecutive admissions</td>
<td>Consecutive admissions to outpatients’ department/day case coronary angiography; Excluded if patho logical Q waves on ECG or regional wall abnormality on echo</td>
</tr>
<tr>
<td>Maintenance</td>
<td>The reference standard was assessed in all patients during their admission 30-day follow-up was obtained in 91/664 patients; reasons for loss to follow-up not stated</td>
<td>12 subjects were lost to 4-week follow-up due to loss of contact</td>
<td>Analysis of results was based upon all 270 patients</td>
<td>Follow-up was longer, so the endpoint of the reference standard was more accurate; 4-month follow-up data was obtained for 389 patients</td>
<td>The number of patients lost to follow-up not stated</td>
</tr>
<tr>
<td>Results</td>
<td>Response criterion: Complete or moderate relief  S0.51 (62/122)  S 0.72 (69/93)  S 0.37 (70/181) 2-unit reduction in pain  S 0.59 (16/254)  S 0.92 (68/74)  S 0.12 (18/149) 2-unit reduction in pain  S 0.92 (68/74)  S 0.63 (102/161) 2-unit reduction in pain  S 0.92 (68/74)  S 0.14 2-unit reduction in pain  S 0.92 (68/74)  S 0.14</td>
<td></td>
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</table>

*Likelihood ratio positive/likelihood ratio negative, diagnostic OR.
mention is made of the dose or timeframe in which the test is administered, or the exact nature of the response; neither does it discuss confounding variables such as other analgesia—which may explain the increased diagnostic OR in this study.

The receiver operating plot (figure 1) shows that the ‘test’ was uninformative in five studies, with all studies near the ‘no information’ diagonal: three just above and two on the line or below. The combined sensitivity was 0.52 (95% CI 0.48 to 0.56) and combined specificity was 0.49 (95% CI 0.46 to 0.52). The diagnostic ORs (table 2) ranged from 0.76 to 1.3 with the CIs of all studies except the Wu et al study crossing the null value of 1.0. The overall diagnostic OR from the combined studies was 1.2 (95% CI 0.97 to 1.5), which is not significant, and the diagnostic OR from the Wu et al study was 1.0. The overall diagnostic OR from the combined studies was 1.2 (95% CI 0.97 to 1.5), which is not significantly different from 1. However, there was moderate heterogeneity ($\chi^2=9.7$, p=0.045), which appeared mostly due to the Wu et al study.

### DISCUSSION

This systematic review of nitroglycerine as a diagnostic test has demonstrated that the accuracy of this ‘test of treatment’ for diagnosis is poor. Four studies showed a poor ability of GTN to accurately discriminate between those with cardiac chest pain and those with non-cardiac pain; with the paper by Wu et al reporting a slightly higher ability but in an outpatient setting. This review confirms that nitroglycerine is an unreliable diagnostic tool for patients presenting with chest pain of uncertain aetiology. The likelihood ratio for nitroglycerine as a diagnostic test is close to 1 in four of the papers, indicating that the post-test probability of a diagnosis of coronary artery disease is almost equivalent to the pre-test probability. It was increased in the paper by Wu et al, but this can be accounted for by the less accurate nature of administration and recording of response to nitroglycerine. The result was consistent across the remaining four papers, irrespective of which pain score was used. Consequently, nitroglycerine is not useful as a triage tool in the emergency room. If it is administered for pain relief, the response should not be taken as an indicator of a coronary cause.

All five studies have some flaws. First, workup bias—patients with ‘positive results’ are more likely to be fully assessed—is present in all studies. In a follow-up letter to Henriksson et al’s study, Evans and Reilly, attempted to correct for the workup bias and suggested that sensitivity should have been 0.53 (rather than 0.55) and specificity 0.84 (rather than 0.59). However, these corrected results would still suggest the ‘test’ is very weak.

Second, the ‘gold standard’ for coronary artery disease is imperfect and the misclassification will tend to underestimate the true accuracy. Finally, these studies were all in the acute care setting, but even then, some degree of selection occurred, and hence there is still the possibility that there are subgroups of patients in the emergency setting where this ‘test’ may be useful. However, none of these flaws is likely to substantially change the conclusions.

These results are limited to the acute care setting, and further research in this setting is unlikely to be fruitful. The one (excluded) study which looked at history of response to nitroglycerine as part of the definition of ‘typical angina’ found inducible ischaemia on stress testing in 14% of patients with typical angina, 11% with atypical angina and 16% with no chest pain. However, we found no studies relevant to the ambulatory care setting of patients presenting with recurrent exertional chest pain. Hence, research is still needed on the usefulness of sublingual nitroglycerine in recurrent chest pain. Meanwhile, practitioners and guidelines should warn against the use of nitroglycerine as a test.

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### Competing interests

None.

### Contributors

Both authors contributed to the searches, data extraction, analysis and writing of the paper.

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