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Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation

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Abstract

Clinical effectiveness and cost-effectiveness of immediate angioplasty for acute myocardial infarction: systematic review and economic evaluation

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Objectives: To review the clinical evidence comparing immediate angioplasty with thrombolysis, and to consider whether it would be cost-effective.

Data sources: Electronic databases. Experts in the field.

Review methods: For clinical effectiveness, a comprehensive review of randomised control trials (RCTs) was used for efficacy, and a selection of observational studies such as case series or audit data used for effectiveness in routine practice. RCTs of thrombolysis were used to assess the relative value of prehospital and hospital thrombolysis. Observational studies were used to assess the representativeness of patients in the RCTs, and to determine whether different groups have different capacity to benefit. Clinical effectiveness was synthesised through a narrative review with full tabulation of results of all included studies and a meta-analysis to provide a precise estimate of absolute clinical benefit. Consideration was given to the effect of the growing use of stents. The economic modelling adopted an NHS perspective to develop a decision-analytical model of cost-effectiveness focusing on opportunity costs over the short term (6 months).

Results: The results were consistent in showing an advantage of immediate angioplasty over hospital thrombolysis. The updated meta-analysis showed that mortality is reduced by about one-third, from 7.6% to 4.9% in the first 6 months, and by about the same in studies of up to 24 months. Reinfarction is reduced by over half, from 7.6% to 3.1%. Stroke is reduced by about two-thirds, from 2.3% with thrombolysis to 0.7% with percutaneous coronary intervention (PCI), with the difference being due to haemorrhagic stroke. The need for coronary artery bypass graft is reduced by about one-third, from 13.2% to 8.4%. Caution is needed in interpreting some of the older trials, as changes such as an increase in stenting and the use of the glycoprotein IIb/IIa inhibitors may improve the results of PCI. There is little evidence comparing prehospital thrombolysis with immediate PCI. Research on thrombolysis followed by PCI, known as 'facilitated PCI', is underway, but results are not yet available. Trials may be done in select centres and results may not be as good in lower volume centres, or out of normal working hours. In addition, much of the marginal mortality benefit of PCI over hospital thrombolysis may be lost if door-to-balloon time were more than an hour longer than door-to-needle time. Conversely, within the initial 6 hours, the later patients present, the greater the relative advantage of PCI. Results suggest that PCI is more cost-effective than thrombolysis, providing additional benefits in health status at some extra cost. In the longer term, the cost difference is expected to be reduced because of higher recurrence and reintervention rates among those who had thrombolysis.

Conclusions: If both interventions were routinely available, the economic analysis favours PCI, given the assumptions of the model. However, very few units in England could offer a routine immediate PCI service at present, and there would be considerable resource implications of setting up such services. Without a detailed survey of existing provision, it is not possible to quantify the implications, but they include both capital and revenue: an increase in catheter laboratory provision and running costs. The greatest problem would be staffing, and that would take some years to

resolve. A gradual incrementalist approach based on clinical networks, with transfer to centres able to offer PCI, may be used. In rural areas, one option may be to promote an increase in prehospital thrombolysis, with PCI for thrombolysis failures. There is a need for data on the long-term consequences of treatment, the quality of life of patients after treatment, and the effects of PCI following thrombolysis failure.

Contents

List of abbreviations

A&E	accident and emergency
AMI	acute myocardial infarction
ARR	absolute risk reduction
BARI	Bypass Angioplasty Revascularisation Investigation
BCIS	British Cardiovascular Intervention Society
BCS	British Cardiac Society
CABG	coronary artery bypass graft
CCU	coronary care unit
CI	confidence interval
CPR	cardiopulmonary resuscitation
DANAMI	Danish Trial in Acute Myocardial Infarction
DARE	Database of Abstracts of Reviews of Effectiveness
DBP	diastolic blood pressure
df	degrees of freedom
DGH	district general hospital
GUSTO	Global Use of Strategies to Open Occluded Coronary Arteries
HRG	Health Resource Group
HS	health status unit
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
ITT	intention-to-treat
MI	myocardial infarction
MTO	medical technical officer
NA	not applicable
NHS CRD	NHS Centre for Reviews and Dissemination
NICE	National Institute for Clinical Excellence
NNT	number needed to treat
ns	not significant
NSF	National Service Framework
OR	odds ratio
PAMI	Primary Angioplasty in Myocardial Infarction
PCI	percutaneous coronary intervention
PCT	primary care trust
PTCA	percutaneous transluminal coronary angioplasty
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RRR	relative risk reduction
rt-PA	recombinant tissue plasminogen activator
SBP	systolic blood pressure

continued

List of abbreviations *continued*

SD	standard deviation
SMM	Norwegian Centre for Health Technology Assessment (Senter for Medisinsk Metodevurdering)
TIMI	Thrombolysis in Myocardial Infarction
t-PA	tissue plasminogen activator
WMD	weighted mean difference

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Description of proposed service

This review examines the clinical and cost-effectiveness of immediate angioplasty in myocardial infarction, with thrombolysis as the main comparator.

Background

The blockage of a coronary artery (coronary thrombosis) can lead to a heart attack (acute myocardial infarction). There are several ways of trying to overcome this blockage. The methods include drug treatment to dissolve the clot (thrombolysis) and physical intervention, either by passing a catheter into the affected artery [angioplasty or percutaneous coronary intervention (PCI)], or bypassing the blocked section by cardiac surgery [coronary artery bypass grafting (CABG)].

Thrombolysis can be given in the community before the patient is sent to hospital, or delayed until after admission. Prehospital thrombolysis is not common in the UK.

Immediate angioplasty is not routinely available in the UK at present; it is much more common in the USA.

Objectives

To review the clinical evidence comparing immediate angioplasty with thrombolysis, and to consider whether it would be cost-effective.

Methods

This report was based on a systematic review of the evidence of clinical effectiveness and an economic analysis of cost-effectiveness based on the clinical review and on cost data from published sources and *de novo* data collection.

Data sources

The search strategy searched six electronic databases (including MEDLINE, Cochrane Library and EMBASE), with English-language limits, for the periods up to December 2002. Bibliographies of related papers were assessed for relevant studies and experts contacted for advice and peer review, and to identify additional published and unpublished references.

Study selection

For clinical effectiveness, a comprehensive review of randomised controlled trials (RCTs) was used for efficacy, and a selection of observational studies such as case series or audit data for effectiveness safety in routine practice. RCTs of thrombolysis were used to assess the relative value of prehospital and hospital thrombolysis. Observational studies were used to assess the representativeness of patients in the RCTs, and to determine whether different groups have different capacity to benefit. They were used to assess the implications of wider diffusion of the technology away from major centres.

Data extraction

Data extraction and quality assessment were undertaken by one reviewer and checked by a second reviewer, with any disagreements resolved through discussion. The quality of systematic reviews, RCTs, controlled clinical trials and economic studies was assessed using criteria recommended by the NHS Centre for Reviews and Dissemination (University of York).

Study synthesis

Clinical effectiveness was synthesised through a narrative review with full tabulation of results of all included studies and a meta-analysis to provide a precise estimate of absolute clinical benefit. Consideration was given to the effect of the growing use of stents. The economic modelling adopted an NHS perspective to develop a decision-analytical model of cost-effectiveness focusing on opportunity costs over the short term (6 months).

Results and conclusion

Number and quality of studies, and summary of benefits

There were several good-quality systematic reviews, including a Cochrane review, as well as an

individual patient meta-analysis and a number of recent trials not included in the reviews. The results were consistent in showing an advantage of immediate angioplasty over hospital thrombolysis. The updated meta-analysis showed that mortality is reduced by about one-third, from 7.6% to 4.9% in the first 6 months, and by about the same in studies of up to 24 months. Reinfarction is reduced by over half, from 7.6% to 3.1%. Stroke is reduced by about two-thirds, from 2.3% with thrombolysis to 0.7% with PCI, with the difference being due to haemorrhagic stroke. The need for CABG is reduced by about one-third, from 13.2% to 8.4%.

Caution is needed in interpreting the older trials, as changes such as an increase in stenting and the use of the glycoprotein IIb/IIa inhibitors may improve the results of PCI. There is little evidence comparing prehospital thrombolysis with immediate PCI. One good quality study from France showed that prehospital thrombolysis with PCI in those in whom thrombolysis failed was as good as universal PCI. Research on thrombolysis followed by PCI, known as facilitated PCI, is underway, but results are not yet available. Further caveats are needed. Trials may be done in select centres and results may not be as good in lower volume centres, or out of normal working hours. In addition, much of the marginal mortality benefit of PCI over hospital thrombolysis may be lost if door-to-balloon time were more than 1 hour longer than door-to-needle time. Conversely, within the initial 6 hours, the later patients present, the greater the relative advantage of PCI.

Cost-effectiveness

If both interventions were routinely available, the economic analysis favours PCI, given the assumptions of the model. Results suggest that PCI is more cost-effective than thrombolysis, providing additional benefits in health status at some extra cost and an incremental cost per unit change in health status under the £30,000 threshold in most instances. In the longer term, the cost difference is expected to be reduced because of higher recurrence and reintervention rates among those who had thrombolysis. The model is not particularly sensitive to variations in probabilities from the clinical effectiveness analysis.

However, very few units in England could offer a routine immediate PCI service at present, and there would be considerable resource implications of setting up such services. Without a detailed survey of existing provision, it is not possible to quantify the implications, but they include both capital and revenue: an increase in catheter laboratory provision and running costs. The greatest problem would be staffing, and that would take some years to resolve.

A gradual incrementalist approach based on clinical networks, with transfer to centres able to offer PCI, could be used. In rural areas, one option could be to promote an increase in prehospital thrombolysis, with PCI for thrombolysis failures.

Need for further research

There is a need for economic data on the long-term consequences of the treatment, the quality of life of patients after treatment and the effects of PCI following thrombolysis failure.

Chapter 1

Aim of the review

The aim of this review is to examine the clinical effectiveness of immediate angioplasty, taking into account its effect on mortality, morbidity and quality of life (QoL), and to estimate its cost-effectiveness compared with other uses of resources. Specifically, it compares immediate angioplasty with hospital and community thrombolysis. In addition to the clinical effectiveness and cost-effectiveness of the interventions, the review considers the delivery of a service and implications for its implementation.

Chapter 2
Background

Description of underlying health problem

The burden of disease from myocardial infarction (MI) is well known and need not be repeated here.[1] The background to this review is the pathological process underlying heart attacks (MI), namely thrombosis in a diseased coronary artery. Standard interventions after MI include measures aimed at reducing cardiac workload and arrhythmias (e.g. β-blockers), reducing further thrombosis (e.g. aspirin) and relieving symptoms (e.g. opiate analgesia, antiemetics). These will not be reviewed here, nor will the use of glycoprotein IIb/IIIa inhibitors, which were the subject of a recent HTA report[2] and National Institute for Clinical Excellence (NICE) guidance.[3]

There are three ways of actively restoring blood flow to an artery blocked by an acute coronary thrombosis:

- pharmacological: giving a thrombolytic drug to dissolve the clot
- physical opening of the artery by angioplasty: passing a catheter with a balloon into the artery, and inflating the balloon once positioned inside the narrowed and blocked section. A stent may be used to hold the artery open after dilatation
- surgical bypass by emergency coronary artery bypass graft (CABG).

In current UK practice, only the first of these is routinely available, but in most areas only after patients are admitted to hospital.

The use of thrombolysis has become more common, although the evidence goes back for many years.[4] The aim is to dissolve the clot and reopen the artery, if possible before irreversible damage has occurred to the heart muscle which has been deprived of oxygen downstream from the occlusion. Thrombolysis has been the subject of recent NICE guidance[5] and underpinned by an HTA report.[6] There are several problems with thrombolysis:

- Not all patients are suitable; in some, thrombolysis may be contraindicated because they are at risk of bleeding (*Table 1* gives details of contraindications).

TABLE 1 *Contraindications to thrombolysis therapy*

Absolute contraindications:
Haemorrhagic stroke or stroke of unknown origin at any time
Ischaemic stroke in preceding 6 months
Central nervous system damage or neoplasms
Recent major trauma/surgery/head injury (within preceding 3 weeks)
Gastrointestinal bleeding within the last month
Known bleeding disorder
Aortic dissection
Relative contraindications:
Transient ischaemic attack in preceding 6 months
Oral anticoagulant therapy
Pregnancy or within 1 week postpartum
Non-compressible punctures
Traumatic resuscitation
Refractory hypertension (systolic blood pressure >180 mmHg)
Advanced liver disease
Infective endocarditis
Active peptic ulcer

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- It does not always work.
- In a small proportion of patients, there are serious side-effects, most notably stroke from cerebral haemorrhage.
- The earlier it is given, the more effective it is, but pain-to-needle time targets are often not met. Recent data suggest that in England just under 70% of patients who have had an MI are receiving thrombolysis within the recommended 30 minutes of arrival at hospital.[7]
- Aspirin should be given in addition to thrombolysis since the combination of aspirin and thrombolysis is much better than either alone.[8]
- The underlying problem in the artery remains, and is a potential focus for another MI.

There is a strong case for prehospital thrombolysis,[10] including areas not close to specialist care, but implementation has been low.[11]

Technology assessment in interventional cardiology is complicated by the pace of change. There is always a risk that studies conducted over periods of more than a few years may be out of date by publication. For example, the Bypass Angioplasty Revascularisation Investigation (BARI) study[12] of angioplasty versus CABG did not involve stenting. By the time its results were published, stenting was becoming common and some of the results had to be reinterpreted. New drugs such as the glycoprotein IIb/IIa inhibitors will improve the results of percutaneous coronary intervention (PCI), especially in high-risk cases,[3] and drug eluting stents (currently being reviewed by NICE)[13] may further reduce the need for revascularisation.

Stents

Stents are small tubes inserted into the artery during angioplasty to hold the artery open, like internal splints. They have three implications for angioplasty. First, the duration of benefit of angioplasty is increased.[14] Early meta-analyses of angioplasty versus CABG showed that by about 6 months, the need for reintervention, by repeat angioplasty or CABG to correct restenosis of the artery, was greater in those who had initial angioplasty. Stents reduce the need for repeat procedures.

Second, stents can be used when angioplasty goes wrong. This only happens in a small proportion of patients but can be serious: collapse of the artery leading to MI, fatal or non-fatal. In the early days of angioplasty, the solution to this was emergency CABG, which was not always possible. The term 'bail-out stenting' was used to describe the situation where a stent was fitted to hold the artery open when angioplasty went wrong. This reduced the need for CABG back-up. With much greater (indeed routine) use of stents as part of angioplasty, emergency CABG is rarely required.

Third, stenting extends the scope of angioplasty. In the early days, angioplasty, or PCI, was used to treat short, proximal, non-calcified stenoses in a single coronary artery branch. Multivessel disease and complex anatomy were referred for CABG. The trend towards the use of several stents per patient, and for stenting more complicated lesions, has expanded the role of angioplasty to a greater proportion of those with symptomatic coronary artery disease. In this report stents are regarded as the norm.

Immediate angioplasty

Angioplasty was initially used in elective cardiology for stable angina, but it has since been used in emergency situations such as unstable angina, to avert MI, and in MI itself. This has been done mainly outside the UK, particularly in the USA, with relatively little in the UK. A review by the Technological Change in Health Care Network, which monitors uptake of new technologies in 17 countries, found that

> "Differences in the use of primary angioplasty are relatively larger than differences in other intensive procedures (for heart disease). Primary angioplasty was used earliest and diffused most rapidly in the United States. Diffusion started later, and has occurred more slowly, in other countries. In Ontario, the United Kingdom and Denmark, the procedure remains very rarely used".[15]

So, one question is whether the NHS should provide immediate angioplasty. If so, it would need to look at the possibilities of providing this in an equitable manner: could someone having an MI at 2 a.m. in a rural area receive the same standard of care as someone having a heart attack at midday in a city? Realistically, this will not be possible. Options include providing PCI in some district general hospital (DGHs) (perhaps for only part of the day), transferring patients to a central facility and having mobile intervention units serving a group of hospitals.

This review will address a number of issues, including;

- Key questions:
  1. Previous reviews have reported that immediate angioplasty is clinically as

effective or better than hospital thrombolysis. Has recent evidence changed this at all?
2. If so, how much more effective is immediate angioplasty? Thrombolysis is known to be effective in reducing mortality after MI.
3. If thrombolysis is given prehospital, how much does that affect the relative benefits compared to angioplasty?
4. If thrombolysis is given but fails, how effective is angioplasty?
5. If immediate angioplasty provides clinical benefits, is it also cost-effective?

- Subsidiary questions:
6. If early angioplasty is both clinically and cost-effective, what would be the implications of implementation, including not just funding but other barriers to implementation?
7. Is there any evidence on the relationship between volume and quality, which might suggest whether there should be a minimum number of procedures per centre, and hence number of centres?
8. Are results in routine practice as good as those seen in the trials?
9. Are some groups of patients more suitable for immediate angioplasty than others?
10. Does the use of stents improve results of angioplasty in acute myocardial infarction (AMI)?

The review will not cover questions such as whether and how readily cardiac surgery back-up needs to be available, since such questions were addressed by the national guidelines agreed by the British Cardiac Society (BCS) and the British Cardiovascular Intervention Society (BCIS).[16] Further, as already discussed, the need is rare in immediate PCI with stenting.

Nor will this review examine the relative merits of different extents of immediate PCI. Some cardiologists treat only the culprit lesion in the artery blocked by the heart attack, whereas others take the opportunity to aim at a complete revascularisation, dealing not only with the culprit lesion but also with other balloonable lesions at the same time.

Trials are underway on a combination approach, sometimes called 'facilitated angioplasty', where early thrombolysis is followed by PCI, but these are unpublished.

This report will include a systematic review of evidence of clinical effectiveness, and an economic analysis of cost-effectiveness based on the clinical review, on cost data from published sources and *de novo* data collection.

Incidence and prevalence

Around 240,000 people experience AMI in England and Wales each year. Up to 50% of people who have an AMI die within 30 days of the event, and over half of these deaths occur before medical assistance arrives or the patient reaches hospital.[5] It is a leading cause of admissions to medical units.[17] A primary care trust (PCT) with 200,000 residents would see 920 people suffer AMIs per year, many of whom are not admitted for care, partly because so many die outside hospital. A DGH serving a population of 500,000 people might admit about 900 people a year with AMI. The actual rates will vary across the country owing to socio-economic inequalities.

However, not all of the 900 admitted would be eligible for PCI, which is usually used for those with ST segment elevation on ECG. Unpublished data from one trust with a catchment of about 500,000 (Murray G: personal communication, 2003) show that just over 900 patients were admitted with MI (or, strictly speaking, coded as such to code KMR1), but only about 300 had ST elevation, and hence were considered for immediate thrombolysis. Of these, only around 200 were classed as 'barn-door' ST elevation MI. Hence, the number of patients in whom immediate PCI would be indicated would be much less than 900, and probably 300 a year or less.

Current service provision

It is estimated that around 50,000 patients currently receive thrombolysis in England and Wales each year.[5] This is just over half of the people admitted with AMI. This number is rising, and the Myocardial Infarction National Audit Project by the Royal College of Physicians estimates that over 70% of eligible people are now receiving thrombolysis, but the proportion eligible is not reported.[18]

Audit data from the BCIS[19] give the following information about number of PCI procedures performed on patients with AMI in 2001 (*Table 2*). It suggests that the proportion of PCIs performed for AMI varies between 0 and 29% in different centres. Data are only available from about one-

TABLE 2 *BCIS audit data, 2001*

	No. of procedures (no. of centres)	% of procedures successful[a] (range of results by centre)	Partial success[b] (range of results by centre)	Repeat PCI (range of results by centre)	CABG (range of results by centre)	Reinfarction (range of results by centre)	Death (range of results by centre)
Primary PCI	352 (21)	90% (56–100)	2.6% (0–11)	1.4% (0–22)	0.9% (0–11)	2.3% (0–22)	4.3% (0–13)
Salvage PCI[c]	578 (22)	86% (50–100)	2.4% (0–7.1)	1.0% (0–3.8)	0.5% (0–5)	1.0% (0–5)	3.8% (0–14)
Reinfarction PCI[d]	258 (19)	90% (50–100)	3.1% (0.18)	2.7% (0–14)	0.8% (0–13)	4.7% (0–18)	3.1% (0–50)
PCI for MI with cardiogenic shock	167 (22)	59% (0–100)	7.8% (0–17)	2.4% (0–25)	2.0% (0–33)	0.6% (0–25)	35% (0–100)

[a] Radiographic success (<50% residual stenosis) without a major adverse cardiac event.
[b] Patients with multivessel disease or multiple sessions in whom not all planned lesions were successfully treated.
[c] When the procedure is carried out after unsuccessful thrombolysis.
[d] When the procedure is carried out for a further MI following thrombolysis.

third of the 64 centres performing interventions. An approximate estimate is that about 4000 procedures are carried out for AMI, which is about 10% of 39,000 PCI procedures reported in the audit for all indications including elective procedures. However, it appears from the table that much of the immediate PCI is for salvage or rescue purposes, rather than for 'routine' immediate PCI. The number is also less than 10% of the number receiving thrombolysis.

Chapter 3

Methods for systematic review and economic evaluation

The a priori methods for systematically reviewing evidence of clinical effectiveness and the economic evaluation were described in the protocol (see Appendix 1). Some changes, additions or points of clarification were made to the methods discussed in the original protocol and these are outlined below.

- The search strategy for assessing clinical efficacy used key databases to find previous good quality systematic reviews, with subsequent searches limited to identifying randomised controlled trials (RCTs) not included in these systematic reviews or published after these systematic reviews. Inclusion was limited to studies in the English language and studies published before December 2002. The systematic reviews and the RCTs, whether included in the previous systematic reviews or not, were quality assessed.
- The evidence from the systematic reviews and RCTs was supplemented with information from selected observational studies, such as case series and audit reports, to assess effectiveness and safety of the interventions within routine practice. A sensitive search for observational studies was undertaken. These were filtered by an information scientist and studies for inclusion were then selected by an experienced reviewer, looking specifically for studies that could help to answer questions 4, 7, 8, 9 and 10 (see section 'Immediate angioplasty', p. 4). Specifically, the observational studies examined whether particular groups have different capacity to benefit and to assess the implications of wider diffusion away from major centres.
- Importantly, it should be noted that the first section in Chapter 4 is based on a systematic review of the evidence from systematic reviews of RCTs and subsequent RCTs, with additional information from observational studies included in the subsections 'Patient selection effects' (p. 20) and 'Comparison of RCTs and observational studies' (p. 24). The following sections, 'Centre effects' (p. 25), 'Stents' (p. 28) and 'Rescue angioplasty after failed thrombolysis' (p. 29), are based on evidence from this systematic review and selected observational studies.

Sources of information, search terms and a flowchart outlining the identification of studies are described in Appendices 2 and 3.

Data were extracted by one reviewer using a standard data extraction form and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion.

The quality of included systematic reviews and RCTs was assessed using criteria recommended by the NHS Centre for Reviews and Dissemination (NHS CRD, University of York) (see Appendix 4).[20] Quality criteria were applied by one reviewer and checked by a second reviewer. Any disagreements were resolved through discussion.

The economic part of the study followed national guidance on health technology assessment.[20] It contains a short critical review of the available cost-effectiveness evidence. However, cost data from large published RCTs were not available and a model was used to adapt data to the problem. A decision tree was used to highlight the most important parameters of the studied technologies.

The economic evaluation adopted an NHS perspective. No attempts were made to estimate costs outside the NHS for patients or other sectors of society. The analysis took the form of a cost-effectiveness analysis with outcomes measured in simple health status terms. Only short-term outcomes (6 months) were used, owing to the lack of available data. Sensitivity analyses of costs, outcomes and probabilities were carried out.

The basis of costing used the concept of opportunity cost. The costs used focused on short-term additional (marginal) costs of operating a primary angioplasty service. That is, investments, training and capacity costs were not used. Possible consequences of the implementation in the NHS will be highlighted.

Chapter 4

Clinical effectiveness

Immediate angioplasty versus hospital thrombolysis

Quantity and quality of previous systematic reviews

Four systematic reviews were identified.[21–24] The review by Zijlstra and colleagues[24] is an update of the review by Weaver and colleagues,[23] but presents data by time of presentation in an individual patient data meta-analysis and will be dealt with in a separate subsection ('Time of presentation', p. 18).

The review by Weaver and colleagues[23] and the Cochrane review by Cucherat and colleagues[21] included the same ten trials.[25–34] However, Weaver and colleagues contacted authors to obtain data on outcomes (mortality, stroke, reinfarction and major bleeding) not reported in some of the original publications, and also obtained data for an additional 33 patients from the authors of one study.[34]

The earlier review by Michels and Yusuf[22] included seven studies; six of these[25,27,28,32,35,36] (or updates thereof) were included in the other reviews, while one study used intracoronary streptokinase[37] and was therefore not relevant. An additional study by Akhras and colleagues[38] was included in the meta-analysis by Ziljstra and colleagues.[24]

A further review has recently been published by the Norwegian Centre for Health Technology Assessment (Senter for Medisinsk Metodevardering, SMM),[39] but it was not possible to use this study as it was not published in English. The conclusions from the English abstract were noted.

Table 3 summarises the quality assessment of the systematic reviews. The Cochrane Review was of high methodological quality, fulfilling all of the NHS CRD criteria.[21] Validity of included studies was not assessed in the review of published trials by Weaver and colleagues,[23] but was reported in the meta-analysis of individual patient data.[24] The older review by Michels and Yusuf[22] is of poorer quality, failing to report validity and sufficient detail of the included studies.

The RCTs included in these reviews, and their quality assessment, are shown in *Table 4*. None of the studies fulfilled all of the NHS CRD criteria for the assessment of good quality RCTs. Three studies[31,32,38] were available in abstract form only, and thus provided only limited information. Of the 11 studies, randomisation was adequate in just three[25,26,29] and partial in four,[27,28,30,40] with the method of randomisation not known in the remaining studies. Allocation concealment was inadequate in four studies,[27,28,30,40] and unknown in four studies,[31,32,38,41] thus leading to possible selection bias in these trials. The groups were similar at baseline in all studies except for Akhras and colleagues,[38] where similarity was unknown. The eligibility criteria for entry into the study were specified by nine studies, being unknown in both DeWood and colleagues[32] and Akhras and colleagues.[38] The blinding of outcome assessors was the most poorly reported criteria, being unknown in all studies except for Grines and colleagues,[27] where it was judged as inadequate. Point estimates and measures of variability were presented for the primary outcome measure in every study, again with the exception of Akhras and colleagues.[38] Data were analysed according to intention-to-treat (ITT) principles by seven studies.[27–30,32,40,41] Three of the studies described

TABLE 3 *Quality assessment of systematic reviews comparing primary PCI with thrombolytic therapy*

Study	Inclusion/exclusion criteria	Thorough search	Validity assessed	Detail	Summaries appropriate
Cucherat *et al.*, 2002[21]	Yes	Yes	Yes	Yes	Yes
Michels and Yusuf, 1995[22]	Yes	Yes	No	No	Yes
Weaver *et al.*, 1997[23] and Zijlstra *et al.*, 2002[24]	Yes	Yes	Weaver: No Zijlstra: Yes	Some	Yes

loss to follow-up inadequately (numbers not specified for each group),[25,26,41] while the remaining studies did not report loss to follow-up.

The studies vary in their length of follow-up, from outcomes measured during hospital stay or at discharge (i.e. immediate) to 24 months after intervention. One study reported outcomes at 6 weeks,[32] six studies reported outcomes at 6 months[25–27,29,41,42] and one study reported outcomes at 8 months of follow-up.[38] Studies with follow-up periods of more than 1 year were limited, with two studies (one RCT[40] and one observational study[43]) reporting outcomes at 12 months, and one study reporting follow-up data at 24 months.[44]

Results of previous systematic reviews

The immediate outcome measures reported in the reviews (*Table 5*) were mortality, reinfarction, stroke, CABG, recurrent ischaemia and the incidence of major bleeding. Weaver and colleagues[23] and Michels and Yusuf[22] also included death and non-fatal reinfarction as a combined end-point. The Cochrane Review[21] pooled the combined end-points reported in the primary studies, but these varied in definition.

Longer term outcome measures reported by the reviews were mortality at 6 or 12 months, and a combined mortality or non-fatal reinfarction outcome at 12 months. Hospital stay was also reported in the original RCTs, but was not combined in a meta-analysis in these reviews (see below for results of updated meta-analysis).

In summary, the results of these reviews are consistent in showing an advantage of immediate angioplasty over hospital thrombolysis on outcomes of mortality [relative risk reduction (RRR) 30%, ARR 2%], reinfarction rates (RRR 50%, ARR 4%), stroke rates (RRR 65%, ARR 1.5%), CABG rates (RRR 30%, ARR 4%), recurrent ischaemia rates (RRR 50%, ARR 8%), and the combined end-point (RRR 46%, ARR 5%). There were no statistically significant differences in the incidence of major bleeding or long-term mortality.

Quantity and quality of new RCTs

Since the publication of the above reviews, two trials have been updated[40,41] (see *Table 4*) and five new RCTs have been identified.[42,44–46] The Danish Trial in Acute Myocardial Infarction (DANAMI)-2 study[47] was available in abstract form only for the analysis undertaken in this study. Aversano and colleagues[42] compared PCI and thrombolysis in hospitals without on-site cardiac surgery. The Air Primary Angioplasty in Mycocardial Infarction (Air-PAMI) trials,[45] randomised patients to on-site thrombolysis or to emergency transfer to a larger hospital for PCI. The PRAGUE study[46] compared patients randomised to thrombolytic therapy in community hospitals, thrombolytic therapy during transportation to angioplasty, and immediate transportation for primary angioplasty without thrombolysis. De Boer and colleagues[44] compared primary PCI with thrombolysis and included elderly patients (aged over 75 years).

Table 6 summarises the quality assessment of the new RCTs that have been published since the reviews. The study by Aversano and colleagues[42] was of high methodological quality, fulfilling all of the NHS CRD quality criteria.[20] The method of randomisation was adequate in all of the studies, with the exception of Grines and colleagues[45] where it was partial. Similarly, allocation concealment was adequate in all of the studies, except in Grines.[45] The blinding of outcome assessors was the most poorly reported criteria, being adequate only in the study by Aversano and colleagues.[42] Point estimates and measure of variability were adequately presented for the primary outcome measures in every study, with the exception of Widimsky.[46] Grines and colleagues[45] was the only study not to analyse the data according to ITT principles. The similarity of groups at baseline, the eligibility criteria and the loss to follow-up were adequately reported by all the new RCTs.

Results of new RCTs

Of the four new RCTs, three compared primary PCI with thrombolytic therapy.[42,44,45] Widimsky and colleagues[46] also investigated a combined approach of thrombolytic therapy during transportation to angioplasty. All four new RCTs reported immediate (in-hospital[42] or 30-day[44,45]) outcome measures of mortality, recurrent infarction, stroke and a composite end-point (death/recurrent infarction/stroke). In addition, three studies reported the need for an additional procedure (PCI and/or CABG),[44–46] one reported the incidence of ischaemia[45] and two studies reported bleeding events.[44,46] Aversano and colleagues[42] reported short-term outcome measures of mortality, recurrent infarction, stroke, incidence of CABG and a composite end-point at 6 weeks, as well as the same longer term outcomes at 6 months, and de Boer and colleagues[44] reported longer term outcome measures of mortality and a combined end-point at 12 and 24 months. Three studies[42,44,45] also reported

TABLE 4 *Quality assessment of RCTs included in systematic reviews*

Study	Random	Allocation concealment	Group similarity	Eligibility	Blinding	Point estimates	ITT	Withdrawal
Garcia *et al.*, 1999[41a]	Unknown	Unknown	Reported	Adequate	Unknown	Adequate	Adequate	Inadequate
Gibbons *et al.*, 1993[25]	Adequate	Adequate	Reported	Adequate	Unknown	Adequate	Inadequate	Inadequate
GUSTO-IIb, 1997[26]	Adequate	Adequate	Reported	Adequate	Unknown	Adequate	Inadequate	Inadequate
Grines *et al.*, 1993[27] (PAMI)	Partial	Inadequate	Reported	Adequate	Inadequate	Adequate	Adequate	Unknown
Ribeiro *et al.*, 1993[28]	Partial	Inadequate	Reported	Adequate	Unknown	Adequate	Adequate	Unknown
Ribichini *et al.*, 1998[40a]	Partial	Inadequate	Reported	Adequate	Unknown	Adequate	Adequate	Unknown
Zijlstra *et al.*, 1997[29]	Adequate	Adequate	Reported	Adequate	Unknown	Adequate	Adequate	Unknown
De Boer *et al.*, 1994[30] (Zwolle)	Partial	Inadequate	Reported	Adequate	Unknown	Adequate	Adequate	Unknown
Grinfeld *et al.*, 1996[31b]	Unknown	Unknown	Reported	Adequate	Unknown	Adequate	Inadequate	Unknown
DeWood *et al.*, 1989[32b]	Unknown	Unknown	Reported	Unknown	Unknown	Adequate	Adequate	Unknown
Akhras *et al.*, 1997[38b]	Unknown	Unknown	Unknown	Unknown	Unknown	Inadequate	Inadequate	Unknown

[a] Quality assessment was performed on the full published studies; however, data in abstract form only were available to Cochrane and Weaver.
[b] Available in abstract form only.
GUSTO, Global Use of Strategies to Open Occluded Coronary Arteries.

TABLE 5 *Meta-analyses of primary PCI versus thrombolysis from previous systematic reviews*

Review details	No. of trials in meta-analysis	No. of patients in meta-analysis		Results[a]
Mortality (in-hospital to 6 weeks as reported by primary studies)				
Cucherat *et al.*, 2002[21]	10	2573	Streptokinase	RR 0.69 (0.35 to 1.39)
			t-PA	RR 0.61 (0.28 to 1.31)
			Accelerated t-PA	RR 0.71 (0.47 to 1.07)
			Total	RR 0.68 (0.50 to 0.95)
				χ^2 9.40 (df = 8) Z = 2.29 (total)
			Total	ARR 2.1%
Weaver *et al.*, 1997[23]	10	2606	Streptokinase	OR 0.66 (0.29 to 1.50), p = 0.38
				ARR 1.9% (–2.7 to 4.1)
			t-PA	OR 0.60 (0.24 to 1.41), p = 0.28
				ARR 2.2% (–2.2 to 4.3)
			Accelerated t-PA	OR 0.68 (0.42 to 1.08), p = 0.10
				ARR 2.2% (–0.5 to 4.0)
			Total	OR 0.66 (0.46 to 0.94), p = 0.02
				ARR 2.1% (0.4 to 3.4)
			Tests for homogeneity: p = 0.24	
Michels and Yusuf, 1995[22]	7	1145	Total	OR 0.56 (0.33 to 0.94)
				χ^2 7.3, p = 0.29
			Total	ARR 2.7%
Reinfarction rates				
Cucherat *et al.*, 2002[21]	5	2118	Streptokinase	RR 0.11 (0.03 to 0.39)
			t-PA	RR 0.39 (0.14 to 1.09)
			Accelerated t-PA	RR 0.72 (0.45 to 1.14)
			Total	RR 0.48 (0.33 to 0.70)
				χ^2 8.23 (df = 4) Z = 3.75 (total)
			Total	ARR 3.8%
Weaver *et al.*, 1997[23]	10	2606	Total	OR 0.53 (0.34 to 0.8)
				ARR 2.4% (1.0 to 3.4)
Stroke rates				
Cucherat *et al.*, 2002[21]	5	2118	Streptokinase	RR 0.41 (0.08 to 2.09)
			t-PA	RR 0.07 (0.00 to 1.19)
			Accelerated t-PA	RR 0.45 (0.18 to 1.13)
			Total	RR 0.34 (0.16 to 0.72)
				χ^2 2.65 (df = 4) Z = 2.83 (total)
			Total	ARR 1.7%
Weaver *et al.*, 1997[23]	10	2606	Streptokinase	OR 0.62 (0.10 to 3.22), p = 0.77
			t-PA	OR 0.00 (0.00 to 0.54), p = 0.02
			Accelerated t-PA	OR 0.43 (0.13 to 1.20), p = 0.12
			Total	OR 0.35 (0.14 to 0.77), p = 0.007
			Total	ARR 1.3%
CABG rates				
Cucherat *et al.*, 2002[21]	4	693	Streptokinase	RR 0.58 (0.24 to 1.37)
			t-PA	RR 0.76 (0.45 to 1.27)
			Accelerated t-PA	No studies
			Total	RR 0.70 (0.45 to 1.09)
				χ^2 2.71 (df = 3) Z = 1.56 (total)
			Total	ARR 3.8%
Recurrent ischaemia rates				
Cucherat *et al.*, 2002[21]	5	1786	Streptokinase	RR 0.80 (0.23 to 2.81)
			t-PA	RR 0.38 (0.25 to 0.57)
			Accelerated t-PA	RR 0.53 (0.34 to 0.81)
			Total	RR 0.46 (0.34 to 0.61)
				χ^2 5.36 (df = 4) Z = 5.41 (total)
			Total	ARR 8.4%

continued

TABLE 5 *Meta-analyses of primary PCI versus thrombolysis from previous systematic reviews (cont'd)*

Review details	No. of trials in meta-analysis	No. of patients in meta-analysis		Results[a]
Incidence of major bleeding				
Cucherat *et al.*, 2002[21]	4	1934	Streptokinase	RR 0.87 (0.35 to 2.20)
			t-PA	RR 1.23 (0.54 to 2.78)
			Accelerated t-PA	RR 1.38 (0.64 to 2.98)
			Total	RR 1.18 (0.73 to 1.90)
				χ^2 0.59 (df = 2) Z = 0.67 (total)
			Total	ARR 0.5%
Weaver *et al.*, 1997[23]	10	2606	Total	OR 1.06 (0.79 to 1.41), p = 0.75
			Total	ARR 0.3%
Combined end-points				
Cucherat *et al.*, 2002[21]	6	2131	**Combined end-point: varied between primary studies**	
			Streptokinase	RR 0.30 (0.17 to 0.53)
			t-PA	RR 0.51 (0.27 to 0.97)
			Accelerated t-PA	RR 0.70 (0.51 to 0.97)
			Total	RR 0.54 (0.42 to 0.70)
				χ^2 9.27 (df = 5) Z = 4.67 (total) (p = 0.10)
			Total	ARR 6.5%
Weaver *et al.*, 1997[23]	10	2606	**Combined end-point: death or non-fatal MI**	
			Streptokinase	OR 0.40 (0.21 to 0.75), p = 0.003
				ARR 7.4% (2.9 to 10.0)
			t-PA	OR 0.51 (0.26 to 0.99), p = 0.05
				ARR 4.8% (0.1 to 7.4)
			Accelerated t-PA	OR 0.70 (0.48 to 1.08), p = 0.05
				ARR 3.3% (0.0, 5.9)
			Total	OR 0.58 (0.44 to 0.76), p < 0.001
				ARR 4.6% (2.6 to 6.3)
			Tests for homogeneity: overall, p = 0.04	
Michels and Yusuf, 1995[22]	7	1145	**Combined end-point: death or non-fatal MI**	
			Total	OR 0.53 (0.35 to 0.80)
			Total	ARR 4.8%
Longer term outcomes				
Cucherat *et al.*, 2002[21]	3	288	**6-months or 1-year mortality**	
			Streptokinase	RR 3.33 (0.14 to 79.64)
			t-PA	RR 1.07 (0.32 to 3.62)[b]
			Accelerated t-PA	No studies
			Total	RR 1.27 (0.42 to 3.89)[b]
				χ^2 0.65 (df = 2) Z = 0.42 (total)
			Total	ARR 1.0%
Michels and Yusuf, 1995[22]	4	393	**12-month mortality**	
			Total	OR 0.91 (0.42 to 2.00)
			Total	ARR 0.4%
			12-month combined mortality or non-fatal reinfarction	
			Total	OR 0.88 (0.45 to 1.72)
			Total	ARR 0.9%

[a] 95% confidence intervals (CIs) are shown in parentheses.
[b] Values in this meta-analysis were found to be incorrect.
ARR, absolute risk reduction; df, degrees of freedom; OR, odds ratio; RR, relative risk; t-PA, tissue plasminogen activator.

TABLE 6 *Quality assessment of new RCTs*

Study	Random	Allocation concealment	Group similarity	Eligibility	Blinding	Point estimates	ITT	Withdrawal
Aversano *et al.*, 2002[42]	Adequate	Adequate	Reported	Adequate	Adequate	Adequate	Adequate	Adequate
De Boer *et al.*, 2002[44]	Adequate	Adequate	Reported	Adequate	Unknown	Adequate	Adequate	Adequate
Grines *et al.*, 2002[45]	Partial	Inadequate	Reported	Adequate	Inadequate	Adequate	Inadequate	Adequate
Widimsky *et al.*, 2000[46]	Adequate	Adequate	Reported	Adequate	Unknown	Inadequate	Adequate	Adequate

length of hospital stay. The outcomes from the studies are presented in *Tables 7* and *8* in order of sample size. The study with three groups by Widimsky and colleagues[46] is reported in a separate table (*Table 9*).

Mortality

Immediate mortality was reported by all four RCTs (*Table 7*). The mortality rates in the PCI group ranged from 5.3 to 8.4%, compared with 6.2 to 22% in the thrombolysis group. The difference between groups was statistically significant only in one study which reported a lower mortality rate in the PCI group compared with the thrombolysis group [7% versus 22%, RR (thrombolysis) 4.0, 95% CI 0.9 to 24.6, $p = 0.04$[44]], but this may be a chance effect since the mortality in the thrombolysis group is much higher than usual. The lower mortality found in the angioplasty group in the Air-PAMI study[27] was not statistically significant (8.4% versus 12.1%, $p = 0.46$), possibly owing to the small sample size, and perhaps because of the delays incurred.

Longer term mortality rates were reported by two studies[42,44] and are shown in *Table 8*. Aversano and colleagues[42] found no statistically significant difference between groups at 6 weeks (5.3% versus 7.1%, $p = 0.44$) or at 6 months (6.2% versus 7.1%, $p = 0.72$). However, de Boer and colleagues[44] reported a higher mortality rate in the thrombolysis group at 12 months (11% versus 29%, RR 3.4, 95% CI 1.0 to 13.5, $p = 0.03$) and also at 24 months (15% versus 32%, RR 2.5, 95% CI 1.0 to 6.2, $p = 0.04$).

Recurrent infarction

Immediate non-fatal recurrent infarction was reported by all four new RCTs (*Table 7*). The reinfarction rates in the PCI group ranged from 1 to 4% compared with 0 to 15% in the thrombolysis group. Two studies directly comparing PCI with thrombolysis found a statistically significant greater incidence of recurrent infarction in thrombolysis patients (4.0% versus 8.8%, $p = 0.04$[42]; 2% versus 15%, $p = 0.01$),[44] and the one study comparing three groups[46] found a statistically significant difference in reinfarction rates between groups (PCI 1%, thrombolysis and PCI 7%, thrombolysis 10%, $p < 0.03$). Conversely, Grines and colleagues[45] reported a higher incidence of reinfarction in the PCI group (1.4%) compared with the thrombolysis group (0%), but this was not statistically significant ($p = 1.00$).

Aversano and colleagues[42] were the only investigators to report recurrent reinfarction rates at short-term (6 weeks) and longer term (6 months) follow-up (*Table 8*). This study found that PCI patients had a lower rate of reinfarction compared with thrombolysis patients, but this was only statistically significant at 6 months' follow-up (5.3% versus 10.6%, $p = 0.04$).

Stroke

All four studies reported stroke rates as immediate outcome measures (*Table 7*). The stroke rates in the PCI group ranged from 0 to 2% compared with 1 to 7% in the thrombolysis group. The incidence of stroke was found to be higher in the thrombolysis group in all four studies, although none reached statistical significance. In the study by Widimsky and colleagues,[46] patients undergoing thrombolytic therapy during transportation to PCI had a higher incidence of stroke (3%) compared with PCI-only patients (0%) and thrombolysis-only patients (1%), although this did not reach statistical significance.

Aversano and colleagues[42] reported stroke rates at short-term (6 weeks) and longer-term (6 months) follow-up (*Table 8*). This study found that PCI patients tended to have a lower rate of stroke compared with thrombolysis patients at both 6 weeks (1.3% versus 3.5%, $p = 0.13$) and 6 months (2.2% versus 4.0%, $p = 0.28$), but these differences were not statistically significant.

Combined end-point

An immediate combined end-point, defined as death, reinfarction or stroke, was reported by all four RCTs (*Table 7*). The incidence of the combined end-point ranged from 8 to 9.8% in the PCI group compared with 13.6 to 29% in the thrombolysis group. Two studies reported significantly lower rates of the combined end-point in the PCI group compared with the thrombolysis group (9.8% versus 16.8%, $p = 0.0342$; 9% versus 29%, RR 4.3, 95% CI 1.2 to 20.0, $p = 0.01$[44]) and the study comparing three groups[46] found a statistically significant difference between groups (PCI 8%, thrombolysis and PCI 15%, thrombolysis 23%, $p < 0.02$). Grines and colleagues[45] also reported the same trend, but the results did not reach statistical significance.

Longer term combined end-point rates were reported by two studies[42,44] (*Table 8*). Aversano and colleagues[42] found a statistically significantly lower incidence of the combined end-point in the PCI group compared with the thrombolysis group at 6 weeks (10.7% versus 17.7%, OR 0.52, 95% CI 0.30 to 0.89, $p = 0.03$) and at 6 months (12.4% versus 19.9%, OR 0.57, 95% CI 0.34 to 0.95,

TABLE 7 *Results of new RCTs of PCI versus thrombolysis: immediate outcomes*

Study details	Immediate outcome measures	PCI *n* (%) unless stated	Thrombolysis *n* (%) unless stated	Between-group differences
Aversano *et al.*, 2002[42]	Mortality	12 (5.3)	14 (6.2)	$p = 0.70$
Country: USA	Recurrent MI	9 (4.0)	20 (8.8)	$p = 0.04$
Design: RCT, multicentre study	Stroke	3 (1.3)	8 (3.5)	$p = 0.13$
Numbers: Total: 451 PCI: 225 Thrombolysis: 226	Composite end-point: death, recurrent MI, stroke	22 (9.8)	38 (16.8)	$p = 0.03$
	Median length of hospital stay (IQR) (days)	4.5 (3–6)	6.0 (4–8)	$p = 0.02$
Grines *et al.*, 2002[45]	30-day mortality	8.4%	12.1%	$p = 0.46$
Countries: USA, Finland, Argentina	Non-fatal MI	1.4%	0	$p = 1.00$
	Disabling stroke	0	4.5%	$p = 0.11$
Design: multicentre RCT	CABG	6 (8.5) (did not receive PCI)	Assume 0	
Numbers: Total: 138 (patients with high-risk MI) PCI (transfer): 71 Thrombolysis: 67	Ischaemia	12.7%	31.8%	$p = 0.007$
	Combined end-point: death, repeat MI, disabling stroke	8.4%	13.6%	OR 0.571 (95% CI 0.191 to 1.709), $p = 0.331$
	Length of hospital stay (days)	6.1 (4.3)	7.5 (4.3)	$p = 0.015$
de Boer *et al.*, 2002[44]	30-day mortality	3 (7)	9 (22)	RR (thrombolysis) 4.0 (95% CI 0.9 to 24.6), $p = 0.04$
Country: The Netherlands				
Design: RCT	Recurrent MI	1 (2)	6 (15)	$p = 0.01$
Numbers: Total: 87 (all >75 years)	Stroke	1 (2)	3 (7)	$p = 0.34$
	Additional CABG/PCI	2 (4)	4 (10)	$p = 0.41$
PCI: 46 Thrombolysis: 41	Composite (death, infarction, stroke)	4 (9)	12 (29)	RR 4.3 (95% CI 1.2 to 20.0), $p = 0.01$
	Days in hospital	5 (3–10)	5 (3–10)	$p = 0.95$
	Bleeding (non-cerebral)	5 (11)	3 (7)	$p = 0.72$

IQR, interquartile range.

$p = 0.03$), implying that any deaths due to angioplasty were outweighed by the advantages of angioplasty over thrombolysis. In addition, de Boer and colleagues[44] found a significantly lower incidence of the combined end-point in the PCI group at both 12 months (13% versus 44%, RR 5.2, 95% CI 1.7 to 18.1, $p = 0.001$) and 24 months (20% versus 44%, RR 3.1, 95% CI 1.4 to 7.0, $p = 0.003$), suggesting that the benefit of angioplasty was maintained in this population.

PCI/CABG

Three RCTs reported the need for PCI and/or CABG procedure as an immediate outcome measure (*Table 7*).[44–46] While this was an additional procedure undertaken on patients in two of the studies,[44,46] in the study by Grines and colleagues[45] 8.5% of the patients originally randomised to PCI did not undergo this procedure, but instead were referred for CABG. There were no statistically significant differences observed between the groups for this outcome.

The only study to report the need for a CABG procedure in the long term was by Aversano and colleagues[42] (*Table 8*). At both 6 weeks and 6 months, a higher proportion of patients in the thrombolysis group required a CABG procedure, but this difference was not statistically significant.

TABLE 8 *Results of new RCTs of PCI versus thrombolysis: longer term outcomes*

Study details	Longer-term outcome measures	PCI *n* (%) unless stated	Thrombolysis *n* (%) unless stated	Between-group differences
Aversano *et al.*, 2002[42] *Country:* USA *Design:* RCT, multicentre study *Numbers:* Total: 451 PCI: 225 Thrombolysis: 226	**Short-term outcome measures (6 weeks)**			
	Mortality	12 (5.3)	16 (7.1)	$p = 0.44$
	Recurrent MI	11 (4.9)	20 (8.8)	$p = 0.09$
	Stroke	3 (1.3)	8 (3.5)	$p = 0.13$
	CABG	28 (12.4)	42 (18.6)	$p = 0.07$
	Composite end-point: death, recurrent MI or stroke	24 (10.7)	40 (17.7)	$p = 0.03$ OR 0.52 (95% CI 0.30 to 0.89)
	Longer term outcome measures (6 months)			
	Mortality	14 (6.2)	16 (7.1)	$p = 0.72$
	Recurrent MI	12 (5.3)	24 (10.6)	$p = 0.04$
	Stroke	5 (2.2)	9 (4.0)	$p = 0.28$
	CABG	30 (13.3)	44 (19.5)	$p = 0.08$
	Composite end-point: death, recurrent MI or stroke	28 (12.4)	45 (19.9)	$p = 0.03$ OR 0.57 (95% CI 0.34 to 0.95)
de Boer *et al.*, 2002[44] *Country:* The Netherlands *Design:* RCT *Numbers:* Total: 87 (all > 75 years) PCI: 46 Thrombolysis: 41	**Longer-term outcome measures (12 months)**			
	Mortality	5 (11)	12 (29)	RR (thrombo) 3.4 (95% CI: 1.0 to 13.5), $p = 0.03$
	Composite end-point: (death, infarction, stroke)	6 (13)	18 (44)	RR 5.2 (95% CI 1.7 to 18.1), $p = 0.001$
	Longer term outcome measures (24 months)			
	Mortality	7 (15)	13 (32)	RR (thrombolysis) 2.5 (95% CI 1.0 to 6.2), $p = 0.04$
	Composite end-point: (death, infarction, stroke)	9 (20)	18 (44)	RR: 3.1 (95% CI 1.4 to 7.0), $p = 0.003$

Ischaemia

Ischaemia was reported by only one study[45] as an immediate outcome measure (*Table 7*). Patients in the PCI group experienced significantly less ischaemia compared to patients in the thrombolysis group (12.7% versus 31.8%, respectively, $p = 0.007$).

Bleeding events

Bleeding was reported as an immediate clinical event in two studies (*Table 7*),[44,46] but there were no statistically significant differences observed between the groups for this outcome.

Mixed results on measures such as mortality and reinfarction have been shown from these newer RCTs, which may in part be attributable to their small sample sizes. On other measures an advantage of immediate angioplasty over hospital thrombolysis was generally shown.

Results of updated meta-analysis

The results of the updated meta-analyses, including the two updated studies[40,41] and four new publications,[42,44–46] are shown in *Figures 1–9*. No statistically significant heterogeneity was observed. Overall, in-hospital or 30-day mortality was 4.9% with angioplasty and 7.6% with thrombolysis. The RRR was 36% (95% CI 51 to 17%). Longer term mortality (6 months to 24 months) was 5.3% and 8.4% for angioplasty and thrombolysis, respectively (RRR 38%, 95% CI 57 to 11%). A statistically significant reduction was also found with angioplasty compared with hospital thrombolysis for stroke (RRR 64%, 95% CI 80 to 36%), reinfarction (RRR 58%,

TABLE 9 *Results of new RCT of transfer PCI versus combination PCI/thrombolysis versus thrombolysis*

Study details	Immediate outcome measures	PCI % unless stated	PCI and thrombolysis % unless stated	Thrombolysis % unless stated	Between-group differences
Widimsky *et al.*, 2000[46]	30 day mortality	7	12	14	ns
Country: Czech Republic	Non-fatal MI	1	7	10	$p < 0.03$
Design: Multicentre RCT	Stroke	0	3	1	ns
Numbers: Total: 300 PCI: 101 Thrombolysis PCI: 100 Thrombolysis: 99	Combined end-point death reinfarction, stroke	8	15	23	$p < 0.02$
	CABG	3	2	3	Not reported
	PCI	4	5	11	Not reported
	Stent thrombosis (*n*)	1	5		Not reported
	Fatal bleeding complications and/or fatal cardiac tamponade only (estimated from figure), related to actual treatment used	0/97 (–4 who also received streptokinase)	8/111 (+7 rescue PCI patients, +4 from PCI group)	0/92 (–7 rescue PCI patients)	Not reported

ns, not significant.

95% CI 70 to 43%), recurrent ischaemia (RRR 59%, 95% CI 68 to 48%), CABG (36%, 95% CI 51 to 16%), and the combined end-point of death or non-fatal reinfarction (44%, 95% CI 61 to 20%). No statistically significant difference in bleeding was found (RR 1.15, 95% CI 0.76 to 1.74).

An additional meta-analysis including studies from the reviews and the new RCTs on hospital stay was performed and the results are shown in *Figure 9*. Data were combined, where available, and expressed in terms of mean and SD, using a random effects model. Combined length of hospital stay favours PCI (weighted mean difference –2.42, 95% CI –3.59 to –1.25); however, this should be viewed with caution as significant heterogeneity was observed (χ^2 test for heterogeneity = 24.21, df = 5, $p = 0.0002$).

Although the inclusion of new trials updates and improves the analysis, one issue is whether the oldest trials should now be discounted, on the grounds that they may not reflect current practice, such as the use of stents and new drugs. The oldest trials may therefore underestimate current benefits. However, the test for heterogeneity was negative, and they have been retained.

In summary, immediate angioplasty shows an advantage over thrombolysis on clinical indices, including mortality (ARR 3%, RRR 36%), longer-term mortality (ARR 3%, RRR 38%), stroke (ARR 2%, RRR 64%), reinfarction (ARR 5%, RRR 58%), recurrent ischaemia (ARR 11%, RRR 59%), CABG (ARR 5%, RRR 36%) and the combined end-point of death or non-fatal reinfarction (ARR 5%, RRR 44%). Hospital stay was shorter with angioplasty (by 2 days). There was no statistically significant difference in bleeding.

Time of presentation

The Primary Coronary Angioplasty versus Thrombolysis (PCAT) collaboration, which included authors from most of the trials, carried out an individual patient data meta-analysis according to time of presentation.[24] All trials from the meta-analysis by Weaver and colleagues[23] were included, with the exception of the DeWood study[48] (individual patient data were not available), plus an additional study[38] not available at the time of the earlier review. This study by Akhras and colleagues was excluded from the Cochrane review (because no clinical end-point was available).

The aim was to examine outcomes by time from onset of symptoms to presentation, defined as hospital admission (three trials) or randomisation (six trials) (unavailable in one trial), classified as early (<2 hours), intermediate (2–4 hours) and

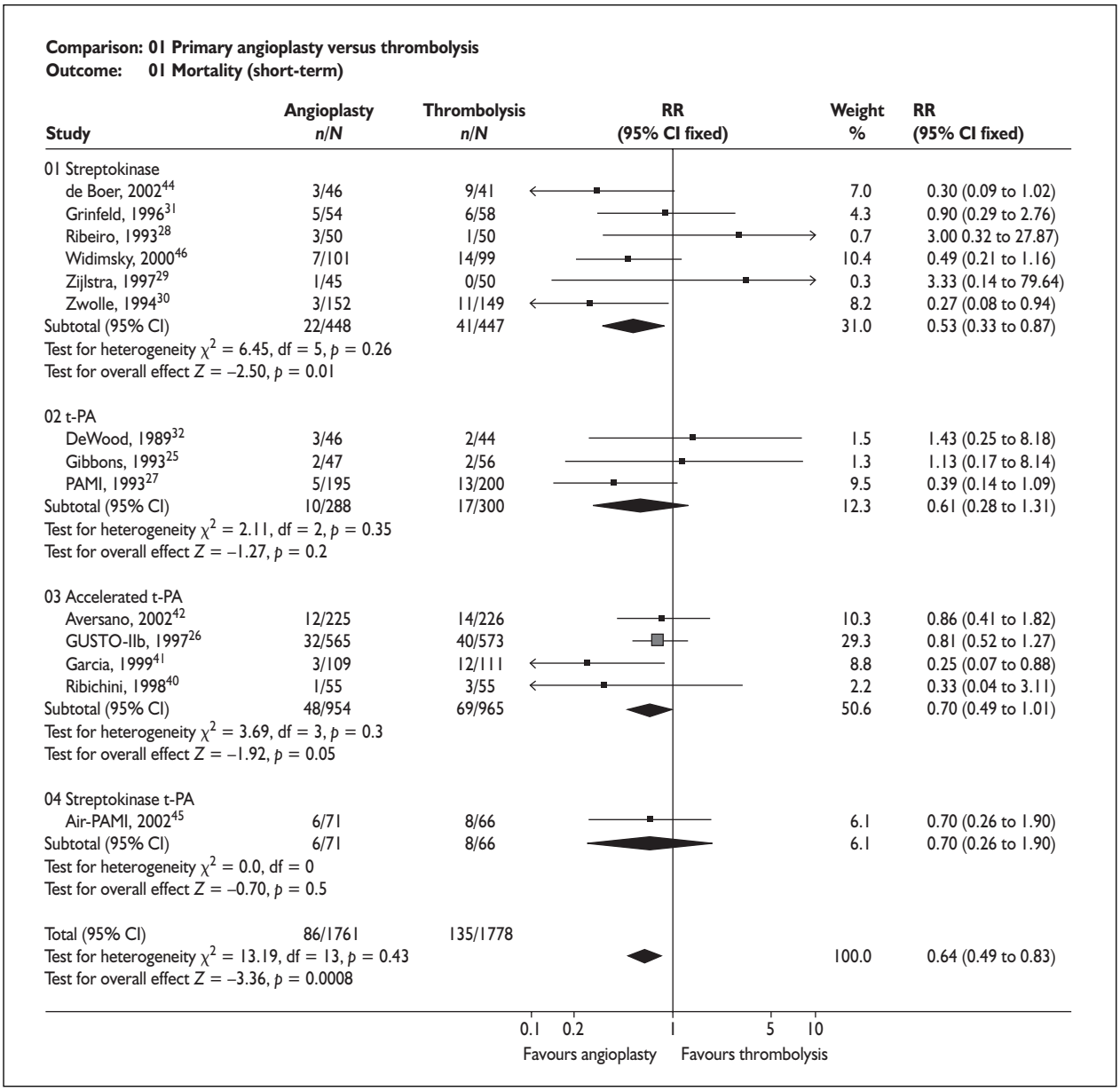

FIGURE 1 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on mortality*

late (> 4 hours) presentation. Median times from presentation to treatment were 69 minutes (25th and 75th percentiles 51 and 90 minutes) for angioplasty and 22 minutes (25th and 75th percentiles 14 and 35 minutes) for thrombolysis. Presentation delay was associated with older age, female gender, diabetes and increased heart rate. The advantage of angioplasty was seen irrespective of time to presentation. *Table 10* shows the combined outcome of death, reinfarction and stroke at 30 days' follow-up.

TABLE 10 *Combined outcome of death, reinfarction and stroke at 30 days*

Presentation	Angioplasty	Thrombolysis
Early	5.8%	12.5%
Intermediate	8.6%	14.2%
Late	7.7%	19.4%

However, it should be noted that not many patients were treated very early (within 1 hour of symptoms) and so it could be argued that neither treatment was being used to best effect, in the 'golden hour'.[49] Furthermore, time to presentation is associated with several variables that are related to prognosis. However, it does appear that outcomes are more affected by time with

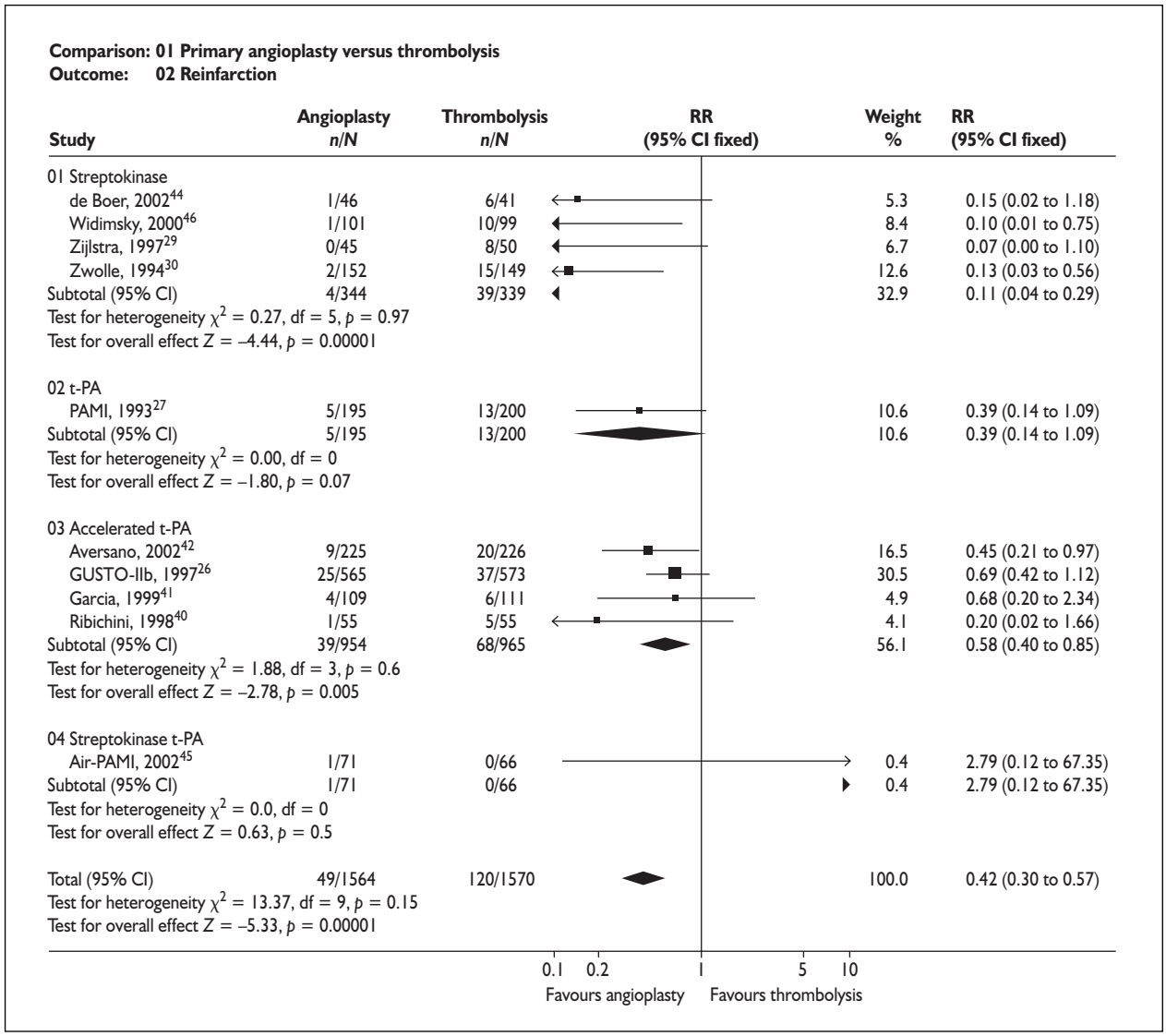

FIGURE 2 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on reinfarction*

thrombolysis than with PCI, and that the later within the 6-hour period the patients present, the greater the advantage of PCI over thrombolysis.

Patient selection effects

To gain an impression of the generalisability of the populations within the included trials to those of the general AMI population, the baseline characteristics of the trial participants are shown in *Tables 11* and *12*.

From these tables it can be seen that with a few minor exceptions the mean ages and the proportions of participants with diabetes, previous MI and anterior location of MI and those of male gender, are similar within studies.

Studies were also sought that examined the effect of different patient characteristics on the difference in effect between PCI and thrombolysis. No studies were found; however, studies were found comparing outcomes in different patient groups undergoing PCI.

Gender

The benefits in terms of relative risk of hospital mortality appear similar in the two genders. The absolute benefits are related to underlying risk, including severity of disease.[50]

Diabetes

Cohort studies suggest that mean survival among diabetic patients is shorter than that in non-

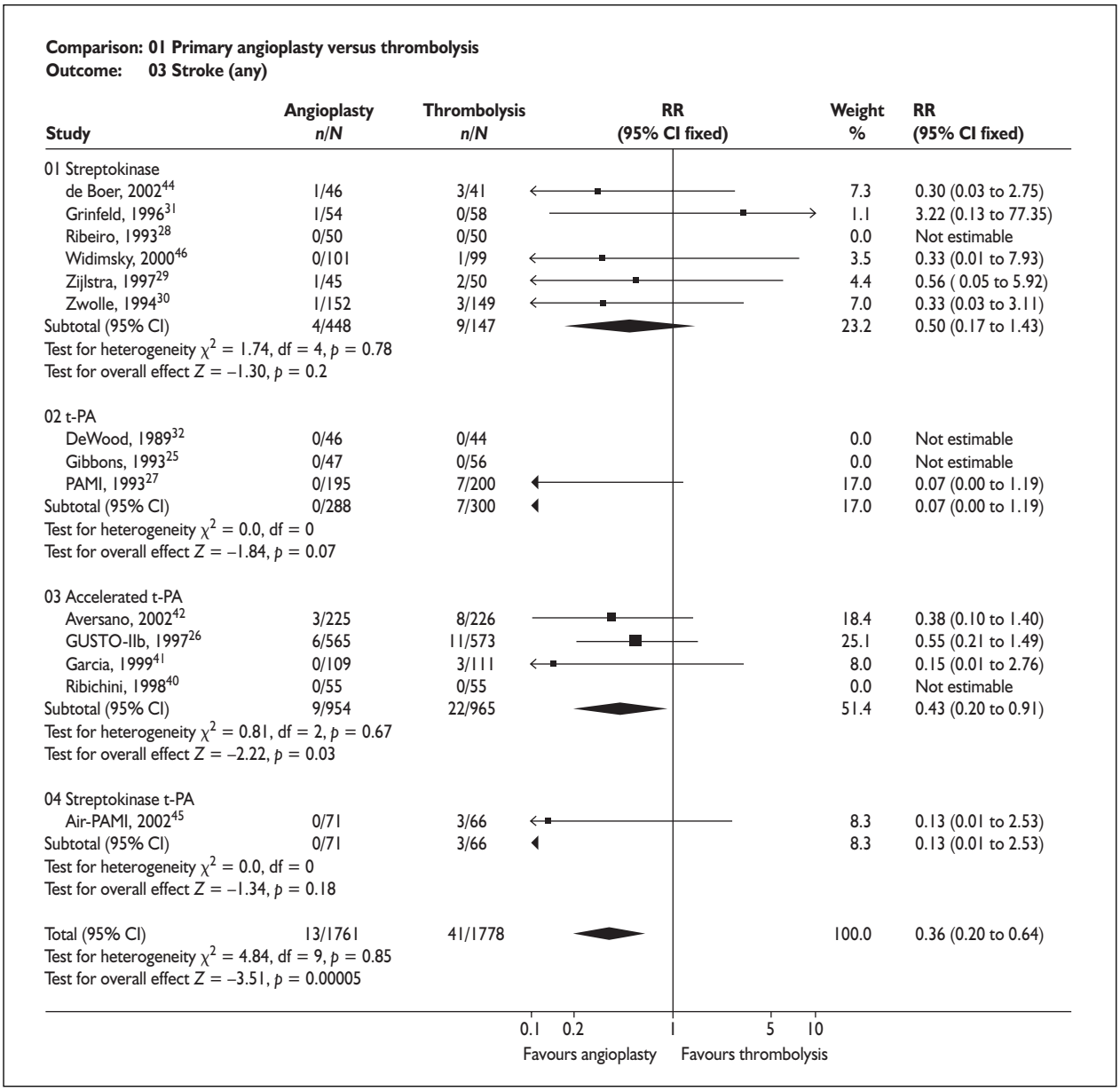

FIGURE 3 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on stroke*

diabetics, after adjustment for confounders. This may be due to more frequent stent thrombosis.[51] In non-Q-wave MI there may be no difference between diabetics and non-diabetics. However, the relative benefit of PCI over thrombolysis appears similar in diabetics and non-diabetics.[50]

Age

Different cohort studies report varying results about the effect of age on survival in patients undergoing PCI. Those people aged over 75 or 80 years may have similar survival after PCI with adjustment for morbidity[52] or may survive less well,[53] although survival may be no worse than the age-matched general population.[54] Only one study compared the effect of age on the relative benefits of PCI and thrombolysis.[55] This suggested that the benefit of PCI over thrombolysis may be less in older than in younger people. This would have considerable implications for absolute numbers to be treated, since the incidence of MI increases with age.

The studies give insufficient detail of age bands; most give mean and some give ranges. It can be seen from *Table 11* that most studies recruited relatively young patients. Without data on the percentage of patients in each age band who were included or not included, the degree of selection bias cannot be assessed, but since the average ages

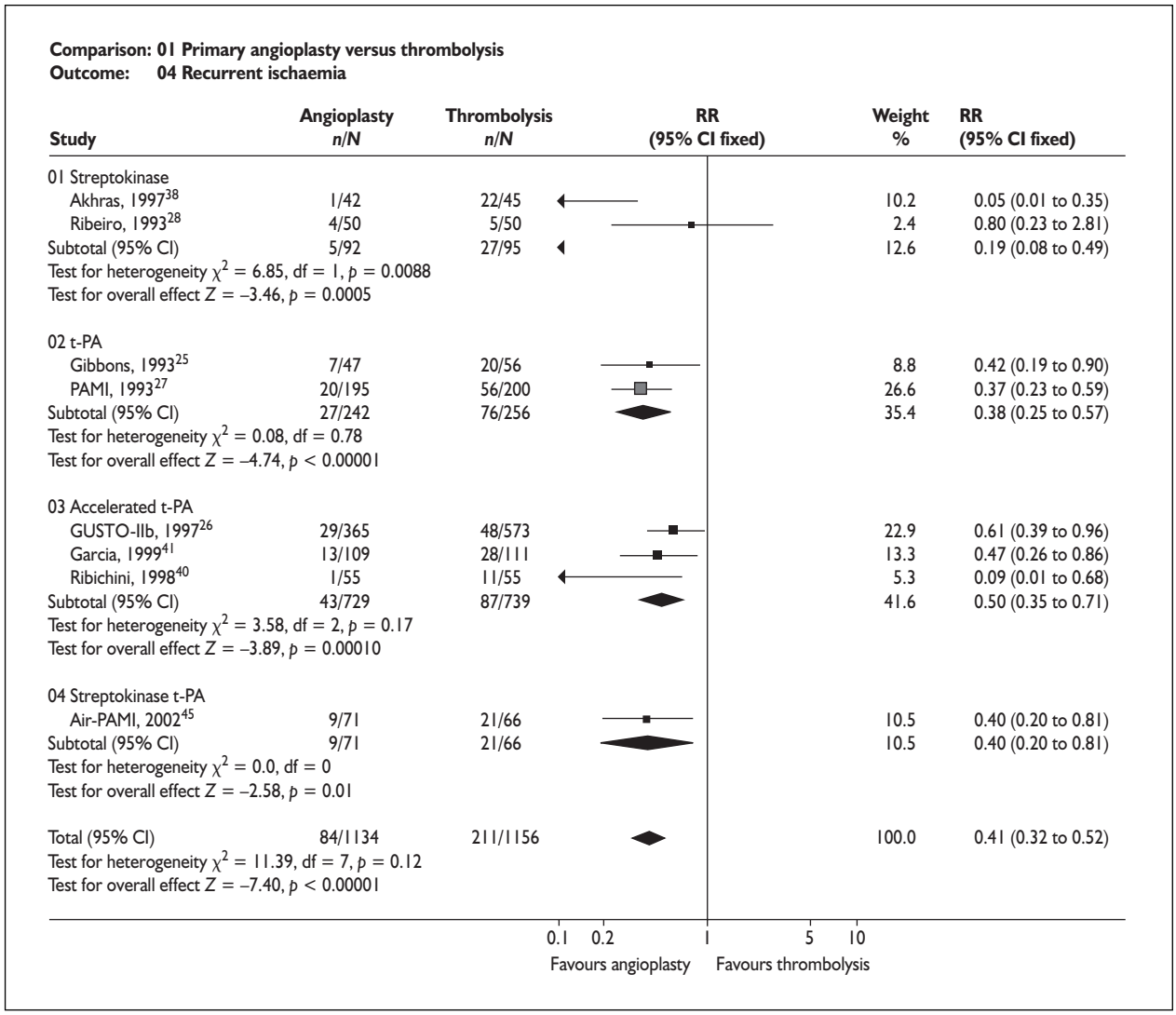

FIGURE 4 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on recurrent ischaemia*

TABLE 11 *Baseline characteristics of participants in RCTs*

Trial name	Mean age (years) (PCI/thrombolysis)	Proportion (%) of participants (PCI/thrombolysis)			
		Male	Diabetes	Previous MI	Anterior MI
Garcia[41]	63/60	84/80	12/17	13/13	No data
Gibbons[25]	60/62	78/71	No data	4/12	32/39
GUSTO-IIb[26]	63/62	75/78	17/13	13/15	No data
Grines[27]	60/60	74/72	13/12	15/14	36/33
Ribeiro[28]	57/55	80/86	12/10	6/16	34/46
Ribichini[40]	63/60	82/85	16/11	18/11	No data
Zijlstra[29]	63/59	80/74	No data	18/20	0/0
de Boer[30]	59/61	84/81	No data	21/14	52/46
Grinfeld[31]	66 (across groups)	71 (across groups)	No data	No data	No data
DeWood[32]	55/55	83/78	No data	No data	No data
Akhras[38]	57 (across groups)	87 (across groups)			

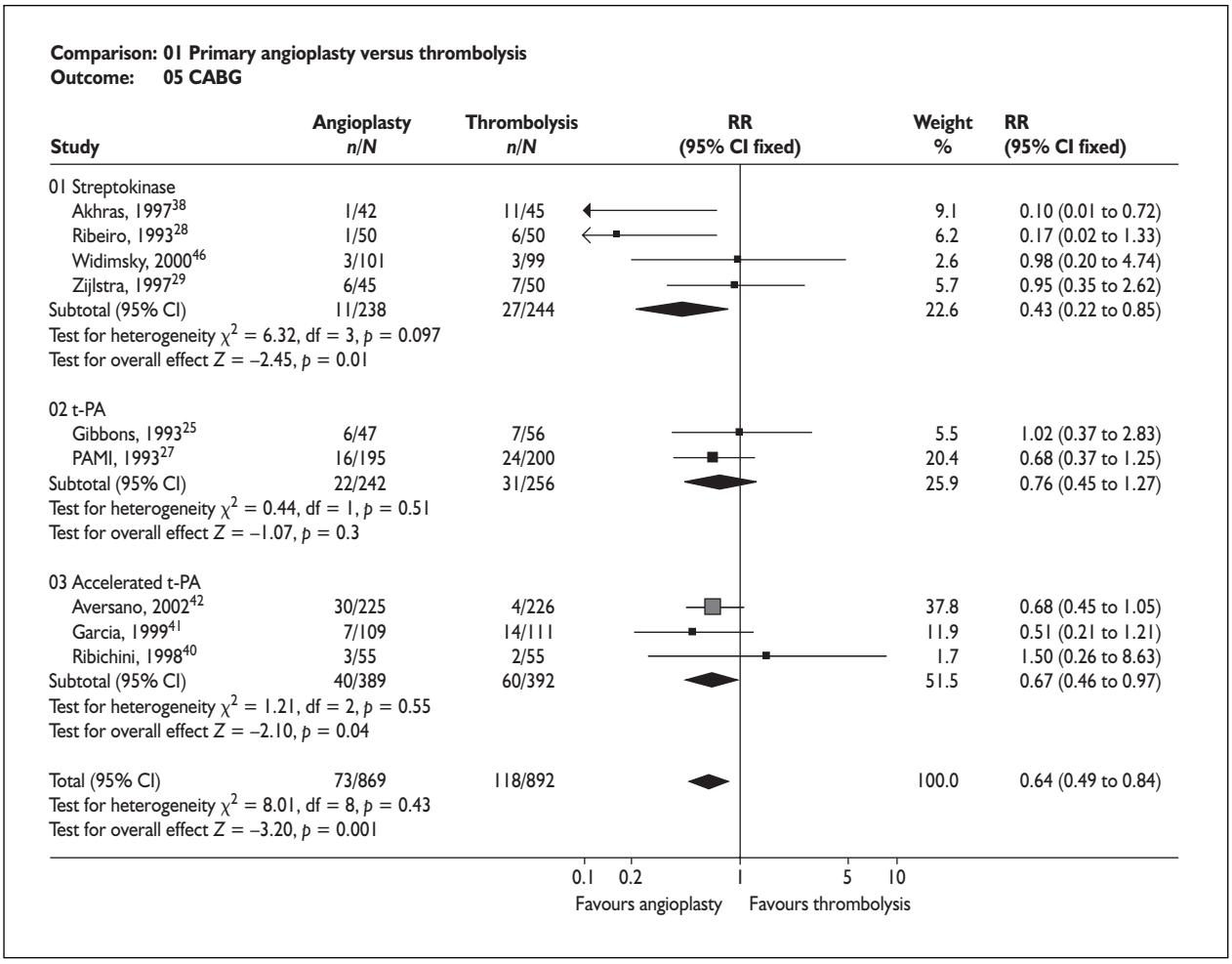

FIGURE 5 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on CABG*

TABLE 12 *Baseline characteristics of participants within new RCTs*

Trial name	Mean age (years) (PCI/thrombolysis)	Proportion (%) of participants (PCI/thrombolysis)			
		Male	Diabetes	Previous MI	Anterior MI
Aversano[42]	64/64	71/70	15/16	16/18	36/36
de Boer[44]	80/81	48/61	24/17	13/17	50/46
Grines[45]	62/64	76/65	23/20	13/14	77/80
Widimsky[46]	61/62/61	71/73/19[a]	No data	9/13/19[a]	47/54/43[a]

[a] PCI/thrombolysis and PCI/thrombolysis.

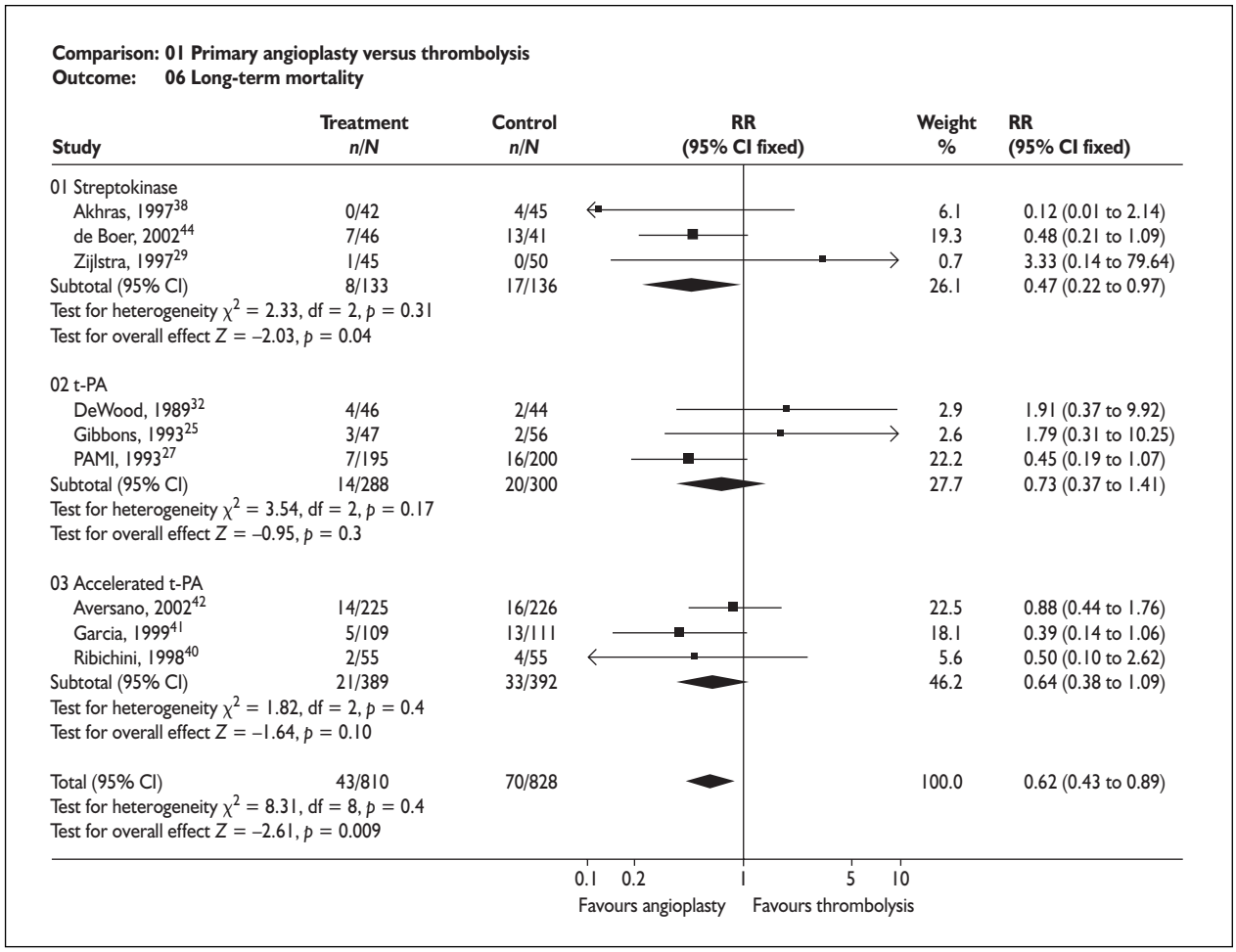

FIGURE 6 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on long-term mortality*

were quite low, and since the prevalence of heart disease increases with age, it appears that there is selection bias in the trials.

The main lack of information is how the above factors influence the relative effects of PCI versus thrombolysis, rather than just the outcome of PCI.

Comparison of RCTs and observational studies

A comparison of the results of the RCTs with those of comparative observational studies may give an impression of the generalisability of the findings of the RCTs to the real-world situation. Three observational studies were identified (see Appendix 5). Two of these observational studies were registry surveys[43,56] and one was a multicentre cohort study.[57] On outcomes of mortality the results of the cohort study echo those of the combined RCTs, with a higher mortality in those given thrombolysis (PCI 4.3% versus thrombolysis 10.3%). The two registry survey studies show no clear difference in rates of mortality between the two interventions.

Reinfarction rates were also shown to be significantly different between groups in the cohort study,[57] in the same direction as shown by the combined RCTs. Only one of the registry studies provided data for reinfarction rates and in this study no statistically significant differences were observed between intervention groups.[56] Rates of stroke and rates of ischaemia were only noted in one of the registry studies[56] and rates reflect those of the combined RCTs (stroke: 0.7% angioplasty, 1.6% thrombolysis; ischaemia: 9.8% angioplasty, 14.6% thrombolysis).

Conflicting results have been shown between one observational study and the combined RCTs on rates of CABG; no statistically significant differences in rates of CABG were observed in the registry study by Tiefenbrunn and colleagues.[56] Major bleeding was reported in two of the included

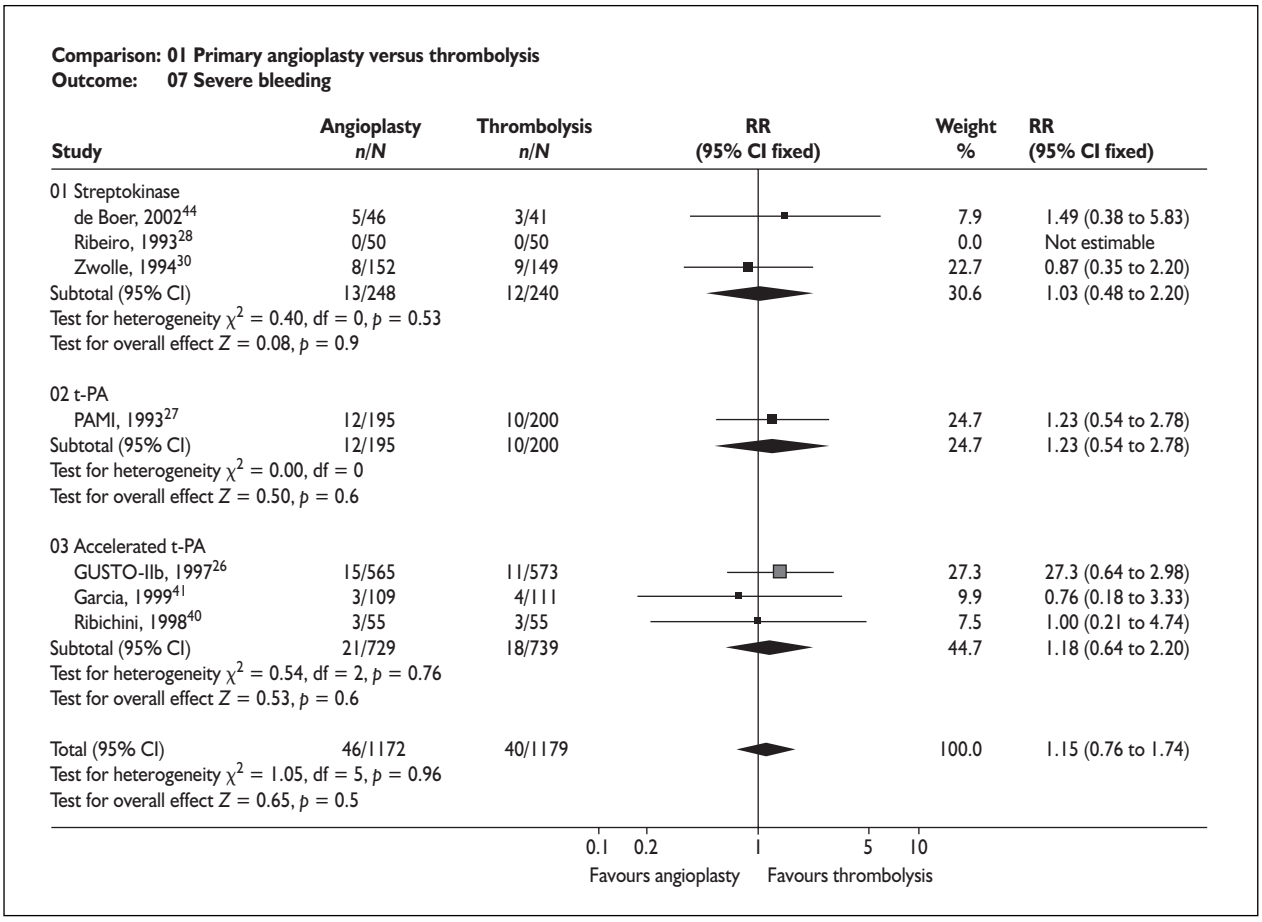

FIGURE 7 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on severe bleeding*

observational studies; the multicentre registry results[57] showed no statistically significant differences in rates (similar to the combined RCTs), but one of the registry studies showed significantly more bleeding in the angioplasty group.[56]

No data were provided on measures of long-term mortality in the observational studies.

Centre effects

One issue is whether the changes seen in trials would be replicated in routine practice. RCTs may be conducted in selected patients in select centres and may not be generalisable, especially if the trial centres are large units experienced in, and organised for, emergency angioplasty.

In a recent editorial, Soljak[58] states that a relation exists between the volume of procedures and the outcome of treatment, and that this holds major promise for improved safety of patients. Recent examples of volume effects include lower mortality rates following cancer surgery,[59] decreased mortality for cardiovascular and cancer procedures[60] and reduced postoperative complications following radical prostatectomy.[61]

If primary angioplasty for AMI is found to be subject to similar effects, then the implication may be that it should only be undertaken in centres of a certain size. There may, however, be a trade-off effect. If only centres with a higher number of patients per annum were to perform angioplasty, patients would have to be transferred from smaller centres to the larger centre. This would have implications not just in terms of resources (principally ambulance costs) but also in terms of morbidity and mortality during transit. A 1997 NHS CRD systematic review[62] of volume effects in a number of procedures concluded that there is no compelling reason to concentrate hospital services further, although this did not look specifically at immediate PCI or care of MI.

In a review of volume effects in primary angioplasty, Hlatky and Dudley[63] state that an

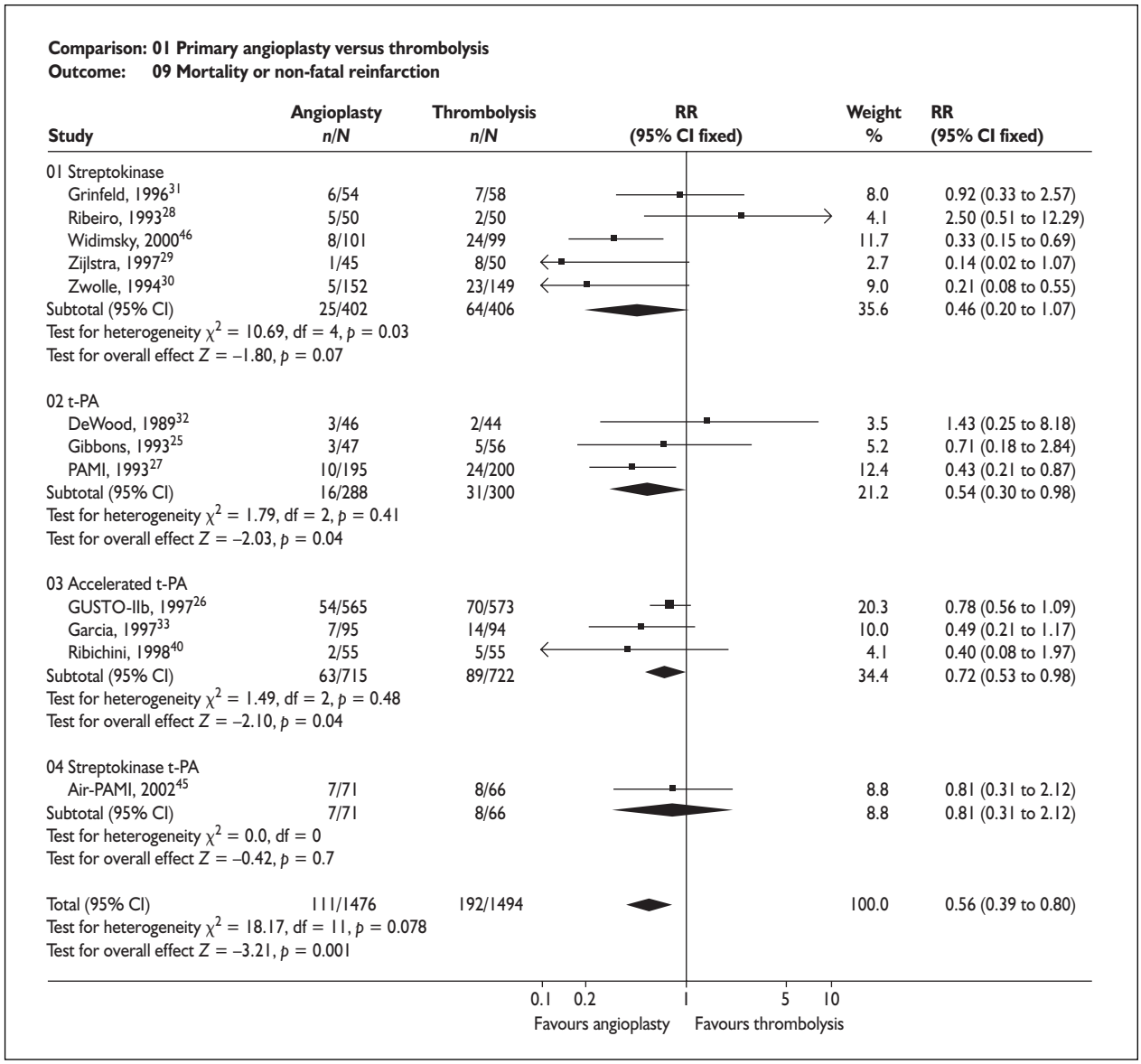

FIGURE 8 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on mortality or non-fatal reinfarction*

"inverse relationship in large studies is shown" and that the "evidence is substantial and compelling". This effect is shown on hospital volume and operator volume. Canto and colleagues[64] showed that hospitals with the highest volumes of primary angioplasty had significantly lower mortality rates than did hospitals performing fewer procedures, but in terms of number of procedures per annum, their quartiles were 5–11, 12–20, 21–33 and over 33. If the average English DGH were to cope with about 200 procedures per annum, with a small number of operators, all units would be in the top quartile. Similarly, Vakili and colleagues[65] reported that higher primary angioplasty volumes led to lower mortality for both hospitals and operators, but low volume was one to 17 PCIs per year for hospitals and one to two for physicians, and high was over 11 for operators and over 57 for hospitals, so again most UK units would be in the high-volume group.

In a study not reviewed by Hlatky and Dudley, results echo the finding that there is a relationship between volume of workload and outcomes. Maynard and colleagues[66] compared angioplasty in rural and urban hospitals, which were in turn subdivided into low-, medium- and high-volume centres. Over 200,000 patients were followed up in 996 hospitals and mortality was shown to be higher in rural hospitals, but was lower in high-volume centres in both areas.

Several issues need to be taken into account when interpreting the results of such studies. Little

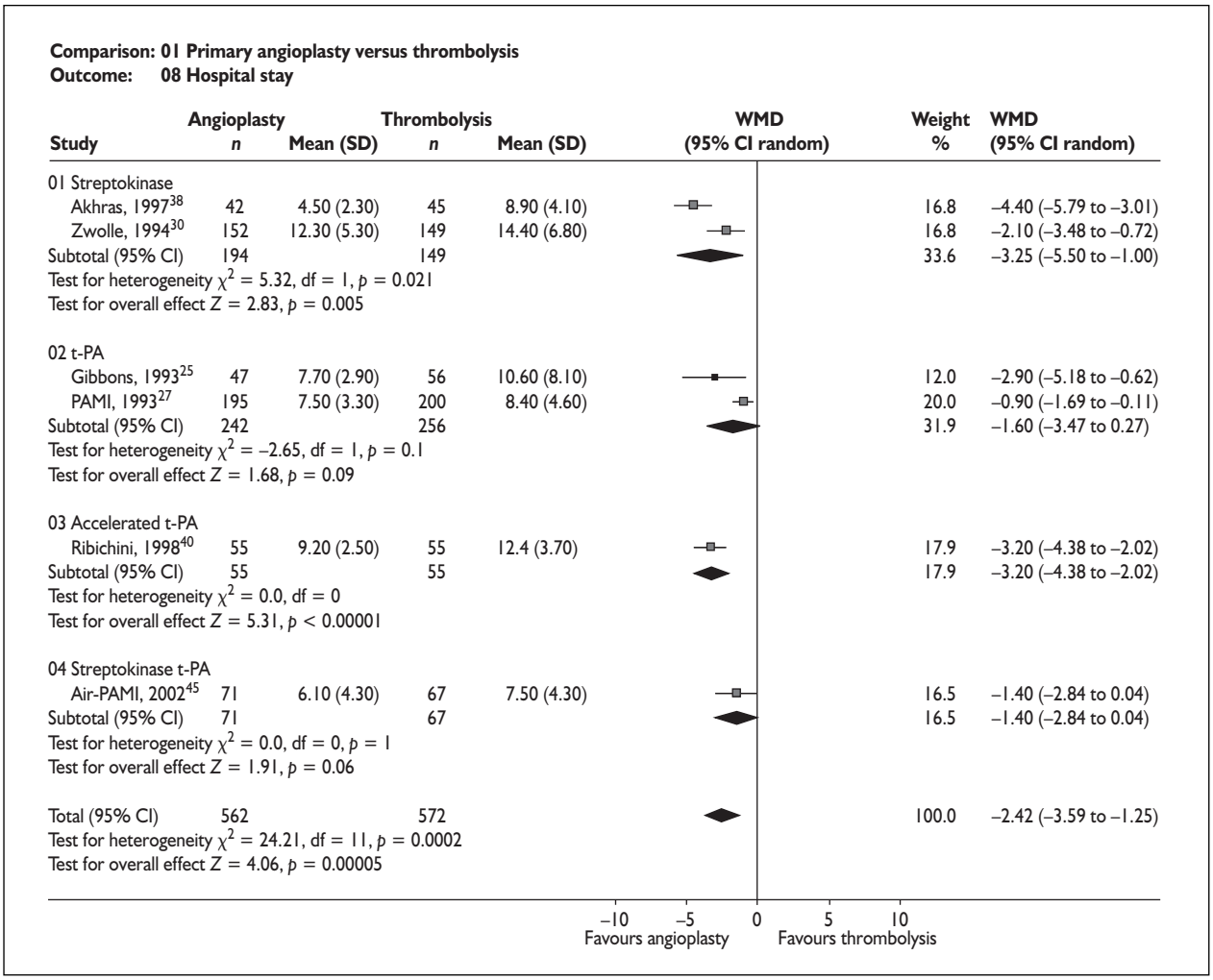

FIGURE 9 *Updated meta-analysis of the effect of angioplasty versus thrombolysis on hospital stay. WMD, weighted mean difference.*

research using any consistent methodology has been undertaken. As it is impractical to randomise patients to high- or low-volume hospitals,[67] most studies have been non-RCTs, but have differed in design, thus making it difficult to summarise results across studies. Differences in patient case-mix and severity of condition have generally not been adjusted for; this means that lower volume hospitals may have a greater spread of severe cases, thereby potentially biasing results. In addition, very large sample sizes are needed to provide sufficient power to document a relationship between mortality and procedure volume.

Finally, there has been little research into the cause of these volume effects. It may not be just hospital volume that is causing the effect, but other factors such as better pathways of care for patients in higher volume centres, the inclusion of other treatments, and differences in care systems. A mixture of results from studies looking at volume effects and recovery from MI may serve as an example of this. Despite showing that high-volume centres carry out more revascularisation procedures such as PCI to patients presenting with MI,[68–70] these studies show conflicting results regarding the effects of high-volume hospitals on mortality rates, from no effect[68,69,71] to higher volume hospitals leading to lower mortality.[70,72] In 446 hospitals classified as low, intermediate and high volume, some 62,000 patients were studied to look at mortality between PCI and thrombolysis therapy.[73] Effects on mortality were in favour of PCI at intermediate- and high-volume hospitals, but at low-volume hospitals no significant differences were shown in mortality rates. The effect on primary angioplasty demonstrated by Canto and colleagues[64] was not evident for thrombolysis. Only at higher volume hospitals did patients undergoing primary angioplasty have lower mortality rates than patients undergoing thrombolysis for AMI.

In summary, the volume issue would probably not be an important issue in England because if PCI were introduced as a routine service, it would be done by high-volume units and operators, probably working through clinical networks, and perhaps with activity centred on regional or subregional centres.

One issue around centres is that of having a central facility to which patients would be transferred, by ambulance. While there may be concerns about people with fragile myocardia being rushed around the country, the evidence from several studies is that transfer plus PCI is better than thrombolysis alone at the base hospital. The DANAMI-2 trial[47] in patients admitted to hospitals without an immediate angioplasty service showed that patients randomised to be transferred to another centre for primary angioplasty did better than those randomised to have thrombolytic therapy in the hospital to which they were first admitted. The primary end-points of death, reinfarction or stroke occurred in 8.5% of the angioplasty group and 14.2% of the thrombolytic group. The PRAGUE-2 study[74] reported similar results, despite transfer differences of up to 120 km. In an associated editorial, Zijlstra notes that transfer for PCI reduced the number of major cardiac events by 70 per 1000 patients, a number needed to treat (NNT) of 14.[75]

Stents

A recent HTA evaluation of stents found seven RCTs comparing angioplasty with and without stents.[14] Some of these trials were available only in abstract form and quality appeared variable. It may be that this reflects the abbreviated reporting rather than underlying design. Overall mortality was unaffected by stent use: MI rates in 6–12 months' follow-up were 2.6% in the stents group and 4.3% in the angioplasty without stents group, but the 95% confidence intervals overlapped (1.5 to 3.7 and 2.8 to 5.8). The main finding of significance was the composite event rate of 14.7% with stents and 30.9% without, but this was dominated by repeat revascularisation (angioplasty or CABG).

Hence, although the key outcomes did not change much, the use of stents at first procedure, at a marginal cost of about £900,[14] reduced subsequent procedures by half. So, for every 100 patients treated, stents would incur an immediate extra cost of £92,000 but reduce costs within the next year by about £43,000, a net increase in price per case of £490. However, these calculations assume that all repeat revascularisations are by PCI. Some would probably be by CABG, which would reduce the cost differential. All costs in the study[14] may now be out of date because of changes in type and price of stents, and costs were based on elective angioplasty.

Successful dissolution of the occluding thrombus by thrombolysis does not affect the underlying arterial narrowing, and reocclusion is common. Wilson and colleagues reviewed the literature on reocclusion rates after thrombolysis and immediate angioplasty, with or without stents.[76] The review provides data on three treatment groups: thrombolysis, angioplasty and angioplasty with stents. Some of the studies were RCTs, but because of non-randomised allocation in some studies (e.g. patients with some types of arterial disease patterns were not considered for stenting), they in effect present three large case series. The main search was on MEDLINE only, but abstracts from conferences were included. There will be an American bias, but that is probably unimportant because most studies come from there anyway. They exclude small studies (under 50 patients having PCI and under 30 with stents).

Bearing in mind the biases and selection effects, they report that occlusion occurs in 25–30% of patients after successful thrombolysis, but that this is reduced by angioplasty to a range of 5–17%, and further by angioplasty plus stenting, to 0–6%, at 6 months. Since stenting is now routine in PCI, it is the last figures that are most relevant.

Maillard and colleagues[77] carried out an RCT in which all patients had angioplasty, but one group had stents used routinely, and one had them used only if necessary. In the later group, 36% of patients had stents, mainly because of a suboptimal result from angioplasty alone (58%) or for poor flow (10%), non-occlusive arterial dissection (15%) or bail-out (18%). The main outcome was a composite one including death, recurrent MI and repeat revascularisation. This was reported in 20% of the routinely stented group and in 28% of the optional stenting group (despite the previous cross-overs) at 1 year. Repeat revascularisations were seen in 18% of the routine stenting group and in 28% of the optional group, and made up the bulk of the composite outcome.

Various observational studies have shown stenting to be safe and effective in rescue PCI,[78] at higher immediate cost but with less frequent later repeat revascularisation.

In summary, stenting is now routine in PCI, and the improved results in outcomes ranging from abrupt occlusion to later restenosis would apply in immediate PCI. It should be assumed that virtually all patients having immediate PCI will be stented.

Rescue angioplasty after failed thrombolysis

None of the included trials randomised patients following failed thrombolysis. Proportions of patients who had angioplasty subsequent to their randomised treatment have been reported, but it is unclear whether these subsequent procedures relate to rescue angioplasty, as the timing of outcomes is not clearly reported.

Three observational studies present data on the outcomes of rescue PCI. Bar and colleagues[79] compared outcomes in patients having primary PCI with those having rescue PCI. Similar rates of mortality, reinfarction and stroke were observed between the two groups. The only statistically significant difference observed was in rates of bleeding; in the rescue PCI groups more patients required blood transfusion.

Juliard and colleagues[80] compared prehospital thrombolysis with primary PCI. In the prehospital group some 50 out of 170 (29%) patients had rescue PCI. No data are presented for this subgroup alone; however, mortality, recurrent ischaemia, and angiographically proven revascularisation rates were not significantly different between the two study groups.

Oude-Ophius and colleagues[81] observed outcomes between patients given community thrombolysis and rescue PCI where required (34%) with those having thrombolysis only. Mortality was significantly higher in the rescue PCI group, but recurrent MI was significantly higher in the thrombolysis-only group.

These studies were not randomised comparisons, and as such their results are more likely to be biased. There were differences in baseline characteristics in two of these studies: in the Bar study,[79] patients in the primary PCI group had more anterior MIs, more previous MIs and more diabetes. Similarly, in the Juliard study,[80] reperfusion rates were faster in PCI groups.

Studies are underway. Meanwhile, the consensus is that when thrombolysis fails (as indicated by continuing pain, failure of ST changes to resolve, etc.) PCI should be considered.

Immediate angioplasty versus community thrombolysis

One recent good quality RCT comparing angioplasty with community (and hence earlier) thrombolysis was found,[82] and is shown in *Tables 13* and *14*. Both services were delivered to high quality. Prehospital thrombolysis was administered by an ambulance team (including a physician) skilled in acute care of MI and accustomed to giving thrombolysis. Angioplasty was provided only by hospitals with experience in routine primary angioplasty for MI and that had a 24-hour on-call angioplasty team.

The main end-point was a composite of death, non-fatal reinfarction or non-fatal disabling stroke at 30 days. Event rates were 8.2% for the thrombolysis group and 6.2% for the angioplasty group. The difference was not statistically significant ($p = 0.29$). Analysis was by ITT, but results show that 26% of the thrombolysis group had rescue angioplasty immediately after failure of thrombolysis, so in practice the prehospital thrombolysis group was treated by a combination of early thrombolysis, rapid transfer to a hospital with interventional cardiology facilities and early angioplasty by an experienced 24-hour team if thrombolysis failed. The study used alteplase, which incurred delays because of the need to prepare infusions. The authors speculate that the use of newer bolus thrombolytics might shorten pain-to-needle time and improve results. The difference in administration time (between thrombolysis and angioplasty) was only 60 minutes, which would be unlikely to be replicated in many places.

Is the apparent benefit of PCI over thrombolysis affected by changes in the lag time of PCI compared to thrombolysis?

An important consideration is whether early thrombolysis might negate the apparent benefit of angioplasty, and how much earlier it would have to be given to do so. The importance to the NHS can then be assessed by considering whether the measures implemented from the National Service Framework (NSF) and NHS Plan, including community thrombolysis, could achieve those time savings.

TABLE 13 *Quality assessment of trial comparing primary angioplasty versus community thrombolysis*

Study	Random	Allocation concealment	Group similarity	Eligibility	Blinding	Point estimates	ITT	Withdrawal
Bonnefoy *et al.*, 2002[82]	Adequate	Adequate	Reported	Adequate	Unclear	Adequate	Adequate	Inadequate

TABLE 14 *Results of trial comparing primary angioplasty versus community thrombolysis*

Study details	Immediate outcome measures	PCI *n* (%) unless stated	Thrombolysis *n* (%) unless stated	Between-group differences
Bonnefoy *et al.*, 2002[82]	Mortality	20 (4.8)	16 (3.8)	Risk difference –0.93 (95% CI –3.67 to 1.81), $p = 0.61$
Country: France	Cardiovascular death	18 (4.3)	16 (3.8)	$p = 0.86$
Design: Multi-centre RCT	Reinfarction	7 (1.7)	15 (3.7)	Risk difference 1.99 (95% CI –0.27 to 4.24), $p = 0.13$
Numbers: Total: 840 PCI: 421 Community thrombolysis: 419	Stroke	0	4 (1)	Risk difference 1.00 (95% CI 0.02 to 1.97), $p = 0.12$
	Composite (death, non-fatal reinfarction, non-fatal stroke)	26 (6.2)	34 (8.2)	Risk difference: 1.96 (95% CI –1.53 to 5.46), $p = 0.29$
	Any angioplasty up to day 30	60 (14.3)	295 (70.4)	
	Overall unplanned angioplasty/CABG	4.7%	34.5%	$p < 0.0001$
	Urgent angioplasty	16 (4)	134 (33)	$p < 0.0001$
	Persistent ischaemia (rescue)	7 (1.7)	106 (26)	
	Recurrent ischaemia	9 (2.1)	28 (6.7)	
	CABG surgery	3 (0.7)	6 (1.5)	
	Severe haemorrhage	8 (2.0)	2 (0.5)	$p = 0.06$
	Recurrent ischaemia (different values reported in Table 2)	16 (4.0)	29 (7.2)	$p = 0.09$
	Ischaemic stroke	0	2 (0.5)	$p = 0.50$
	Haemorrhagic stroke	0	2 (0.5)	$p = 0.50$

An estimate of the time difference at which thrombolysis is equally effective to angioplasty was estimated by Kent and colleagues[83] in a meta-regression of studies in the meta-analysis of Weaver and colleagues.[23] They concluded that the treatments appeared to be equivalent when the time to PCI was 50 minutes longer than thrombolysis. They suggest, however, that treatment delay is likely to be a marker for poor quality angioplasty; therefore, true equivalence may occur after a longer interval if service quality can be assured. Similar findings were also reported in a recent meta-regression analysis[84] using data from the primary sources of a quantitative review by Keeley and colleagues.[85] The analysis suggests that the short-term (4–6 weeks) mortality benefit of primary PCI may be lost if the door-to-balloon time is delayed by over 1 hour compared with thrombolytic therapy door-to-needle time. Others have examined the effect of time of day on outcome in PCI, and found no effect.[86,87] Studies have suggested that the mortality after PCI is unchanged if the procedure is delayed by up to 6 hours,[88,89] although this may not hold for high-risk patients.

The NSF for coronary heart disease aims for a standard of 60 minutes between calling for professional help and thrombolysis (Standard six). In most cases this is to be met by reaching hospital in less than 30 minutes from calling for help and being given treatment within 30 minutes of arrival. Other models, for example out-of-hospital thrombolysis, will be considered where a call-to-door time of 30 minutes cannot be achieved. Reports suggest that door-to-needle times under 30 minutes are achievable.[90] The NHS Plan aimed for times of 20 minutes by 2003. The NHS Plan also announced a 3-year programme to train and equip paramedics to administer thrombolysis and save up to 3000 lives a year. Early information suggests that the roll-out of community thrombolysis is slow, although possibly increasing. The Department of Health reports that very few ambulance services or GPs have started to administer thrombolysis.

In cities, the use of community thrombolysis cannot (by definition) shorten call-to-needle times by more than 30 minutes compared with rapid hospital care, provided the NSF target of call-to-door time of 30 minutes is achieved. Rural areas are likely to be different.[91] The clinical trials report a median difference in call-to-treatment time of 55 minutes between hospital thrombolysis and PCI. Therefore, in most areas community thrombolysis is unlikely to alter the generalisability of the findings of this report, provided the NSF targets are met.

Chapter 5
Economic analysis

Literature review

A search of the literature was undertaken to identify economic evaluations of PCI or thrombolysis for AMI. Details of the methodology and search strategy are presented in Appendices 2 and 3. In addition, the search aimed to identify information related to the costs and QoL associated with patients undergoing PCI or thrombolysis for AMI. The searches identified 59 papers with economic aspects in the scope of the study. Most of these contained little or no detailed information about costs or effects, although 17 were relevant to the general area of the study.[92–108] One article reviewed methodological issues.[101] Six were excluded from the review as they did not meet the inclusion criteria, being letters,[98] other diagnoses,[99] overviews[100,101,103] and a study of patient preferences.[108] Ten studies were considered to have a general relevance to this study. Most of these studies used cost information based on patient charges or insurance costs (*Table 15*). Only two RCTs[93,94] were found; these were also based on fixed cost elements from charges to patients or their insurance. No study contained detailed marginal cost information from the UK. As a consequence, no studies were included in a systematic review of the cost-effectiveness of PCI compared with thrombolysis for AMI. However, a brief summary of the ten studies was produced (*Table 15*).

Table 15 provides information on where the studies have been conducted, the type of study design used, and the types of costing and outcome measures that have been used. Only one study[95] measured outcomes in terms of patient preferences or quality of life. The others define outcomes in terms of survival or a composite measure of survival, infarction and stroke.[92–97,105–107] All studies use charges or insurance claims as a measure of costs, except for the paper by Lee,[97] which compares marginal hospital costs. None of the studies provided sufficient detailed data to allow them to be used as a basis for developing an economic evaluation within the UK.

The majority of studies appear to favour PCI over thrombolysis from a budgetary point of view as the costs are lower, with thrombolysis costing between 4 and 9% more than PCI.[93–95] When the outcomes (i.e. survival and health status) are taken into account the results suggest that there is limited difference between the two treatment options and conclusions become more uncertain. Although some studies have produced a cost-effectiveness analysis, the value of the outcomes in terms of quality of life is uncertain, whether a consequence of poor quality evidence or absence of data. Only the study by Lieu and colleagues[95] provides an incremental cost-effectiveness ratio (ICER) showing that PCI provides additional quality-adjusted life-years (QALYs) at a cost of US$12,000 per QALY. The cost analyses were not conducted using a detailed marginal cost perspective.

TABLE 15 *Studies used in the economic analysis, in reverse order of publication*

Study	Country	Type of study	Costs	Outcomes
Sagmeister *et al.*, 2000[104]	Switzerland	Meta analysis	Insurance	Survival
Mullner *et al.*, 1999[92]	Austria	Overview	Charges	Survival
Amit *et al.*, 1999[105]	The Netherlands	Overview	Charges	Composite
Zijlstra, *et al.*, 1999[93]	The Netherlands	RCT	Insurance	Survival
Boersma *et al.*, 1998[106]	The Netherlands	Meta-analysis	?	Survival
Brodie, 1998[107]	USA	Overview	Charges	Composite
Talley, 1998[96]	USA	Overview	Charges	Composite
Lee, 1997[97]	Republic of Korea	Comment	Marginal cost	?
Lieu *et al.*, 1997[95]	USA	Overview	Charges	QALYs
Stone *et al.*, 1997[94]	USA	RCT	Charges	Composite

?, Unknown.

Estimating UK cost-effectiveness

The review of the literature on the cost-effectiveness of PCI compared with thrombolysis for AMI showed that there are no economic evaluations directly relevant to the UK. As a consequence, an economic evaluation was developed in this review to assess the cost-effectiveness of PCI compared with thrombolysis for AMI within the UK, using evidence from the systematic review of clinical effectiveness, data from published studies identified in the review of cost-effectiveness, and from NHS hospital trusts in the UK. The subsequent sections give a brief description of the components of the economic evaluation, including its structure, the sources of information for benefits and costs, and the results of the analysis.

Economic model structure

The economic evaluation developed for this assessment was based on a deterministic approach using a 6-month decision-analytical model examining the benefits and costs of PCI compared with thrombolysis for AMI. The deterministic approach was used as it involves using fewer assumptions than a probabilistic approach which, given the limited data available, may have led to greater uncertainty. In effect, the model presents the probabilities of an average patient experiencing particular events (i.e. health states or treatment options) during the period of the evaluation, the consequences of which can be assessed in terms of benefits to the patients (survival and quality of life) and the costs that are incurred. The structure of the model, which is presented in *Figure 10*, was developed using evidence from the systematic review of clinical effectiveness, the review of economic evaluations and expert advice. It represents the key states that were thought would determine the cost effectiveness of the alternative treatment options for people suffering from AMI. The model takes a 6-month perspective focusing on the early acute hospital period. It was considered that a longer period would involve a broader spectrum of additional healthcare interventions and it was deemed that these lay outside the scope of the assessment. In addition, data on the benefits and costs of these additional interventions were limited and inclusion in the model would necessitate several assumptions that may have led to additional uncertainty. The economic evaluation focused on estimating the ICER, that is, the marginal cost per QALY (or other outcome) from using PCI instead of thrombolysis. The intention was to allow recommendations as to the most appropriate intervention given current capacity (i.e. facilities, equipment and staff) within the NHS. As a consequence, the evaluation does not consider capital costs, training costs or other overhead costs associated with developing or providing the service. Indirect costs were excluded from the analysis as the primary question to be addressed was the most cost-effective treatment, rather than assessing the costs of developing a service within the UK. Uncertainty in the model parameters would be investigated through sensitivity analysis, with different values used for specific variables of the model to test how assumptions influence the outcome (e.g. quality of life, probability of PCI outcomes following failed thrombolysis).

The model shows that patients suffering from AMI have three treatment options: PCI, thrombolysis, and PCI when thrombolysis is contraindicated. In addition, patients who receive thrombolysis that fails may undergo PCI. All alternatives are compared to a base-case scenario of symptomatic and supportive treatment only (e.g. pain relief, β-blockers).

Thrombolysis treatment can have a range of outcomes. The treatment may succeed (pTs in *Figure 10*) and patients may regain full health with a QoL valued at 1. If the treatment fails (pFT), the patient may die (pFTd), resulting in a QoL valued at 0. However, the patient may survive but with ongoing short- or long-term morbidity (e.g. non-fatal bleeding, ischaemia, stroke or reinfarction) (pFTm). These morbidities will reduce QoL between death and full health (ET). Alternatively, the patient may leave the study (pFLT) or receive angioplasty secondary to the thrombolysis (pRP), with the possible outcomes of morbidity ($p = p$TPm), mortality ($p = p$TPd) or success (pTPs). QoL for these different outcomes was assumed to be valued at 0 for patients who died, 1 for those whom the treatment was successful, and somewhere between 0 and 1 for those suffering from morbidity (ETP). The cost of treatment with thrombolysis was defined in the model as CTr, with the additional cost of angioplasty as CTP.

Where PCI was the treatment for AMI, patients have a probability of experiencing one of three possible outcomes: morbidity (pPm), death (pPd) or success (pPs). As with the thrombolysis outcomes, success would return the patient to full health and a QoL valued at 1, death following treatment was valued as having a QoL of 0, and

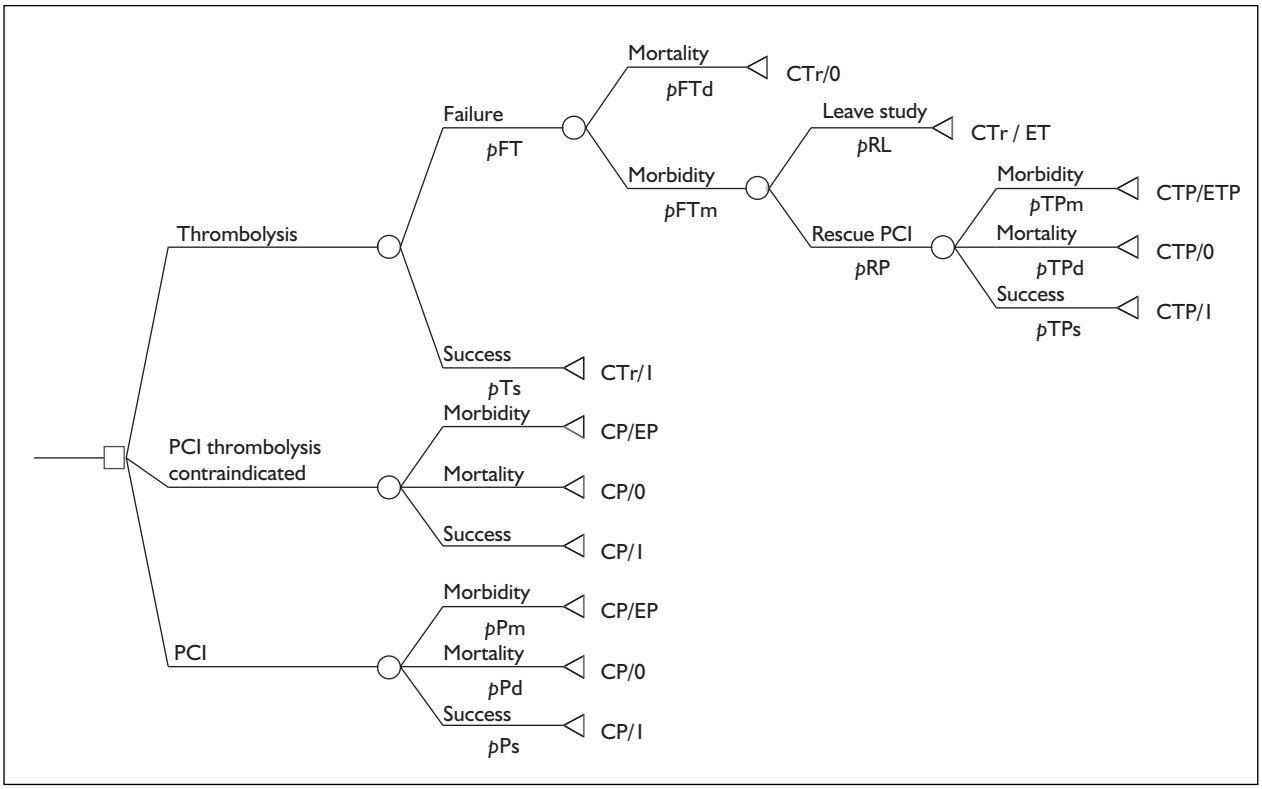

FIGURE 10 *Decision tree of the treatment alternatives*

morbidity was thought to be valued somewhere between 0 and 1 (EP). The cost of PCI was specified in the model as CP. Patients treated with PCI where thrombolysis was contraindicated were assumed to have similar probabilities for the different outcomes, QoL and costs. The decision that thrombolysis is contraindicated is undertaken in the diagnosis phase, before the model starts. In this instance, there is no real choice between PCI and thrombolysis when considering management of the patient's condition and this arm is only included in the model for illustrative purposes.

Estimation of net benefits

Estimation of the net benefits in an economic evaluation usually examines the effects of a health intervention on the years of life gained and the QoL experienced by the patient. Within this evaluation the short period adopted of 6 months' duration limits the usefulness of incorporating life-years gained. As a consequence, the model focuses on probability of patient survival within that period and the change in health status experienced by the patient. Recommendations as to the most beneficial intervention will be based on differences in the health status measure rather than the calculation of QALYs.

Methods used to assess health status

It was assumed in the economic evaluation that patients who died following an intervention would have a health status of zero (0). In contrast, those patients in whom the treatment was deemed to be successful would have been restored to full health and discharged home, and as a consequence would have a health status of one (1). The health status of patients who survived but suffered from some morbidity event would lie somewhere between the values adopted for those patients who either died or survived, and would depend on the nature of their condition. AMI and the different forms of treatment may be associated with several different morbid conditions, including bleeding, ischaemia, stroke and reinfarction. It is likely that these morbid effects would necessitate further interventions. Unfortunately, the limited evidence available on the benefits and costs of such interventions prevented their inclusion in the evaluation. As a consequence, it was decided to assume that patients suffering such morbidity following their intervention would experience an average or composite non-fatal effect. Only the study by Solomon and colleagues[108] provided an estimate of health status for such a group of patients, setting a low health status value of 0.1 for patients suffering a non-fatal disabling stroke. As most survivors will have better outcomes than

TABLE 16 *Aggregate probabilities for morbidity*

	Incidence		
	PCI	**Thrombolysis**	**Source**
Reinfarction	0.03	0.08	*Figure 2*
Stroke	0.01	0.03	*Figure 3*
Ischaemia	0.07	0.18	*Figure 4*
CABG	0.08	0.13	*Figure 5*
Bleeding	0.04	0.03	*Figure 7*
Total	0.24	0.45	

disabling stroke, their health status will be better. With very limited evidence available to assess health status for these patients, it was decided arbitrarily that survivors with ischaemic heart disease-related morbidities would have a health status score of 0.5, with the sensitivity analysis assessing health status values of 0.3–0.7.

Methods used to assess survival

Evidence from the meta-analyses in the systematic review of clinical effectiveness (see section 'Results of updated meta-analysis', p. 17) and from audit data for 2001 from the BCIS was used to derive the transition probabilities used in the evaluation, specifying the proportion of patients who would survive, die or suffer subsequent morbidity. The different transition probabilities are shown in *Tables 16* and *17*, along with the source of the data.

The BCIS survey for 2001 shows that patients with AMI who undergo PCI have a probability of success and restoration of full health (pPs) of 0.90 and mortality (pPd) of 0.05. It was assumed that the remaining patients would have a probability of 0.05 of suffering from a range of morbidities (pPm). Evidence from the systematic review of clinical effectiveness suggested that patients undergoing PCI could have a higher probability of morbidity, with patients having a probability of 0.24, including reinfarction (0.03), stroke (0.01), ischaemia (0.07), CABG (0.08) and bleeding (0.04). As the BCIS survey provides data on actual activity in the UK, it was decided to use this in the base case. As there was no evidence to the contrary, it was assumed that those patients undergoing PCI owing to thrombolysis being contraindicated would have the same probabilities of survival, mortality and morbidity as the PCI group.

Patients who received thrombolysis had a probability of failure of treatment (pFT) of 0.53, comprising a probability of mortality (pTd) of 0.08 and a probability of morbidity (pTm) of 0.45. As such, patients had a probability of success and a return to full health (pTs = 1 – pTd + pTm) of 0.47. The probability of morbidity comes from a composite encompassing reinfarction, stroke, ischaemia, CABG and bleeding (pTm) (*Table 16*). Patients whose thrombolysis treatment failed owing to morbidity would have a probability of undergoing PCI as a rescue strategy (pRP) of 0.79. Of those undergoing rescue PCI, the probability of success (pTPs) was 0.86, morbidity (pTPm) 0.10 and mortality (pTPd) 0.038.

Estimation of net costs

As the economic evaluation examines the incremental cost-effectiveness it focuses on the marginal costs of the interventions, including staff costs, direct ward costs, and costs for the use of equipment, pharmaceuticals and other materials. It excludes indirect costs such as capital costs, training costs or overheads. Costs originate from Southampton University Hospitals Trust (UK) and from a study by McKenzie and colleagues[110] and are average costs for the different scenarios at 2003 prices. Further details of NHS cost data are outlined in Appendix 6.

It was assumed that patients undergoing thrombolysis would be assessed as probable heart attack patients in accident and emergency (A&E) by a triage nurse, with an ECG and possibly an X-ray. Such low-cost investigations in A&E were thought to cost £107 [Healthcare Resource Group (HRG) V05 2002/03 prices]. Following admission to the coronary care unit (CCU) the patient would receive streptokinase (£92.13), reteplase plus heparin and enoxaparin (£430.64) or tenecteplase plus heparin and enoxaparin (£514.39). The patient would remain on the CCU for 2–3 days at a cost of £469 per day (total cost £938–1407), before transfer to a cardiology ward for 7.2–9.4 days at £278 per day including support costs (total cost £2001.60–2613.20). The patient is also likely to undergo an angiography during the stay. This will involve approximately 20 minutes in theatre with a cardiologist, a radiographer, a technician and two nurses, costing £178.92 with other non-staff costs. Depending on the drug used and the days spent on the CCU and ward, the average total costs for thrombolysis varied. In the evaluation it was assumed that patients would receive the reteplase option with a cost ranging from £3656.16 to £4736.76, with the use of streptokinase examined in the sensitivity analysis.

The cost of PCI included assessment in A&E as a probable heart attack patient by a triage nurse

TABLE 17 *Model specifications in summary*

Variable	Code in *Figure 10*	Value	Source
Outcomes			
Morbidity QoL outcome from thrombolysis	ET=EP	0.5 (range 0.3–0.7)	Assumption; no evidence available
Morbidity QoL outcome from PCI	EP	0.5 (range 0.3–0.7)	Assumption; no evidence available
Morbidity QoL outcome from thrombolysis after rescue primary angioplasty	ETP=EP	0.5 (range 0.3–0.7)	Assumption; no evidence available
Probabilities			
Failure of thrombolysis	*p*FT=1–*p*Ts	0.53	See *p*Ts
Successful survival after thrombolysis	*p*Ts=1–*p*Td–*p*Tm	0.47	See *p*Td, *p*Tm
Mortality probability from thrombolysis	*p*Td	0.08	*Figure 1*
Morbidity probability from thrombolysis	*p*Tm	0.45	*Table 16*
Mortality at failed thrombolysis[a]	*p*FTd=*p*Td/*p*FT	0.15	See *p*Td, *p*FT
Morbidity at failed thrombolysis[a]	*p*FTm=*p*Tm/*p*FT	0.85	See *p*Tm, *p*FT
Leave study for other treatment	*p*RL=1–*p*RP	0.21	See *p*RP
Rescue PCI probability	*p*RP	0.79	Schweiger *et al.*, 2001[109]
Mortality probability after rescue PCI	*p*TPd	0.038	*Table 2*; BCIS
Morbidity probability after rescue PCI	*p*TPm=1–*p*TPs–*p*TPd	0.10	*Table 2*; BCIS (estimate)
Successful survival after rescue PCI	*p*TPs	0.86	*Table 2*; BCIS
Successful survival after PCI	*p*Ps	0.90	*Table 2*; BCIS
Mortality probability from PCI	pPd	0.05	*Figure 1*
Morbidity probability from PCI	*p*Pm=1–*p*Ps–*p*Pd	0.05	*Table 2*; BCIS (estimate)

[a] The modelling software calculates the probabilities at the different stages in the decision tree to ensure the total probability equals 1. *p*FTd and *p*FTm represent a recalculation of *p*Td and *p*Tm, so the combined probabilities equal 1.

with an ECG and X-ray at a cost of £107 (HRG V05 2002/03 prices). The patient would be admitted to the CCU and stay for 2–3 days at a cost of £469 per day (total cost £938–1407). The angioplasty procedure would take approximately 60 minutes, involving a cardiologist, a radiographer, a technician and two nurses, at a cost of £2034. After the stay on the CCU, the patient would then be transferred to the cardiology ward for 7.2–9.4 days, at a total cost of £2001.60–2613.20 (£278 per day). In addition, the patient would require abciximab (£800) and clopidrogrel (£35). Depending on the time spent on CCU and the cardiology ward the average total cost for the treatment would vary between £5915.60 and £6996.20 per patient.

For patients who underwent PCI after thrombolysis had failed, the costs of care are likely to include a proportion of the costs of undergoing the two forms of treatment. It is assumed that patients will undergo assessment for thrombolysis in A&E (£107) and incur the costs of the reteplase treatment (£430.64). It is likely that failure of thrombolysis will be identified within a few hours of the procedure in CCU and patients will undergo the PCI option, involving some investigational procedures (£179), the procedure itself (£2034), drug costs (£835) and a stay on the CCU (£938–1407 including the cost of CCU support for thrombolysis care) and on the cardiology ward (£2002–2613). Patients may vary in the procedures followed, with some differences in the investigational procedures used and their length of stay. The effects of different thrombolytic agents will also be assessed in the sensitivity analysis, examining the use of streptokinase. As a consequence, the analysis will examine total costs for this element ranging from £6526 to £7606.

The average total costs for these different scenarios and the variations highlighted in the different length of time spent on the CCU and cardiology wards were examined through sensitivity analysis. Similarly, the difference in the

drug costs for thrombolysis was examined in the sensitivity analysis.

Discounting of the benefits and costs was not undertaken owing to the short-term perspective adopted of 6 months. In addition, it was assumed that the treatments were similar enough that annual capital costs would not differ. As such, costs such as those for the stay on the CCU and cardiology ward costs include the operative costs of equipment. They do not include the costs of administration or other overhead costs, which would be likely to differ between hospitals. As discussed previously, the limited time-frame reflects the lack of data on long-term outcomes, particularly morbidity.

Estimation of cost-effectiveness

The results from the economic evaluation for the base case and for alternative cost options are presented in *Tables 18* and *19*. The costs for the average patient of each treatment arm are compared with the health status of those patients having undergone treatment. The overall result is presented as an average cost–utility ratio for each arm (cost per health status) and also as an incremental cost–utility ratio, that is the cost of moving routine treatment from the least to the most cost-effective, and the aggregated change in health status that this change can generate.

Using the assumptions stated earlier, the base-case analysis shows that the short-term clinical effects are more favourable using PCI compared with thrombolysis for uncomplicated MI at an additional cost. The results show an incremental cost per case of £543 for PCI compared with thrombolysis and a better result in terms of health status from using PCI [0.925 health status unit (HS)] instead of thrombolysis (0.841 HS) (*Table 18*), producing an ICER of £6473.

It was evident from the assessment of the clinical pathways and net costs for PCI and thrombolysis that the length of stay on the CCU and cardiology ward may vary (see Appendix 6). In the base case

TABLE 18 *Base-case costs and effects of treatment options*

	Cost (£)	Incremental cost (£)	Effectiveness (HS)	Incremental effectiveness (HS)	Cost-effectiveness (£/HS)	ICER (£/HS)
PCI hospital cost £5916, thrombolysis cost £4737 per case,[a] rescue PCI £6526 (max./min.)						
Thrombolysis	5373[b]		0.841		6388	
PCI	5916	543	0.925	0.084	6396	6473

[a] Represents average costs of thrombolysis treatment alone.
[b] Represents average costs for patients undergoing thrombolysis option, including a proportion undergoing angioplasty following failed thrombolysis.

TABLE 19 *Cost-effectiveness with alternative hospital cost options PCI £5916 to £6997 and thrombolysis £3656 to £4737*

	Cost (£)	Incremental cost (£)	Effectiveness (HS)	Incremental effectiveness (HS)	Cost-effectiveness (£/HS)	ICER (£/HS)
PCI hospital cost £6997, thrombolysis cost £3656 per case[a], rescue PCI £6526 (min./max)						
Thrombolysis	4676[b]		0.841		5560	
PCI	6997	2321	0.925	0.084	7564	27,664
PCI hospital cost £5916, thrombolysis cost £3656 per case[a], rescue PCI £6526 (min./min.)						
Thrombolysis	4676[b]		0.841		5560	
PCI	5916	1240	0.925	0.084	6396	14,778
PCI hospital cost £6997, thrombolysis cost £4737 per case[a], rescue PCI £6526 (max./max.)						
Thrombolysis	5373[b]		0.841		6388	
PCI	6997	1624	0.925	0.084	7564	19,359

[a] Represents average costs of thrombolysis treatment alone.
[b] Represents average costs for patients undergoing thrombolysis option, including a proportion undergoing angioplasty following failed thrombolysis.

presented in *Table 18* and the analysis presented in *Table 19* these differences are examined through different estimates of the net costs for the two treatment options. In none of the alternatives presented does the incremental cost-effectiveness favour thrombolysis treatment.

Sensitivity analysis

In the base-case model reteplase [recombinant tissue plasminogen activator (rt-PA)] was used as the drug for thrombolysis treatment, which is an expensive option providing a worst case scenario. As a contrast to the base-case model, subsequent models were specified varying the net costs from differences in drug costs, using the least expensive thrombolytic drug, streptokinase, as the alternative to PCI (*Table 20*). By using streptokinase as the thrombolytic agent, the drug costs decrease from £431 to £92. A sensitivity analysis showed that a decrease in the cost of thrombolysis using streptokinase resulted in an ICER of £3329 to £29,093 favouring PCI.

For those patients who suffered from some morbidity event as a consequence of AMI or the subsequent treatment, the base-case model assumed that they would have a health status value of 0.5. As there was a lack of evidence about the effects of morbidity on health status for these patients, the sensitivity analysis assessed the effects of varying the health status value from 0.3 to 0.7 (*Table 21*). Reducing the health status to 0.3 changed the ICER to between £1590 and £5250 per unit change in health status in favour of PCI, whereas increasing the health status to 0.7 changed the ICER to between £2348 and £7754 per health status unit, making PCI still cost-effective. Similarly, with limited information on

TABLE 20 *Sensitivity analysis from using streptokinase instead of reteplase (treatment cost PCI/thrombolysis)*

	Cost (£)	Incremental cost (£)	Effectiveness (HS)	Incremental effectiveness (HS)	Cost-effectiveness (£/HS)	ICER (£/HS)
PCI hospital cost £5916, thrombolysis cost £3657 per case[a], rescue PCI £6187						
Thrombolysis	4556[b]		0.841		5417	
PCI	5916	1360	0.925	0.084	6396	16,207
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £6187						
Thrombolysis	5253[b]		0.841		6245	
PCI	5916	664	0.925	0.084	6396	7910
PCI hospital cost £6997, thrombolysis cost £3657 per case[a], rescue PCI £6187						
Thrombolysis	4556[b]		0.841		5417	
PCI	6997	2441	0.925	0.084	7564	29,093
PCI hospital cost £6997, thrombolysis cost £4737 per case[a], rescue PCI £6187						
Thrombolysis	5253[b]		0.841		6245	
PCI	6997	1745	0.925	0.084	7564	20,796
PCI hospital cost £5916, thrombolysis cost £3657 per case[a], rescue PCI £7268						
Thrombolysis	4941[b]		0.841		5874	
PCI	5916	975	0.925	0.084	6396	11,626
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £7268						
Thrombolysis	5795[b]		0.841		6702	
PCI	5916	121	0.925	0.084	6396	3329
PCI hospital cost £6997, thrombolysis cost £3657 per case[a], rescue PCI £7268						
Thrombolysis	5207[b]		0.841		5874	
PCI	6997	1790	0.925	0.084	7564	24,512
PCI hospital cost £6997, thrombolysis cost £4737 per case[a], rescue PCI £7268						
Thrombolysis	5795[b]		0.841		6702	
PCI	6997	1202	0.925	0.084	7564	16,215

[a] Represents average costs of thrombolysis treatment alone.
[b] Represents average costs for patients undergoing thrombolysis option, including a proportion undergoing angioplasty following failed thrombolysis.

TABLE 21 *Sensitivity analysis of morbidity and rescue PCI assumptions*

	Cost (£)	Incremental cost (£)	Effectiveness (HS)	Incremental effectiveness (HS)	Cost-effectiveness (£/HS)	ICER (£/HS)
(a) Changes to proportion of patients suffering from morbidity						
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £6526, health status coefficient = 0.3						
Thrombolysis	5390[b]		0.815		6615	
PCI	5916	525	0.915	0.100	6466	5250
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £6526, health status coefficient = 0.7						
Thrombolysis	5390[b]		0.8673		6216	
PCI	5916	525	0.9350	0.0677	6327	7754
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £7607, health status coefficient = 0.3						
Thrombolysis	5757[b]		0.815		7064	
PCI	5916	159	0.915	0.100	6466	1590
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £7607, health status coefficient = 0.7						
Thrombolysis	5390[b]		0.8673		6638	
PCI	5916	159	0.9350	0.0677	6327	2348
(b) Changes to proportion of patients undergoing rescue PCI following failed thrombolysis						
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £7607, probability of undergoing rescue PCI = 0.9						
Thrombolysis	5899[b]		0.8615		6848	
PCI	5916	17	0.9250	0.0635	6396	268
PCI hospital cost £5916, thrombolysis cost £4737 per case[a], rescue PCI £7607, probability of undergoing rescue PCI = 0.1						
Thrombolysis	4866[b]		0.713		6820	
PCI	5916	1050	0.925	0.212	6396	4964

[a] Represents average costs of thrombolysis treatment alone.
[b] Represents average costs for patients undergoing thrombolysis option, including a proportion undergoing angioplasty following failed thrombolysis.

the proportion of patients who received rescue PCI after failed thrombolysis it was decided to examine the effects of varying the proportion from 0.79 in the base case to 0.1 and 0.9 in the sensitivity analysis. Irrespective of the proportion of patients receiving rescue PCI after failed thrombolysis, PCI was the cost-effective option, with the ICER ranging from £268 to £4964 per health status unit.

Discussion of economic results

The results of the base case and sensitivity analyses show that PCI appears to be more cost-effective than thrombolysis for people with AMI. The base-case analysis showed that PCI provided additional health status at a higher cost per unit change in health status. Sensitivity analysis examining variations in net costs associated with changes in the length of stay on CCU and cardiology units, the cost of thrombolytic drug treatment, the health status associated with people suffering non-morbid conditions and the proportion of people receiving rescue PCI following failed thrombolysis showed that the ICER varied from £268 to £29,093 per unit change in health status.

The results of the economic evaluation should be appraised within the possible limitations of the analysis. First, the economic evaluation focuses on the short-term effects of the treatment options on people who have suffered an AMI. In being limited to the first 6 months, the evaluation does not include a measure of the length of survival or the long-term effects on health status or any other consequences or costs. Zijlstra and colleagues[93] examined the longer term consequences of treatment with PCI, finding some additional benefits in reductions in the need for future angioplasty and the opportunity to treat other lesions at the same time, but increased likelihood of finding lesions that require revascularisation. Despite these additional costs, it was felt by Zijlstra and colleagues[93] that the benefits of PCI were

strengthened. Second, the estimates of health status were simplistic, valuing death as 0, successful treatment as 1 and morbidity as ranging from 0.3 to 0.7. Although these values are crude estimates of changes in health status and do not include any patient preferences, the sensitivity analysis does include a reasonably wide range of values with limited effect on the incremental cost-effectiveness. In addition, the transition probabilities for mortality and morbidity, and as a consequence success, are assumed to be the same for immediate angioplasty and angioplasty where thrombolysis is contraindicated. These assumptions were made owing to a lack of evidence and are a limitation. Third, published cost data were of uncertain relevance and quality, originating from other countries and including charges rather than marginal costs, differing procedures and varying actuarial techniques for distributing indirect costs. As a consequence, defined marginal costs from the NHS statistics were used to simulate the likely costs within the UK. The costs originate from Southampton University Hospitals Trust (UK), whose mean costs are thought to be about 4% below the mean cost of all NHS trusts in 2002.

Chapter 6

Discussion

Factors relevant to the NHS

This review has suggested that the outcomes after heart attacks could be improved by immediate PCI at lower cost, provided the training and capacity of staff are sufficient, and that PCI would be cost-effective. Indeed, the current European guidelines (2003)[9] and US guidelines (1999)[111] both advocate primary PCI as the preferred treatment if performed by an experienced team in a timely fashion (Europe: <90 minutes from first medical contact to treatment; USA: <90 ± 30 minutes from admission to balloon inflation).

There are barriers to making PCI widely available for the immediate treatment of MI.[112] One difficulty is the availability of catheter laboratories. These were mainly in regional centres, where cardiac surgery is also carried out. Laboratories have now been established in district hospitals. While many of these do not or would not undertake PCI,[112] their increasing availability may help central teams in larger hospitals to do so. There is not yet sufficient capacity to undertake large numbers of additional procedures. The existing PCI facilities are mainly set up to carry out elective procedures, although some centres are performing emergency PCI on an ad hoc basis. PCI is a procedure done by cardiologists, of whom there is currently a shortage. Other staff, including other doctors, nurses and paramedics, can undertake thrombolysis. However, there are also shortages of trained catheter laboratory nurses, physiological measurement technicians and radiographers. A change of practice to PCI rather than thrombolysis would require a change of job plan for cardiologists and an expansion in numbers, over and above the increase already planned for the elective service. To provide a service to the whole community would require good ambulance services to transfer patients quickly to the specialist units. The ambulance services are being improved. This would add to the current demands on ambulance services to increase 999 response times and, in some areas, to increase provision of community thrombolysis by ambulance paramedics. Ambulance services are also gearing up to provide more community thrombolysis.

There are, however, opportunities to enable a change of practice to be introduced. There appears to be an enthusiasm for PCI among clinicians, and some are already undertaking this as an emergency. Coronary heart disease is one of the priority disease areas for healthcare providers and is supported by the NSF. Clinical networks are emerging that will enable a coordinated service to be provided within regions, with routine treatment provided in local hospitals and more invasive treatment at specialist centres. The ongoing accreditation of district general hospitals, including those without on-site cardiac surgery, for angiography and elective PCI will free resources in the specialist centres for emergency work. The work of a clinical network need not necessarily incur additional costs. For example, emergency PCI could reduce the number of elective angiograms and revascularisation procedures. It has been suggested that because PCI allows more rapid recovery, hospital stay may be shorter than after thrombolysis, resulting in beds being freed for other purposes. Phased introduction of PCI appears to be feasible provided it is done with the appropriate training of new staff and the savings in bed-days that have been suggested. An incrementalist approach starting with thrombolysis failure would be one option.

A final consideration for the NHS is the impact that a major policy change would have on outcomes in the population. The NSF for coronary heart disease, which does not advocate emergency PCI, has been widely accepted as the basis for good care of patients. For the first time a national audit scheme has been established (at the Royal College of Physicians) and is demonstrating improvements in the care of patients with MI.[18] The dilemma is whether the apparent benefits of emergency PCI in individual patients in trials can be achieved in the NHS. Ease of delivery and established infrastructure for prehospital thrombolysis may reduce the relative advantage of PCI in improving public health. This is an issue beyond the scope of this review, being a question of service delivery, but merits careful consideration by NHS policy makers.

Statement of principal findings

The main findings of the systematic review, other assessments and economic evaluation are discussed in this section.

Systematic review of immediate angioplasty versus hospital thrombolysis

Four previous systematic reviews of 11 RCTs, two updated RCTs and four new RCTs were included in the systematic review of clinical effectiveness of immediate angioplasty compared with hospital thrombolysis. The meta-analyses of the four previous systematic reviews showed statistically significant benefit for people receiving immediate angioplasty over hospital thrombolysis on outcomes of mortality (30% reduced risk, ARR 2%), reinfarction rates (50% reduced risk, ARR 4%), stroke rates (65% reduced risk, ARR 1.5%), CABG rates (30% reduced risk, ARR 4%) and recurrent ischaemia rates (50% reduced risk, ARR 8%). There were no statistically significant differences in the incidence of major bleeding and long-term outcomes of mortality and non-fatal infarction between the different interventions. These results are reflected in a Norwegian review,[39] which concluded that primary PCI is better than thrombolysis for patients with AMI admitted to an invasive centre, and that the combined outcome of death, reinfarction or stroke in the acute phase is nearly halved. One such outcome is avoided for every 16 patients treated with PCI. Results were still significantly in favour of PCI more than 1 year after the infarction. Similarly, a recent meta-analysis by Keeley and colleagues[85] found primary percutaneous transluminal coronary angioplasty (PTCA) to be significantly more effective than thrombolytic therapy for ST-segment elevation AMI on death, non-fatal reinfarction, stroke and a combined end-point of these outcomes. The effects remained at long-term follow-up (6–18 months), irrespective of thrombolytic agent used and whether or not patients were transferred for primary PTCA.

The six additional RCTs judged to be of adequate methodological quality were included in a new meta-analysis. As with the previous meta-analyses, this showed that compared with thrombolysis immediate angioplasty had statistically significant beneficial effect on in-hospital or 30-day mortality (ARR 3%, RRR 36%), longer term mortality (ARR 3%, RRR 38%), stroke (ARR 2%, RRR 64%), reinfarction (ARR 5%, RRR 58%), recurrent ischaemia (ARR 11%, RRR 59%), CABG (ARR 5%, RRR 36%) and the combined end-point of death or non-fatal reinfarction (ARR 5%, RRR 44%). There was no statistically significant difference in bleeding.

For every 1000 patients treated by immediate PCI rather than hospital thrombolysis, an additional 23 lives would be saved, 43 fewer would suffer reinfarction and 11 fewer strokes would occur.

The recently published DANAMI-2 RCT[112] also found that patients presenting with acute MI had a significantly better composite outcome of death, reinfarction or stroke at 30 days after primary angioplasty compared with thrombolysis. This benefit over on-site thrombolysis was maintained regardless of whether patients underwent PCI on-site at an invasive treatment centre or were transferred from a community hospital.

One issue not illuminated by the evidence is whether the relative advantage of angioplasty has been increased by the availability of stents. There may be two benefits: an immediate increase in safety and a reduced need for CABG, and a longer term benefit of a reduced need for revascularisation, as shown in the STRESS[114] and BENESTENT[115] studies in elective PCI.

The importance of time of presentation, up to 'over 4 hours', was assessed using ten RCTs in which the median times from presentation to treatment were 69 minutes for angioplasty and 22 minutes for thrombolysis. Delay in presentation was associated with older age, female gender, diabetes and increased heart rate. Despite the longer time to treatment, the benefits of angioplasty outweighed those of thrombolysis when assessing death, reinfarction and stroke, at all intervals between onset of symptoms and presentation.

Systematic review of immediate angioplasty versus community thrombolysis

One reasonably good quality RCT compared immediate angioplasty with community thrombolysis, with both services delivered to a high specification and quality. There was no statistically significant difference between immediate angioplasty and community thrombolysis on a composite measure of death, non-fatal reinfarction and non-fatal disabling stroke at 30 days (6% versus 8%, respectively). It is likely that this is due to a combination of the use of a thrombolytic that had a long pain-to-needle time and that 26% of patients receiving thrombolysis had rescue angioplasty after failure of thrombolysis.

Non-systematic evaluation of rescue angioplasty after failed thrombolysis

Three observational studies were selected to assess rescue PCI. These studies either showed limited difference when comparing rescue PCI with other interventions on outcomes of mortality, reinfarction or stroke, or reported outcomes for rescue PCI as part of another intervention limiting any assessment.

Non-systematic review of volume effects

Although a good quality systematic review suggested no compelling evidence to concentrate hospital services, other selected studies assessing the effects of the volume of primary angioplasty procedures performed by hospitals and operators showed that increased volume resulted in lower mortality. Included studies were quasi-experimental or observational, with limited assessment of potential confounders, such as differences in patient case-mix and provision of care. However, in practice, any service provided in England would be based on units considered high volume as defined in these studies.

Non-systematic review of patient selection effects

No studies were found assessing the effects of patient characteristics on the difference in effect between PCI and thrombolysis. Studies assessing the effects of patient characteristics on the outcomes following PCI showed that women have poorer outcomes than men and people with diabetes have shorter survival than non-diabetics. The effects of age were less clear, with different studies showing either no difference with age or older people having poorer outcomes.

Non-systematic review of timelag to treatment

The effect of timelag to treatment on short-term mortality following PCI or thrombolysis was assessed in two studies, both of which were meta-regression analyses of RCTs included in systematic reviews. It was reported that a relative delay of 50 minutes[83] or 62 minutes[84] in performing PCI compared with thrombolysis would produce a worse chance of survival. However, both studies were limited by ecological bias and the potential for confounding by factors such as the quality of service. Other studies have suggested that PCI can be delayed by up to 6 hours without a detrimental effect on outcomes, whereas thrombolysis cannot.

Economic evaluation

The economic evaluation showed that PCI appears to be cost-effective compared with thrombolysis for people with AMI, with PCI providing additional benefits in health status at a higher cost. Sensitivity analysis showed that the relationship was consistent when taking account of changes in drug costs and differences in health status.

The economic assessment used data from high-quality evidence of clinical effectiveness of PCI versus hospital thrombolysis. Cost data from UK sources were used, but will not be the same in every cardiology department. Different hospitals can apply their own costs, or more often, estimates of these, since few departments currently offer a PCI service. The analysis in the economics section of this review takes a conservative cost-effectiveness approach and does not consider the initial capital and non-recurring costs of setting up services from scratch. Some cardiology departments would need an extra catheterisation room (since otherwise elective angiography or PCI may repeatedly be postponed in order to deal with emergencies), which would have a significant capital cost for room, imaging equipment, and so on.

If a 24-hour service were to be provided, there would be staffing implications. To perform PCI requires more experienced staff than thrombolysis. At the very least, there would need to be a 24-hour specialist registrar rota with sufficient time for PCI. Cardiology units may not have specialist registrars in cardiology, but may be covered out of hours by general medical registrars. The time cost of PCI may mean that double cover is required in some units. Again, each unit would have to review its workload, consider the time costs based on expected number of emergency PCIs, and estimate staffing and other implications. Those providing 24-hour services would need to consider whether the performance would vary by time of day. The experienced group from Zwolle[116] found that the mortality among patients admitted between 19.00 and 08.00 hours was 4.2%, compared with 1.9% in those admitted between 08.00 hours and 18.00 hours. Since the difference in mortality between hospital thrombolysis and immediate PCI is only 2.7%, this study could be interpreted as showing that the difference may fall to 0.4% for those admitted out of normal hours. Further research into the reasons is needed; the Zwolle group identified several possible reasons. Each hospital providing a 24-hour service should audit its results by time of day.

Similarly, each strategic health authority, in liaison with its PCTs and cardiac networks, would have to assess the options, which include:

- no provision of immediate PCI: the 'do nothing' option
- provision in DGHs by the DGH team: probably unrealistic in most DGHs for staffing reasons, although some are piloting such a service (Murray G: personal communication)
- transferring patients to a tertiary referral centre for immediate PCI
- creating a mobile intervention team.

Further information is needed before the economics of PCI after thrombolysis (i.e. facilitated PCI rather than PCI after failure of thrombolysis) and research are underway. Studies looking at medium-term (2–5 years) outcomes after both forms of treatment would also be useful.

Strengths and limitations of the review

This review has certain strengths, including the following:

- It is independent of vested interest.
- The systematic review applies consistent methods of critical appraisal and presentation.
- The systematic review was guided by the principles for undertaking a systematic review. Before undertaking the systematic review, the methods of the review were set out in a research protocol (Appendix 1). The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods used to undertake the different stages of the review. All sections of the review that did not adhere to a systematic approach are clearly identified.
- An advisory group informed the review through peer review.

In contrast, there were certain limitations placed upon the review:

- The clinical evidence came from outside the UK, mainly from the USA.
- There is little evidence comparing prehospital thrombolysis with angioplasty; since the benefits of thrombolysis are greater when given earlier, this could affect the relative cost-effectiveness.
- Observational studies, sought to provide information on results in 'real-life' routine care, were from outside the UK with limited information on confounding variables.
- The costs used for the economic evaluation were based on available published information and data from a local NHS trust, and will not apply to all hospitals. Costs for PCI were extrapolated from elective angioplasty services, and one would expect less efficient throughput with unplanned procedures, and hence perhaps higher unit costs. The timescale and resources did not permit a survey of cardiology units.
- The cost-effectiveness analysis assumes a steady state when immediate angioplasty is available in the UK as in the USA, and does not allow for start-up costs.

Other issues

One of the key issues is the low use of prehospital thrombolysis. If an increase in this procedure, by GPs or ambulance staff, were to improve outcomes, this would affect the marginal benefits of immediate PCI. However, any such expansion may be sought more in areas (which may be not only rural) where time to specialist care was greater, whereas in cities the pain-to-care time may give angioplasty the advantage.

Research needs

If it were to be decided in principle that British hospitals ought to provide an immediate angioplasty service, then a detailed survey of what would be required to provide that service would be needed, before implementation and running costs could be accurately predicted through modelling studies. Some units already perform immediate PCI for some patients.

Analysis of the relative costs and benefits of combination treatment (early thrombolysis followed by PCI in most or selected patients) will need to await results of clinical trials.

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Responsibility for the final report rests with the Southampton Health Technology Assessments Centre, Wessex Institute for Health Research and Development, University of Southampton, and our panel of advisors are not responsible for any flaws.

Contributions of authors

N Waugh (Professor of Public Health) devised the protocol. P Royle (Senior Researcher) carries out the searches. D Hartwell (Research Fellow), E Loveman (Senior Researcher), J Colquitt (Senior Researcher) and H Brodin (Senior Research Fellow) devised the inclusion criteria. D Hartwell, E Loveman, J Colquitt, H Brodon and N Waugh carried out the data extraction. H Bodin, L Vale (Research Fellow), L MacKenzie (Research Fellow) and A Clegg (Senior Research Fellow) were responsible for the economic evaluation. D Hartwell, E Loveman, J Colquitt, N Waugh, A Clegg, P Davidson (Specialist Registrar in Public Health), H Brodin, P Royle and L Vale all contributed to drafting the report.

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Appendix 1

Methods from research protocol

The report will include a systematic review of evidence of clinical effectiveness, and an economic analysis of cost-effectiveness based on the clinical review and on cost data from published sources and *de novo* data collection.

Search strategy

Searches for clinical efficacy will start with the Cochrane Library. Preliminary searches show that there is a relevant Cochrane review, and searches will be restricted to the years since the searches for that were done. The bibliographic databases used will be MEDLINE and Cochrane only. The register of projects held by INAHTA will be checked, and member agencies asked about new projects.

Searches for economic studies will use the standard strategies and sources, such as MEDLINE and HEED.

Inclusion and exclusion criteria

For clinical effectiveness, a comprehensive review of RCTs will be used for efficacy, and a selection of observational studies such as case series or audit data used for effectiveness safety in routine practice. RCTs of thrombolysis will be used to assess the relative value of prehospital and hospital thrombolysis. Observational studies will be used to assess the representativeness of patients in the RCTs, and to determine whether different groups have different capacity to benefit. They will also be used to assess the implications of wider diffusion of the technology away from major centres.

Data extraction strategy

The quality of the existing systematic reviews will be assessed. Their inclusions will be quality assessed to ensure that the included studies would be deemed satisfactory using CRD criteria. Data on outcomes will be summarised in a table from previous reviews and new RCTs.

Quality assessment strategy

The checklists in CRD4 will be used, for RCTs, CCTs and economic studies.

Methods of analysis/synthesis

Assuming the data are suitable, a precise estimate of absolute clinical benefit will be derived from the systematic reviews and new RCTs.

Consideration will be given to the effect of the growing use of stents.

Methods for estimating quality of life, costs and cost-effectiveness and/or cost/QALY

Quality of life data will be sought from published studies, if given.

Costs will be sought from published studies, and from our costing collaboration with the Southampton University Hospitals Trust.

The cost-effectiveness model will include timing issues.

INAHTA, International Network of Agencies for Health Technology Assessment; HEED, Health Economic Evaluations Database; CCT, controlled clinical trial.

Appendix 2

Sources of information, including databases searched and search terms used

The databases were searched for published studies, and recently completed and ongoing research. All searches were limited to English language only.

Search strategies for clinical effectiveness

Searches for recent RCTs

Cochrane Library – all sections (2002, Issue 3)
#1 (((ANGIOPLAST* or PCI) or PCI) OR (PERCUTANEOUS NEXT (CORONARY next INTERVENTION)))#2 (MYOCARDIAL next INFARCTION)#3 (#1 and #2)#4 FIBRINOLYTIC-AGENTS*:ME#5 THROMBOLYTIC-THERAPY*:ME#6 (FIBRINOL* or THROMBOLY*)#7 ((#4 or #5) or #6)#8 (#3 and #7)

National Research Register (2002, Issue 3)
Same strategy as for the Cochrane Library.

MEDLINE (WebSPIRS) (1996 to July 2002)
((angioplast* or PCI or pci or percutaneous coronary intervention) and ((explode 'Myocardial-Infarction' / all subheadings in MIME,MJME) or (myocardial infarction)) and ((explode 'Fibrinolytic-Agents' / all subheadings in MIME,MJME) or (explode 'Thrombolytic-Therapy' / all subheadings in MIME,MJME) or (fibrinol*) or (thromboly*))) and (((pt=randomized-controlled-trial) and (English in la)) or (PT=META-ANALYSIS))

Searches for observational studies for data on real-life effectiveness or outcomes

MEDLINE (WebSPIRS) (1996 to July 2002)
(((((angioplast* or PCI or pci or percutaneous coronary intervention) and (explode 'Myocardial-Infarction' / all subheadings in MIME,MJME)) and (acute near (MI or myocardial infarction))) and ((explode 'Cohort-Studies' / all subheadings in MIME,MJME) or (explode 'Outcome-Assessment-Health-Care' / all subheadings in MIME,MJME))) and (LA=ENGLISH) and (PY=1997-2002)) not ((((((angioplast* or PCI or pci or percutaneous coronary intervention) and (explode 'Myocardial-Infarction' / all subheadings in MIME,MJME)) and (acute near (MI or myocardial infarction))) and ((explode 'Cohort-Studies' / all subheadings in MIME,MJME) or (explode 'Outcome-Assessment-Health-Care' / all subheadings in MIME,MJME))) and (LA=ENGLISH) and (PY=1997-2002)) and (PT=RANDOMIZED-CONTROLLED-TRIAL))

Search strategies for economic evaluations

MEDLINE (WebSPIRS) (1980 to July 2002)
((((angioplast* or PCI or pci or percutaneous coronary intervention) and ((explode 'Economics-' / all subheadings in MIME,MJME) or ((explode 'Quality-Adjusted-Life-Years' / all subheadings in MIME,MJME) or (explode 'Quality-of-Life' / all subheadings in MIME,MJME)) or (cost* or economic*) or (wellbeing or well-being) or (hrqol or qol or hr-qol or euroqol or euro-qol or health utilit*) or ((quality near2 life) or QALY*))) and (English in la)) and (LA=ENGLISH) and (PY=1997-2002)) and ((explode 'Myocardial-Infarction' / all subheadings in MIME,MJME) or (myocardial infarction and (PY=1997-2002)))

EMBASE (WebSPIRS) (1997 to July 2002)
(((angioplast* or PCI or pci or percutaneous coronary intervention) and ((explode 'quality-of-life' / all subheadings) or ('quality-adjusted-life-year' / all subheadings) or (explode 'health-economics' / all subheadings) or (explode 'economics-' / all subheadings) or (cost* or economic*) or (health utilit* or hrqol or qol or hr-qol or euroqol or euro-qol) or ((quality near3 life) or qaly* or wellbeing or well-being))) and (English in la)) and ((explode 'heart-infarction' / all subheadings) or (myocardial infarction))

NHS EED (web version) (searched on 18 July 2002)
Angioplasty$ and myocardial infarction
(All records added since 1997 were scanned.)

EconLit (1997 to July 2002)
(angioplast* or PCI or pci or percutaneous coronary intervention) and (PY=1997-2002)

Additional searching

Bibliographies: all references of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

Websites of the following organisations were searched:

- BCIS, audit data: http://www.bcis.org.uk/audit/index.html
- European Society of Cardiology: http://www.escardio.org/
- American Heart Association: http://www.americanheart.org/
- American College of Cardiology: http://www.acc.org/

Experts were contacted for advice and peer review, and to identify additional published and unpublished references and any currently ongoing studies.

Appendix 3

Flowcharts of included studies

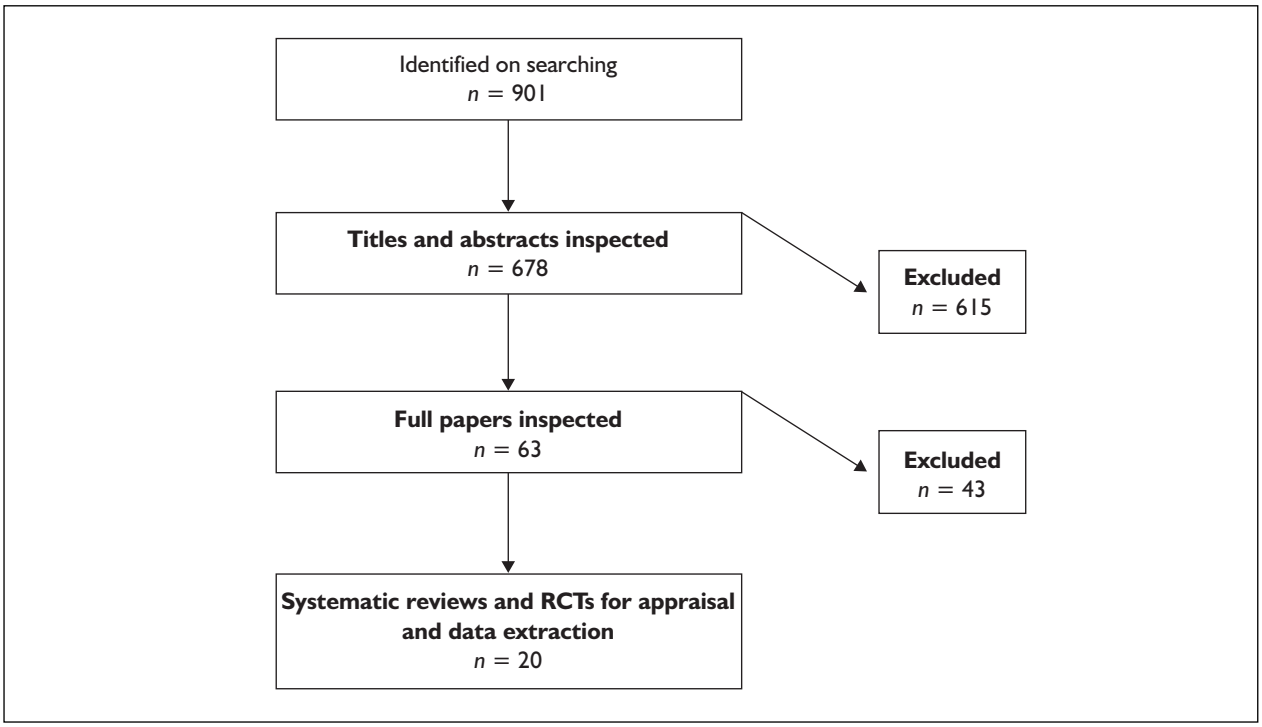

FIGURE 11 *Flowchart of identification of studies (RCTs and systematic reviews) for the clinical effectiveness systematic review. (The number of references identified on initial searching includes duplicates from searches across multiple databases as well as references that were obviously inappropriate.)*

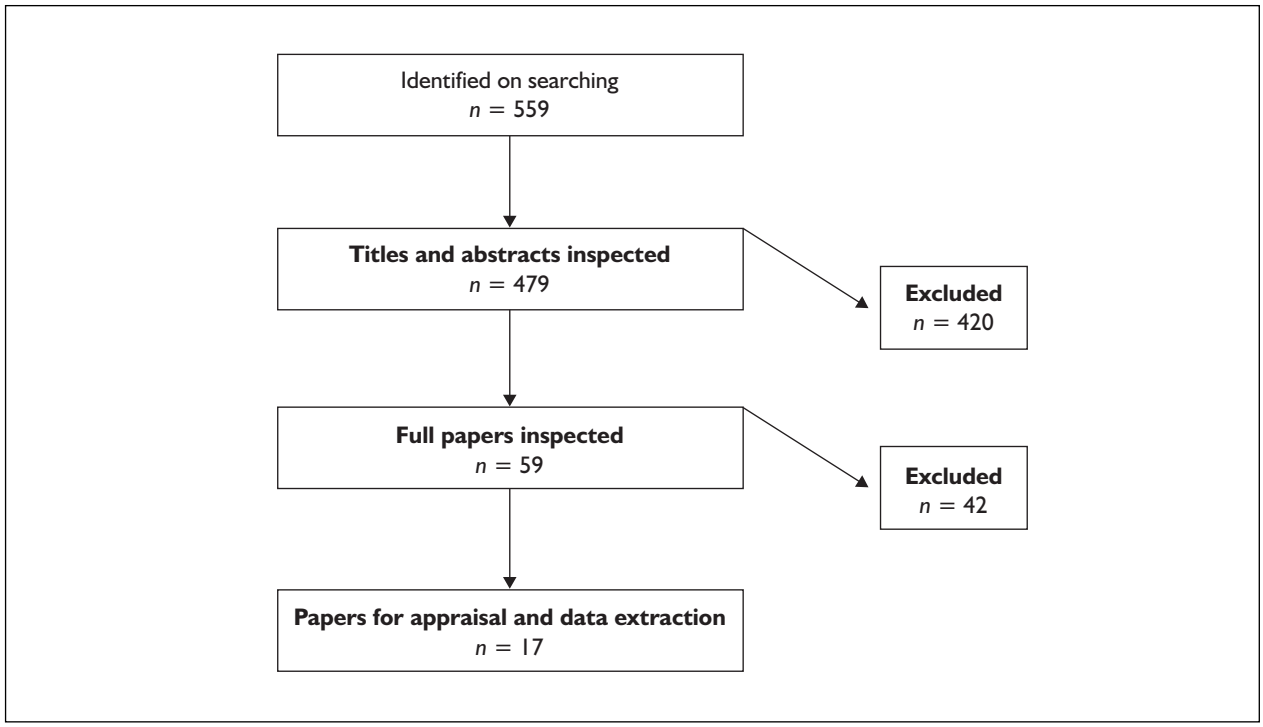

FIGURE 12 *Flowchart of identification of studies for the cost-effectiveness review. (The number of references identified on initial searching includes duplicates from searches across multiple databases as well as references that were obviously inappropriate.)*

Appendix 4

Quality assessment criteria

TABLE 22 *Quality criteria for RCTs: CRD Report 4*

1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	NA
7. Was the patient blinded?	NA
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention-to-treat analysis?	
10. Were withdrawals and dropouts completely described?	

NA, not applicable.

Appendix 5

Data extraction

Data extraction for reviews

Study detail

Reference and design	Intervention
Cucherat *et al.*, 2002[21] *Study design:* Cochrane review and meta-analysis *No. of trials:* 10 *No. of patients:* Total: 2573	*Treatment interventions in study selection:* primary balloon angioplasty without stenting versus intravenous thrombolytic therapy Two studies using intracoronary thrombolysis and not intravenous thrombolysis were excluded. Four trials used streptokinase Three trials used t-PA over 3–4 hours Three trials used accelerated t-PA, an optimal thrombolysis therapy (accelerated alteplase infusion)

Results

Patients
Delay from onset of symptoms of 6 or 12 hours. Average age 55–66 years. Most (70–83%) were male

Mortality	
Streptokinase	RR 0.69 (95% CI 0.35 to 1.39)
t-PA	RR 0.61 (95% CI 0.28 to 1.31)
Accelerated t-PA	RR 0.71 (95% CI 0.47 to 1.07)
Total	RR 0.68 (95% CI 0.50 to 0.95), χ^2 9.40 (df = 8), Z = 2.29 (total)
Total	ARR 2.1%
Reinfarction	
Streptokinase	RR 0.11 (95% CI 0.03 to 0.39)
t-PA	RR 0.39 (95% CI 0.14 to 1.09)
Accelerated t-PA	RR 0.72 (95% CI 0.45 to 1.14)
Total	RR 0.48 (95% CI 0.33, 0.70), χ^2 8.23 (df = 4), Z = 3.75 (total)
Total	ARR 3.8%
Stroke	
Streptokinase	RR 0.41 (95% CI 0.08 to 2.09)
t-PA	RR 0.07 (95% CI 0.00 to 1.19)
Accelerated t-PA	RR 0.45 (95% CI 0.18 to 1.13)
Total	RR 0.34 (95% CI 0.16 to 0.72), χ^2 2.65 (df = 4), Z = 2.83 (total)
Total	ARR 1.7%
Combined end-point (varied between studies)	
Streptokinase	RR 0.30 (95% CI 0.17 to 0.53)
t-PA	RR 0.51 (95% CI 0.27 to 0.97)
Accelerated t-PA	RR 0.70 (95% CI 0.51 to 0.97)
Total	RR 0.54 (95% CI 0.42 to 0.70), χ^2 9.27 (df = 5), Z = 4.67 (total) (p = 0.10)
Total	ARR 6.5%
Recurrent ischaemia	
Streptokinase	RR 0.80 (95% CI 0.23 to 2.81)
t-PA	RR 0.38 (95% CI 0.25 to 0.57)
Accelerated t-PA	RR 0.53 (95% CI 0.34 to 0.81)
Total	RR 0.46 (95% CI 0.34 to 0.61), χ^2 5.36 (df = 4), Z = 5.41 (total)
Total	ARR 8.4%

continued

Results (cont'd)

Major bleeding	
Streptokinase	RR 0.87 (95% CI 0.35 to 2.20)
t-PA	RR 1.23 (95% CI 0.54 to 2.78)
Accelerated t-PA	RR 1.38 (95% CI 0.64 to 2.98)
Total	RR 1.18 (95% CI 0.73 to 1.90), χ^2 0.59 (df = 2), Z = 0.67 (total)
Total	ARR 0.5%
CABG	
Streptokinase	RR 0.58 (95% CI 0.24 to 1.37)
t-PA	RR 0.76 (95% CI 0.45 to 1.27)
Accelerated t-PA	No studies
Total	RR 0.70 (95% CI 0.45 to 1.09), χ^2 2.71 (df = 3), Z = 1.56 (total)
Total	ARR 3.8%
Long-term mortality (only three studies: prevents any interpretation of the result)	
Streptokinase	RR 3.33 (95% CI 0.14 to 79.64)
t-PA	RR 1.07 (95% CI 0.32 to 3.62)[a]
Accelerated t-PA	No studies
Total	RR 1.27 (95% CI 0.42 to 3.89),[a] χ^2 0.65 (df = 2), Z = 0.42 (total)
Total	ARR 1.0%

[a] Values for DeWood (1989) and Gibbons (1993) incorrect in this meta-analysis.
ARR calculated by reviewer.

Quality assessment for reviews using the CRD DARE criteria

Quality item	Yes/No/Uncertain	Methodological comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes	
2. Is there evidence of a substantial effort to search for all relevant research?	Yes	MEDLINE and EMBASE only databases searched. Searched reference lists and abstracts. May have missed some trials
3. Is the validity of included studies adequately assessed?	Yes	
4. Is sufficient detail of the individual studies presented?	Yes	
5. Are the primary studies summarised appropriately?	Yes	

Study detail

Reference and design	Intervention
Michels and Yusuf, 1995[22] *Study design:* meta-analysis *No. of trials:* 7 trials of primary PCTA vs thrombolysis 16 trials of rescue PCI (various subcategories) *No. of patients:* Total: 8496 (both groups 1145 (group 1)	*Treatment interventions in study selection:* 7 RCTs of PCI vs thrombolysis: 2 PCI vs i.v. streptokinase within 6 hours 1 PCI vs intracoronary streptokinase within 12 hours 1 PCI vs tPA within 6 hours 1 PCI vs tPA within 12 hours 1 PCI vs tPA (no detail) 1 PCI vs thrombolysis (no detail) 16 RCTs of rescue PCI (subgroups)

Results

1. Primary PCI vs thrombolytic therapy:
In-hospital or 6-week mortality: OR 0.56 (95% CI 0.33 to 0.94), χ^2 7.3, $p = 0.29$; ARR 2.7%
Mortality and non-fatal MI at 6 weeks combined: OR 0.53 (95% CI 0.35 to 0.80); ARR 4.8%
Mortality at 1 year: OR 0.91 (95% CI 0.42 to 2.00); ARR 0.4%
Mortality or non-fatal MI at 1 year: OR 0.88 (95% CI 0.45 to 1.72); ARR 0.9%
Mortality between weeks 6 and 52 among 6-week survivors: OR 1.00 (95% CI 0.14 to 7.16)

2. PCI after thrombolytic therapy
2a. Immediate vs no PCI: χ^2 5.2, $p = 0.27$
In-hospital or 6-week mortality: OR 1.09 (95% CI 0.73 to 1.61)
Mortality and non-fatal MI at 6 weeks combined: OR 0.89 (95% CI 0.65 to 1.21)
Mortality at 1 year: OR 1.05 (95% CI 0.75 to 1.48)
Mortality or non-fatal MI at 1 year: OR 0.90 (95% CI 0.68 to 1.18)
Mortality between weeks 6 and 52 among 6-week survivors: OR 1.12 (95% CI 0.58 to 2.17)

2b. Early vs no PCI: χ^2 4.8, $p = 0.44$
In-hospital or 6-week mortality: OR 1.08 (95% CI 0.84 to 1.39)
Mortality and non-fatal MI at 6 weeks combined: OR 1.06 (95% CI 0.89 to 1.25)
Mortality at 1 year: OR 0.93 (95% CI 0.74, 1.17)
Mortality or non-fatal MI at 1 year: OR 0.99 (95% CI 0.84 to 1.16)
Mortality between weeks 6 and 52 among 6-week survivors: OR 0.61 (95% CI 0.42 to 0.88)

2c. Delayed vs no PCI: χ^2 1.1, $p = 0.3$
In-hospital or 6-week mortality: OR 1.33 (95% CI 0.49 to 3.63)
Mortality and non-fatal MI at 6 weeks combined: OR 1.78 (95% CI 0.99 to 3.19)
Mortality at 1 year: OR 6.79 (95% CI 1.32 to 35.03)
Mortality or non-fatal MI at 1 year: OR 2.24 (95% CI 1.19 to 4.19)
Mortality between weeks 6 and 52 among 6-week survivors: OR 8.35 (95% CI 0.52 to 135)

2d. Immediate vs delayed PCI: χ^2 0.6, $p = 0.74$
In-hospital or 6-week mortality: OR 1.46 (95% CI 0.71 to 2.97)
Mortality and non-fatal MI at 6 weeks combined: OR 1.61 (95% CI 0.91 to 2.86)
Mortality at 1 year: OR 1.31 (95% CI 0.68 to 2.51)
Mortality or non-fatal MI at 1 year: OR 1.38 (95% CI 0.81 to 2.34)
Mortality between weeks 6 and 52 among 6-week survivors: OR 0.81 (95% CI 0.22 to 3.02)

2e. Rescue vs no PCI: χ^2 1.0, $p = 0.33$
In-hospital or 6-week mortality: OR 0.38 (95% CI 0.13 to 1.06)
Mortality and non-fatal MI at 6 weeks combined: OR 0.44 (95% CI 0.16 to 1.21)
Mortality at 1 year: OR 0.17 (95% CI 0.02 to 1.15)
Mortality or non-fatal MI at 1 year: OR 0.47 (95% CI 0.09 to 2.58)
Mortality between weeks 6 and 52 among 6-week survivors: NA

Summary PCI vs no PCI (2a+2b+2c+2e):
In-hospital or 6-week mortality: OR 1.07 (95% CI 0.86 to 1.34)
Mortality and non-fatal MI at 6 weeks combined: OR 1.06 (95% CI 0.91 to 1.22)
Mortality at 1 year: OR 1.00 (95% CI 0.82 to 1.21)
Mortality or non-fatal MI at 1 year: OR 0.94 (95% CI 0.82 to 1.08)
Mortality between weeks 6 and 52 among 6-week survivors: OR 0.71 (95% CI 0.51 to 0.99)

Summary of more aggressive vs less aggressive interventions (2a+2b+2c+2d+2e):
In-hospital or 6-week mortality: OR 1.10 (95% CI 0.89 to 1.35)
Mortality and non-fatal MI at 6 weeks combined: OR 1.07 (95% CI 0.92 to 1.24)
Mortality at 1 year: OR 1.01 (95% CI 0.84 to 1.23)
Mortality or non-fatal MI at 1 year: OR 0.95 (95% CI 0.83 to 1.10)
Mortality between weeks 6 and 52 among 6-week survivors: OR 0.74 (95% CI 0.53 to 1.02)

Routine PCI vs no PCI: χ^2 12.3, $p = 0.14$
In-hospital or 6-week mortality: OR 1.03 (95% CI 0.80 to 1.33)
Mortality and non-fatal MI at 6 weeks combined: OR 1.03 (95% CI 0.85 to 1.24)
Mortality at 1 year: OR 0.93 (95% CI 0.74 to 1.18)
Mortality or non-fatal MI at 1 year: OR 0.94 (95% CI 0.79 to 1.11)
Mortality between weeks 6 and 52 among 6 week survivors: OR 0.58 (95% CI 0.39 to 0.87)

continued

Results (cont'd)

Elective PCI vs no PCI: χ^2 1.6, $p = 0.82$ In-hospital or 6-week mortality: OR 1.22 (95% CI 0.85 to 1.77) Mortality and non-fatal MI at 6 weeks combined: OR 1.11 (95% CI 0.88 to 1.42) Mortality at 1 year: OR 1.16 (95% CI 0.81 to 1.66) Mortality or non-fatal MI at 1 year: OR 1.07 (95% CI 0.84 to 1.36) Mortality between weeks 6 and 52 among 6-week survivors: OR 1.12 (95% CI 0.61 to 2.06)
ARR calculated by reviewer.

Quality assessment for reviews using the CRD DARE criteria

Quality item	Yes/No/Uncertain	Methodological comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes	Study design, intervention, outcomes defined, no specific participant characteristics defined.
2. Is there evidence of a substantial effort to search for all relevant research?	Yes	MEDLINE and Index Medicus only databases searched, but extensive hand searching
3. Is the validity of included studies adequately assessed?	No	
4. Is sufficient detail of the individual studies presented?	No	No details of patient numbers or patient characteristics; interventions not always clearly defined
5. Are the primary studies summarised appropriately?	Yes	Test of heterogeneity and Mantel–Hansel technique
DARE, Database of Abstracts of Reviews of Effectiveness.		

Study detail

Reference and design	Intervention
Weaver *et al.*, 1997[23] Zijlstra *et al.*, 2002[24] *Study design:* meta-analysis: Weaver comparing PCI with thrombolysis, Zijlstra comparing the same but also by time of presentation by an individual patient data meta-analysis *No. of trials:* Weaver: $n = 10$ Zijlstra: $n = 10$ *No. of patients:* Weaver: Total: 2606 PCI: 1290 Thrombolysis: 1316 Zijlstra: Total: 2635 PCI: 1302 Thrombolysis: 1333	*Treatment interventions in study selection:* Weaver: 4 trials PCI vs streptokinase 1 hour 3 trials PCI vs t-Pa 3–4 hour 3 trials PCI vs t-Pa 90 minutes Zijlstra: 5 trials PCI vs streptokinase 1 hour 3 trials PCI vs t-Pa 90 minutes 2 trials PCI vs t-PA 3–4 hours (including one 'duteplase') Trials included in the two reviews are the same, but used for different analysis, except: Zijlstra review does not include one study for which they were unable to collect individual patient data (DeWood, 1990).[49] Zijlstra included one additional trial identified subsequent to Weaver meta-analysis (Akhras, 1997)[38] *Eligibility criteria:* details are noted in Table 1 of the Weaver review. Eligible patients required randomisation within 12 hours of onset of ischaemic symptoms, and no major contraindications to the use of thrombolytic drug therapy. Limited discussion of generalisability, only of the use of 'high-risk' or 'low-risk' patients

Results (all from Weaver[23])[a]

	30-day mortality, *n* (%)		
Trial name	**PCI**	**Thrombolysis**	**Event rate (95% CI)**
Ziljstra[35]	3/152 (2.0)	11/149 (7.4)	
Ribeiro[28]	3/50 (6.0)	1/50 (2.0)	
Grinfeld[31]	5/54 (9.3)	6/58 (10.3)	
Ziljstra[29]	1/45 (2.2)	0/50	
Subtotal streptokinase	12/301 (4.0)	18/307 (5.9)	OR 0.66 (0.29 to 1.50), $p = 0.38$, ARR 1.9 (–2.7 to 4.1), NNT 52 (24 to ?)
DeWood[32]	3/46 (6.5)	2/44 (4.5)	
Grines[27]	5/195 (2.6)	13/200 (6.5)	
Gibbons[25]	2/47 (4.3)	2/56 (3.6)	
Subtotal t-PA	10/288 (3.5)	17/300 (5.7)	OR 0.60 (0.24 to 1.41), $p = 0.28$, ARR 2.2 (–2.2 to 4.3), NNT 45 (23 to ?)
Ribichini[40]	0/41	1/42 (2.4)	
Garcia[41]	3/95 (3.2)	10/94 (10.6)	
GUSTO[26]	32/565 (5.7)	40/573 (7.0)	
Subtotal accelerated t-PA	35/701 (5.0)	51/709 (7.2)	OR 0.68 (0.42 to 1.08), $p = 0.10$, ARR 2.2 (–0.5 to 4.0), NNT 46 (25 to ?)
Total	57/1290 (4.4)	86/1316 (6.5)	Favouring PCI: OR 0.66 (0.46 to 0.94), $p = 0.02$, ARR 2.1 (0.4 to 3.4), NNT 47 (29 to 250)
Tests for homogeneity: Streptokinase trials $p = 0.08$, t-PA trials $p = 0.33$, accelerated t-PA trials $p = 0.21$, thrombolytic regimen, $p = 0.96$, overall $p = 0.24$.			
	Mortality and non-fatal MI		
Trial name	**PCI**	**Thrombolysis**	**Event rate (95% CI)**
Ziljstra[35]	5/152 (3.3)	23/149 (15.4)	
Ribeiro[28]	5/50 (10.0)	2/50 (4.0)	
Grinfeld[31]	6/54 (11.1)	7/58 (12.1)	
Ziljstra[29]	1/45 (2.2)	8/50 (16.0)	
Subtotal streptokinase	17/301 (5.6)	40/307 (13.0)	OR 0.40 (0.21 to 0.75), $p = 0.003$, ARR 7.4 (2.9 to 10.0), NNT 14 (10 to 34)
DeWood[32]	3/46 (6.5)	2/44 (4.5)	
Grines[27]	10/195 (5.1)	24/200 (12.0)	
Gibbons[25]	3/47 (6.4)	5/56 (8.9)	
Subtotal t-PA	16/288 (5.6)	31/300 (10.3)	OR 0.51 (0.26 to 0.99), $p = 0.05$, ARR 4.8 (0.1 to 7.4), NNT 21 (14 to 1000)
Ribichini[40]	0/41	1/42 (2.4)	
Garcia[41]	7/95 (7.4)	14/94 (14.9)	
GUSTO[26]	54/565 (9.6)	70/573 (12.2)	
Subtotal accelerated t-PA	61/701 (8.7)	85/709 (12.0)	OR 0.70 (0.48 to 1.08), $p = 0.05$, ARR 3.3 (0.0 to 5.9), NNT 30 (17 to ?)
Total	94/1290 (7.2)	156/1316 (11.9)	In favour of PCI: OR 0.58 (0.44 to 0.76), $p < 0.001$, ARR 4.6 (2.6 to 6.3), NNT 22 (16 to 38)
Tests for homogeneity: streptokinase trials $p = 0.008$, t-PA trials $p = 0.35$, accelerated t-PA trials $p = 0.59$, thrombolytic regimen $p = 0.25$, overall $p = 0.04$.			
	Non-fatal reinfarction		
Trial name	**PCI**	**Thrombolysis**	**Event rate (95% CI)**
Combined only	2.9%	5.3%	OR 0.53 (0.34 to 0.8), ARR 2.4 (1.0 to 3.4), NNT 41 (29 to 100)

continued

Results (all from Weaver[23])[a] (cont'd)

Trial name	Total stroke: PCI	Total stroke: Thrombolysis	Event rate (95% CI)
Ziljstra[35]	1/152 (0.7)	3/149 (2.0)	0.32, $p = 0.77$
Ribeiro[28]	0/50	0/50	Undefined
Grinfeld[31]	1/54 (1.9)	0/58	Undefined
Ziljstra[29]	1/45 (2.2)	2/50 (4.0)	0.32, $p = 0.77$
Subtotal streptokinase	3/301 (1.0)	5/307 (1.6)	0.62 (0.10 to 3.22), $p = 0.77$
DeWood[32]	0/46	0/44	Undefined
Grines[27]	0/195	7/200 (3.5)	0.0
Gibbons[25]	0/47	0/56	Undefined
Subtotal t-PA	0/288	7/300 (2.3)	OR 0.00 (0.00 to 0.54) $p = 0.02$
Ribichini[40]	0/41	0/42	Undefined
Garcia[41]	0/95	3/94	0.0
GUSTO[26]	6/565 (1.1)	11/573 (1.9)	0.55 (0.16 to 1.63), $p = 0.12$
Subtotal accelerated t-PA	6/701 (0.86)	14/709 (2.0)	0.43 (0.13 to 1.20), $p = 0.12$
Total	9/1290 (0.7)[a]	26/1316 (2.0)[a]	OR 0.35 (0.14 to 0.77), $p = 0.007$ ARR 1.3% (calculated by reviewer)

Tests for homogeneity: overall, $p = 0.15$.
[a] Percentages are pooled results and ORs calculated by exact method using all trials.

Trial name	At least one major bleeding incident: PCI	At least one major bleeding incident: Thrombolysis	Event rate (95% CI)
Total only	8.8%	8.4%	OR 1.06 (0.79 to 1.41), $p = 0.75$ ARR 0.3% (calculated by reviewer)

[a] Data from Zijlstra not documented as reports data at time of presentation only.

Quality assessment for reviews using the CRD DARE criteria

Quality item	Yes/No/Uncertain	Methodological comments
1. Are any inclusion/exclusion criteria reported relating to the primary studies which address the review question?	Yes	RCT, randomisation ≤ 12 hours symptoms, ECG ST elevation ≥ 1 mm in two leads, no contraindication
2. Is there evidence of a substantial effort to search for all relevant research?	Yes	MEDLINE the only database searched: possible that some trials may be missed, but did handsearch and contact authors
3. Is the validity of included studies adequately assessed?	Yes for Zijlstra (randomisation only for Weaver)	Randomised, reporting of exclusions, extent of blinding, follow-up period: resolved any differences between published and individual data with trial investigators
4. Is sufficient detail of the individual studies presented?	Some	Some data presented on age, follow-up period, duration symptoms, no data on gender and settings
5. Are the primary studies summarised appropriately?	Yes	Weaver: meta-analysis of trials, Zijlstra: IPD analysis

Data extraction for RCTs within reviews

Study details

Reference and design	Intervention
Akhras *et al.*, 1997[38] (abstract) UK *Study design:* RCT *No. of patients:* Total: 87 PCI: 42 Thrombolysis: 45	*Treatment intervention:* 1. Primary PCI: on-site 2. Thrombolytic therapy: *Type:* streptokinase *Dose and duration:* not reported *Where given:* hospital *Eligibility criteria:* <12-hour history. All but three in thrombolysis group also had angiography (but unsure if PCI) at some point

Baseline characteristics

n (%) unless stated	Data presented for total group only
Age ± SD (years)	57 ±12
Gender (males/females)	76/19

Results

Longer term outcomes, *n*	PCI (*n* = 42)	Thrombolysis (*n* = 45)	Comparisons between groups
Mortality at 8 months	0	4	Not reported
CABG at 8 months	1	11	Not reported
Recurrent ischaemia	1	22	Not reported
Length of hospital stay ± SD (days)	4.5 ± 2.3	8.9 ± 4.1	$p = 0.0001$

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Unknown	
2. Was the treatment allocation concealed?	Unknown	
3. Were the groups similar at baseline in terms of prognostic factors?	Unknown	Not reported for individual groups
4. Were the eligibility criteria specified?	Unknown	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate	
7. Did the analyses include an intention-to-treat analysis?	Inadequate	
8. Were withdrawals and dropouts completely described?	Unknown	Unsure of numbers in either group at 8 months

Study details

Reference and design	Intervention
de Boer *et al.*, 1994[30] (Zwolle study) The Netherlands *Study design:* RCT, single-centre study *No. of patients:* Total: 301 1: 152 2: 149 The 301 patients in this study include the 142 patients evaluated in Zijlstra *et al.*, 1993[35]	*Treatment intervention:* 1. Primary PCI (on-site) (patients underwent angiography before PCI) 2. Thrombolytic therapy: *Type:* i.v. streptokinase *Dose and duration:* 1.5×10^6 U over 1 hour *Where given:* hospital *Eligibility criteria:* symptoms of AMI for > 30 minutes (criteria defined), presentation within 6 hours, or between 6 and 24 hours if evidence of continuing ischaemia, age <76 years, no contraindication to thrombolysis

Baseline characteristics

n (%) unless stated	PCI	Thrombolysis	Comparisons between groups
Time from onset to admission ± SD (minutes)	195 ± 227	176 ± 172	$p = 0.43$
Age ± SD (years)	59 ± 10	61 ± 9	$p = 0.06$
Gender (male)	127 (84)	121 (81)	$p = 0.59$
Previous MI	32 (21)	21 (14)	$p = 0.11$
Anterior MI	79 (52)	68 (46)	$p = 0.27$

Additional results

Longer term outcomes	PCI	Thrombolysis	Comparisons between groups
Length of hospital stay ± SD (assume days)	12.3 (5.3)	14.4 ± 6.8	$p = 0.003$
Comments: Veen *et al.* (1999)[117] compared angiography results from PCI patients in the Zwolle trial with thrombolysis patients in the APRICOT trial (APRICOT compares thrombolysis).			

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Partial	Closed envelope system. No further description
2. Was the treatment allocation concealed?	Inadequate	Envelopes subject to manipulation
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Baseline characteristics similar
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	States ITT in text
8. Were withdrawals and dropouts completely described?	Unknown	Assume no dropouts, but not stated in text

Study details

Reference and design	Intervention
DeWood *et al.*, 1989[32] Abstract only USA *Study design:* RCT *No. of patients:* Total: 36 1: 18 2: 18	*Treatment intervention:* 1. Direct PCI 2. Thrombolytic therapy *Type:* r-tPA *Dose and duration:* 0.4 megaunits (MU) kg^{-1} for 1 hour, 0.07 MU kg^{-1} per hour for 3 hours *Where given:* hospital *Eligibility criteria:* within 6 hours of early Q-wave MI

Baseline characteristics

n (%) unless stated	PCI (*n* = 18)	Thrombolysis (*n* = 18)	Comparison between groups
Age ± SD (years)	55 ± 11	55 ± 10	*p* = ns
Gender (Male)	15 (83)	14 (78)	*p* = ns

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Unknown	Method not stated
2. Was the treatment allocation concealed?	Unknown	
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Age, gender and global EF reported only
4. Were the eligibility criteria specified?	Unknown	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to treat-analysis?	Adequate	States ITT
8. Were withdrawals and dropouts completely described?	Unknown	No details in text, but assume no dropouts

Study details

Reference and design	Intervention
Garcia *et al.*, 1997[33] and 1999[41]; Elizaga *et al.*, 1993[36] Spain *Study design:* RCT *No. of patients:* Total: 220 1: 109 2: 111 31 of these patients were also included in the GUSTO-IIb trial, 1997[26] (Garcia, 1997, in abstract form, included in Cochrane review)	*Treatment intervention:* 1. Primary PCI 2. Systemic thrombolysis: *Type:* accelerated t-PA, alteplase *Dose and duration:* front-loaded regimen, 15-mg i.v. bolus, infusion of 0.75 mg kg^{-1} over 30 minutes (max. 50 mg), 0.50 mg kg^{-1} over 60 minutes (max. 35 mg) *Where given:* hospital *Eligibility criteria:* patients with anterior acute MI. Chest pain between 30 minutes and 5 hours without response to nitrates and ECG changes defined *Exclusions:* contraindications to thrombolysis, left bundle branch block, age <18 years and females of childbearing age

Baseline characteristics

***n* (%) unless stated**	**PCI (*n* = 109)**	**Thrombolysis (*n* = 111)**	**Comparison between groups**
Age (median, 25th and 75th percentiles) (years)	63 (53, 71)	60 (53, 74)	*p* = ns
Gender (male)	91 (84)	89 (80)	*p* = ns
Diabetes	13 (12)	19 (17)	*p* = ns
Previous MI	14 (13)	14 (13)	*p* = ns
Time from onset of symptoms to: (median, 25th and 75th percentiles) (minutes)	First balloon inflation: 197 (150, 250) Admission: 120 (85, 180)	Start of t-PA infusion: 150 (105, 215) Admission: 120 (80, 175)	*p* = ns
Length of stay (median, 25th and 75th percentiles) (days)	15 (11, 20)	15 (12, 19)	*p* = ns

Results from updated publication (1999)

Immediate outcome measures (in hospital)	**PCI (*n* = 109)**	**Thrombolysis (*n* = 111)**	**Comparison between groups**
Mortality	3 (2.8)	12 (10.8)	*p* = 0.02
Non-fatal reinfarction	4 (3.7)	6 (5.5)	ns
Stroke	0	3 (2.7%)	*p* = 0.08
Combined (death, reinfarction or stroke)	7 (6.4)	20 (1.7)	*p* = 0.01
Bleeding requiring transfusion	3 (2.8)	4 (3.6)	ns
Ischaemia (angina or stress test)	13 (11.9)	28 (25.2)	*p* = 0.01
PCI	17 (15.6)	39 (35.1)	*p* = 0.001
CABG	7 (6.4)	14 (12.6)	*p* = 0.12
Long-term measures at 6 months, *n* (%)	**PCI (*n* = 99)**	**Thrombolysis (*n* = 91)**	**Comparison between groups**
Mortality	5 (4.6)	13 (11.7)	ns
Non-fatal reinfarction	6 (5.5)	8 (7.2)	ns
Ischaemia (unstable angina)	5 (5.1)	9 (9.9)	ns
PCI	11 (11.2)	13 (14.4)	ns
CABG	1 (1)	3 (3.3)	ns

Quality criteria (CRD Report 4) from updated publication (1999)

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Unknown	Method of randomisation not stated
2. Was the treatment allocation concealed?	Unknown	
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Characteristics similar except for hypercholesterolaemia, higher in thrombolysis group (33% vs 21%)
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	
8. Were withdrawals and dropouts completely described?	Inadequate	Percentages given for each group, but numerator and denominator not given and not deducible. Reasons not given. Four not eligible for follow-up: groups and reasons not clear

Study details

Reference and design	Intervention
Gibbons *et al.*, 1993[25] USA *Study design:* RCT, single-centre study *No. of patients:* Total: 103 (end of study) (108 patients randomised, but end-point data not available for five) 1: 47 2: 56	*Treatment intervention:* 1. Primary PCI on-site (angiography first) Time from onset of chest pain to first balloon inflation = 277 ± 144 minutes 2. Thrombolytic therapy: *Type:* double-chain t-PA (duteplase) *Dose and duration:* 0.6×10^6 units kg^{-1} body weight over 4 hours *Where given:* hospital Time from onset of chest pain to start of infusion = 232 ± 174 minutes *Eligibility criteria:* AMI (criteria defined), pain for >30 minutes and ≤ 12 hours. *Exclusions:* cardiogenic shock, contraindications to thrombolytic therapy

Baseline characteristics

n (%) unless otherwise stated	PCI	Thrombolysis	Comparisons between groups
Time to treatment ± SD (minutes)	277 ± 144	232 ± 174	ns
Pain to randomisation = within 4 hours of symptoms in:	35	43	ns
Age ± SD (all < 80 years)	60 ± 11	62 ± 13	ns
Gender (male/female)	37/10	40/16	ns
Previous MI	2	7	ns
Previous surgery or angioplasty	1	2	ns
Anterior MI	15	22	ns

Additional results

Longer term outcomes	PCI	Thrombolysis	Comparisons between groups
Hospital days ± SD	7.7 ± 2.9	10.6 ± SD 8.1	$p = 0.01$
Coronary care days ± SD	4.0 ± 2.6	4.3 ± SD 3.6	$p = 0.6$
Comments: In PCI group, angioplasty not necessary in two patients at angiography. In thrombolysis group, five patients did not receive thrombolysis therapy (all had PCI owing to complications); 16 patients receiving thrombolysis therapy later underwent PCI.			

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Adequate	Computer-generated randomisation schedule
2. Was the treatment allocation concealed?	Adequate	
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Baseline characteristics similar for 103 patients. However, thrombolysis patients randomised in <4 hours (from onset of chest pain) were treated sooner than PCI patients
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Inadequate	States uses ITT, but does not. 108 patients randomised initially. End-point data not available for five patients. Imputed or measured data on 103 patients are presented.
8. Were withdrawals and dropouts completely described?	Inadequate	108 patients randomised. No data available for five patients (reasons given), but does not specify which group(s)

Study details

Reference and design	Intervention
Grines *et al.*, 1993[27] (PAMI) USA, France *Study design:* multicentre RCT *No. of patients:* Total: 395 1: 195 2: 200	*Treatment intervention:* 1. Primary PCI 2. Thrombolytic therapy: *Type:* t-PA, activase *Dose and duration:* 100 mg (or 1.25 mg kg^{-1} for patients <65 kg) over 3 hours *Where given:* hospital *Eligibility criteria:* patients of any age who presented within 12 hours of onset of ischaemic chest pain *Exclusions:* inability to provide informed consent, dementia, complete left bundle-branch block, cardiogenic shock, higher than normal risk of bleeding

Baseline characteristics

% unless stated	PCI (*n* = 195)	tPA (*n* = 200)	Comparison between groups
Age ± SD (range) (years)	60 ± 11 (29–84)	60 ± 11 (32–85)	
Gender (male)	74	72	
Diabetes	13	12	
Previous congestive heart failure	1	2	
Previous MI	15	14	
Location of current infarct, anterior	36	33	
Time from pain to treatment[a] SD (minutes)	181 ±119 to randomisation +60 ± 41 to treatment	197 ± 150 to randomisation +31 ± 22 to treatment	

[a] Treatment defined at administration of bolus of t-PA or angiography of the infarct-related vessel.

Additional results

	PCI (*n* = 195)	tPA (*n* = 200)	Comparison between groups
Length of stay ± SD (days)	7.5±3.3	8.4±4.6	$p = 0.03$

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Partial	Sealed envelopes, no further description
2. Was the treatment allocation concealed?	Inadequate	Sealed envelopes may be manipulated
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Similar characteristics
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Inadequate	Independent nurse reviewed medical charts, no mention of blinding
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	States ITT
8. Were withdrawals and dropouts completely described?	Unknown	No details in text

Study details

Reference and design	Intervention
Grinfeld *et al.*, 1996[31] (abstract) Argentina *Study design:* RCT, single-centre study *No. of patients:* Total: 112 1: 54 2: 58	*Treatment intervention:* 1. Primary PCI on-site 2. Thrombolytic therapy: *Type:* streptokinase *Dose and duration:* 1.5 K U *Where given:* hospital *Eligibility criteria:* presentation within 12 hours, eligible for thrombolysis *Exclusions:* cardiogenic shock, left bundle branch block

Baseline characteristics

Outcome	PCI	Thrombolysis	Comparisons between groups
Time from symptoms to randomisation ± SD (minutes)	242 ± 138	258 ± 162	ns
Age (not reported for individual groups) ± SD (years)		66 ± 23	
Gender (male) (not reported for individual groups)		71%	

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Unknown	States 'randomised', but no further details
2. Was the treatment allocation concealed?	Unknown	
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Baseline characteristics reported in text as similar in both groups
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Inadequate	Not reported
8. Were withdrawals and dropouts completely described?	Unknown	Assume no dropouts, but not stated in text

Study details

Reference and design	Intervention
GUSTO-IIb, 1997[26] International *Study design:* RCT (multicentre study) *No. of patients:* Total:1138 PCI: 565 Thrombolysis: 573	*Treatment intervention:* 1. Primary PCI on-site 2. Thrombolytic therapy: *Type:* t-PA 90 minutes *Dose and duration:* 15-mg bolus, 0.75 mg kg^{-1} body weight for 30 minutes, 0.50 mg kg^{-1} for 60 minutes (max. dose of 100 mg) *Where given:* hospital *Eligibility criteria:* presentation within 12 hours of symptoms *Exclusions* (criteria as in GUSTO trial[118]): taking warfarin at time of enrolment or had active bleeding, history of stroke, contraindication to heparin therapy or renal insufficiency, SBP >200 mmHg, DBP >110 mmHg, women of childbearing potential
DBP, diastolic blood pressure; SBP, systolic blood pressure.	

Baseline characteristics

n (%) unless stated	PCI	Thrombolysis	Comparisons between groups
Median time to treatment (25th and 75th percentiles) (hours)	3.8 (3.0, 5.3)	3.0 (2.0, 4.3)	Not reported
Median age (25th and 75th percentiles) (years)	63.5 (52.5, 71.0)	61.9 (52.0, 70.1)	Not reported
Age >75 years	82 (14.5)	79 (13.8)	Not reported
Gender (female)	139 (24.6)	121 (21.5)	Not reported
Diabetes	99 (17.5)	77 (13.4)	Not reported
Previous MI	73 (12.9)	85 (14.8)	Not reported
Previous CABG	12 (2.1)	16 (2.8)	Not reported
Previous angioplasty	29 (5.1)	28 (4.9)	Not reported

Additional results

Longer term outcomes	PCI group	Thrombolysis	Comparisons between groups
Median length of stay on intensive care unit (25th and 75th percentiles) (days)	3 (2, 4)	3.5 (2.5, 5)	Not reported
Median length of stay in hospital (25th and 75th percentiles) (days)	8 (6,12)	10 (7, 14)	Not reported
See also Birnbaum *et al.*, (2001):[119] part of GUSTO which subdivides patients into two grades depending on ECG changes and analyses the same outcomes.			

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Adequate	24-hour randomisation centre
2. Was the treatment allocation concealed?	Adequate	24-hour randomisation centre
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Similar characteristics
4. Were the eligibility criteria specified?	Adequate	Reported on p. 1622: Participants
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Inadequate	States ITT
8. Were withdrawals and dropouts completely described?	Inadequate	Numbers not specified for each group

Study details

Reference and design	Intervention
Ribeiro *et al.*, 1993[28] Brazil *Study design:* RCT *No. of patients:* Total: 100 1: 50 2: 50	*Treatment intervention:* 1. Primary PCI 2. Thrombolytic therapy *Type:* i.v. streptokinase *Dose and duration:* 1.2×10^6 U over 1 hour *Where given:* hospital *Eligibility criteria:* consecutive patients presenting with acute MI. Chest discomfort typical of ischaemia of 20 minutes to 6 hours duration *Exclusions:* relief of chest pain by sublingual nitroglycerine, history of stroke within 6 months, history of major surgery or trauma within 6 months, history of abnormal bleeding so as to contraindicate use of thrombolytics, history of prior CABG, age $\geq$ 75 years, prior Q-wave MI in the same infarct distribution as the index infarction

Baseline characteristics

% unless stated	PCI (n = 50)	Thrombolysis (n = 50)	Comparison between groups
Age ± SD (years)	57±10	55±10	p = ns
Gender (Male)	80	86	p = ns
Diabetes	12	10	p = ns
Previous angina	38	34	p = ns
Previous MI	6	16	p = ns
Anterior MI	34	46	p = ns
Time to treatment (mean SD) (minutes)	238 ± 112	179 ± 98	p = 0.005
Length of stay: not reported.			

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Partial	Closed envelope system without patient stratification. No further details
2. Was the treatment allocation concealed?	Inadequate	Envelopes may be subject to manipulation
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Similar baseline characteristics, but thrombolysis group treated earlier
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	Assume no dropouts, but not clearly stated in text
8. Were withdrawals and dropouts completely described?	Unknown	

Study details

Reference and design	Intervention
Ribichini *et al.*, 1996[34] and 1998[40] Italy *Study design:* RCT *No. of patients:* Total: 110 'high risk' 1: 55 2: 55 (Ribichini, 1996, in abstract form, included in Cochrane review)	*Treatment intervention:* *1. Primary PCI* *2. Thrombolytic therapy* *Type:* rt-PA *Dose and duration:* accelerated, weight adjusted treatment according to GUSTO protocol. *Where given:* hospital Unscheduled catheterisation performed in cases of failure of thrombolysis or recurrence of ischaemia *Eligibility criteria:* <80 years, presenting within 6 hours of symptom onset (typical chest pain lasting more than 30 minutes), criteria excluding small, low-risk, posterior AMI, informed consent *Exclusions:* formal contraindications to thrombolysis or to anticoagulation with herapin, cardiogenic shock or blood pressure <80 mmHg, anticipated impossibility of percutaneous femoral vascular access

Baseline characteristics

n (%) unless stated	PCI (*n* = 55)	rt-PA (*n* = 55)	Comparison between groups
Gender (male)	45 (82)	47 (85)	$p = 0.9$
Age ± SD (assume range) (years)	63.4 ± 8.4 (42–80)	60.2 ± 9.6 (36–80)	$p = 0.07$
Diabetes	9 (16.3)	6 (10.9%)	$p = 0.6$
Previous bypass surgery	4 (7.3)	3 (5.5)	$p = 0.9$
Previous PCI	1 (1.8)	0	$p = 0.9$
Previous MI	10 (18.2)	6 (10.9)	$p = 0.5$
Prehospital delay ± SD (range) (minutes)	152.5 ± 65.7 (25–355)	154.7 ± 69.6 (45–345)	$p = 0.9$
In-hospital delay ± SD (range) (minutes)[a]	53.2 ± 11.7 (25–75)	36.5 ± 10.3 (21–90)	$p = 0.0001$

[a] From arrival at A&E to beginning of treatment.

Results from updated publication (1998)

Immediate outcomes (in hospital), *n* (%)	**PCI (*n* = 55)**	**rt-PA (*n* = 55)**	**Comparison between groups**
Mortality	1 (1.8)	3 (5.5)	$p = 0.6$
Non-fatal reinfarction	1 (1.8)	5 (9.1)	$p = 0.2$
Combined mortality or reinfarction	2 (3.6)	5 (9.1)	$p = 0.4$
Angina	1 (1.8)	11 (20)	$p = 0.002$
PCI		15 (27.3)	Not tested
CABG	3 (5.5)	2 (3.6)	$p = 0.6$
Stroke	0	0	
Bleeding requiring transfusion	3 (5.5)	3 (5.5)	Not tested
Heart failure	3 (5.5)	10 (18)	$p = 0.04$
Length of stay ± SD (days)	9.2 ± 2.5 (4–15)	12.4 ± 3.7 (6–28)	$p = 0.0001$
Long-term outcomes at 1 year, *n* (%)	**PCI (*n* = 55)**	**rt-PA (*n* = 55)**	**Comparison between groups**
Mortality	2 (3.6)	4 (7.3)	$p = 0.7$
Reinfarction	2 (3.6)	5 (9.1)	$p = 0.4$
Angina	2 (3.6)	18 (32.7)	$p = 0.0001$
PCI after randomisation	3 (5.50	24 (43.6)	$p = 0.0001$
CABG	3 (5.5)	11 (20)	$p = 0.05$
Heart failure requiring admission	2 (3.6)	1 (1.8)	$p = 0.5$

Quality criteria (CRD Report 4) from updated publication (1998)

Quality item	**Coding**	**Methodological comments**
1. Was the assignment to the treatment groups really random?	Partial	Sealed envelopes, no further description
2. Was the treatment allocation concealed?	Inadequate	Sealed envelopes may be subject to manipulation
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Characteristics similar except for higher heart rate at admission for rt-PA. Delay to start of treatment was longer for PCI
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	
8. Were withdrawals and dropouts completely described?	Unknown	Assume no dropouts, but not clearly stated in text.

Study details

Reference and design	Intervention
Zijlstra *et al.*, 1997[29] The Netherlands *Study design:* RCT, single-centre study *No. of patients:* Total: 240 PCI (low risk): 45 Thrombolysis (low risk): 50 PCI (high risk): 145	*Treatment intervention:* 1. Primary PCI on-site (angiography followed by PCI was performed in 92% of patients randomised to this group) Time from hospital admission to first balloon inflation = 68 ± 21 minutes 2. Thrombolytic therapy: *Type:* i.v. streptokinase *Dose and duration:* 1.5×10^6 IU *Where given:* hospital Time from hospital admission to start of streptokinase infusion = 29 ± 17 minutes *Eligibility criteria:* symptoms >30 minutes, within 6 hours of onset, or between 6 and 24 hours if signs of ongoing ischaemia, *Exclusions:* life expectancy <6 months, conditions resulting in severe impairment of QoL

Baseline characteristics

% unless stated	PCI	Thrombolysis	Comparisons between groups
Time from symptom onset	No details only from admission to treatment given		
Age ± SD (year)	63 ± 11	59 ± 12	Not reported
Gender (male)	80	74	Not reported
Previous MI	18	20	Not reported
Anterior MI	0	0	Not reported
Comments: Patients were classified into low or high risk on entering the trial. Low-risk patients were randomised to PCI or thrombolytic therapy; high-risk patients were treated with angiography and then PCI where suitable. Main comparator is between treatments in low-risk patients only.			

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Adequate	Randomly allocated by telephone. No further description
2. Was the treatment allocation concealed?	Adequate	
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Similar for most baseline characteristics, but multivessel disease was more common in PCI group
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	Unclear: reports numbers at 6 months as the same
8. Were withdrawals and dropouts completely described?	Unknown	

Data extraction for new RCTS

Study details

Reference and design	Intervention
Aversano *et al.*, 2002[42] USA *Study design:* RCT, multicentre study *No. of patients:* Total: 451 1: 225 2: 226	*Treatment intervention:* 1. Primary PCI (PCI) on-site (no previous on-site cardiac surgical or PCI programme) 2. Thrombolytic therapy: *Type:* accelerated t-PA *Dose and duration:* bolus dose of 15 mg, and infusion of 0.75 mg kg^{-1} for 30 minutes followed by 0.5 mg kg^{-1} for 60 minutes *Where given:* hospital *Eligibility criteria:* eligible to receive thrombolytic therapy, aged ≥ 18 years, could provide informed consent, had chest discomfort or any other symptom compatible with myocardial ischaemia of ≥ 30 minutes and <12 hours duration. Patients were not excluded because of prior or recent MI, any co-morbid condition (including those that might limit survival to < 6 months) or prior PCI or CABG *Exclusions:* unable to give informed consent, taking metformin with creatinine level >1.5 mg dL^{-1} (men) or 1.4 mg dL^{-1} (women), true idiosyncratic reactions to aspirin or radiographic contrast media, not eligible for thrombolytic therapy

Baseline characteristics

n (%) unless stated	PCI (*n* = 225)	Thrombolysis (*n* = 226)	Comparisons between groups
Age (mean ± SD) (years)	63.7 ± 12.7	63.9 ± 12.1	$p = 0.82$
White race	179 (90)	191 (91)	$p = 0.17$
Gender (male)	160 (71)	160 (70)	$p = 0.99$
Diabetes	33 (15)	37 (16)	$p = 0.62$
Prior CABG	10 (4)	14 (6)	$p = 0.41$
Prior PCI	17 (8)	21 (9)	$p = 0.51$
Prior MI	35 (16)	40 (18)	$p = 0.54$
Anterior infarction	81 (36)	82 (36)	$p = 0.99$
Time to treatment (IQR) (minutes)	Door to balloon: 101.5 (82, 121) Symptom to admission: 90.5 (59, 170)	Door to therapy: median 46 (30, 65) Symptom to admission: 90 (60, 200)	Not reported

Results for ITT analysis

Immediate outcome measures (discharge), *n* (%)	**PCI (*n* = 225)**	**Thrombolysis (*n* = 226)**	**Comparisons between groups**
Mortality	12 (5.3)	14 (6.2)	$p = 0.70$
Recurrent MI	9 (4.0)	20 (8.8)	$p = 0.04$
Stroke	3 (1.3)	8 (3.5)	$p = 0.13$
Composite end-point: death, recurrent MI or stroke	22 (9.8)	38 (16.8)	$p = 0.03$
Median length of hospital stay (IQR) (days)	4.5 (3, 6)	6.0 (4, 8)	$p = 0.02$
Short-term outcome measures (6 weeks), *n* (%)	**PCI (*n* = 225)**	**Thrombolysis (*n* = 226)**	**Comparisons between groups**
Mortality	12 (5.3)	16 (7.1)	$p = 0.44$
Recurrent MI	11 (4.9)	20 (8.8)	$p = 0.09$
Stroke	3 (1.3)	8 (3.5)	$p = 0.13$
CABG	28 (12.4)	42 (18.6)	$p = 0.07$
Composite end-point: death, recurrent MI or stroke	24 (10.7)	40 (17.7)	$p = 0.03$ OR 0.52 (95% CI 0.30 to 0.89)
Longer term outcome measures (6 months), *n* (%)	**PCI (*n* = 225)**	**Thrombolysis (*n* = 226)**	**Comparisons between groups**
Mortality	14 (6.2)	16 (7.1)	$p = 0.72$
Recurrent MI	12 (5.3)	24 (10.6)	$p = 0.04$
Stroke	5 (2.2)	9 (4.0)	$p = 0.28$
CABG	30 (13.3)	44 (19.5)	$p = 0.08$
Composite end-point: death, recurrent MI or stroke	28 (12.4)	45 (19.9)	$p = 0.03$ OR 0.57 (95% CI 0.34 to 0.95)
Comments: analysis by treatment actually received also reported: outcomes favour PCI even more.			

Quality criteria (CRD Report 4) for RCTs

Quality item	**Coding**	**Methodological comments**
1. Was the assignment to the treatment groups really random?	Adequate	Computer-generated block randomisation used; separate treatment schedules used for each site; treatment assignments made using an automated telephone response system at the trial data coordinating centre
2. Was the treatment allocation concealed?	Adequate	
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	No significant difference for baseline characteristics
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Adequate	Recurrent MI events reviewed by two cardiologists not associated with trial and blinded to treatment; similarly for stroke events with neurologist
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	ITT performed for all randomised patients regardless of eventual treatment. Results are presented for ITT and also for treatment received. Flow diagram clearly explains numbers of patients receiving which treatment
8. Were withdrawals and dropouts completely described?	Adequate	None lost to follow-up or discontinued. Flow diagram as above

Study details

Reference and design	Intervention
De Boer *et al.*, 2002[44] The Netherlands *Study design:* RCT *No. of patients:* Total: 87 (all >75 years) PCI: 46 Thrombolysis: 41	*Treatment intervention:* 1. On-site angiography with primary PCI at investigator's discretion 2. Thrombolytic therapy: *Type:* streptokinase *Dose and duration:* 1.5×10^6 U over 1 hour *Where given:* hospital *Eligibility criteria:* ≥ 76 years, no contraindications for thrombolytic therapy, presented within 6 hours of symptoms (or between 6 and 24 hours if there was evidence of continuing ischaemia)

Baseline characteristics

n (%) unless stated	PCI	Thrombolysis	Comparisons between groups
Time to balloon/needle, mean ± SD (range) (minutes)	59 ± 19 (33–120)	31 ± 15	Not tested
Age (range) (years)	80 (77–84)	81 (78–84)	$p = 0.17$
Gender (male)	22 (48)	25 (61)	$p = 0.31$
Diabetes	11 (24)	7 (17)	$p = 0.60$
Previous MI	6 (13)	7 (17)	$p = 0.82$
Previous CABG	3 (7)	4 (10)	$p = 0.47$
Anterior MI	23 (50)	19 (46)	$p = 0.89$

Results

Immediate outcome measures, *n* (%)	PCI (*n* = 46)	Thrombolysis (*n* = 41)	Comparisons between groups
30-day mortality	3 (7)	9 (22)[a]	RR (thrombolysis) 4.0 (95% CI 0.9 to 24.6), $p = 0.04$[a]
Recurrent MI	1 (2)	6 (15)	$p = 0.01$
Stroke	1 (2)	3 (7)	$p = 0.34$
Additional CABG/PCI	2 (4)	4 (10)	$p = 0.41$
Composite end-point: death, MI, stroke	4 (9)	12 (29)	RR 4.3 (95% CI 1.2 to 20.0), $p = 0.01$
Bleeding (non-cerebral)	5 (11)	3 (7)	$p = 0.72$
Longer term outcome measures, *n* (%)	**PCI (*n* = 46)**	**Thrombolysis (*n* = 41)**	**Comparisons between groups**
Mortality at 12 months	5 (11)	12 (29)	RR (thrombolysis) 3.4 (95% CI: 1.0 to 13.5), $p = 0.03$
Mortality at 24 months	7 (15)	13(32)	RR (thrombolysis) 2.5 (95% CI 1.0 to 6.2), $p = 0.04$
Composite end-point: death, MI, stroke at 12 months	6 (13)	18 (44)	$p = 0.001$, RR 5.2 (95% CI 1.7 to 18.1)
Composite end-point: death, MI, stroke at 24 months	9 (20)	18 (44)	$p = 0.003$, RR 3.1 (95% CI 1.4 to 7.0)[b]
Days in hospital	5 (3–10)	5 (3–10)	$p = 0.95$

[a] values for thrombolysis and *p*-value in Table 2 [8 (20) and $p = 0.07$ respectively] are different to the text.
[b] *p*-Value reported as $p = 0.01$ in Table 2.

Comments: PCI group: angiography 45 (one died before) then angioplasty in 41 of these (two CABG, two conservative treatment). 21 patients had stenting.
Six PCI and four thrombolysis patients treated >6 hours from symptoms.
Before randomisation a catheter laboratory needed to be available.

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Adequate	Telephone randomisation service
2. Was the treatment allocation concealed?	Adequate	Telephone randomisation service
3. Were the groups similar at baseline in terms of prognostic factors?	Adequate	
4. Were the eligibility criteria specified?	Adequate	All >75 years
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	States uses principle of ITT
8. Were withdrawals and dropouts completely described?	Adequate	None lost to follow-up

Study details

Reference and design	Intervention
Grines *et al.*, 2002[45] (Air-PAMI) USA, Finland, Argentina *Study design:* multicentre RCT Patients with high-risk MI *No. of patients:* Total: 138 1: 71 2: 67	*Treatment intervention:* 1. Angiography then primary PCI (following emergency transfer by air or ground) 2. Thrombolytic therapy (on-site): *Type:* drug use according to that considered standard of care for the participating hospital *Dose and duration:* 68% received a fibrin-specific agent (alteplace or reteplase); 32% received streptokinase *Where given:* hospital *Eligibility criteria:* onset of AMI <12 hours, one or more of the following criteria for high risk had to be met: age >70 years, heart rate >100 beats per minute, SBP <100 mmHg in absence of volume depletion, Killip class II/III or an ECG demonstrating left bundle branch block or anterior MI *Exclusions:* ineligible for thrombolytic therapy (history of stroke or transient cerebral event in past 6 months, major surgery or active gastrointestinal bleeding within previous 2 months, organ biopsy within 2 weeks, CPR lasting ≥ 10 minutes or resulting in rib fracture, SBP >200 mmHg or DBP >110 mmHg), had cardiogenic shock (DBP ≤ 80 mmHg in the absence of bradycardia or requiring vasopressors) or life expectancy <1 year *Generalisability:* high-risk patients
CPR, cardiopulmonary resuscitation.	

Baseline characteristics

% unless stated	Transfer PCI group (n = 71)	Thrombolysis group (n = 66)	Comparisons between groups
Age (mean ± SD)	62 ± 12	64 ± 12	$p = 0.59$
Gender (male)	76	65	$p = 0.16$
Previous MI	13	14	$p = 0.89$
Previous CABG	3	3	$p = 1.00$
Diabetes	23	20	$p = 0.68$
Anterior MI	77	80	$p = 0.68$
Time from emergency room to treatment (mean ± SD) (minutes)	174 ± 80	63 ± 39	$p < 0.0001$

Results

Immediate outcome measures, %	Transfer PCI* (n = 71)	Thrombolysis (n = 66)	Comparisons between groups
30-day mortality	8.4	12.1	p = 0.46
Non-fatal MI	1.4	0	p = 1.00
Disabling stroke	0	4.5	p = 0.11
CABG	6 (8.5%)[a]	Assume 0	
Ischaemia	12.7	31.8	p = 0.007
Combined end-point: death, repeat MI, disabling stroke	8.4	13.6	OR 0.571 (95% CI 0.191 to 1.709), p = 0.331
Length of hospital stay ± SD (days)	6.1±4.3	7.5±4.3	p = 0.015

[a] Eight did not receive PCI: six (8.5%) referred for CABG; two (2.8%) treated medically.

Quality criteria (CRD Report 4) for RCTs

Quality item	Coding	Methodological comments
1. Was the assignment to the treatment groups really random?	Partial	Randomisation stratified by site. US sites used telephone randomisation from the study coordinating centre, but non-US sites used sealed envelopes
2. Was the treatment allocation concealed?	Inadequate	Sealed envelopes may be subject to manipulation
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	No significant difference in most baseline characteristics, but hypertension more common in PCI group
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Inadequate	Blinding not stated, but deducible from procedures that the outcome assessors were not blinded, although events were reviewed by a blinded clinical events committee
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate	
7. Did the analyses include an intention-to-treat analysis?	Inadequate	
8. Were withdrawals and dropouts completely described?	Adequate	One lost from thrombolysis group

Study details

Reference and design	Intervention
Widimsky *et al.*, 2000[46] Czech Republic *Study design:* RCT (multicentre study) *No. of patients:* Total: 300 PCI: 101 Thrombolysis PCI: 100 Thrombolysis: 99	*Treatment intervention:* 1. Transferred for primary PCI 2. Transferred for PCI with thrombolytic therapy during transfer: *Type:* i.v. streptokinase *Dose and duration:* assume 1.5 ml U^{-1} over 45–60 minutes *Where given:* on route to district hospital 3. Immediate thrombolytic therapy: *Type:* i.v. streptokinase *Dose and duration:* 1.5 ml U^{-1} over 45–60 minutes *Where given:* community hospital *Eligibility criteria:* presentation within 6 hours of symptoms *Exclusions:* terminal phase of cardiogenic shock, contraindication to thrombolysis, transport problems, absence of femoral artery pulses.

Baseline characteristics

***n* unless stated**	**PCI (*n* = 101)**	**Thrombolysis PCTA (*n* = 100)**	**Thrombolysis (*n* = 99)**	**Comparisons between groups**
Time (symptoms to randomisation)[a] (minutes)	135	127	122	Not reported
Age ± SD	61 ± 12	62 ± 11	61 ± 10	Not reported
Gender (males)	72	73	68	Not reported
Previous MI	9	13	19	Not reported
Anterior MI	48	54	43	Not reported

[a] Details in Figure 1 only, but totals given are to reperfusion (thus including thrombolysis therapy and balloon); therefore, taken until randomisation only to standardise.

Results

Immediate outcome measures (within 30 days), %	**PCI (*n* = 101)**	**Thrombolysis PCTA (*n* = 100)**	**Thrombolysis (*n* = 9)**	**Comparisons between groups**
30-day mortality	7	12	14	ns
Non-fatal MI	1	7	10	$p < 0.03$
Stroke	0	3	1	ns
Combined end-point: death reinfarction, stroke	8	15	23	$p < 0.02$
CABG	3	2	3	Not reported
PCI	4	5	11	Not reported
Stent thrombosis (*n*)	1	5		Not reported
Fatal bleeding complications and/or fatal cardiac tamponade only (estimated from figure); related to actual treatment used	0/97 (–4 who also received streptokinase)	8/111 (+7 rescue PCI patients, +4 from PCI group)	0/92 (–7 rescue PCI patients)	Not reported

Comments: stenting occurred in 79% of interventions in each group of angioplasty. Significant procedure-related complications occurred immediately in one patient in the thrombolysis group (rescue angioplasty), two each in combined and PCTA groups. Angioplasty actually undertaken in 91 of PCI group and 82 of thrombolysis PCI group.

Quality criteria (CRD Report 4) for RCTs

Quality item	**Coding**	**Methodological comments**
1. Was the assignment to the treatment groups really random?	Adequate	Telephone randomisation
2. Was the treatment allocation concealed?	Adequate	By telephone, assume OK
3. Were the groups similar at baseline in terms of prognostic factors?	Reported	Possible differences in anterior infarction, previous infarct and Killip class
4. Were the eligibility criteria specified?	Adequate	
5. Were outcome assessors blinded to the treatment allocation?	Unknown	
6. Were the point estimates and measure of variability presented for the primary outcome measure?	Inadequate	
7. Did the analyses include an intention-to-treat analysis?	Adequate	States analysed using ITT principle (assumed adequate as reported, but difficult to establish as numbers not given in presentation of data)
8. Were withdrawals and dropouts completely described?	Adequate	

Data extraction of RCT for immediate angioplasty versus community thrombolysis

Study details

Reference and design	Intervention
Bonnefoy *et al.*, 2002[82] [on behalf of the Comparison of Angioplasty and Prehospital Thrombolysis in acute Myocardial infarction (CAPTIM) study group] France *Study design:* randomised multicentre trial *No. of patients:* Total: 840 1: 421 2: 419	*Aim:* to find out whether PCI was better than prehospital fibrinolysis followed by transfer to a centre with interventional facilities for possible rescue angioplasty *Treatment intervention:* 1. Primary PCI 2. Prehospital thrombolytic therapy: *Type:* alteplase *Dose and duration:* 15-mg bolus followed by infusion of 0.75 mg kg^{-1} (not exceeding 50 mg) over 30 minutes and then 0.50 mg kg^{-1} (not exceeding 35 mg) over 60 minutes, up to a total dose of 100 mg *Where given:* most at home or workplace *Eligibility criteria:* presentation within 6 hours of symptoms *Exclusions:* known bleeding disorders, or any contraindication to fibrinolysis, severe renal or hepatic insufficiency, aortofemoral bypass or any condition that could hamper femoral artery bypass, cardiogenic shock, history of CABG, current oral anticoagulant treatment, duration of transfer to hospital expected to exceed 1 hour All patients were transferred to a centre with emergency angioplasty. Ambulance teams included a physician, and a physician diagnosed AMI in 94.8% of cases

Baseline characteristics

n (%) unless stated	PCI (*n* = 421)	Thrombolysis (*n* = 419)	Comparisons between groups
Time from onset to randomisation (IQR) (minutes)	108 (76, 162)	107 (76, 158)	Not reported
Time from onset to treatment (IQR) (minutes)	190 (149, 255)	130 (95, 180)	Not reported
Age (mean, IQR) (years)	58 (50, 68)	58 (49, 69)	Not reported
Age >75 years	40 (9.5)	42 (10)	Not reported
Gender (male/female)	343 (81.5)/78 (18.5)	345 (82.5)/74 (17.5)	Not reported
Diabetes	57 (13.5)	46 (11.1)	Not reported
Previous MI	28 (6.7)	34 (8.2)	Not reported
Previous CABG	5 (1.2)	0	Not reported
Anterior MI	178 (42.7)	166 (40.2)	Not reported
Previous angioplasty	18 (4.3)	22 (5.3)	Not reported
States that groups were balanced, but no evidence of statistical testing noted.			

Results

Immediate outcome measures (within 30 days), *n* (%)	**PCI (*n* = 421)**	**Thrombolysis (*n* = 419)**	**Comparisons between groups**
Mortality	20 (4.8)	16 (3.8)	Risk difference –0.93 (95% CI –3.67 to 1.81), $p = 0.61$
Cardiovascular death	18 (4.3)	16 (3.8)	$p = 0.86$
Reinfarction	7 (1.7)	15 (3.7)	Risk difference 1.99 (95% CI 0.27 to 4.24), $p = 0.13$
Stroke	0	4 (1)	Risk difference 1.00 (95% CI 0.02 to 1.97), $p = 0.12$
Composite end-point (death, non-fatal reinfarction, non-fatal stroke)	26 (6.2)	34 (8.2)	Risk difference 1.96 (95% CI –1.53 to 5.46), $p = 0.29$
Any angioplasty up to day 30	60 (14.3)	295 (70.4)	
Overall unplanned Angioplasty/CABG	4.7%	34.5%	$p < 0.0001$
Urgent angioplasty	16 (4)	134 (33)	$p < 0.0001$
Persistent ischaemia (rescue)	7 (1.7)	106 (26)	
Recurrent ischaemia	9 (2.1)	28 (6.7)	
CABG surgery	3 (0.7)	6 (1.5)	
Severe haemorrhage	8 (2.0)	2 (0.5)	$p = 0.06$
Recurrent ischaemia (different values reported in Table 2)	16 (4.0)	29 (7.2)	$p = 0.09$
Ischaemic stroke	0	2 (0.5)	$p = 0.50$
Haemorrhagic stroke	0	2 (0.5)	$p = 0.50$

Comments: some patients in the thrombolysis group had PCI (5), and 14 neither. 16 PCI patients did not undergo angiography, and 41 had angiography but not angioplasty. Stenting undertaken in some PCI patients.

Data extraction for observational studies of rescue angioplasty

Study details

Reference and design	**Intervention**
Bar *et al.*, 2000[79] The Netherlands *Study design:* retrospective cohort study *No. of patients:* Total: 759 1: 317 2: 442	*Aim:* to demonstrate that rescue PCI treatment has the same success rate or differs by ≤ 5% compared with standard treatment *Treatment intervention:* 1. Rescue PCI after treatment with thrombolysis 2. Primary PCI The reasons for thrombolytic therapy or primary PCI could not be described by the retrospective analysis, and a change in attitude towards PCI over time was observed *Eligibility criteria:* 1987–1997: clinical and ECG signs of AMI, chest pain ≥ 30 minutes. Initially only patients <70 years had therapy in case treatment delay between chest pain and intervention was <4 hours. Since 1989 no upper age criterion used, and treatment delay increased to 6 hours. In case of persistent pain and ST segment elevation, patients with longer delays could also undergo an intervention

Baseline characteristics

***n* (%) unless stated**	**Rescue PCI (*n* = 317)**	**Primary PCI (*n* = 442)**	**Comparisons between groups**
Age ± SD (years)	59.6 ± 12.0	61.1 ± 11.6	$p = 0.08$
Gender (males)	235 (74.0)	323 (73.1)	$p = 0.81$
Anterior infarct	151 (47.6)	224 (50.7)	$p = 0.07$
History of infarct	68 (21.5)	106 (24.0)	$p = 0.09$
Diabetes	25 (7.9)	46 (10.4)	$p < 0.05$
Pain to PCI, median (range) (minutes)			
PCI centre	240 (60–945)	195 (50–1430)	
Transfer from other hospitals	315 (95–710)	220 (105–1245)	
Median	269	204	

Results

Immediate outcome measures *n*	**Rescue PCI (*n* = 317)**	**Primary PCI (*n* = 442)**	**Comparisons between groups**
Successful PCI	286 (90.2)	404 (91.4)	$p = 0.67$ (effect size –1.2%, 90% CI –4.7 to –2.3)
In-hospital mortality	15 (4.7)	29 (6.6)	$p = 0.37$
Reinfarction	16 (5.1)	29 (6.6)	$p = 0.47$
Stroke	3 (0.9)	3 (0.7)	$p = 1.00$
CABG	12 (3.8)	20 (4.5)	$p = 0.75$
Recurrent angina	44 (13.9)	56 (12.7)	$p = 0.70$
Hospital stay ± SD (days)	8.2 ± 7.5	8.1± 9.7	$p = 0.46$
Blood transfusion	13 (4.1)	6 (1.4)	$p < 0.05$
11 patients (six rescue, five primary) lost to follow-up.			
Longer term outcome measures, *n* (%)	**Rescue PCI (*n* = 296)**	**Primary PCI (*n* = 408)**	**Comparisons between groups**
Mortality at 1year	8 (2.7)	15 (3.7)	$p = 0.63$
Reinfarction	6 (2.0)	6 (2.0)	$p = 1.00$
No. of later interventions:			
Repeat PCI	22 (7.4)	21 (5.1)	$p = 0.27$
CABG	11 (3.7)	15 (3.7)	$p = 1.00$
Heat failure	8 (2.7)	21 (5.1)	$p = 0.39$
Recurrent angina	50 (16.9)	77 (18.6)	$p = 0.60$

Study details

Reference and design	Intervention
Juliard *et al.*, 1999[80] France *Study design:* prospective cohort study with matched controls *No. of patients:* Total: 340 1: 170 (of whom 50 rescue PCI after failed thrombolysis) 2: 170	*Aim:* to compare hospital outcomes and artery patency in patients with AMI treated with prehospital thrombolysis and standby rescue PCI compared with matched patients treated with primary PCI *Treatment intervention:* 1. Prehospital thrombolysis with standby rescue PCI: (a) rt-PA, $n = 110$: 100 mg over 90 minutes in 46 patients; accelerated rt-PA (15-mg bolus followed by an infusion of 0.75 mg kg^{-1} over 30 minutes and then an infusion of 0.5 mg kg^{-1} over 60 minutes) in 61 patients; and double bolus rt-PA (double bolus of 50 mg given 30 minutes apart) in 3 patients (b) streptokinase, $n = 45$: 1.5×10^6 IU over 60 minutes (c) eminase, $n = 15$: 30-IU bolus *Where given:* community Coronary angiography performed 90 minutes after initiation of thrombolytic therapy. Patients underwent emergency rescue PCI for failed thrombolysis if the TIMI was grade 0–1 ($n = 50$). Patients with TIMI grade 2 or 3 were treated medically ($n = 120$) 2. Primary PCI *Eligibility criteria:* patients with AMI of <6 hours duration (chest pain lasting >30 minutes and resistant to nitrates with typical ECG changes), eligibility for thrombolysis. Diagnosis confirmed by creatinine kinase elevation *Exclusions:* Related to risk of bleeding: prolonged CPR (>30 minutes), SBP >200 mmHg, oral anticoagulant therapy, history of stroke or transient ischaemic attack, known bleeding disorder, inability to communicate, recent intramuscular or intra-arterial puncture, gastrointestinal bleeding, surgery, major trauma, urological bleeding or haemoptysis within previous 3 months

Baseline characteristics

n (%) unless stated	Prehospital thrombolysis ($n = 170$)	Primary PCI ($n = 170$)	Comparisons between groups
Age ± SD (years)	56 ± 12	57 ± 13	
Gender (male)	147 (86)	147 (86)	
Anterior MI	84 (49)	84 (49)	
Previous MI	14 (8)	26 (15)	
Diabetes	24 (14)	22 (13)	
Time from pain to reperfusion (angiograph proven) ± SD (minutes)	264 ± 78	232 ± 94	$p < 0.02$
Time from pain to therapy ± SD (minutes)	151 ± 61	Not reported	
Time from pain to admission ± SD (minutes)	209 ± 92	181 ± 90	$p < 0.03$

Results

Results focus mainly on thrombolysis group. For thrombolysis patients ($n = 170$):

At 90-minute coronary angiography, infarct-related artery patency was TIMI grade 3 in 108/170 (64%), TIMI grade 2 in 12/170 (7%) and TIMI 0 or 1 (i.e. thrombolysis failure) in 50/170 (29%)

Of the patients who underwent rescue PCI, TIMI grade 3 was achieved in 47/50 (94%)

Overall, 155/170 (91%) achieved TIMI grade 3 and 12/170 (7%) achieved TIMI grade 2, on average 113 minutes after the start of thrombolysis

There were 7/170 (4%) in-hospital deaths: two haemorrhagic strokes, three heart failures, one free wall rupture (a few hours after thrombolytic therapy) and one ventricular septal defect (<24 hours after successful rescue PCI)

Mortality was 3% (5/155) in patients achieving TIMI flow 3, 8% (1/12) in TIMI flow 2 and 33% (1/3) in TIMI 0 or 1, $p = 0.054$

14/170 (8%) patients had severe haemorrhagic complications, and 12/170 (7%) received transfusions

140/163 patients underwent predischarge angiography: 11/140 (8%) had silent reocclusion, 125/140 (89%) TIMI flow 3 and 4/140 (3%) TIMI flow 2

In-hospital outcome measures, *n* (%)	**Prehospital thrombolysis (*n* = 170)**	**Primary PCI (*n* = 170)**	**Comparisons between groups**
Angiographically proven TIMI 3 flow (final)	91%	91%	p = ns
Mortality	7 (4.1)	8 (4.7)	p = ns
Recurrent ischaemia	12 (7)	11 (6.4)	p = ns
CABG	8 (4.7)	9 (5.3)	p = ns
Reocclusion (angiographic)	16 (10)	7 (4.5)	$p < 0.05$
Ventricular fibrillation	6 (3.5)	5 (2.9)	p = ns

Length of stay: not reported.

Study details

Reference and design	**Intervention**
Oude-Ophius *et al.*, 1999[81] The Netherlands *Study design:* observational *No. of patients:* Total: 165 of 1265 consecutive AMI patients transferred for rescue PCI (c. 13%) Thrombolysis: 66 who had clinical signs of reperfusion on transfer Thrombolysis angiography: 41 without clinical signs of reperfusion on transfer given angiography only Thrombolysis angiography/PCI: 57 without clinical signs of reperfusion on transfer given angiography and rescue PCI	*Aim:* to study safety, feasibility and clinical outcome of patients with AMI initially treated with a thrombolytic agent in the community hospital with early referral to a PCI centre for rescue PCI when needed *Treatment intervention* 1. Thrombolytic therapy *Type:* either streptokinase or t-PA (numbers not given) *Dose and duration:* streptokinase: 1.5×10^6, t-PA: dose not reported *Where given:* hospital *followed by* 2. Transfer for PCI if fitted criteria: ECG evidence of large AMI (sum of ST-segment deviation >1.5 mV), Killip class 3–4 and or severe hypotension (SBP <90 mmHg) and ECG evidence of right ventricular involvement (presence of ST segment elevation in lead V4R) 3. On arrival, reperfusion status evaluated clinically and if absent or inconclusive given angiography 4. If no reperfusion on angiography given PCI *Eligibility criteria:* indication for early referral for intentional rescue PCI was large AMI (criteria defined). Rescue PCI if no signs of reperfusion once transferred (criteria defined)

Baseline characteristics

***n* (%) unless stated**	**Total (*n* = 165)**	**Thrombolysis only (*n* = 67)**	**Thrombolysis and angiography (*n* = 41)**	**Thrombolysis and PCI (*n* = 57)**	**Comparisons between groups**
Median time to arrive at PCI centre (25th and 75th percentiles) (minutes)	150 (110, 120)	Not reported	187 (146, 255)		Not reported
Age (mean ± SD) (years)	59 ± 11	59 ± 11	58 ± 11	60 ± 10	Not reported
Gender (male)	141 (85)	56 (84)	36 (88)	49 (86)	Not reported
Anterior MI	94 (57)	35 (52)	25 (61)	34 (60)	Not reported

Results

In-hospital outcome measures, *n* (%)	**Total (*n* = 165)**	**Thrombolysis group (*n* = 66)**	**Thrombolysis and angiography (*n* = 41)**	**Thrombolysis and PCI (*n* = 57)**	**Comparisons between groups**
30-day mortality	10 (6)	0	3 (7)	6 (11)	$p < 0.05$
Recurrent MI	14 (8)	11 (17)	2 (5)	1 (2)	$p < 0.01$
Stroke	0	0	0	0	ns
CABG	6 (4)	3 (5)	3 (7)	0	ns
Emergency PCI	12 (7)	9 (14)	2 (5)	1 (2)	$p < 0.05$
Elective PCI	5 (3)	3 (5)	2 (5)	0	ns
Bleeding leading to transfusion	5 (3)	2(3)	2 (5)	1 (2)	ns
1-year follow-up, *n* (%)	**Total (*n* = 152)**	**Thrombolysis group (*n* = 65)**	**Thrombolysis and angiography (*n* = 37)**	**Thrombolysis and PCI (*n* = 50)**	**Comparisons between groups**
Mortality at 1 year	2 (1)	1 (2)	1 (3)	0	ns
Heart failure	8 (5)	6 (9)	0	2 (4)	ns
PCI	8 (5)	2 (3)	4 (11)	2 (4)	ns
CABG					
Other					
Recurrent MI	7 (5)	3 (5)	2 (5)	2 (4)	ns
QoL					
Comments: time delays reported in Table 2 and complications during transfer also reported. Also reports bleeding. Three lost to follow-up: one in each group, known to be alive.					

Data extraction of observational studies for comparison of generalisability

Study details

Reference and design	Intervention
Danchin *et al.*, 1999[43] France *Study design:* prospective registry survey *No. of patients:* Total: 735 treated, but 1-year data available for 721 (98%) 1: 152 2: 569	*Aim:* to document 1-year outcome in all patients who received early reperfusion therapy (admitted within 6 hours of onset of chest pain) for AMI by either thrombolysis or primary PCI *Treatment intervention:* 1. Primary PCI (on-site within 24 hours of hospital admission) 2. Thrombolytic therapy (i.v.) *Type:* not reported *Dose and duration:* not reported *Where given:* hospital *Eligibility criteria:* AMI (48 hours from symptom onset). All patients were admitted within 6 hours of chest pain. PCI performed within 24 hours of admission without previous or concomitant use of thrombolytic therapy

Baseline characteristics

***n* (%) unless stated**	**PCI (*n* = 152)**	**Thrombolysis (*n* = 569)**	**Comparisons between groups**
Age ± SD (years)	60.9 ± 12.7	61.3 ± 12.6	*p* = ns
Gender (male/female)	127/25 (84/16)	468/101 (82/18)	*p* = ns
Diabetes	18 (12)	81 (14)	*p* = ns
Prior MI	25 (16)	71 (12.5)	*p* = ns
History of angina pectoris	62 (41)	200 (35)	*p* = ns
History of congestive heart failure	4 (3)	15 (3)	*p* = ns
Anterior location of MI	52 (34)	197 (35)	*p* = ns
Time to hospital admission (median, quartiles) (minutes)	150 (91, 200)	150 (110, 225)	*p* = ns

Results

Immediate outcome measures, *n* (%)	**PCI (*n* = 152)**	**Thrombolysis (*n* = 569)**	**Comparisons between groups**
5-day mortality	10 (6.6)	32 (5.6)	*p* = ns
30-day mortality	(9.2%)	(7.6%)	*p* = ns
Rescue PCI[a]	–	53 (9)	
Longer term outcome measures (1 year), *n* (%)	**PCI (*n* = 152)**	**Thrombolysis (*n* = 569)**	**Comparisons between groups**
Overall probability of survival	(85.5%)	(89.5%)	*p* = 0.18
≥ 1 revascularisation procedure performed	55 (36)	292 (51)[b]	*p* < 0.005

[a] Within 24 hours of admission.
[b] Includes rescue PCI in thrombolysis group.
Length of stay: not reported.

Comments:
Univariate and multivariate analyses were performed to calculate predictors of 1-year risk of death and 1-year outcomes in patients alive at 5 days

Study details

Reference and design	Intervention
Tiefenbrunn *et al.*, 1998[56] USA *Study design:* observational: retrospective registry review *No. of patients:* Total: 28,757 PCI: 4052 (with no contraindication to thrombolytic therapy) Thrombolysis: 24,705	*Aim:* to compare outcomes after primary PCI or thrombolytic therapy for AMI *Treatment intervention:* 1. Primary PCI (on-site within 12 hours of MI) 2. Thrombolytic therapy (within 12 hours of MI) *Type:* alteplase (rt-PA) *Dose and duration:* dose varied, but reported that accelerated dose regimen (infusion completed within 100 minutes) used in 92% patients *Where given:* hospital *Eligibility criteria:* AMI according to local hospital criteria, therapy within 12 hours of symptom onset. Data analysis limited to patients with a minimal 48-hour hospital stay (or death)

Baseline characteristics

% unless stated	PCI	Thrombolysis	Comparisons between groups
Median duration of onset to treatment (25th and 75th percentiles) (minutes)	216 (152, 329)	145 (95, 230)	$p = 0.0001$
Age (years)	60.5	61.1	$p = 0.01$
Age >75 years	15.6	15.1	ns
Gender (male)	72.5	70.1	$p = 0.002$
Previous MI	18.8	18.0	ns
Previous CABG	7.3	6.5	ns
Previous congestive heart failure	3.5	3.5	ns
Diabetes	17.1	18.4	$p = 0.05$
Anterior MI	39.1	35.7	$p = 0.0001$
Previous PCI	13.0	6.8	$p = 0.0001$

Results

Immediate outcome measures in those not in cardiogenic shock, %	**PCI (*n* = approx. 3882)**	**Thrombolysis (*n* = approx. 24384)**	**Comparisons between groups**
In-hospital mortality	5.2	5.4	ns
Combined end-points: mortality plus stroke	5.6	6.2	ns
Ischaemia	9.8	14.6	$p < 0.001$
Recurrent MI	2.5	2.9	ns
Stroke	0.7	1.6	$p < 0.0001$
Immediate CABG	2.5	Assume nil	Not reported
Heart failure	10.6	10.6%	ns
Subsequent procedures	Repeat PCI: 15.5	Rescue PCI: 3.5	Not reported
		Elective PCI: 18.6	Not reported
	Elective CABG: 6.5	Elective CABG: 7.3	Not reported
Major bleeding	4.0	3.2	$p < 0.01$
Immediate outcome measures in those in cardiogenic shock (%)	**PCI (*n* = approx. 170)**	**Thrombolysis (*n* = approx. 321)**	**Comparisons between groups**
In-hospital mortality	52.3	32.4	$p < 0.0001$
Comments: multiple regression performed to assess variables that may predict increased mortality. Bleeding, ischaemia and late cardiogenic shock reported.			

Study details

Reference and design	Intervention
Zahn *et al.*, 1997[57] Germany *Study design:* Prospective multicentre observational study with matched controls (1 PCI: 3 thrombolysis). 136 centres including tertiary care centres and smaller hospitals *No. of patients:* Total: 593 1: 156 2: 437	*Treatment intervention:* 1. Primary PCI 2. Thrombolytic therapy: *Type:* 68% streptokinase, 15.6% t-PA, 8.9% urokinase, 5.5% combinations or other thrombolytic substances, 2% not specified *Dose and duration:* most common protocols: 1.5×10^6 U streptokinase within 1 hour or 100 mg t-PA within 1.5 hours (accelerated t-PA regimen) *Where given:* intrahospital and prehospital thrombolysis included. Clinical routine setting at tertiary care centres *Eligibility criteria:* All patients with Q-wave AMI presenting within 96 hours after onset of pain were registered prospectively. Matching criteria: age ± 5 years, gender, location of infarction, SBP ± 20 mmHg, previous MI, prehospital delay ± 60 minutes. *Exclusions:* bundle branch block or requiring resuscitation

Baseline characteristics

n (%) unless stated	PCI (*n* = 156)	Thrombolysis (*n* = 437)	Comparisons between groups
Age ± SD (years)	61 ± 11	61 ± 10	
Gender (male)	114 (73)	326 (74)	
Anterior infarct	72 (46)	200 (46)	
Previous MI	19 (12.2)	49 (11.2)	
Door-to-treatment time ± SD (minutes)	142 ± 263	53 ± 127	$p = 0.0001$

Results

Immediate outcome measures, *n* (%)	PCI (*n* unclear)	Thrombolysis (*n* unclear)	Comparisons between groups
In-hospital death, *n* = 556	6 (4.3)	43 (10.3)	OR 0.39 (95% CI 0.17 to 0.92)
Death within 48 hours, *n* = 593	3 (1.9)	23 (5.3)	OR 0.35 (95% CI 0.11 to 1.14)
Reinfarction, *n* = 273	2 (3)	22 (10.6)	OR 0.26 (95% CI 0.07 to 1.05)
Non-fatal MI or death, *n* = 273	4 (6.1)	36 (17.4)	OR 0.31 (95% CI 0.11 to 0.85)
Major bleeding, *n* = 592	4 (2.6)	9 (2)	
Major bleeding with transfusion, *n* = 592	1 (0.7)	3 (0.7)	
Cerebral bleeding, *n* = 592	0	2 (0.5)	
Length of stay: not reported.			

Appendix 6

Health economics

Cost estimates from the NHS trust: Angioplasty compared with thrombolysis study for treatment of AMI

Cost area				Cost	Comment
Thrombolysis route					
1. *Visit to A&E*					A patient would be assessed as a probable heart attack patient in A&E. The triage nurses in A&E maintain contact with the thrombolytic nurses from CCU so patients can be identified early
An ECG and possibly an X-ray might be done in A&E				£107	This is the HRG cost for a low-cost investigation in A&E (HRG V05), and at 2002/03 cost base. It is the A&E direct costs plus share of support services, mainly pathology and radiology. This has been calculated by top–down costing and not by a bottom–up profile
2. *Admission to CCU*					
Input of thrombolytic drug:					
	Streptokinase	£92.23	1.5-MU injection		Now becoming less popular
However, the following drugs are now used in preference to streptokinase:					
	Reteplase (rTPA)	£411.25	10 units plus 10 units		Cost is total
plus	Heparin	£0.35	5000-unit injection		
plus	Enoxaparin	£19.04	4 x 80-mg injections		Unit cost £4.76
	Total	£430.64			
or	Tenecteplase (TNK)	£495	via injection		NB. This is the price negotiated by this trust; may be higher elsewhere
plus	Heparin	£0.35	5000-unit injection		Unit cost £4.76
	Enoxaparin	£19.04	4 × 80-mg injections		
	Total	£514.39			
				£473	Average of reteplase and tenecteplase drug packages
Cost per day in CCU:					
Direct costs only				£418	Excluding overheads and use of support services, at 2002/03 cost base
Direct costs plus support services				£469	Includes use of pathology, radiology, etc., not identified specifically in profiling
					Typically a patient would spend 48–72 hours on CCU before transferring to a cardiology ward for the remainder of their stay
					A typical length of stay for a thrombolysis patient is 1 week

continued

Cost area			Cost	Comment
3. *Cost per day on cardiology ward*				
Marginal, i.e. excluding overheads			£178	This is the direct cost element of the excess bed-day cost, inflated to 2002/03 cost base
			£278	This is the direct plus support services element of the excess bed-day cost at 2002/03 cost base
4. *Angiography might be done a few days into the stay*				
Cost for angiography (assumes 20 minutes in theatres)				
		Rate per minute	Total for procedure	Staffing is same as for angioplasty
Staff:	One cardiologist	£0.77	£15.45	For details of staff grades used, see
	One radiographer	£0.25	£4.90	Angioplasty section below
	One technician (MTO)	£0.24	£4.80	
	Two nurses	£0.19	£3.77	
Non-staff:	Dyes and other consumables		£150.00	
TOTAL			**£178.92**	
Angioplasty route				
1. *Visit to A&E*				A patient would be assessed as a probable heart attack patient in A&E. The triage nurses in A&E maintain contact with the thrombolytic nurses from CCU so patients can be identified early
An ECG and possibly an X-ray might be done in A&E			£107	This is the HRG cost for a low-cost investigation in A&E (HRG V05), and at 2002/03 cost base. It is the A&E direct costs plus share of support services, mainly pathology and radiology. This has been calculated by top–down costing and not by a bottom–up profile
2. *Admission to CCU*				
Cost per day in CCU:				
Direct costs only			£418	Excluding overheads and use of support services, at 2002/03 cost base
Direct costs plus support services			£469	Includes use of pathology, radiology, etc., not allowed for elsewhere in profiling
3. *Angioplasty*				
Typically 60 minutes in theatre (including angiography)				
		Rate per minute	Total for procedure	
Staff:	One cardiologist	£0.77	£46.35	Rate is consultant with discretionary points
	One radiographer	£0.25	£14.71	Senior radiographer grade, average of grades 1 and 2
	One technician (MTO)	£0.24	£17.75	Grade MTO 4 assumed
	Two nurses	£0.19	£22.63	Two grade E nurses assumed
	Total		£101.43	
Non-staff:	*Breakdown of prosthesis and consumables costs*			
	Stents:			
	Bare metal stents:			
	Range in costs £500–700 + VAT	£705		An average of 90% of these patients would require stenting, and they would need an average of 1.3 stents (this is a slightly smaller number of stents than for angioplasties as a whole)

continued

Cost area			Cost	Comment
	Hence adjusted cost for stent		£825	
	Drug-eluting stent: Now used in about 25% of patients	£1300+VAT	£382	NB. Stent costs are averages as the number required for an individual patient varies, and the individual price depends on the supplier. The drug-eluting stents have been used increasingly at SUHT since April 2002, but the market price is likely to reduce in the future as more suppliers become licensed for production
	Balloon catheter: Range in costs £190–350 + VAT		£317	
	Guiding catheters: £45+VAT	Three used	£159	
	Fem stop	Estimate	£100	
Non-staff:	Dyes and other consumables for angiography		£150	
Non-staff total			£1933	
Angioplasty total staff and non-staff costs			£2034	
4. *Cost per day on cardiology ward* Marginal, i.e. excluding overheads			£178	This is the direct cost element of the excess bed-day cost, inflated to 2002/03 cost base
			£278	This is the direct plus support services element of the excess bed-day cost at 2002/03 cost base
Additional costs for angioplasty patients				
Drugs:				
Abciximab Cost is £280 per vial; several would be used per patient			£800	Confirmed by pharmacy
Clopidogrel £35 per 28-tab pack; one would be used			£35	Confirmed by pharmacy

Drugs not included in the above calculations: a group of drugs called glycoprotein IIB/IIIA inhibitors (e.g. eptifibatide and tirofiban) are being used with some 'unstable' patients before angioplasty.
The average cost per patient is likely to be some £515. This has not been included in the above calculations.
MTO, medical technical officer; SUHT, Southampton University Hospitals NHS Trust.

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We look forward to hearing from you.

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