International Journal of Technology Assessment in Health Care, **22:4** (2006), 484–496.

Reanalysis of systematic reviews: The case of invasive strategies for acute coronary syndromes

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Objectives: The objective of this study was to collect all systematic reviews on invasive strategies for acute coronary syndromes (ACS) and reanalyze the data in these reviews to reach combined estimates, as well as to make predictions on the effectiveness and risk of harm so as to facilitate relevant decision making in health care.
Methods: The data sources used were the following electronic databases, searched from 1994 to September 2004: Cochrane Database of Systematic Reviews; Cochrane Central Register of Controlled Trials; DARE, HTA, EED (NHS CRD); MEDLINE(R) In-Process, Other Non-Indexed Citations, MEDLINE(R), and PubMed (2000 to 2004). References to the identified systematic reviews were checked. An ancillary search to identify recent randomized controlled trials (RCTs) covering the period from January 2003 to January 2006 was done in MEDLINE(R). We included systematic reviews of RCTs on patients with ACS. In unstable angina and non–ST-elevation myocardial infarction (UA/NSTEMI), eligible reviews had to compare early routine invasive strategy with early selective invasive strategy. In ST-elevation myocardial infarction (STEMI), a comparison between primary percutaneous coronary intervention (PCI) and thrombolytic therapy was required. The methodological quality of the reviews was assessed, and a standardized data extraction form was used. Results for the main outcomes of the RCTs in the reviews were reanalyzed. An additional search of those RCTs not included in the meta-analyses was performed for UA/NSTEMI and short-term morality data on STEMI. Bayesian models were constructed to estimate the uncertainty about a possible treatment effect and to make predictions and probability statements. Main results are based on these analyses. Mortality was considered as the primary outcome measure.
Results: One systematic review on invasive strategies was identified for UA/NSTEMI and nine on invasive strategies for STEMI. Five reviews of the latter that were published after the year 2000 were included for the final analysis. The median quality score was 10.5 (range, 7–13; $n = 6$) on a scale from 0 to 18 points. An updated literature search identified one further RCT on UA/NSTEMI. Regarding NSTEMI and mortality, the average risk difference favoring an early invasive treatment strategy compared with early conservative strategy was .6 percent (95 percent credible interval [CrI], −2.1 to 1.0). Predicted risk (relative risk/risk difference scales) of doing harm was 26.7/26.6 percent. Regarding STEMI and mortality, the absolute risk reduction in favor of primary PCI over thrombolysis

Conflict of Interest Statements: No conflicts of interest to declare. Role of the funding source: This work has been carried out without external funding.

was 4.1 percent (95 percent CrI, −7.1 to −1.1) when PCI was compared with streptokinase and 1.2 percent (95 percent CrI, −2.7 to .2) when compared with fibrin-specific thrombolytics. Predicted risk of harm was 8.9/5.3 percent and 8.0/13.3 percent, respectively.
Conclusions: There seems to be at present no solid evidence for survival benefit on early invasive strategy for UA/NSTEMI as a broad diagnostic group, and the risk of doing harm should be considered. Also, the evidence for PCI to decrease early mortality after STEMI is scanty. Estimations of predicted harm may further aid decisions on whether to implement the new treatment over the old one. It may also give an additional dimension for interpreting the results of any meta-analysis.

Keywords: Acute coronary syndrome, Myocardial infarction, Unstable angina, ST-elevation, PCI, Thrombolysis, Invasive, Conservative, Strategy

Acute coronary syndromes (ACS) are a major health problem in industrialized countries, and it is becoming an increasingly significant problem in developing countries with a large number of hospitalizations (2;9). In 2001, there were 1,680,000 unique discharges for ACS in the United States. Applying a conservative estimate of 30 percent of the ACS patients, an estimated 500,000 ST-elevation myocardial infarction (STEMI) events are encountered per year in the United States (American Heart Association, 2004). Thus, ACS represents the most common diagnosis for hospital admission, and although improvements in medical therapy have resulted in a dramatic decline in mortality from acute myocardial infarction (MI), it remains the most common cause of in-hospital death in industrialized nations (5).

In patients with ACS without STEMI (NSTEMI), the early selective invasive strategy includes ischemia-guided use of medical therapy followed by angiography and revascularization for angina or stress-induced myocardial ischemia if necessary. The early routine invasive strategy includes cardiac catheterization followed by percutaneous coronary intervention within 48 hours of symptom-onset. FRISC-II, TACTICS, TIMI-18, and RITA-3 were the first studies indicating that high-risk patients benefit from early revascularization and that medical therapy is also important. Although these trials support an early invasive approach in intermediate- and high-risk patients, other trials support a more conservative approach in those without electrocardiographic changes or enzyme elevations (6).

The target of reperfusion therapy for STEMI is to get rapid and constant patency of the infarct-related artery. Thrombolytic therapy is quickly available, but it restores flow in only approximately 60 percent of cases. Primary percutaneous coronary intervention (PCI) is successful in over 90 percent of cases but requires the availability of an experienced interventional team (28). Individual trials had not shown a clear mortality benefit with primary PCI, but a recent meta-analysis of twenty-three trials comparing primary PCI with fibrinolytic therapy estimated that PCI was associated with improved survival (24).

There is controversy about the effect of an early routine invasive strategy on mortality in patients with NSTEMI (3). Similarly, current evidence on the widespread implementation of primary PCI over thrombolytic therapy for STEMI is widely discussed (8;10;13;23;36). Our aim was to collect all systematic reviews on invasive strategies for ACS and reanalyze the data in these reviews so as to reach combined estimates, as well as to make predictions on the effectiveness and risk of harm, so as to facilitate relevant decision making in health care. An update of the meta-analyses for UA/NSTEMI and short-term morality data on STEMI was also done by searching the latest randomized controlled trials (RCTs).

METHODS

Paper selection, validity assessment, data abstraction, and qualitative synthesis of the data were performed independently by two of the authors (P. Kuukasjärvi and A. Malmivaara). 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. This study is structured according to the recommendations of the QUOROM statement (32).

Searching

Electronic databases were searched for meta-analyses and systematic reviews of ACS without language restriction from 1994 to September 2004. The databases used for the search were EBM Reviews—Cochrane Database of Systematic Reviews (2nd Quarter 2004) (OVID); EBM Reviews—Cochrane Central Register of Controlled Trials (2nd Quarter 2004) (OVID); DARE, HTA, EED (NHS CRD); Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations, Ovid MEDLINE(R) to August, Week 4, 2004. In addition, PubMed from 2000 to 2004 was searched. References in the systematic reviews were checked.

Search strategies were planned by an information specialist for each database. The following Medical Subject Heading (MeSH) search terms were used: angina, unstable; Exp Myocardial infarction; acute disease; meta-analysis.

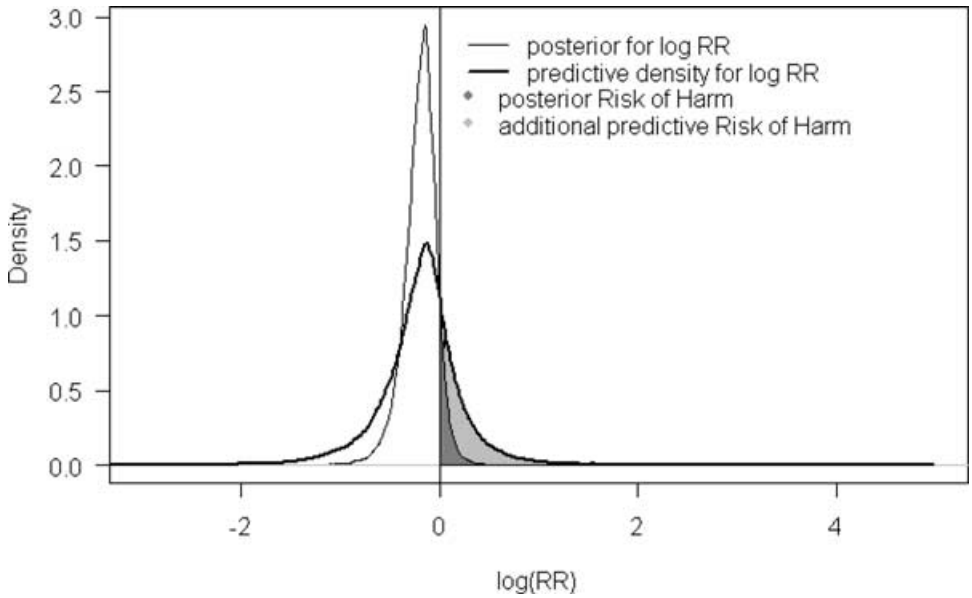

Figure 1. Posterior density of relative risk on log-scale (logRR) for updated non–ST-elevation myocardial infarction (NSTEMI) meta-analysis (nine randomized controlled trials) and predictive density for new study. The dark gray area gives the probability that an early invasive treatment strategy is harmful compared with an early conservative treatment strategy based on the original studies. The light gray area gives the additional risk of doing harm by inference for a new study effect, exchangeable with studies performed.

Selecting

The abstracts identified were reviewed using the screening criteria regarding study design, population, intervention, control intervention, and outcome. We included systematic reviews of RCTs on patients with ACS. For NSTEMI, the early selective invasive strategy had to be compared with early routine invasive strategy. For STEMI, a comparison between primary PCI and thrombolytic therapy was required. At least one of the following outcomes had to be reported: mortality, myocardial infarction (MI), angina pectoris, revascularization, or stroke. All studies judged to be potentially relevant were retrieved for detailed evaluation.

Systematic reviews before 2000 were excluded if RCTs in these reviews were covered by the later works included in this review. We excluded studies focusing on economic evaluation. To be eligible, a systematic review had to have intent to cover all relevant studies and to do a qualitative or quantitative synthesis of the included studies. Researchers were not precluded from knowing the journal or authors of the reviews.

Validity Assessment

The methodological quality of the reviews was assessed by using a modified version of a quality scale of research overviews. The scale combines nine items, each ranging from zero to two points, resulting in a maximum score of eighteen points (34).

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 included systematic reviews were tabulated.

Data Synthesis and Reanalysis

The primary outcome measure was mortality; other outcomes that were considered as secondary outcome measures are not reported here. Mortality refers to all-cause mortality, although this definition is not explicitly defined in all the papers. In systematic reviews using individual patient data (IPD), no further analyses were made and these reviews are presented separately. We reanalyzed mortality data as given in the reviews by using Bayesian random effects meta-analysis. WinBUGS 1.4.1 (39) software was used by

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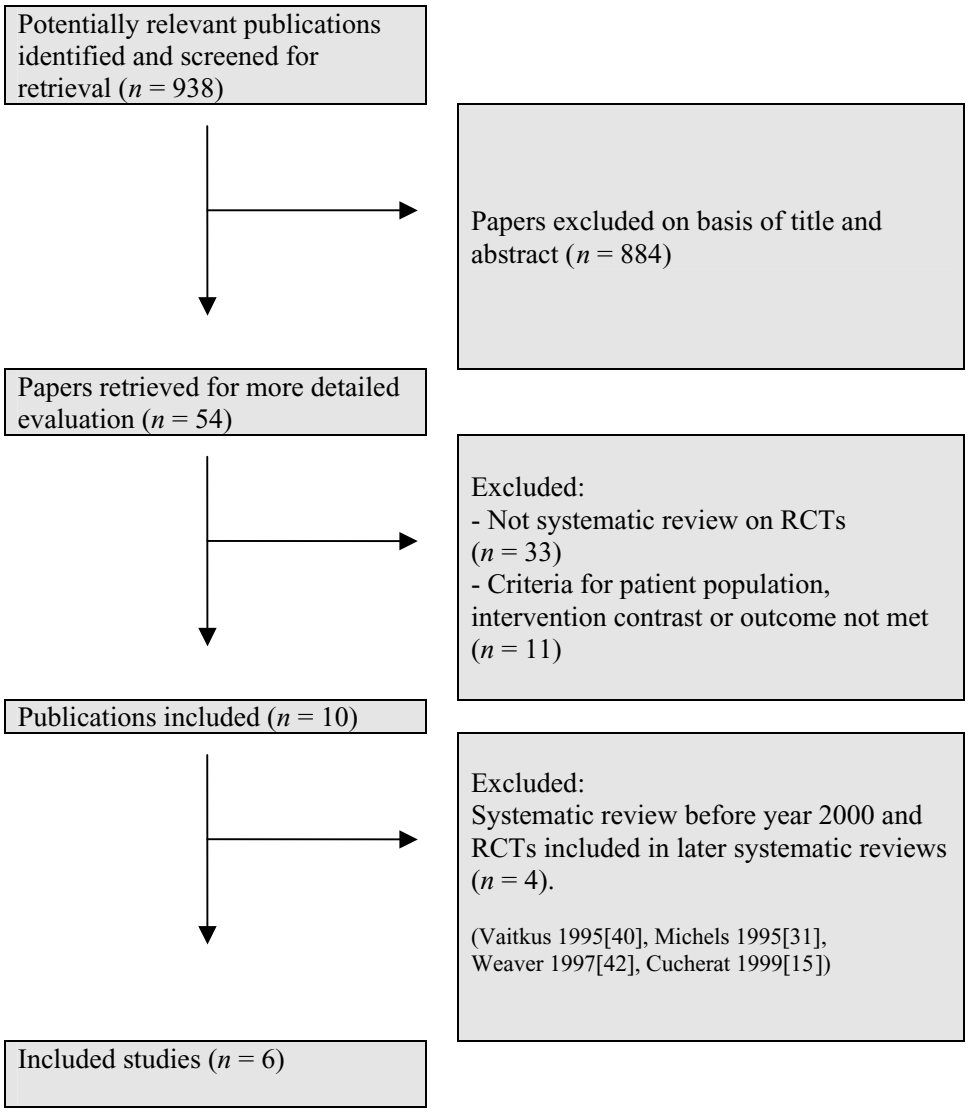

Figure 2. Flow diagram of inclusion/exclusion of systematic reviews. RCTs, randomized controlled trials.

applying the absolute risk difference model (method[b]) and the log relative risk scale model of Warn et al. (41), with their adjustment suggestions for zero counts in the treatment group also being adopted. Vague uniform priors were used for the between-study variance τ^2 (a Uniform[0,2] prior on τ in the risk difference model and a Uniform[0,10] prior on τ in the log relative risk model). A sensitivity check was done by also applying an Inverse Gamma(.001,.001) prior on the between-study variance τ^2 in the log relative risk model, and as in Warn et al. (41), we observed similar log relative risks but slightly smaller values for the between-study variance τ^2. For the inference, two MCMC chains were run and convergence was assessed by evaluating graphically the Gelman and Rubin statistic after 10,000 samples. If convergence could be assumed, 50,000 samples per chain were run for summary statistics.

Simultaneously, uncertainty about the probable treatment effect in a particular population outside the study population was expressed by inference for a new study effect, exchangeable with the studies performed. This predictive distribution achieved by simulation may be a more appropriate summary of the treatment effect than the mean summary effect per se (12;38). The risk of doing harm by the new treatment when compared with the old treatment (early invasive strategy over early conservative strategy, primary PCI over thrombolysis) was estimated by posterior distribution densities (see Figure 1). Codes used for WinBUGS are available from the authors. All plots were made with R 2.1.0 (35).

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Table 1. Characteristics of the Systematic Reviews.

Paper	Objective of the paper	Information source	No. of studies included	Population sum
Bavry et al. 2004 (3)	The primary aim was to determine whether a routine invasive approach, with adjunctive use of glycoprotein IIb/IIIa inhibitors and intracoronary stents, improves survival over standard medical therapy. Modification of treatment effect across additional variables that are available from patient trials, such as gender and troponin status, will also be assessed.	MEDLINE, EMBASE, CRISP, metaRegister of Controlled Trials, and Cochrane databases for randomized clinical trials. Hand-searched relevant journals, corresponded with investigators and experts in the field, and used the Science Citation Index to cross-reference any articles that met selection criteria.	5 RCTs	6,766
Keeley et al. 2003 (24)	The aim was to provide an updated quantitative analysis of the results of the randomized trials of primary PTCA versus thrombolytic therapy in AMI.	Medline. Searched scientific sessions abstracts in the New England Journal of Medicine, Journal of the American College of Cardiology, Circulation, European Heart Journal, Heart, and Clinical Cardiology, and questioned the principal investigators of most trials to ensure validity of the data, obtain additional unpublished data, and to verify that the study was randomized in design.	23 RCTs	7,739
Dalby et al. 2003 (16)	The primary aim of the meta-analysis was to compare immediate local thrombolytic drug treatment with transfer for primary PCI in the treatment of AMI.	Medline. Papers from major cardiac conferences. Cochrane Database was searched and national and international colleagues were consulted.	6 RCTs	3,750
Grines et al. 2003 (21)	Primary PCI versus thrombolysis with 6-month follow-up. Detailed overview using individual patient data.	Medline Jan 1985 to Jan 1998. Hand search Circulation, JACC, Eur Heart J Jan 1993 to Jan 1998. Expert contact.	11 RCTs	2,725
Wiseth et al. 2002 (43)	An attempt was made to identify and retrieve all RCTs that compare acute PCI with thrombolysis in AMI.	Studies referred to in the Cochrane report on PCI for AMI (43). Medline, EMBASE. Assessed the abstracts from the most important international cardiological conferences in 2001 and 2002 (European Society of Cardiology, American College of Cardiology, and American Heart Association).	17 RCTs	6,873
Zijlstra et al. 2002 (44)	The clinical characteristics and outcome of patients with early (<2 hr), intermediate (2–4 hr), and late (>4 hr) presentation treated by primary angioplasty or thrombolytic therapy for acute myocardial infarction were examined.	Medline. Scientific session abstracts in Circulation, JACC, Eur Heart J Jan 1993 to Mar 1996. Contact to primary investigator for each trial for data, additional studies or problems with any published study.	10 RCTs	2,635

RCTs, randomized controlled trials; PTCA, percutaneous transluminal coronary angioplasty; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction.

Both relative risks (RR) and risk differences (RD) are shown. In the results section, risk differences are given offering direct access to number needed to treat (NNT) formulation (NNT = 1/RD). Predicted risk of harm is estimated by a Bayesian model 2 on RR and RD scales.

Ancillary Search for RCTs

An additional MEDLINE search by an information specialist was conducted later during the publication process to identify recent RCTs covering the period from January 2003 to January 2006. Search strategy included MeSH terms exp

Table 2. Quality of the Identified Systematic Reviews.

Paper	Search methods	*Comprehensiveness* of the search	Inclusion criteria	Avoidance of selection bias	Definition of the validity assessment criteria	Validity assessment criteria used	Summarize methods used	Accessibility of the study	Data and analysis supports reviewers' conclusions	Total (max 18 points)
Bavry et al. 2004 (3)	2	2	2	1	0	0	1	1	1	10
Keeley et al. 2003 (24)	1	2	1	0	0	0	1	1	2	8
Dalby et al. 2003 (16)	1	2	2	0	0	0	2	2	2	11
Grines et al. 2003 (21)	1	2	1	0	1	0	2	2	2	11
Wiseth et al. 2002 (43)	2	2	1	1	2	0	2	2	1	13
Zijlstra et al. 2002 (44)	1	2	1	0	1	0	1	1	0	7

Myocardial Infarction, exp Angina, Unstable and Acute Disease. Possible new RCTs were considered as additional data to update the meta-analyses identified by the first-line literature search.

RESULTS

Trial Flow

In the primary searches, 938 potentially relevant publications were identified: 9 in the Cochrane Database of Systematic Reviews; 76 in the Cochrane Central Register of Controlled Trials; 412 in DARE, HTA, EED (NHS CRD); 369 in Ovid MEDLINE(R) In-Process, Other Non-Indexed Citations and Ovid MEDLINE(R), and 72 in PubMed. The flow diagram of inclusion/exclusion of the systematic reviews is shown in Figure 2.

We found one systematic review on UA/NSTEMI comparing early selective invasive strategy to early routine invasive strategy (3). Nine systematic reviews were identified on invasive strategies for STEMI with a comparison between primary PCI and thrombolytic therapy. Five (16;21;24;43;44) of these systematic reviews were published in or after 2000 and were taken for the final analysis. The trials in the four (15;31;40;42) excluded systematic reviews were covered in the included systematic reviews but not two (17;33) rather old trials.

In the ancillary search for RCTs, we found 704 potentially relevant publications. A total of 686 papers were excluded on the base of title and abstract. Eighteen papers were retrieved for more detailed evaluation. No RCTs were found to add to the meta-analysis for short-term outcome on STEMI by Keeley et al. (24). One RCT (ICTUS-study [18]) was found in addition to the trials identified by Bavry et al. (3) for the meta-analysis on UA/NSTEMI. A 5-year follow-up for RITA-3 data was noted (20).

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 sum of the population.

The quality of the six systematic reviews included in this overview is summarized in Table 2. Median quality score was 10.5 (range, 7–13) on a scale with a maximum of 18 points. Selecting papers for systematic reviews was done by two assessors in only two of the included systematic reviews. Quality assessment, even if described, was not reported in any of the six reviews.

Data Synthesis

Reanalyses of the mortality data available in the included systematic reviews are shown in Table 3. From Keeley's meta-analysis, the SHOCK trial was excluded because of distinct patient characteristics (cardiogenic shock).

https://doi.org/10.1017/S0266462306051415 Published online by Cambridge University Press

Table 3. Relative Risks and Absolute Risk Differences for Mortality.

Paper	Focus of the review	RR (CrI)	RD (CrI)	Risk of harm (RR)	Risk of harm (RD)
A. Bavry et al. (2004) (5 RCTs)[a]	Early invasive versus early conservative strategy in NSTEMI				
Bayesian model 1		.62 (.17 to 1.53)	−.010 (−.050 to .016)	9.0%	14.5%
Bayesian model 2		.64 (.04 to 6.69)	−.010 (−.089 to .054)	24.5%	26.7%
B. Updated meta-analysis (9 RCTs)[b]	Early invasive versus early conservative strategy in NSTEMI				
Bayesian model 1		.84 (.56 to 1.10)	−.006 (−.021 to .010)	8.9%	16.2%
Bayesian model 2		.85 (.32 to 1.87)	−.006 (−.045 to .034)	26.7%	26.6%
C. Keeley et al. (2003) (24) (22 RCTs)	Primary PCI versus thrombolytic therapy in AMI				
Bayesian model 1					
All studies		63 (.47 to .79)	−.019 (−.032 to −.008)	.0%	.1%
Streptokinase		45 (.19 to .80)	−.041 (−.071 to −.011)	.9%	.7%
Fibrin-specific		72 (.51 to .92)	−.012 (−.027 to .002)	.5%	4.5%
Bayesian model 2					
All studies		.65 (.31 to 1.13)	−.019 (−.046 to .006)	4.6%	5.1%
Streptokinase		.46 (.07 to 2.25)	−.041 (−.097 to .016)	8.9%	5.3%
Fibrin specific		.73 (.35 to 1.27)	−.012 (−.041 to .015)	8.0%	13.3%
D. Dalby et al. (2003) (16) (6 RCTs)	PCI center transport versus immediate thrombolysis in AMI				
Bayesian model 1		.77 (.51 to 1.13)	−.012 (−.039 to .013)	6.9%	16.6%
Bayesian model 2		.77 (.32 to 1.80)	−.012 (−.065 to .039)	14.9%	23.8%
E. Wiseth et al. (2002) (43) (6 RCTs)	PCI versus thrombolysis in AMI with at least 12 months of follow-up				
Bayesian model 1		.69 (.42 to 1.03)	−.040 (−.084 to .001)	3.0%	2.6%
Bayesian model 2		.70 (.24 to 1.78)	−.040 (−.131 to .046)	12.0%	10.1%

Note. Bayesian model 1 indicates Bayesian random effect meta-analysis. Bayesian model 2 indicates Bayesian random effect meta-analysis with prediction.
[a] FRISC-II, TRUCS, TACTICS-TIMI 18, VINO, RITA-3.
[b] TIMI IIIb, VANQVISH, MATE, FRISC-II, TRUCS, TACTICS-TIMI 18, VINO, RITA-3, ICTUS.
RR, relative risk; CrI, 95% credible interval; RD, risk difference; RCT, randomized controlled trials; NSTEMI, non–ST-elevation myocardial infarction; PCI, percutaneous coronary intervention; AMI, acute myocardial infarction;

The meta-analysis by Bavry et al. (3) identified eight RCTs, but they excluded the three oldest trials (TIMI IIIB (1), MATE (27), VANQVISH (7)) before the era of stents and glycoprotein inhibitors. We included these trials and the ICTUS-trial (18) for our updated meta-analysis. Mortality data were extracted from the original trials (1;7;11;18;19;26;27;30;37).

NSTEMI, Mortality

The average risk difference favoring early invasive treatment strategy compared with early conservative strategy was 1.0 percent (95 percent credible interval [CrI], −5.0 to 1.6) (Table 3; Figure 3). Predicted risk (RR/RD scales) of doing harm was 24.5 percent/26.7 percent. The updated meta-analysis with nine RCTs showed an average risk difference of .6 percent (95 percent CrI, −2.1 to 1.0), and the predicted risk of doing harm was 26.7/26.6 percent (Table 3, Figures 2 and 4).

STEMI, Mortality

Average risk difference favoring primary PCI over thrombolysis was 4.1 percent (95 percent CrI, −7.1 to −1.1) when PCI was compared with streptokinase and 1.2 percent (95 percent CrI, −2.7 to .2) when compared with fibrin-specific thrombolytics. Predicted risk of harm was 8.9 percent/5.3 percent and 8.0 percent/13.3 percent, respectively (Table 3; Figure 5).

Absolute risk reduction favoring PCI center transport over immediate thrombolysis was 1.2 percent (95 percent CrI, −3.9 to 1.3) for primary PCI with a predicted risk of harm of 14.9 percent/23.8 percent (Table 3; Figure 6). In studies of at least a 1-year follow-up, there was a 4.0 percent (95 percent CrI, −8.4 to .1) risk difference in mortality favoring primary PCI with a 12.0 percent/10.1 percent predicted risk of harm (Table 3; Figure 7).

Results from individual patient data meta-analyses comparing angioplasty to thrombolysis in STEMI showed a

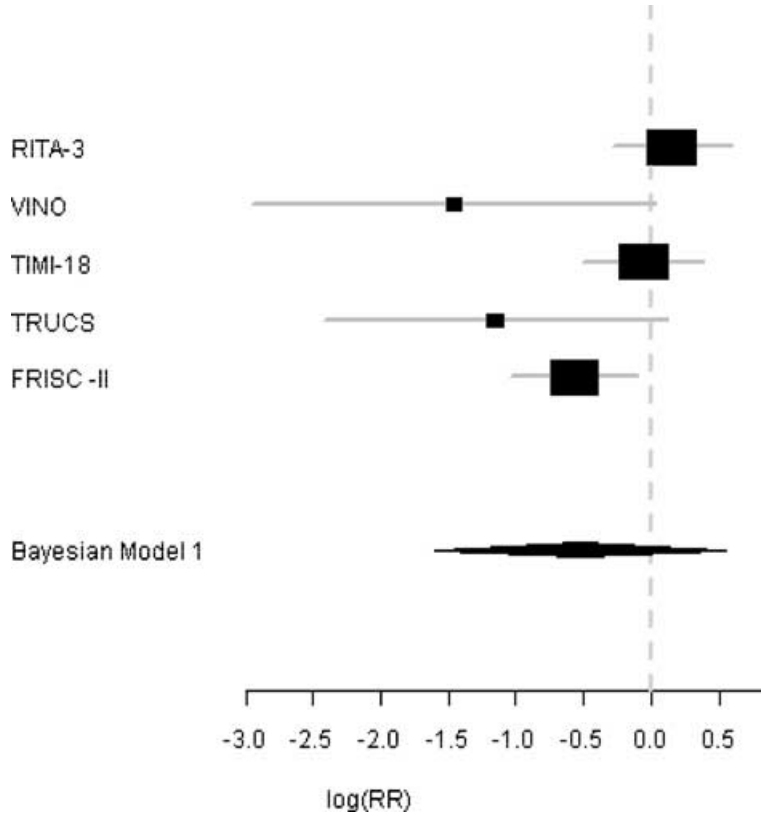

Figure 3. Reanalysis of the data of randomized controlled trials adopted from Bavry et al. (3), comparing early invasive strategy to early conservative strategy in patients with non–ST-segment elevation acute coronary syndrome (follow-up, 6–12 months).

30-day mortality odds ratio = .62 for primary angioplasty; $p = .01$ (44). In the other study, the mortality rate at 30 days was 4.3 percent for percutaneous transluminal coronary angioplasty (PTCA) and 6.9 percent for thrombolytic therapy (RR = .62, 95 percent confidence interval [CI], .44–.86). At 6 months, the mortality rate was 6.2 percent for PTCA and 8.2 percent for thrombolysis (RR = .73, 95 percent CI, .55–.98) (21).

DISCUSSION

Our overview of the systematic reviews on invasive strategies for ACS was based on one updated systematic review for UA/NSTEMI and five systematic reviews for STEMI. The average risk difference for mortality favoring an early invasive treatment strategy compared with an early conservative strategy for UA/NSTEMI was .6 percent. At the same time, predicted risk of doing harm by early invasive strategy was up to 27 percent. Similarly, risk difference favoring primary PCI over thrombolysis for STEMI was 1 percent when PCI was compared with the best medical treatment, here fibrin-specific thrombolytics. Predicted risk of harm by primary PCI was up to 13 percent.

Internal Validity

Three recent systematic reviews (4;14;29) for UA/STEMI, not submitted to reanalysis here, used the same RCTs to compare an early invasive treatment strategy to an early conservative strategy as in the present study. We included the recent data in the ICTUS-study. No RCTs were found to add to the Keeley et al. (24) short-term mortality data. A health technology assessment (HTA) report by Hartwell et al. (22) published in 2005 was noted as the latest systematic review comparing primary PCI with thrombolysis for STEMI, with no trial data to add. Most probably, the present meta-analysis covers the relevant studies of ACS for these comparisons. However, the methodological quality scores of the reviews were mediocre, raising concern about their internal validity, especially due to the poor reporting of the way of selecting papers and the lack of reporting of the validity of RCTs.

External Validity

Assessment of the external validity of RCTs is difficult, because patients in clinical practice are dissimilar, in varying degrees, to the patients recruited for a trial. Trials usually aim for efficacy, that is, patients and interventions in an ideal setting. Thus, there is a risk of overestimating the effectiveness for ordinary practice.

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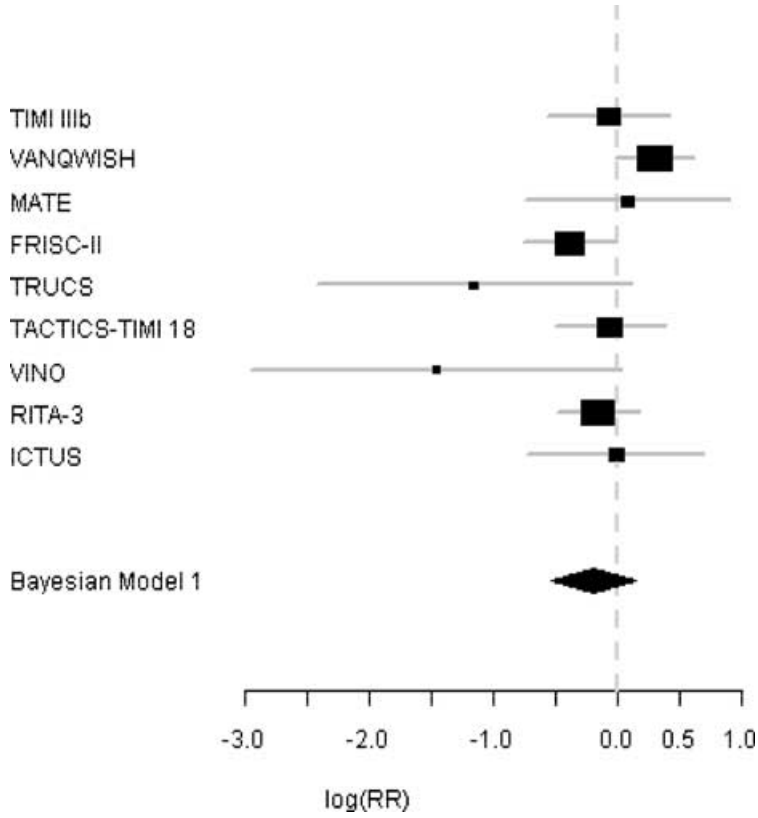

Figure 4. Updated meta-analysis comparing early invasive strategy to early conservative strategy in patients with non–ST-segment elevation acute coronary syndrome (follow-up, 6–24 months).

Trial data depict the past, whereas decision making aims to appraise what happens in the future. Therefore, prediction is a reasonable way to interpret the results. A Bayesian approach gives the possibility to make predictions and probability statements. Predictive distribution provides a more comprehensive summary of the treatment effect by including heterogeneity between patients, treatment protocols, and clinical praxis (38). Consequently, uncertainty increases and credibility intervals become wider. Predictive distribution may also aid in planning a new study. It may give an additional dimension for any meta-analysis.

Interpretation

In patients with UA/NSTEMI, an early invasive treatment strategy gives no statistically significant survival benefit when compared with an early conservative strategy. There is considerable predicted risk that the new approach will cause more harm than good (up to 27 percent for mortality), assuming the patient selection and standard of care equals that in the included trials.

In patients with STEMI, there was no statistically significant short-term (4–6 weeks) survival benefit for PCI over thrombolysis with fibrin-specific drugs and the predicted risk of harm was up to 13 percent. However, risk reduction for PCI versus streptokinase thrombolysis studies was statistically significant (4 percent), although there was still a 9 percent risk of doing harm by PCI. Trials focusing on PCI center transport showed no statistically significant decrease of mortality, and the risk of predicted harm was here estimated to be up to 24 percent. Concerning studies with at least 12 months of follow-up, there was no statistically significant mortality decrease and the predicted risk of harm is up to 12 percent.

Potential Biases

We have undertaken an overview of systematic reviews and used data from primary studies given in the reviews, but not assessed the quality of the original studies. However, mortality data for the updated UA/NSTEMI meta-analysis was extracted from original trials. We have used the data on absolute numbers of patients having the presented outcome on an intention-to-treat basis and have not done any subgroup analyses.

Publication bias as an inherent validity issue for any systematic review may favor the effectiveness of interventions and cannot be evaluated in this study. The sample size of many RCTs included in the systematic reviews was small, and the number of trials in some meta-analyses was few.

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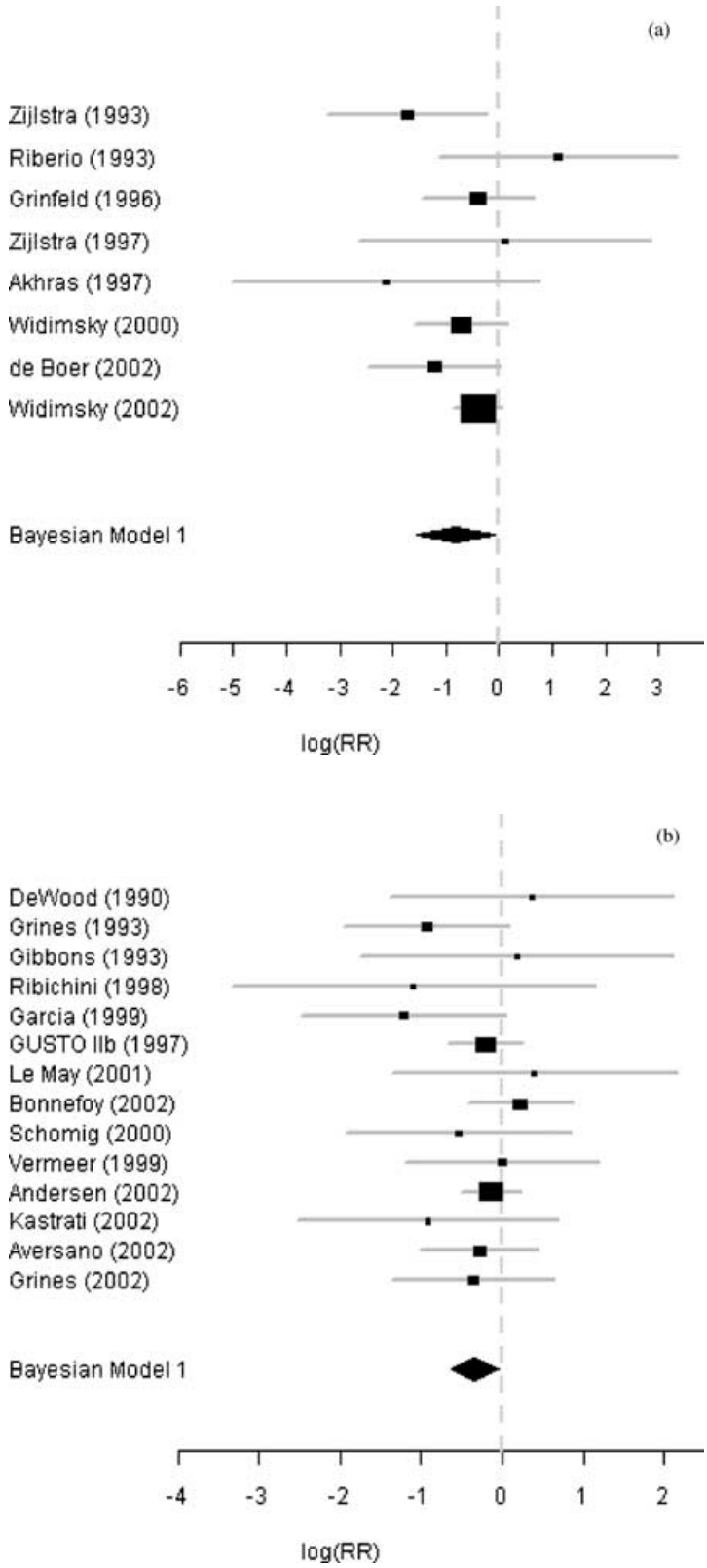

Figure 5. (a) Reanalysis of the data of randomized controlled trials (RCTs) adopted from Keeley et al. (24), comparing primary percutaneous coronary intervention (PCI) to thrombolytic therapy in acute myocardial infarction (AMI), streptokinase trials (follow-up 4–6 weeks). (b) Reanalysis of the data of RCTs adopted from Keeley et al. (24), comparing primary PCI to thrombolytic therapy in AMI, fibrin-specific trials (follow-up, 4–6 weeks).

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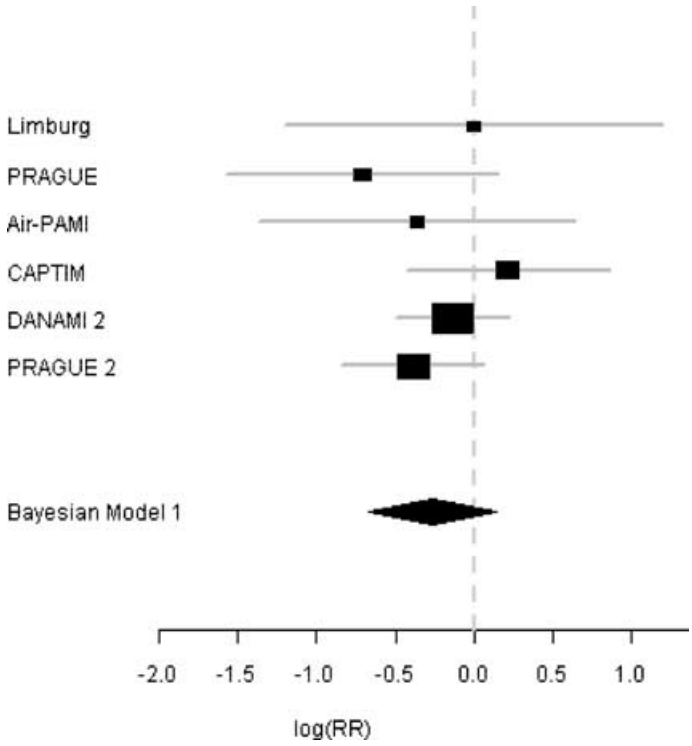

Figure 6. Reanalysis of the data of randomized controlled trials (RCTs) adopted from Dalby et al. (16) comparing angioplasty to thrombolysis in acute myocardial infarction (AMI), with special focus to percutaneous coronary intervention (PCI) center transport versus immediate thrombolysis (follow-up, 1 month).

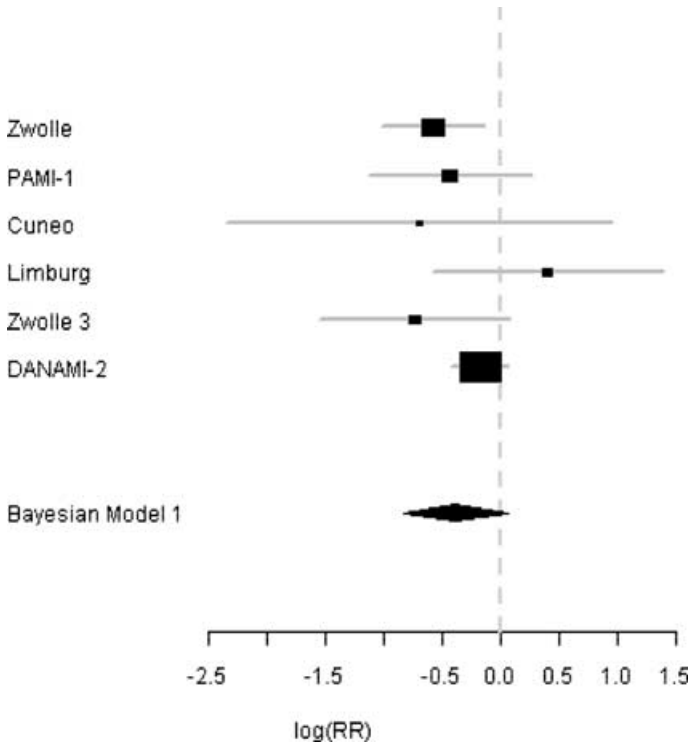

Figure 7. Reanalysis of the data of randomized controlled trials (RCTs) adopted from Wiseth et al. (43) comparing primary percutaneous coronary intervention (PCI) to thrombolytic therapy with at least 12 months follow-up in patients with acute myocardial infarction (AMI).

https://doi.org/10.1017/S0266462306051415 Published online by Cambridge University Press

Future Research Agenda

Mortality has been the only end point considered here; therefore, other end points (i.e., re-infarction, angina pectoris, re-hospitalization) should also be analyzed in the way presented here. Similarly, all the presented intervention comparisons warrant formal systematic reviews.

Facilitated PCI (thrombolysis plus PCI) to optimize the benefits of pharmacological and mechanical reperfusion is an important issue for future studies (25). Organizational and cost-effectiveness questions need local appraisal. Statistical methods for meta-analysis and the use of a Bayesian approach need to be further evaluated.

CONCLUSIONS

There seems to be, at present, no solid evidence of a survival benefit for the early invasive strategy for UA/NSTEMI as a broad diagnostic group, and the risk of doing harm should be considered. Also, the evidence of PCI decreasing early mortality after STEMI is scanty. An estimation of predicted harm may give an additional dimension for interpreting the results of any meta-analysis.

POLICY IMPLICATIONS

The analysis method presented here gives information for the decision maker on the probability of the intervention being harmful as well as it being beneficial. The current data show that there is considerable risk of harm (increase in mortality) if the early invasive strategy for UA/NSTEMI is applied routinely. The analysis method may aid decision making on whether to implement a new treatment over the old one.

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