International Journal of Technology Assessment in Health Care, **22:2** (2006), 219–234.

Overview of systematic reviews on invasive treatment of stable coronary artery disease

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Objectives: The aim of the study was to evaluate the validity of the systematic reviews as a source of best evidence and to present and interpret the evidence of the systematic reviews on effectiveness of surgery and percutaneous interventions for stable coronary artery disease.
Methods: Electronic databases were searched without language restriction from January 1966 to March 2004. The databases used included the Cochrane Database of Systematic Reviews, the Cochrane Central Register of Controlled Trials, DARE, the Health Technology Assessment Database, MEDLINE(R), MEDLINE(R) In-Process & Other Non-Indexed Citations. We included systematic reviews of randomized clinical trials on patients with stable coronary heart disease undergoing percutaneous coronary intervention or coronary artery bypass surgery in comparison with medical treatment or a comparison between invasive techniques. At least one of the following outcomes had to be reported: death, myocardial infarction, angina pectoris, revascularization. The methodological quality was assessed using a modified version of the scale devised by Oxman and Guyatt (1991). A standardized data-extraction form was used. The method used to evaluate clinical relevance was carried out with updated method guidelines from the Cochrane Back Research Group. Quantitative synthesis of the effectiveness data is presented.
Results: We found nineteen systematic reviews. The median score of validity was 13 points (range, 6–17 points), with a maximum of 18 points. Coronary artery bypass surgery gives better relief of angina, and the need for repeated procedures is reduced

Information specialist Riitta Grahn is acknowledged for performing searches and for numerous consultations during the work. This work had no external funding.

after bypass surgery compared with percutaneous interventions. There is inconsistent evidence as to whether bypass surgery improves survival compared with percutaneous intervention. A smaller need for repeated procedures exists after bare metal stent and even more so after drug-eluting stent placement than after percutaneous intervention without stent placement. However, according to the current evidence, these treatment alternatives do not differ in terms of mortality or myocardial infarction.
Conclusions: We found some high-quality systematic reviews. There was evidence on the potential of invasive treatments to provide symptomatic relief. Surgery seems to provide a longer-lasting effect than percutaneous interventions with bare metal stents or without stents. Evidence in favor of drug-eluting stents so far is based on short-term follow-up and mostly on patients with single-vessel disease.

Keywords: Angioplasty, Percutaneous coronary, Coronary artery bypass, Meta-analysis, Review

Ischemic heart disease is the leading cause of death in the European Union (6) and other industrialized nations. Although deaths from coronary heart disease have decreased notably during the past few decades, especially among people of working-age, an aging population shifts the focus of treatment to older groups of patients with a higher comorbidity and an increasing number of hospital discharges (6). New interventions have been developed rapidly, and older treatment options have been improved. In 2000, over 1,202,000 percutaneous coronary intervention (PCIs) and 519,000 coronary artery bypass graft (CABGs) were carried out in the United States (20). In Great Britain, almost 39,000 PCIs were performed in 2001 and approximately 25,000 CABGs in 2000 (9).

Myocardial revascularization aims to alleviate ischemic symptoms and to prevent myocardial infarction, arrhythmias, or heart failure and, thus, reduce mortality (20). When invasive treatment is indicated, the selection of the appropriate myocardial revascularization technique can be challenging and is at least partly subjective. The operative risk, co-morbidities, coronary anatomy, and the patient's preferences play a role in the decision. Therefore, to arrive at a balanced decision, reliable comparative data on the health benefits and adverse effects of different revascularization procedures should be available (2).

Systematic reviews gather and combine evidence in a structured and rigorous manner. A comprehensive summary of scientific studies is useful as a basis for decisions (12). Many systematic reviews have compared medical treatment, percutaneous interventions, and surgical treatment for coronary artery disease. These comparisons typically cover only two treatment options. However, in clinical decision making, the choice is between several treatment options, even though they are seldom unequivocally interchangeable.

Our intention was to summarize evidence on the clinical effectiveness of coronary interventions in patients with stable coronary heart disease.To attain this target, we evaluated the reliability of the systematic reviews as a source of best evidence and interpret the results of the systematic reviews.

METHODS

Paper selection, validity assessment, data abstraction, and qualitative synthesis of the data were performed independently by two of the authors (P.K., A.M.). The selections made and the data collected were compared in each phase, and consensus was required from the two authors on each item. Disagreements were solved in a consensus meeting by checking the original data once more

Searching

Electronic databases were searched for meta-analyses and systematic reviews of invasive treatment of stable coronary heart disease without language restriction from January 1966 to March 2004. The databases used for the search were as follows: EBM Reviews—Cochrane Database of Systematic Reviews (3rd Quarter 2003) (OVID); EBM Reviews—Cochrane Central Register of Controlled Trials (4th Quarter 2003) (OVID); DARE (NHS CRD); the Health Technology Assessment (HTA) (NHS CRD); MEDLINE(R) from 1966 to February 2004, week4; MEDLINE(R) In-Process & Other Non-Indexed Citations to March 9, 2004. A focused search for coronary stents was performed in DARE, NHS Economic Evaluation Database, and HTA. A Science Citation Index search of the identified systematic reviews was performed in May 2004, and references to the systematic reviews identified were checked.

Search strategies were planned by an information specialist for each database. The following medical section head search terms were used: Angioplasty, Transluminal, Percutaneous Coronary, Coronary Artery Bypass, Comparative Study, Meta-Analysis, Review, Stents. Other keywords were balloon, bypass, angioplasty, cabg, pci, ptca, versus, vs, compare, alternate, systematic.

Selecting

The abstracts identified were reviewed using the screening criteria in the study eligibility form regarding study design, population, intervention, control intervention, and outcome. We included systematic reviews of randomized controlled

trials (RCTs) on patients with stable coronary heart disease undergoing percutaneous coronary intervention or coronary artery bypass surgery in comparison with medical treatment or comparison between invasive techniques. At least one of the following outcomes had to be reported: death, myocardial infarction, angina pectoris, revascularization. All papers judged to be potentially relevant were retrieved for detailed evaluation.

Reviews before 1994 were considered out of date and were excluded. We excluded studies focusing on acute coronary syndrome. For the report to be included as a systematic review, we expected intent to cover all relevant studies and a qualitative or quantitative synthesis of the included papers. Researchers were not precluded from knowing the source or authors of the reviews.

Validity Assessment

The methodological quality of the reviews was assessed by using a modified version (11) of a quality scale of research overviews (16). The scale combines nine items, each ranging from 0 to 2 points, resulting in a maximum score of 18 points.

Data Abstraction

The following main topics were covered in the standardized data-extraction form: framing the study question, identifying relevant literature, inclusion criteria for articles, assessing the quality of the literature, data synthesis, and results and applicability.

Study Characteristics

The baseline characteristics of the studies included and the inclusion criteria were tabulated. Primary outcome measures were defined as (i) mortality, (ii) myocardial infarction, (iii) revascularization, and (iv) angina pectoris. Any other outcome measures reported were regarded as secondary outcomes. The outcome measures in chosen articles were cited as given. Systematic reviews were divided into groups according to intervention contrasts: (i) CABG versus medical treatment, (ii) PCI without stents versus medical treatment, (iii) PCI with or without stents versus CABG, (iv) PCI with stents versus PCI without stents, (v) PCI with drug-eluting stent versus PCI with bare metal stent, and (vi) off-pump versus on-pump CABG.

Data Synthesis

The clinical effectiveness was evaluated on the basis of one intervention being more effective than the other or no detected difference between interventions. Quantitative results were described.

Clinical Relevance

The method used to evaluate clinical relevance was carried out using updated method guidelines from the Cochrane Back Research Group, which contained the following questions (24). Question 1 was evaluated by one of the authors (P.K.) and the rest by two of the authors (P.K., A.M.).

1. Are the patient populations included in the meta-analysis and systematic reviews described in enough detail to enable you to decide whether they are comparable with those that you see in your practice?
2. Are the interventions described in enough detail to allow you to provide the same treatment for your patients?
3. Are the treatment settings described well enough so that you can provide the same setting for your patients?
4. Were all four clinically relevant outcomes reported?
5. Are both the treatment benefits and complications presented?

RESULTS

Trial Flow

In the primary searches, 1,114 potentially relevant publications were identified: 4 in the Cochrane Database of Systematic Reviews, 8 in the Cochrane Central Register of Controlled Trials, 17 in DARE, 10 in the Health Technology Assessment Database, 1,007 in MEDLINE, and 45 in MEDLINE(R) In-Process & Other Non-Indexed Citations. A search focused on stents found twenty-three articles. The flow diagram of the systematic reviews is shown in Figure 1. After this selection process had been completed, sixteen reviews were included for the study. FinOHTA's (Finnish Office for Health Care Technology Assessment) continuous screening of HTA Internet resources revealed three other reviews that also fulfilled our criteria (1;7;14). A forward search in the Science Citation Index for these systematic reviews produced 489 citations but no further reviews were used. These nineteen reviews form the basis of this review.

Study Characteristics

Table 1 shows the study characteristics of the systematic reviews and contains information describing the objective of the study, the information source, the number of studies included, and the population sum with follow-up times. Table 2 shows inclusion criteria of the trials in the systematic reviews eligible for this report to describe patient populations.

The quality of the nineteen identified systematic reviews is summarized in Table 3. Three papers did not give data on the information sources. Reviewers were not precluded from knowing the source or authors of the studies, and only seven of nineteen studies explicitly reported article selection criteria. A quality assessment of the studies included was ignored in eleven papers. Other quality aspects were quite well considered, and the median score was 13 points (range, 6–17 points).

Clinical Relevance

Most reviews describe the patient population adequately, but four were unclear about age and gender distribution, disease

https://doi.org/10.1017/S026646230605104X Published online by Cambridge University Press

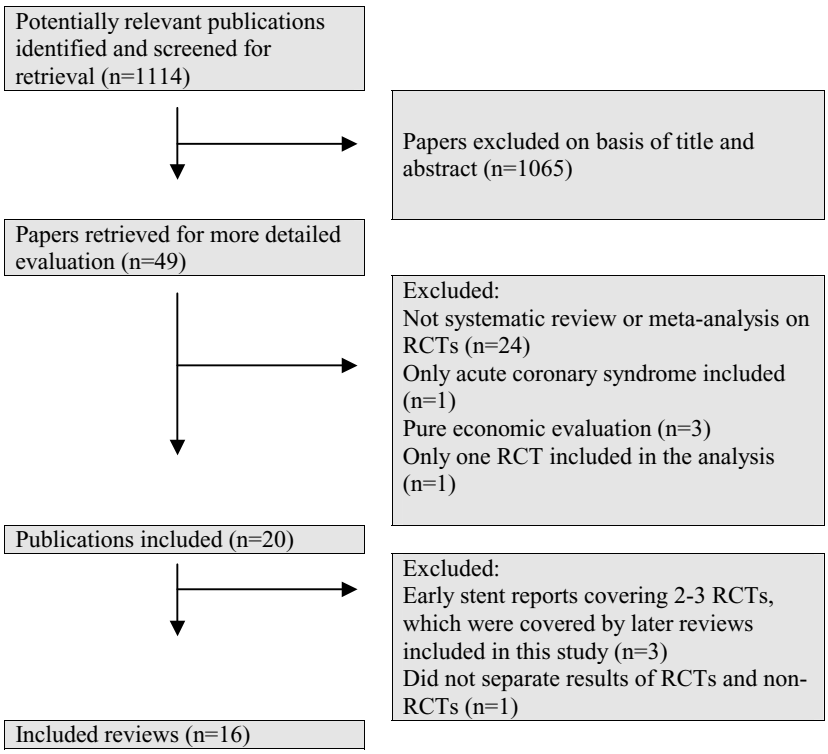

Figure 1. Flow diagram of inclusion/exclusion of systematic reviews. RCT, randomized clinical trial.

severity, and extent (1;7;17;19). The description of interventions was sufficient for judging applicability, but settings were poorly described. All primary outcomes, as defined in this study, were given in six reviews (2;5;10;18;21;22). At least one primary end point and complications were described in only nine of the reviews, hampering the evaluation of trade-offs between benefits and harms (1;5;7;8;14;15;19;22;25).

Data Synthesis

Quantitative results were given in thirteen papers (2–5;9;10;13–15;17;19;22;25). The remaining six reports gave a descriptive synthesis of the collected data (1;7;8;18;21;23). Because of this heterogeneity, we summarized clinical effectiveness qualitatively. Most of the reviews showed no effectiveness in survival rates or the risk of myocardial infarction (Table 4). Systematic reviews comparing off-pump and on-pump surgery reported only surrogate end points or perioperative outcomes. Results by outcome where effectiveness was shown are summarized below.

The risk of death can be reduced by CABG compared with medical treatment in high-risk patients (21;23;25). In two of eight reports where death was given as the outcome measure, CABG was considered to reduce mortality compared with a percutaneous procedure (10;21).

In one systematic review, the risk of nonfatal *myocardial infarction* was found to be lower after PCI with stent than after CABG at 3 years (risk difference [RD], −2.9 percent; 95 percent confidence interval [CI], −5.1—0.6 percent; $p = .01$) (10).

Repeated Revascularization. Bucher et al. (5) observed an increased need for CABG after PCI without stent (relative risk, 1.59; 95 percent CI, 1.09–2.32) compared with medical treatment. The need for repeated revascularization constantly has been reported to be greater after performing percutaneous procedures than after CABG in all ten referred papers. PCI with stenting was also found to be associated with a higher risk of repeated revascularization: 19.0 percent for stenting versus 4.7 percent for CABG (odds ratio [OR], 4.6; 95 percent CI, 3.5–5.9; follow-up 16 months) (2). According to Hoffman et al. (10) the risk of additional PCI or CABG was higher after PCI (including four studies with stent) than after CABG (RDs, 24 percent to 38 percent; $p = .001$, follow-up 8 years). Hill et al. (9) reported that data for single-vessel trials is limited, but in the one reporting trial, CABG shows benefits over stents. Two studies on multiple-vessel disease (ARTS and SOS) reported a statistically significant advantage of CABG over PCI with stenting (OR, 0.16; 95 percent CI, 0.12–0.23) (9) at 1 year.

In the hierarchical Bayesian meta-analysis of Brophy et al. (4), there was no evidence to suggest a difference between routine coronary stenting and PCI without stenting in terms of a need for coronary artery bypass surgery (OR, 1.01; credible interval, 0.79–1.31). Coronary stenting reduced the need for repeated PCI (OR, 0.59; credible interval,

https://doi.org/10.1017/S026646230605104X Published online by Cambridge University Press

Table 1. Study Characteristics of the Systematic Reviews

	Objective of the paper	Information sources	Number of studies included	Population sum	Follow-up
1. CABG vs medical treatment					
Yusuf et al. (25)	The primary objective was to assess the effectiveness of CABG compared with initial medical therapy of up to 10 years mortality among patients with stable CAD. The secondary aims were to assess the interaction between the extent of CAD and the degree of LV dysfunction and the effect of CABG surgery.	Not stated	7 RCTs	1,324 CABG 1,325 medical tx	Up to 10 years
Sculpher et al. (21)	To update earlier reviews of the effectiveness of treatment for chronic stable angina and (i) assess medical tx and newer technologies such as stents (ii) a broader assessment of patient benefits (iii) consideration of costs and cost effectiveness.	Clinical effectiveness: MEDLINE, Health Planning and Administration, NHS CRD DARE database, BIDS, Cochrane Library, Dissertation Abstracts Online, EMBASE, PsycINFO, Social SciRearch. HRQoL MEDLINE. Expert panel feedback. Only English language, studies not included RAND or SBU 1982–93. 1982–96—12/1997.	197 total. 148 clinical effectiveness, 24 health-related QoL, 25 cost and cost-effectiveness. RCTs: Medical tx vs CABG 8, Medical tx vs PTCA 5, PTCA vs CABG 9, PTCA with non-medical adjuncts 12 papers	Not stated	Up to 10 years
Solomon and Gersh (23)	To review the available data on the treatment of chronic stable angina and formulate a rational approach for the use of pharmacological therapy, PTCA, and CABG.	MEDLINE, abstract presented at AHA and ACC meetings, reference list of identified articles. 1976–1996, English-language.	3 medical tx vs PTCA (3 RCTs) 7 medical tx vs CABG (3 RCTs) 9 PTCA vs CABG (6 RCTs)	Not stated	Up to 10 years
2. PCI without stent (PTCA) vs medical treatment					
Sculpher et al. (21)	See above				Up to 3 years
Solomon and Gersh (23)	See above				Up to 2 years
Bucher et al. (5)	Whether PTCA is superior to medical tx in non-acute CAD.	MEDLINE, Embase, Cochrane database, Biological Abstracts, Health Periodicals Database, PASCAL. Citations from relevant articles and previous reviews. 1979–1998, only English.	6 RCTs	PTCA, 953; Medical tx, 951	6–57 months

Table 1. Continued

	Objective of the paper	Information sources	Number of studies included	Population sum	Follow-up
3. PCI without stent (PTCA)/PCI with stent vs CABG					
Gunnell et al. (8)	To review, from the purhaser's perspective, the current state of knowledge of techniques for investigation and treating CAD. The study was based on evidence from past and continuing RCTs.	Medline 1990–1993. Papers before 1990 were obtained from two RAND publications in 1991 and from papers obtained using Medline search. Hand search of relevant journals July 1993–June 1994.	Total 10, 6 RCTs	Not stated	1–3 years
Pocock et al. (19)	Report on a meta-analysis combining the evidence from PTCA vs CABG trials to assess the relative merits of the two approaches.	Own expertise, cardiological meeting, "collective awareness"	8 RCTs	3,371: 1,661 CABG, 1,710 PTCA	Mean 2.7 years (1–4.7)
Sim et al. (22)	A meta-analysis of all reported randomized trials directly comparing CABG with PTCA in patients with multivessel disease.	Medline, BIOSIS. English language studies, 1985–1995	5 RCTs	Total 2,943: 1,449 CABG, 1,494 PTCA	1–3 years
Solomon and Gersh (23)	See above				1–5 years
Perleth (18)	(i) What is the comparative effectiveness of PTCA/CABG as an initial therapy when they are considered interchangeable? (ii) What are the indications of PTCA/CABG? (iii) What is the long-term prognosis of the used method?	MEDLINE, EMBASE, HealthStar, Cochrane library, DARE, INAHTA project database (Cochrane), Reference lists and Internet until 1998 in electronic databases, complemented until Nov 1999.	RCTs 9. Systematic reviews, meta-analyses and HTAs 8	From RCTs 5,272	1–8 years
Sculpher et al. (21)	See above				Up to 5 years
Meads et al. (13)	1. What are the effects and effectiveness of elective stent insertion versus PTCA in subacute IHD, particularly stable angina and unstable angina? 2. What are the effects and effectiveness of elective stent insertion versus CABG in subacute IHD, particularly stable angina and unstable angina?	Electronic databases (MEDLINE, EMBASE, BIDS ISI, The Cochrane Library), Internet sites, and hand-searches of cardiology conference abstracts and 1999 issues of cardiology journals. Lead researchers and local clinical experts were contacted. Manufacturers' submissions to the National Institute for Clinical Excellence were searched. Search up to Nov 1999.	RCTs: 25 stent vs PTCA and 3 stent vs CABG in subacute IHD	Not stated	Up to 30 days

Biondi-Zoccai et al. (2)	A systematic overview of the reported RCTs that directly compared a strategy of coronary revascularization with CABG vs percutaneous coronary stenting in patients with CAD.	MEDLINE, ISI Current Contents, LILACS, the Cochrane Collaboration Controlled Trials Register Jan 1986–Feb 2003. Meta-Register of the Current Controlled Trials and the National Research Register (National Health Service-NHS, UK). Conference proceedings from the 1998–2002 American College of Cardiology, American Heart Association, European Society of Cardiology and Transcatheter Cardiovascular Therapeutics annual scientific sessions were hand-searched. Major reviews on coronary stents were systematically searched in MEDLINE, in the Database of Abstracts of Reviews of Effectiveness (DARE), in the NHS Economic Evaluation Database and in the Health Technology Assessment Database. Cross-references and quoted papers were checked and experts contacted to identify other relevant trials. No language restriction.	9 RCTs	3,283	Average 28 months (6–36)
Hill et al. (9)	Effectiveness and cost-effectiveness of the use of coronary artery stents in patients with CHD.	MEDLINE, EMBASE, Science Citation Index/Web of Science, Cochrane Trials Register (CCTR) (2002, 4), Cochrane Database of Systematic Reviews (CDSR), Health Technology Assessment (HTA), Database of Abstracts of Reviews of Effectiveness (DARE), Science Citation Index/ISI Proceedings. Reference lists of included studies and pharmaceutical company submissions were searched for to identify other relevant studies. Hand searching of recent issues of cardiology journals, hand-searching of cardiology conference proceedings. Internet resources. Searching was limited to English language reports. Search period 1990 Dec 2002.	RCTs: Stent vs PTCA 50 (11 AMI), Stent vs CABG 6, Stent vs DES 12	PTCA > 16,500; CABG, 3,085; DES, 4,367	6–12 (36) months

Table 1. Continued

	Objective of the paper	Information sources	Number of studies included	Population sum	Follow-up
3. PCI without stent (PTCA)/PCI with stent vs CABG					
Hoffman et al. (10)	Probabilities of death, nonfatal MI, angina, and revascularization for up to 8 years following initial CABG or PTCA. Examine relative benefits in subgroups with isolated proximal LAD, multivessel disease, diabetes, and trials with and without stents in the initial PTCA strategy.	MEDLINE, bibliographies of retrieved articles, including previous meta-analyses, personal files, and expert consultation. 1966–2001. One paper 2002.	13 RCTs	7,964	1–8 years
4. PCI with stent vs PCI without stent (PTCA)					
Sculpher et al. (21)	See above				1–5 years
Meads et al. (13)	See above				0.5–5 years
Brophy (3)	To summarize results from all randomized clinical trials comparing routine coronary stenting with standard PTCA.	PubMed, MEDLINE, hand-searching 9 journals, references from original articles and 3 reviews. Clinical trials only, reviews excluded, search period 1993–June 2002.	RCTs 29	9,918	6–16 months
Hill et al. (9)	See above				0.5–5 years
Nordmann et al. (15)	To evaluate whether the routine use of stents compared with balloon angioplasty reduces mortality and improves clinical outcome in patients with non-acute coronary artery disease.	MEDLINE, Embase, Pascal, Index Medicus, the Cochrane Library, and abstracts from cardiology conferences. We searched for all references of relevant articles for additional trials and, if necessary, contacted authors of identified trials to ask for additional information. 1979–March 2003.	RCTs 19	8,004	Up to 12 months
5. Drug-eluting stent vs bare metal stent					
Brophy et al. (4)	This report aims to (i) summarize our knowledge regarding drug-eluting stents, (ii) interpret this scientific evidence in the MUHC context, and (iii) provide estimates of the expected costs and benefits so as to assist the administration in deciding on the appropriate place for this technology.	Not stated	RCTs 7	RCTs: 1,621treatment + 1,567 control	Up to 1 year
Hill et al. (9)	See above				6–12 month (RAVEL-study 2 years)
Grip and Brorsson (7)	Not stated	Hill, (9) + PubMed until 25 Feb 2004	RCTs 7, one register study	3,559	9–12 months

6. Off-pump vs on-pump surgery					
MSAC (14)	This report summarizes the assessment of current evidence for off-pump coronary artery bypass surgery in the treatment of coronary artery disease.	Cochrane Library, Current Contents, EMBASE, HealthStar, MEDLINE, SCI, Clinical Trials Database (US), NHS CRD (UK), NHS HTA (UK), National Research Register (UK), Ann Thoracic J, Heart Lung and Circulation, JACC. Australian Medical Index; Consumers' Health Forum (Australia); National Heart Foundation (Australia); Cardiothoracic Surgery Network database; United States Veterans Affairs database; The Pennsylvania Consumer Guide to CABG Surgery; MedMark Medical Bookmarks (http://members.kr.inter.net/medmark/chest/); Cardiac Surgery Information home page (http://heart-surgeon.com/); and Cardiothoracic Surgery, CPG Infobase (Canadian Medical Association) (http://www.cma.ca/cpgs/cardtho.htm). No language restriction. Until October 2001.	32 studies, 7 RCTs	RCTs: 232 patients	Mostly perioperative follow-up, one study mean 13.4 months follow-up
NICE (1)	This overview has been prepared to assist members of IPAC, advice on the safety and efficacy of an interventional procedure previously reviewed by SERNIP.	MEDLINE, PREMEDLINE, EMBASE, Current Contents, PubMed, Cochrane Library and Science Citation Index. The York Centre for Reviews and Dissemination, Clinicaltrials.gov, National Research Register, SIGLE, Grey Literature Reports (2002), relevant online journals and the Internet were also searched. Conference abstracts and manufacturer's information. Until November 2002 without language restriction.	RCTs 4, one HTA with 7 RCTs	Not stated	Up to 1 year
Parolari et al. (17)	The aim of this study is to assess the differences in clinical outcomes between CABG and OPCAB by meta-analysis of data published in randomized trials.	MEDLINE and PubMed databases from January 1990 to May 2002, to which a manual bibliography review was added. The Cochrane Controlled Trials Register and the Cochrane Medical Editors Trial Amnesty of unpublished clinical trials were searched using the same strategy. English language.	RCTs 9.	1,090: 558 CABG, 532 OPCAB	30 days

RCT, randomized clinical trial; tx, treatment; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass graft; OPCAB, off-pump coronary artery bypass; PCI, percutaneous coronary intervention; LV, left ventricle; CAD, coronary artery disease; MI, myocardial infarction; LAD, left anterior descending; AHA, American Heart Association; ACC, American College of Cardiology; DES, drug-eluting stent; QoL, quality of life.

Table 2. Inclusion Criteria of Trials in the Systematic Reviews

	Design	Population	Intervention	Control intervention	Outcome	Follow-up	Exlusion criteria
1. CABG vs medical treatment							
Yusuf et al. (25)	Randomly assigned CABG or medical tx	Stable CHD not severe enough to necessitate surgery on grounds of symptoms alone or MI	CABG	Medical tx. (Overall population beta-blocker 47.4%, antiplatelet agents 3.2%.)	Not stated	At least 10 years	Surgery necessary, MI
Sculpher et al. (21)	For non-drug studies, one of the following: RCT, UK-based observational study (>1,000 patients or comparative), North American, Australasian or European observational study (>1,000 patients)	Chronic stable angina	PTCA; CABG	Medical tx	Clinical effectiveness, HRQoL	Not stated	Not stated
Solomon and Gersh (23)	Primary research articles, meta-analyses	Chronic stable angina	PTCA, CABG	Medical tx	Not stated	Not stated	Not stated
2. PCI without stent (PTCA) vs medical treatment							
Sculpher et al. (21)	See above						
Solomon and Gersh (23)	See above						
Bucher et al. (5)	Random allocation	Non-acute coronary heart disease	PTCA	Medical tx	Not stated	Not stated	Acute myocardial infarction for at least 1 week before randomization
3. PCI without stent (PTCA)/PCI with stent vs CABG							
Gunnell et al. (8)	RCT	Coronary disease, angina, unstable angina	PTCA	CABG (drug)	Not stated	Not stated	Not stated
Pocock et al. (19)	Randomized trials	angina	PTCA	CABG	Deaths, MI, additional CABG, additional PTCA	Not stated	Not stated
Sim et al. (22)	Randomized trials	Multivessel disease	CABG	PTCA	Death, death+ non-fatal MI, freedom from angina, or with CABG, or with PTCA	Not stated	Not stated
Solomon and Gersh (23)	See above						
Perleth (18)	RCT, HTA, systematic review or meta-analysis based on RCTs	Not stated	PTCA	CABG	Not stated	Not stated	Not stated
Sculpher et al. (21)	See above						

Meads et al. (13)	RCT	Adults with IHD in native or graft vessels (subacute IHD and AMI)	Elective insertion of coronary artery stents	Elective PTCA or CABG	Outcomes defined as one or more of: combined event rate (or event-free survival), death, MI, angina, target vessel revascularization, CABG, repeat PTCA, angiographic outcomes	Not stated	1. not finished recruiting 2. only interim results 3. results of only some of participants 4. no detail of number of patients 5. not comparison elective stenting vs PTCA or CABG
Biondi-Zoccai et al. (2)	RCT	Not stated	Percutaneous coronary revascularization with stenting	CABG	Death, non-fatal MI or stroke, revascularization, freedom from angina (CCS <2), death or MI or stroke	≥1 month	(i) equivocal treatment allocation process, (ii) severe imbalances in major baseline characteristics among study groups, (iii) incomplete (<80%) follow-up, and (iv) non-systematic (<90%) coronary stent use over total percutaneous procedures
Hill et al. (9)	RCT	1. Adults with CAD in native or graft vessels 2. Patients with stable angina or Acute Coronary Syndrome, which includes AMI (ST segment elevation and depression, Q wave and non-Q wave) and unstable angina	Coronary artery stents of any type inserted as an elective procedure	1.PTCA without stent vs PTCA with stent 2. Stent vs CABG 3. Non drug-eluting stent vs drug-eluting stent	Included if they reported one or more of the following outcomes: combined event rate or event free survival; death; AMI; target vessel revascularization (TVR); repeat treatment (PTCA, Stent or CABG) and binary stenosis (greater than 50%)	Not stated	RCTs that continue recruit patients, provide only unplanned, interim findings, provide data on only a subgroup of patients. Comparisons of PTCA with stents with medical management, single-vessel vs multiple-vessel stenting, various stent designs, anticoagulant or antiplatelet comparisons, PTCA or stenting to other PCI interventions
Hoffman et al. (10)	RCT	Multivessel or proximal LAD in candidates for either procedure	CABG	PTCA, 4 papers with stents	Not stated	Not stated	AWESOME because of patient with severe left ventricular dysfunction, ongoing/recent MI, prior heart surgery
4. PCI with stent vs PCI without stent (PTCA)							
Sculpher et al. (21)	See above						
Meads et al. (13)	See above						
Brophy (3)	RCT	Not stated	Routine stenting	PTCA	Death, MI, repeated angioplasty of the target lesion	At least 6 months follow-up	Acute MI, comparison with other percutaneous, medical or surgical techniques, comparative studies of different stent models

Table 2. Continued

	Design	Population	Intervention	Control intervention	Outcome	Follow-up	Exlusion criteria
Hill et al. (9)	See above						
Nordmann et al. (15)	Randomization to stents or balloon angioplasty prior the procedure	Intervention in native coronary artery	Stent	PTCA	Reporting death or MI	At least 6 months' follow-up	Patients with AMI where angioplasty was done within 48 hr after diagnosis, trials that exclusively randomized patients to provisional stenting and trials where patients were randomized after angioplasty only
5. Drug-eluting stent vs bare metal stent							
Brophy et al. (4)	RCT + observational	Not stated	DES	BMS	Not stated	Not stated	Not stated
Hill et al. (9)	See above						
Grip and Brorsson (7)	RCT + one register study	Not stated	DES	BMS	Not stated	Not stated	Not stated
6. Off-pump vs on-pump surgery							
MSAC (14)	RCT, CCT; letters, conference material, commentary, editorials and abstracts were included as background information for both procedures	Non-pregnant adult (= 18 years of age) human patients undergoing treatment for single- or multiple-vessel coronary artery disease	The included studies related to the use of coronary artery bypass surgery performed on a beating heart without the aid of CPB; specifically, OPCAB performed in conjunction with a mechanical (not hand-held) coronary tissue stabilizer. OPCAB via full median sternotomy.	CABG, via full median sternotomy, with centrally cannulated CPB on an asystolic or beating heart	Perioperative and postoperative mortality (short- and long-term). Perioperative and postoperative morbidity. Perioperative and early postoperative factors. Evaluation of graft patency. Convalescence of patients	Not stated	Data derived from patients who underwent OPCAB in a hybrid procedure with PTCA or in conjunction with any other cardiac procedure, such as mitral valve repair, use of more than one category of mechanical stabilizer were excluded. Pooling of data from different surgical approaches was excluded unless the data subset for the full median sternotomy approach could be separated from the aggregate data
NICE (1)	RCTs, other controlled or comparative studies, case series, and case reports	Not stated	Not stated	Not stated	Safety and efficacy data	Not stated	Not stated

Parolari et al. (17)	Prospective randomized studies comparing CABG and OPCAB	(i) Low- to average-risk patients included in the study (studies performed only on high-risk or very high-risk patients were excluded); 2) Average number of grafts per patient at least two	OPCAB	CABG, myocardial protection with cardioplegia in the CABG group	Data about three major perioperative complications (death, myocardial infarction, and stroke) occurring during the first 30 days postoperatively reported in the study	The first 30 days postoperatively	Studies performed only on high-risk or very high-risk patients

CABG, coronary artery bypass graft; CHD, coronary heart disease; CAD, coronary artery disease; tx, treatment; MI, myocardial infarction; HRQoL, health-related quality of life; PTCA, percutaneous transluminal coronary angioplasty; RCT, randomized controlled trial; UK, United Kingdom; PCI, percutaneous coronary intervention; HTA, health technology assessment; IHD, ischemic heart disease; AMI, acute myocardial infarction; CCS, Canadian Cardiovascular Society class; LAD, left anterior descending; OPCAB, off-pump coronary artery bypass.

Table 3. Quality Assessment for Each of the 19 Identified Eligible Systematic Reviews

Author, year	Search methods	Comprehensiveness of the search	Inclusion criteria	Avoidance of selection bias	Definition of the validity assessment criteria	Validity assessment criteria used	Summarize methods reported	Accessibility of the study combination method	Data and analysis supports the reviewers' conclusions	Total (max 18 points)
Nordmann et al. (15)	2	2	2	1	2	2	2	2	2	17
Meads et al. (13)	2	2	2	1	2	2	2	2	2	17
Hill et al. (9)	2	2	2	1	2	2	2	2	2	17
Bucher et al. (5)	2	2	2	1	2	2	2	2	2	17
Perleth (18)	2	2	2	0	2	2	2	2	2	16
Biondi-Zoccai et al. (2)	2	2	2	0	2	2	2	2	2	16
Sculpher et al. (21)	2	2	2	1	2	2	1	1	1	14
MSAC (14)	2	2	2	0	1	1	2	2	2	14
Parolari et al. (17)	2	2	2	1	0	0	2	2	2	13
Brophy et al. (4)	2	2	2	1	0	0	2	2	2	13
Hoffman et al. (10)	2	2	2	0	0	0	2	2	2	12
Sim et al. (22)	2	2	1	0	0	0	2	2	2	11
Gunnell et al. (8)	2	2	2	0	0	0	2	2	1	11
Grip and Brorsson (7)	2	1	2	0	0	0	2	2	2	11
Yusuf et al. (25)	0	0	2	0	0	0	2	2	2	8
Solomon and Gersh (23)	2	2	1	0	0	0	1	1	1	8
Brophy (3)	0	0	2	0	0	0	2	2	2	8
Pocock et al. (19)	0	0	1	0	0	0	2	2	2	7
NICE (1)	1	2	0	0	0	0	1	1	1	6

Table 4. Summary of Effectiveness Data for Death, MI, Revascularization, and Angina Provided by the 19 Systematic Reviews on Six Intervention Contrasts[a]

Intervention contrast (Intervention vs control)	Outcome	No. of meta-analyses and systematic reviews	Intervention more effective	No detected difference	Control more effective
1. CABG vs medical treatment		3			
	Death		3		
	MI				
	Revascularization				
	Angina		1		
2. PCI without stent (PTCA) vs medical treatment		3			
	Death			2	
	MI			3	
	Revascularization				1
	Angina		3		
3. PCI without stent (PTCA)/PCI with stent vs CABG		10			
	Death			6	2
	MI		1	6	
	Revascularization				10
	Angina				7
4. PCI with stent vs PCI without stent (PTCA)		5			
	Death			4	
	MI			4	
	Revascularization		4		
	Angina				
5. Drug-eluting stent vs bare metal stent		3			
	Death			3	
	MI			3	
	Revascularization		2		
	Angina				
6. Off-pump vs on-pump surgery		3			
	Death				
	MI				
	Revascularization				
	Angina				

[a] Numbers of reviews in terms of differences in effectiveness in each intervention contrast is shown. There is overlapping due to more than one intervention contrast in some reviews.
MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

0.50–0.68). Routine stenting probably reduces the need for repeated angioplasty by fewer than 4 to 5 per 100 persons treated compared with PCI with provisional stenting. Nordmann et al. (15) reported additional events prevented per 1,000 patients (95 percent CI) treated with stents rather than balloon angioplasty at three time points (30 days, 6 months, and 12 months): revascularization of the target vessel 3 (−2 to 8), 55 (40 to 71), and 46 (25 to 66); coronary artery bypass grafting −1 (−6 to 4), 3 (−5 to 10), and 0 (−10 to 10).

In a comparison between drug-eluting stents and bare metal stents, Brophy (3) reported a reduced need for revascularization at 6 months (OR, 0.35; 95 percent CI, 0.27–0.44), but no difference in the subsequent CABG rate. Grip and Brorsson (7) reported that the need for repeated procedures is lower with drug-eluting stents than with bare metal stents: paclitaxel stent 3.3 percent versus BMS 12.2 percent; sirolimus stent 4.0 percent versus BMS 20.6 percent, with follow-up times of between 9 and 12 months.

CABG and PCI appear to relieve *angina pectoris* better than medical treatment (21;23). CABG was found to give invariable relief of angina in seven of seven studies that compared percutaneous procedures with CABG and that reported angina as the outcome. Biondi-Zoccai et al. (2) found that stenting was associated with a significantly higher risk of symptomatic angina (Canadian Cardiovascular Society class [CCS], 2 or higher): 18.4 percent for stenting versus 8.9 percent for CABG (OR, 2.3; 95 percent CI, 1.8–2.8; follow-up, 12 months). In a report by Hoffman et al. (10), patients treated with CABG had a 10 percent ($p = .001$) lower risk of angina than those treated with PCI after 1 and 3 years. After 5 years, the risk difference was 5.3 percent ($p =$ not significant), respectively.

DISCUSSION

Several systematic reviews and meta-analyses have been conducted on invasive treatments for stable coronary heart

https://doi.org/10.1017/S026646230605104X Published online by Cambridge University Press

disease. These reviews provide an important source for clinical and health policy decision making, as well as for clinical guidelines. Thus, there is a dire need for a critical appraisal of the content and methodological quality of the reviews. A systematic review of systematic reviews can give an overall view of the current knowledge of the effectiveness of invasive treatments for stable coronary heart disease. A broader understanding seems important as there are several intervention options available and the systematic reviews focus only on one intervention contrast at a time. From a health policy point of view, the manifold differences in intervention frequencies call for a better understanding of this field: in the United States, invasive procedures are carried out five times as often as in the United Kingdom (9;20).

The reviews identified in the current study address all the clinically important intervention contrasts relevant to invasive treatment for stable ischemic heart disease. However, many review articles did not describe in detail the patient populations included and present only some of the relevant outcome characteristics. Some reviews use composite end points, and appraisal of the specific outcomes is not possible. Adverse effects of intervention are rarely reported. There are also shortcomings in the design of the reviews: a lack of unbiased selection of the primary studies is common and validity assessments of the trials are often lacking. The heterogeneity of the primary studies is only reported in some of the reviews.

As we have undertaken an overview of systematic reviews, and not assessed the primary studies, all inferences on the effectiveness must be considered with due caution. We may conclude that CABG is more effective than medical treatment in terms of reducing mortality among high-risk patients as defined by Yusuf et al. (25), although the data do not reflect the current treatment praxis, neither operative nor conservative. PCI without stenting is also more effective than medical treatment in terms of angina relief, but again, data from the referred trials are too old to warrant valid conclusions for today because of advances both in interventional techniques and in medical treatment. CABG gives better relief for angina, and the need for repeated procedures is less frequent after CABG than after percutaneous interventions. PCI with bare metal stent is better than PCI without stent in terms of a less-frequent need for repeated percutaneous coronary procedures, although there is no evidence of any difference in mortality or in the rate of myocardial infarctions. Apparently, repeated percutaneous coronary procedures are done less frequently after drug-eluting stents than after bare metal stents, but there is no evidence of a difference in the need for bypass grafting or in mortality or myocardial infarctions. The data are insufficient to draw any conclusions on whether off-pump is more effective than on-pump CABG.

Subgroup analyses, for example, on the best indications for each intervention, rarely have been executed, perhaps sometimes because of a lack of data (9;10;15;18). This finding hampers our chances of making conclusions about optimal treatments in major subgroups. However, Hoffman et al. (10) showed that, for diabetic patients, CABG provided a significant survival advantage over PCI at 4 years but not at 6.5 years. Our inference of the review by Perleth (18) is that CABG is more powerful than PCI without stents in providing 5-year survival in diabetic patients in comparison with medical treatment. Hill et al. (9) also concluded that diabetics are a particularly high-risk group after stenting but not after CABG. Limited existing data indicate that the benefits of drug-eluting stents are maintained in diabetics (9).

There are some weaknesses and potential biases in our methodology. Some reviews base their inferences not only on RCTs but also on health technology appraisals and even on cohort studies, making the inference chain not transparent. The case mix of patients in some reviews includes some unstable anginas, which constitutes a potential confounding factor in our review. Publication bias as an inherent validity issue for any systematic review may favor the effectiveness of interventions.

As some of the current systematic reviews clearly are out of date because of rapidly evolving invasive and medical treatment, we think that there is a need for rigorously designed systematic reviews on all the important intervention contrasts. In particular, a systematic review on PCI versus contemporary medical treatment would be valuable. Because of the rapid diffusion of new technology, cumulative meta-analyses might be the design of choice. We think that all trialists should consider whether it is ethically acceptable to add a medical treatment arm in all studies on invasive treatment of coronary heart disease.

We conclude that the evidence for invasive treatment on survival is limited, partly because of difficulties in detecting differences in rare end points. Revascularization appears not to decrease the risk of myocardial infarction. Evidence is much stronger on the potential of invasive treatments to provide symptomatic relief. Surgery seems to provide a longer-lasting effect than percutaneous interventions with bare metal stents or without stents. Evidence in favor of drug-eluting stents to date is based on short-term follow-up and mostly on patients with single-vessel disease. As progress has also been made in medical treatment, there is an urgent need for more data on the effectiveness of all the treatment options.

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REFERENCES

1. ASERNIP-S. *Interventional procedure overview of off-pump coronary artery bypass (OPCAB)*. London: NICE; 2002.
2. Biondi-Zoccai GG, Abbate A, Agostoni P, et al. Stenting versus surgical bypass grafting for coronary artery disease: Systematic overview and meta-analysis of randomized trials. *Ital Heart J*. 2003;4:271-280.
3. Brophy J. An evaluation of drug eluting (coated) stents for percutaneous coronary interventions; What should their role be at the McGill University Health Centre (MUHC)? Montreal: The Technology Assessment Unit (TAU) at McGill University Health Centre (MUHC); 2003.
4. Brophy JM, Belisle P, Joseph L. Evidence for use of coronary stents. A hierarchical bayesian meta-analysis. [see comment][summary for patients in *Ann Intern Med*. 2003;138:I15; PMID: 12755584]. *Ann Intern Med*. 2003;138:777-786.
5. Bucher HC, Hengstler P, Schindler C, Guyatt GH. Percutaneous transluminal coronary angioplasty versus medical treatment for non-acute coronary heart disease: Meta-analysis of randomised controlled trials. [see comment]. *BMJ*. 2000;321:73-77.
6. *European health for all database*. Copenhagen, Denmark: WHO Regional Office for Europe; 2004.
7. Grip L, Brorsson B. *Läkemedelsavgivande stentar i hjärtats kransartärer*. Stockholm, Sweden: SBU; 2004.
8. Gunnell D, Harvey I, Smith L. The invasive management of angina: Issues for consumers and commissioners. *J Epidemiol Community Health*. 1995;49:335-343.
9. Hill R, Bagust A, Bakhai A, et al. Coronary artery stents: A rapid systematic review and economic evaluation. *Health Technol Assess*. 2004;8:iii-iv, 1-242.
10. Hoffman SN, TenBrook JA, Wolf MP, et al. A meta-analysis of randomized controlled trials comparing coronary artery bypass graft with percutaneous transluminal coronary angioplasty: One- to eight-year outcomes. *J Am Coll Cardiol*. 2003;41:1293-1304.
11. Hoving JL, Gross AR, Gasner D, et al. A critical appraisal of review articles on the effectiveness of conservative treatment for neck pain. *Spine*. 2001;26:196-205.
12. Khan K, Kunz R, Kleijnen J, Antes G. Systematic reviews to support evidence-based medicine. How to review and apply findings of healthcare research. London: Royal Society of Medicine Press Ltd; 2003.
13. Meads C, Cummins C, Jolly K, et al. Coronary artery stents in the treatment of ischaemic heart disease: A rapid and systematic review. *Health Technol Assess*. 2000;4:1-153.
14. Medical Services Advisory Committee. Off-pump coronary artery bypass (OPCAB) with the aid of tissue stabilisers. Canberra, Australia: MSAC; 2001. Report No. MSAC reference 11.
15. Nordmann AJ, Hengstler P, Leimenstoll BM, et al. Clinical outcomes of stents versus balloon angioplasty in non-acute coronary artery disease. A meta-analysis of randomized controlled trials. *Eur Heart J*. 2004;25:69-80.
16. Oxman AD, Guyatt GH. Validation of an index of the quality of review articles. *J Clin Epidemiol*. 1991;44:1271-1278.
17. Parolari A, Alamanni F, Cannata A, et al. Off-pump versus on-pump coronary artery bypass: Meta-analysis of currently available randomized trials. *Ann Thorac Surg*. 2003;76:37-40.
18. Perleth M. *Vergleichende Effektivität und Differentialindikation von Ballondilatation (PTCA) versus Bypasschirurgie bei Ein- und Mehrgefäßerkrankungen der Hertzkranzgefäße*. Hannover, Deutschland: Aufbau einer Datenbasis "Evaluation medizinischer Verfahren und Technologien" in der Bundesrepublik; 2000.
19. Pocock SJ, Henderson RA, Rickards AF, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. [see comment]. *Lancet*. 1995;346:1184-1189.
20. Rihal CS, Raco DL, Gersh BJ, Yusuf S. Indications for coronary artery bypass surgery and percutaneous coronary intervention in chronic stable angina: Review of the evidence and methodological considerations. *Circulation*. 2003;108:2439-2345.
21. Sculpher MJ, Petticrew M, Kelland JL, et al. Resource allocation for chronic stable angina: A systematic review of effectiveness, costs and cost-effectiveness of alternative interventions. *Health Technol Assess*. 1998;2:i-iv, 1-176.
22. Sim I, Gupta M, McDonald K, Bourassa MG, Hlatky MA. A meta-analysis of randomized trials comparing coronary artery bypass grafting with percutaneous transluminal coronary angioplasty in multivessel coronary artery disease. *Am J Cardiol*. 1995;76:1025-9.
23. Solomon AJ, Gersh BJ. Management of chronic stable angina: Medical therapy, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft surgery. Lessons from the randomized trials. *Ann Intern Med*. 1998;128:216-223.
24. van Tulder M, Furlan A, Bombardier C, Bouter L. Updated method guidelines for systematic reviews in the Cochrane collaboration back review group. *Spine*. 2003;28:1290-1299.
25. Yusuf S, Zucker D, Peduzzi P, et al. Effect of coronary artery bypass graft surgery on survival: Overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. [see comment][erratum appears in *Lancet*. 1994;344:1446]. *Lancet*. 1994;344:563-570.