Stenting versus surgical bypass grafting for coronary artery disease: systematic overview and meta-analysis of randomized trials

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Background. **Coronary angioplasty and coronary artery bypass grafting (CABG) are both major techniques for the management of coronary artery disease, but CABG is associated with a lower incidence of repeat revascularization. Recent studies comparing angioplasty with stenting vs CABG have yielded conflicting results, with some suggesting improved survival with stenting, and others the opposite. We thus undertook a systematic overview of the randomized trials comparing stenting vs CABG in coronary artery disease.**

Methods. **MEDLINE (January 1986-February 2003), ISI Current Contents, the Cochrane Controlled Trial Register, LILACS and the American Heart Association, American College of Cardiology, European Society of Cardiology, and Transcatheter Cardiovascular Therapeutics conference proceedings were among the databases we searched. Abstraction was performed in a non-blinded manner on pre-specified forms. The random-effect odds ratios for death, myocardial infarction, stroke, repeat revascularization, and symptomatic angina were computed for the longest available follow-up.**

Results. **Nine randomized trials (3283 patients, representing only 6% of all screened subjects) with an average follow-up of 28 months were included in the analysis, while four studies were excluded because they were still unpublished, ongoing, or with non-systematic stenting. No study used drug-eluting stents. The odds ratios for stenting vs CABG were 0.82 (95% confidence interval-CI 0.57-1.18, p = 0.3) for the occurrence of death, non-fatal myocardial infarction or stroke, 4.6 (95% CI 3.5-5.9, p < 0.00001) for repeat revascularization, and 2.3 (95% CI 1.8-2.8, p < 0.00001) for symptomatic angina. Heterogeneity tests were not statistically significant. The results of sensitivity analysis were similar even after stratification for single vessel, off-pump, single center or high-quality studies.**

Conclusions. **Overall and event-free survival after conventional stenting for coronary artery disease are similar to those after CABG, but surgery is still associated with a significantly lower incidence of repeat revascularization and symptoms. The role of next-generation drug-eluting stents in widening the indications for stenting and overcoming restenosis will need to be assessed in future observational and randomized studies comparing stenting vs CABG.**

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Introduction

Myocardial revascularization is the cornerstone of the modern management of coronary artery disease (CAD), and over the last two decades coronary artery bypass grafting (CABG) was shown to reduce mortality by one third in patients with CAD in comparison to expectant medical therapy, with even greater benefits in patients with severe or multivessel CAD[1]. Interventional revascularization by means of percutaneous transluminal coronary angioplasty (PTCA) has been compared to surgical revascularization in clinical trials and meta-analyses[2,3]. Overall, PTCA and CABG seemed to provide similar short-term benefits, but at long-term follow-up CABG appeared superior to PTCA, in particular because of fewer repeat revascularization and symptoms of angina. In particular, the risk of repeat revascularization after angioplasty was 10-fold higher than that after CABG[2].

Since the first implantation of coronary stents in humans in 1986[4], these devices have been increasingly used in percutaneous coronary revascularization, and several trials have been undertaken in an attempt to compare percutaneous coronary stenting to CABG, both in single and multiple vessel disease[5]. These studies have however yielded conflicting results, as some suggested an increased perioperative morbidity and mortality in patients undergoing surgery[6], and others showed an improved survival after surgical revascularization in comparison to coronary stenting,

especially at long-term follow-up[7]. Overall, no trial had enough power to exclude a clinically relevant difference between the two approaches in terms of mortality or of the incidence of myocardial infarction during follow-up.

Systematic overviews search, retrieve and thoroughly assess available sources of clinical evidence, and meta-analytic techniques can pool the results of trials with a similar design to achieve more precise effect estimates, to assess risk differences with greater statistical power, and to overcome apparent inconsistencies among similar studies which may be due to random error, while emphasizing potential statistical or clinical heterogeneity[8,9]. We thus performed a systematic overview of the reported randomized controlled trials that directly compared a strategy of coronary revascularization with CABG vs percutaneous coronary stenting in patients with CAD.

Methods

Search strategy. MEDLINE, ISI Current Contents, LILACS, and the Cochrane Collaboration Controlled Trials Register were searched by a trained investigator (GGL B-Z) for eligible studies published between January 1986 and February 2003. An additional search involved the meta-Register of the Current Controlled Trials and the National Research Register (National Health Service-NHS, UK). Search key words included: "random*"; "coronary"; "stent*"; "cardiac surgery", "by-pass", "bypass", "CABG" or "MIDCAB*". The MEDLINE search was performed according to the recommendations of Robinson and Dickersin[10]. No language restriction was used.

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.

Selection criteria. Inclusion criteria for retrieved studies were: a) controlled comparison of CABG vs percutaneous coronary revascularization with stenting, b) randomized treatment allocation, c) intention-to-treat analysis, and d) follow-up ≥ 1 month. Exclusion criteria were: a) equivocal treatment allocation process, b) severe imbalances in major baseline characteristics among study groups, c) incomplete (< 80%) follow-up, and d) non-systematic (< 90%) coronary stent use over total percutaneous procedures.

Data abstraction and validity assessment. Data abstraction was independently performed by two unblinded reviewers (GGL B-Z, P A), on pre-specified structured data collection forms. Divergences were resolved by consensus. The study quality was evaluated by the same two investigators according to a score modified from Jadad et al.[11], and expressed on an ordinal scale, allocating 1 point for the presence of each of the following: a) statement of objectives, b) explicit inclusion and exclusion criteria, c) description of interventions, d) objective means of follow-up, e) description of the assessment of adverse events, f) power analysis, g) description of statistical methods, h) multicenter design, i) discussion of withdrawals, and j) details on the long-term medical treatment after revascularization (including drugs influencing restenosis or disease progression rate).

Study characteristics. The outcomes of interest were death, non-fatal myocardial infarction, stroke, repeat revascularization, freedom from angina and the composite endpoint of death or non-fatal myocardial infarction or stroke, assessed by the intention-to-treat, with the longest follow-up reported for each trial and outcome. Freedom from angina was defined as angina allocated to a Canadian Cardiovascular Society class (CCS) < 2[12].

Data analysis and synthesis. Statistical analysis was performed using the Review Manager 4.1.1 freeware package[13]. Binary outcomes from individual studies were to be combined with both the Mantel-Haenszel fixed effect model and the DerSimonian and Laird random effect model[8]. In case of borderline or significant statistical heterogeneity ($p < 0.10$ at the χ^2 test), results were reported according to the random effects model only, which overall is more robust and conservative[8,14,15]. Odds ratios (OR) with 95% confidence intervals (CI) were used as summary statistics for the comparison between CABG and stenting. Reported values were two-tailed and hypothesis testing results were considered statistically significant at the p value of 0.05.

Sensitivity and subgroup analysis were performed using the following categories: a) on-pump vs off-pump CABG, b) single vs multiple vessel CAD, c) single center vs multicenter studies, d) higher than median quality vs lower than median quality studies, and e) after exclusion of studies published only as abstract. Further sensitivity analysis to assess the reliability of effect estimates and potential publication bias was performed adding a hypothetical next trial (sized as the second-largest retrieved trial, but with an effect opposite to the summary estimate), according to a modified Rosenthal file drawer method[9]. Formal χ^2 tests were performed to investigate the heterogeneity between trials (the respective scores, degrees of freedom-df, and p values are reported)[8,9]. Power analysis and the calculation of the number-needed-to-treat (NNT, with 95% CI) were also computed[9].

This study was performed in compliance with the Cochrane Collaboration[8] and the Quality of Reporting of Meta-Analyses (QUORUM) guidelines[16].

Results

Search results and study selection. The process of systematic overview is summarized in figure 1: 942 citations were found in MEDLINE whereas others were obtained by searching the additional data sources. Several papers were excluded because of their non-experimental design[17], including the use of historical controls[18], or because of duplicate publication[19]. We finally identified 13 eligible randomized clinical trials, and complete articles were retrieved when applicable and checked for compliance to the inclusion and exclusion criteria (Tables I and II)[6,7,18,20-29]. We excluded one study comparing stenting vs CABG in diabetics because it is still ongoing[28], and two studies comparing stenting and off-pump CABG in isolated left anterior descending coronary disease because still unpublished and with an ongoing follow-up (the authors were contacted but could not provide detailed data) (GD Angelini and PPT de Jaegere, personal communications). One further study comparing percutaneous coronary intervention vs CABG in patients with medically refractory myocardial ischemia was excluded from the review because of the incomplete (average 54%) use of stenting in percutaneous coronary intervention[24]. Data abstraction of the remaining studies was performed, and individual researchers contacted in case of incomplete reporting or apparent data inconsistencies.

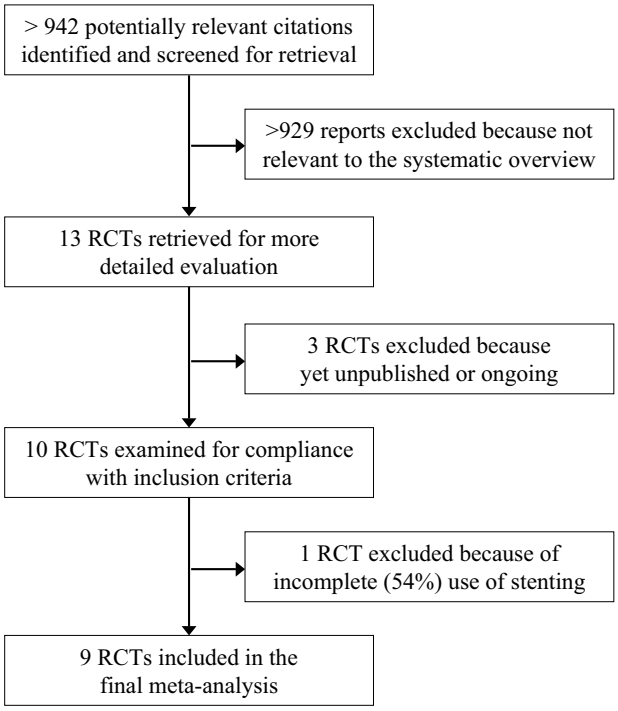


Figure 1. *Flow diagram of the systematic overview process. RCT = randomized controlled trial.*

Study and patient characteristics. The 9 studies included in the final analysis randomized 3283 patients, 1646 to CABG and 1637 to coronary stenting (Table III)[6,7,20,22,23,25-27,29]. The subjects enrolled in individual studies accounted for approximately only 6% of the total patients screened at entry, mostly because of the difficulty in obtaining informed consent to the randomization process or in reaching consensus between interventional cardiologists and surgeons on the potential equivalence of revascularization with both stenting and CABG.

Three studies (2643 patients) enrolled only subjects with multivessel CAD (Table III)[6,7,22]. Five studies (596 patients) involved only patients with proximal left anterior descending coronary disease[20,23,25-27]. A recently reported study compared stenting with retroperfusion vs CABG in 13 patients with left main and in 31 subjects with left-main equivalent (ostial lesions of both the left anterior descending coronary artery and circumflex artery), all of whom at high surgical risk (Parsonnet score > 6)[29]. This study was, together with the trial by Grip et al.[23], reported only as an abstract. Both

Table I. Description of the studies included in the meta-analysis.

Study	Years	Principal investigator	Location	No. patients	Primary endpoint	Follow-up (months)	CAD
ARTS[22]	1997-1998	Serruys PW	America, Europe, Oceania	1205	Death, MI, stroke, RR	36	MV
Cisowski et al.[26]	2000-2001	Cisowski M	Poland	100	Death, MI, RR	6	LAD
Diegeler et al.[25]	1997-2001	Diegeler A	Germany	220	Death, MI, RR	6	LAD
Drenth et al.[27]	1997-1999	Drenth DJ	Netherlands	102	Death, MI, stroke, RR	35	LAD
ERACI II[6]	1996-1998	Rodriguez A	Argentine	450	Death, MI, stroke, RR	36	MV
Grip et al.[23]	2001*	Grip L	Sweden	53	Quality of life	6	LAD
Pohl et al.[29]	2002*	Pohl T	Germany	44	Death	12	LM
SIMA[20]	1994-1998	Goy JJ	Europe	121	Death, MI, RR	29	LAD
SoS[7]	1996-1999	Stables RH	Canada, Europe	988	RR	24	MV

CAD = coronary artery disease; LAD = left anterior descending; LM = left main or left main equivalent; MI = myocardial infarction; MV = multivessel; RR = repeat revascularization. * year of publication.

Table II. Major excluded studies.

Study	Years	Principal investigator	No. participants	Primary endpoint	Reason for exclusion
Angelini et al.	Ongoing	Angelini GD	NA	NA	Unpublished
AWESOME[24]	1994-2000	Morrison DA	454	Death	Incomplete (54%) stent use
CARDIA[28]	Ongoing	Kapur A	600	Death, MI, stroke	Ongoing
GABI 2[18]	1996-1997	Baldus S	136	Freedom from angina	Historical CABG group
Octopus[21]	1998-2000	Eefting FD	280	Death, MI, stroke, RR	Unpublished

CABG = coronary artery bypass graft; MI = non-fatal myocardial infarction; NA = not available; RR = repeat revascularization.

Table III. Description of the populations and interventions of included studies.

Study	Age (years)	Males (%)	Previous MI (%)	DM (%)	ACS (%)	EF* (%)	Diseased vessels (%)			GP IIb/IIIa inhibitors (%)	IMA (%)	Off-pump CABG (%)	Quality**
							1	2	3				
ARTS[22]	61	77	43	18	36	61	1	68	31	0	95	NA	9
Cisowski et al.[26]	55	83	NA	7	9	> 40	100	0	0	NA	100	100	6
Diegeler et al.[25]	62	75	45	30	NA	63	100	0	0	2	100	95	7
Drenth et al.[27]	61	77	21	12	0	NA	100	0	0	0	100	96	8
ERACI II[6]	62	79	28	17	92	> 35	0	39	56§	28	86	0	9
Grip et al.[23]	NA	NA	NA	NA	NA	NA	100	0	0	NA	100	100	2
Pohl et al.[29]	70	NA	NA	NA	NA	NA	0	70§§	0	NA	NA	NA	2
SIMA[20]	60	80	2	12	NA	67	100	0	0	0	90	10	10
SoS[7]	62	79	46	15	24	57	0	57	43§§§	8	93	3	9

ACS = acute coronary syndromes; CABG = coronary artery bypass graft; DM = diabetes mellitus; EF = ejection fraction; GP = glycoprotein; IMA = internal mammary artery grafting; MI = myocardial infarction; NA = not available. * mean, unless otherwise stated; ** quality score was expressed on an ordinal scale, allocating 1 point for the presence of each of the following: a) explicit statement of objectives, b) description of inclusion and exclusion criteria, c) clear description of interventions, d) objective means of follow-up, including adjudication of non-fatal MI, e) description of the assessment of adverse events, f) justification for sample size, g) description of statistical methods, h) multicenter design, i) discussion of withdrawals and dropouts, and j) detailed data on the long-term medical treatment after revascularization (including drugs likely to modify the restenosis or disease progression rate, such as statins); § 4.7% left main disease; §§ 30% left main disease, 70% left main equivalent; §§§ 1% left main disease.

these trials were included with caution in the analysis despite the lack of complete published reports.

The mean age was 63 years. On average, males accounted for 81% and diabetics for 18% of subjects. Recent acute coronary syndromes were quite common (on average 40% of subjects), especially for multivessel disease studies (92% for ERACI II, 36% for ARTS, and 24% for SoS). Overall, a conserved baseline ejection fraction was however a prerequisite for enrolment, thus leading to the exclusion or limited representation of very high risk patients such as those with severe left ventricular dysfunction.

The use of glycoprotein IIb/IIIa inhibitors during stenting was sparse and uncommon (overall 13%), except for a 28% use in the ERACI II trial, which indeed mostly included patients with recent unstable angina. No study reported the implantation of new-generation drug-eluting or radiation-emitting intracoronary devices. Off-pump CABG was the only technique of surgical revascularization in 4 trials (252 patients, including a small portion of patients enrolled in the other trials)[23,25-27], and internal mammary artery grafts were used on average in 90% of surgical interventions.

Overall results. Event rates are presented in figure 2. The results of the meta-analysis are presented according to a random effect method, because of a trend towards statistical heterogeneity for the outcome of death (p = 0.084, Fig. 3A). Coronary revascularization by means of stenting or CABG appeared to confer a similar survival benefit, respectively 96.2 vs 95.9% (OR for death 0.87, 95% CI 0.48-1.57, p = 0.6) at long-term follow-up (average 28 months) (Fig. 3A). Similarly, the comparison of the two revascularization strategies did not show significant differences in the long-term risk of myocardial infarction (OR 0.95, 95% CI 0.60-1.51, p = 0.8, follow-up 16 months), stroke (OR 0.85, 95% CI 0.46-1.57, p = 0.6, follow-up 10 months), or the combined endpoint of death, myocardial infarction or stroke, 8.3% for stenting vs 10.8% for CABG (OR 0.82, 95% CI 0.57-1.18, p = 0.3, follow-up 16 months) (Fig. 3B). Stenting was instead associated with a significantly increased risk of repeat revascularization, 19.0% for stenting vs 4.7% for CABG (OR 4.6, 95% CI 3.5-5.9, p < 0.00001, follow-up 16 months) or symptomatic angina (CCS 2), 18.4% for stenting vs 8.9% for CABG (OR 2.3, 95%

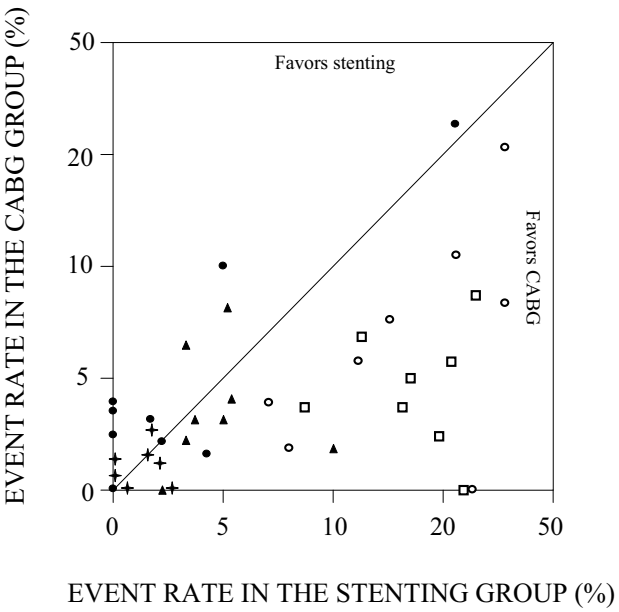


Figure 2. *L'Abbé plot of the risk of adverse events in the individual studies for both stenting* (abscissa) *and coronary artery bypass graft (CABG,* ordinate). ● *death;* ▲ *non-fatal myocardial infarction;* ✦ *stroke;* □ *repeat revascularization;* ○ *CCS 2.*

CI 1.8-2.8, p < 0.00001, follow-up 12 months) (Fig. 4). These findings translate into an estimated number of patients requiring revascularization, or NNT, by means of CABG vs stenting of 7 (6-11) to avoid a repeat revascularization and into a NNT of 10 (7-17) to be angina free, thus both favoring CABG over stenting at a follow-up of 16 and 12 months respectively.

Additional analysis. Heterogeneity testing did not disclose any significant departure from the assumption of statistical homogeneity for any of the outcomes of interest, despite a non-significant trend towards heterogeneity only in the risk of death (χ^2 12.53, df = 7, p = 0.084) (Fig. 3A). In particular, when analysis in the risk of death was performed after the stratification of studies into single vs multivessel disease, the multivessel disease group showed significant heterogeneity (χ^2 10.75, df = 3, p = 0.013). The overall and subgroup heterogeneity were both mostly due to the SoS trial, as after exclusion of this study statistical heterogeneity was no longer evident (overall χ^2 2.57, df = 6, p = 0.86; multivessel group only χ^2 1.41, df = 2, p = 0.49). The results of the meta-analysis after exclusion of the SoS study were similar to those calculated including this trial, thus showing that the summary estimates were robust and not significantly prone to deviations related to lack of homogeneity (Table IV).

Indeed, the results of the SoS trial have been already discussed by the SoS investigators, who interestingly reported, as a potential explanation of this heterogeneity, the exceedingly high rate of cancer death in the group of patients allocated to stenting (8 deaths out of a total of 22, vs 1 out of 8 in the CABG group)[7].

Calculations of OR were also performed according to a fixed effect model, yielding similar results with regard to both the direction and significance of the overall effect, thus confirming the robustness of the overall results (Table IV). We nonetheless chose to present data according to a random effect model in compliance with the design of the present overview.

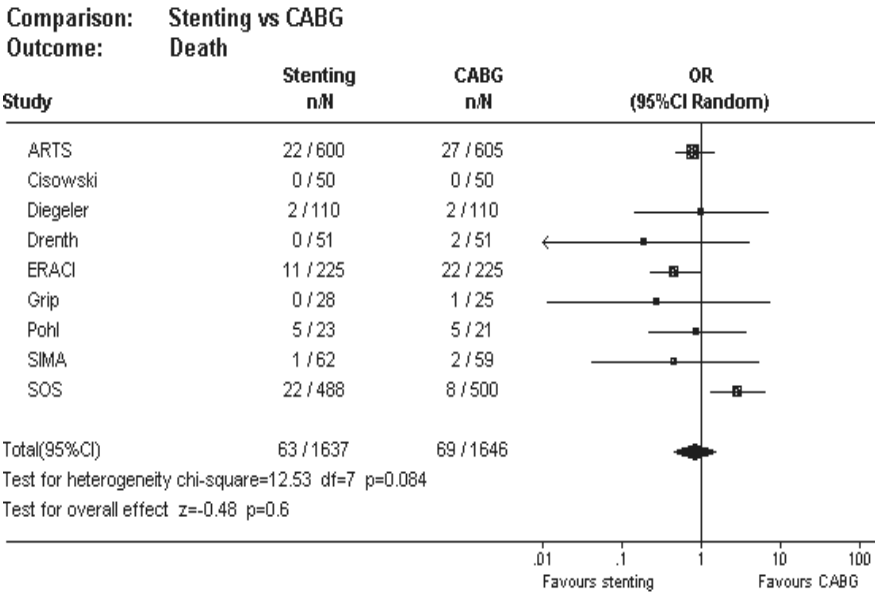
Stratification and sensitivity analysis not including the studies in which a cardiopulmonary extracorporeal circulation for CABG was employed (on-pump vs off-pump studies), showed that results were similar to those obtained in the comprehensive analysis. Findings were also similar after pre-specified stratification in higher than median vs lower than median quality studies, single vs multicenter studies and single vs multivessel coronary disease (Table IV).

Power analysis showed that in 8 studies (3239 patients) the pooled comparison of stenting vs CABG had an 80% power (with a two-tailed α of 0.05) in detecting a 3.5% absolute reduction in the risk of the composite endpoint of death, myocardial infarction or stroke. Using a modified Rosenthal file drawer method to assess the reliability of summary estimates of the risk of the composite endpoint of death, myocardial infarction or stroke, we added a hypothetical study sized as the second largest study (988 patients), with a direction of effect opposite to that of the pooled estimate, in order to simulate the addition of a real but yet unpublished study in the near future[9]. Calculations made after inclusion of such a hypothetical study showed that the results were similar, both in direction and significance, to those obtained before inclusion of the said study (OR 0.89, 95% CI 0.66-1.21, p = 0.5).

The above findings confirm the overall robustness and reliability of the present meta-analysis, even though changes in direction or significance of summary estimates after inclusion of future and unpredicted studies obviously cannot be ruled out.

Discussion

The present systematic overview of the published randomized trials comparing conventional stenting and CABG in patients with CAD shows that stenting compares favorably with surgical revascularization in terms of overall survival and of freedom from major adverse cardiovascular events (death, myocardial infarction or stroke). Bare metal stenting is however still fraught by a significantly increased risk of repeat revascularization in comparison to CABG. Accordingly, CABG is associated with a significantly higher rate of angina-free status. The results of this meta-analysis appear quite robust in the light of the lack of significant statistical heterogeneity and of significant departures from overall conclusions when analyzing study subgroups such as off-pump CABG, multicenter design, higher quality reports or multivessel disease.



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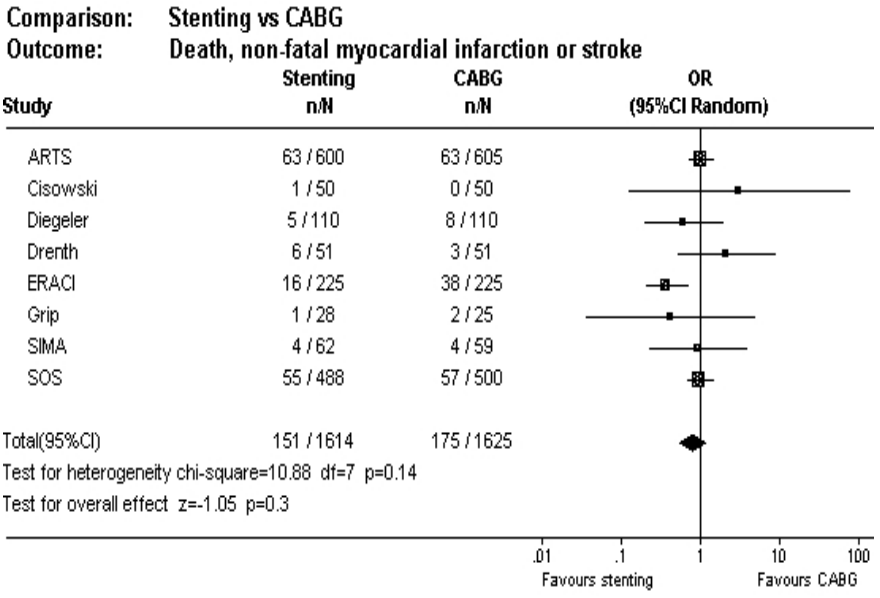

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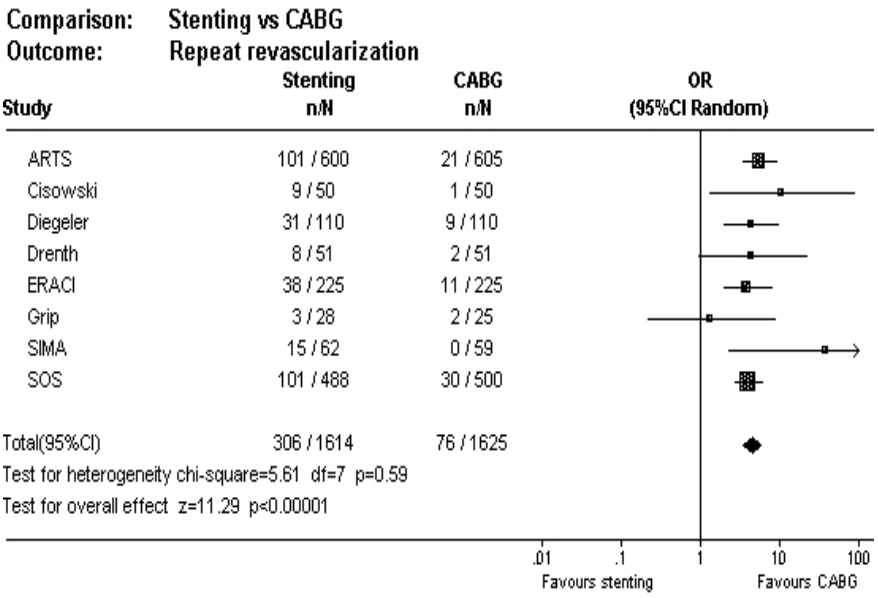
Figure 3. A: *overall risk of death (average follow-up 28 months).* B: *overall risk of the combined endpoint of death, non-fatal myocardial infarction or stroke (average follow-up 16 months; Grip et al. did not report any data on stroke). CABG = coronary artery bypass graft; CI = confidence interval; df = degrees of freedom; OR = odds ratio.*

Implications for clinical practice. Since the development of bypass techniques, myocardial revascularization has been shown to improve outcomes in patients with CAD[1]. At the same time, percutaneous coronary revascularization techniques were introduced and continuously improved. Restenosis at the site of balloon dilation was however soon recognized as an important limitation of PTCA, affecting about one third of patients[30]. In fact, pooled analysis of trials comparing PTCA vs CABG, have already shown that in selected patients with single or multivessel CAD the early and long-term risks of death were similar for both revascularization techniques (2.9-3.9% for PTCA vs 2.3-3.7% for CABG)[2,3]. An equivalent long-term risk for both PTCA and CABG was also evident for the combined endpoint of death or non-fatal myocardial infarction (respectively 9.8 vs 10.1%)[3]. However, significant and clinically relevant differences strongly favored CABG over PTCA both in terms of an increased freedom from angina (80.7 vs 73.1%) and of a reduced rate of repeat revascularization (7 vs 42.6%)[3]. Most of these differences could be ascribed to the early or late complications of PTCA, such as abrupt vessel closure or restenosis.



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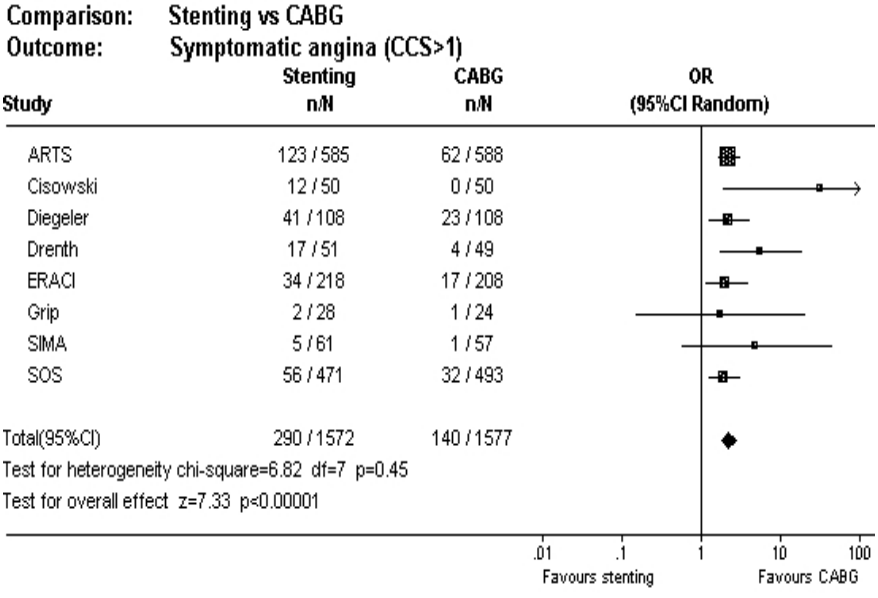

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Figure 4. A: *overall risk of repeat revascularization (average follow-up 16 months).* B: *overall risk of symptomatic angina (CCS > 1) (average follow-up 12 months). CABG = coronary artery bypass graft; CI = confidence interval; df = degrees of freedom; OR = odds ratio.*

A major step forward for interventional techniques was the introduction of bare metal stents in the late 80's[4]. These were later to become one of the most important tools for the improvement of the early and long-term results, in particular in reducing the restenosis rate[30]. Recently, several randomized trials have compared the efficacy and safety of coronary stenting to CABG, with partially conflicting results. To the best of our knowledge, there is currently no systematic and comprehensive overview of the randomized trials comparing stenting vs CABG. Notably, the most recent published systematic overviews of coronary stenting are almost 3 years old, and could not include a significant number of randomized trials, thus being underpowered in comparison to the present meta-analysis[5,31].

Indeed, the results of the present systematic overview comparing stenting vs CABG appear quite relevant for current clinical practice, as they show that in a large and heterogeneous population of patients with CAD, stenting and CABG appear to confer a similar survival benefit and are associated with similar rates of the combined endpoint of death, non-fatal myocardial infarction or stroke. Nonetheless, even though stenting has considerably improved the outlook after

Table IV. Subgroup and sensitivity analysis of studies comparing stenting vs coronary artery bypass graft (CABG).

Subgroup or statistical model for sensitivity analysis	No. studies	No. patients	Risk of death, MI or stroke		
			OR*	95% CI	p
Excluding studies reported only as abstract	7	3186	0.83	0.57-1.23	0.4
Fixed effect model	8	3239	0.86	0.68-1.08	0.19
Higher than median quality studies	4	2764	0.81	0.54-1.21	0.3
Multicenter design studies	4	2764	0.81	0.54-1.21	0.3
Off-pump CABG studies	4	475	0.97	0.43-2.19	0.9
Overall, excluding the SoS trial	7	2251	0.81	0.46-1.29	0.3
Overall including the AWESOME trial§	10	3737	0.89	0.58-1.38	0.6
Pohl et al. and AWESOME combined§	2	498	0.92	0.60-1.42	0.5
Single vessel disease studies	5	596	0.96	0.47-1.96	0.9

CI = confidence interval; MI = myocardial infarction; OR = odds ratio. * OR > 1 favors CABG, < 1 favors stenting; § risk of death is reported for the analysis including the AWESOME study because the composite endpoint was not reported for this trial.

percutaneous intervention in comparison to PTCA, CABG still appears superior to interventional revascularization with conventional stenting in terms of both symptomatic benefit and of freedom from later revascularization. Actually, pooled analyses of trials comparing CABG to percutaneous revascularization before and after the widespread use of stents show that bare metal stents have reduced the rate of repeat revascularization from 44% with balloon only intervention to 19% with coronary stenting. This is still inferior to the 4.7% rate of repeat revascularization typical of CABG in similar patients, but represents a significant improvement.

Clinically, we may thus conclude that in a large population of patients with single or multivessel coronary disease, including a relevant subset of subjects with a moderately impaired ventricular function, diabetes, a previous myocardial infarction or recent acute coronary syndromes, the less invasive percutaneous revascularization means of coronary stenting yields clinical results similar to those of the more invasive and costly CABG both in terms of the risk of death and of the combined endpoint of death, non-fatal myocardial infarction or stroke, albeit at the price of an increased rate of recurrence of angina or later repeat revascularization.

Internal and external validity. One of the major caveats of the present study when extrapolating its findings is the overall low randomized to screened ratio of individual trials comparing percutaneous revascularization and CABG. This low rate severely limits the widespread applicability of the single as well as pooled study results. Unfortunately, conventional stenting and new surgical techniques have not brought substantial improvements in this field, as on average only 6% of the screened patients could be included in the trials hereby analyzed (similar to the overall 5% in trials comparing PTCA to CABG)[3].

Several other limitations of the included studies must be borne in mind. In particular, in several trials patients known to be poor candidates for percutaneous revascularization, such as those with bifurcation or ostial lesions, a small luminal vessel diameter or widespread coronary disease were probably excluded[32]. Glycoprotein IIb/IIIa inhibitors were used only sparsely and implanted stents were sometimes of older design than those currently used in interventional practice. In none of the included trials could the role of the volume of interventions per operator and institution be examined, even though this may significantly impact on the outcome after both CABG and stenting. In addition, medical therapy was assumed to be similar in patients randomized to stenting and CABG, even though some authors have suggested an improved compliance with medical therapy after CABG, thus potentially leading to an overall superiority of surgery. The enrolment criteria were often different in the included studies, and thus the included patients cannot be considered strictly similar in different trials. The potential equivalence of revascularization (including complete revascularization) was an inclusion criterion in some studies, but not in all. Moreover, the available follow-up might not be long enough to reliably exclude differences in stenting vs CABG or to define the exact role of complete vs adequate revascularization, as arterial grafts remain patent even after decades and could thus become significantly superior to percutaneous interventions only several years after revascularization. Finally, subjects at high risk for restenosis, disease progression and perioperative mortality were poorly represented, in particular due to the frequent exclusion of subjects with left ventricular dysfunction and to the relative paucity of diabetics (as both are known to benefit more from surgery than from coronary intervention)[1].

Interestingly, considering the two trials that have enrolled high-risk subjects (elderly, depressed left ventricular function)[24,29], the outlook after revascularization with CABG or stenting was quite similar, even though the long-term survival was still quite poor (only 77-80%).

Overall, we must remember that the choice of the technique of revascularization is still very complex and partly subjective, as the cardiac operative risk, non-cardiac comorbidities, coronary anatomy and the patient's preferences may on the whole play a greater role in decision making than the brute rates of major and minor adverse events during follow-up for the chosen revascularization procedure.

Potential biases and limitations of the present study. The limitations of systematic overviews and meta-analytic methods are well known[15]. Among the potential limitations of this study, two trials could not be included because the authors did not provide detailed data. Moreover, we found, for the outcome of death, an overall non-significant trend towards statistical heterogeneity and a significant heterogeneity in the subgroup of studies on multivessel disease. Sensitivity analysis was performed to assess findings of the meta-analysis after exclusion of the study most responsible for such heterogeneity (the SoS study). The results were similar to the pooled estimates obtained when all studies were included and did not depend much on the outcomes from the SoS trial (Table IV). Finally, no economic or cost-effectiveness analysis was performed in this study, and thus no quantitative conclusion can be drawn on the economic comparison of stenting vs CABG in a resource conscious health care setting.

Avenues for future research and analysis. The results of this systematic overview provide an updated and thorough comparison of CABG and stenting in the management of CAD. However, they represent an accurate summary of what has been already achieved and established in the field, but do not whatsoever say the final word in this fast-changing field of clinical medicine. Indeed, cardiac bypass surgery has significantly evolved in terms of improved techniques, surgical materials and selection of candidates. The development of off-pump mini-invasive CABG, in particular, heralds a promise of a reduced morbidity and an improved safety of cardiac surgery. However, some drawbacks of mini-invasive thoracotomy have been envisaged, and there is still no firm consensus on whether off-pump CABG can represent an alternative to on-pump CABG in the near future.

More recently, medicated stents have been introduced in clinical practice to address a major complication of bare metal stenting, in-stent restenosis[33,34]. The process of in-stent smooth muscle hyperplasia is indeed a troublesome late complication of coronary stenting and may itself constitute an indication to repeat coronary intervention or bypass surgery[33]. Medicated stents are characterized by their ability to release antiproliferative agents *in situ* in the coronary vessel, thus decreasing or abolishing the restenosis process[35]. The long-term follow-up data for single vessel coronary disease stenting with drug-eluting stents are very promising, especially for the sirolimus-eluting stents, but a thorough assessment of the role of these devices in overcoming restenosis in severe CAD such as multivessel or proximal left anterior descending coronary disease is still not possible[34,35]. The ARTS II registry comparison of sirolimus-eluting stents vs CABG in multivessel disease is close to initiation and should provide important information, whilst awaiting formal randomized trials[35]. The latter will surely help reshape our current approach to revascularization in CAD.

In conclusion, the present meta-analysis of randomized studies of stenting vs CABG in the management of CAD shows that stenting yields a similar overall survival to surgical revascularization as well as a similar rate of freedom from major adverse clinical events, such as death, non-fatal myocardial infarction or stroke. Conventional bare metal stenting is however still fraught by a significantly increased risk of repeat revascularization in comparison to CABG. Accordingly, CABG is associated with a significantly higher rate of angina-free status. The role of next-generation drug-eluting stents in overcoming restenosis will need to be assessed in future observational and randomized studies of stenting vs CABG.

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