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A Meta-Analysis of Randomized Controlled Trials Comparing Coronary Artery Bypass Graft With Percutaneous Transluminal Coronary Angioplasty: One- to Eight-Year Outcomes

Stuart N. Hoffman, DO,* John A. TenBrook, Jr, MD,* Michael P. Wolf, MD,*
Stephen G. Pauker, MD, FACC,*† Deeb N. Salem, MD, FACC,*† John B. Wong, MD*
Boston, Massachusetts

OBJECTIVES We performed a meta-analysis of randomized trials comparing coronary artery bypass graft surgery (CABG) with percutaneous transluminal coronary angioplasty (PTCA) for the treatment of coronary artery disease, incorporating new trials and examining long-term outcomes.

BACKGROUND Previous meta-analyses of trials comparing CABG with PTCA have reported short- and intermediate-term outcomes, but since then longer term follow-up and newer trials have been published.

METHODS We performed a meta-analysis of 13 randomized trials on 7,964 patients comparing PTCA with CABG.

RESULTS We found a 1.9% absolute survival advantage favoring CABG over PTCA for all trials at five years ($p < 0.02$), but no significant advantage at one, three, or eight years. In subgroup analysis of multivessel disease, CABG provided significant survival advantage at both five and eight years. Patients randomized to PTCA had more repeat revascularizations at all time points (risk difference [RD] 24% to 38%, $p < 0.001$); with stents, this RD was reduced to 15% at one and three years. Stents also resulted in a significant decrease in nonfatal myocardial infarction at three years when compared with CABG. For diabetic patients, CABG provided a significant survival advantage over PTCA at 4 years but not at 6.5 years.

CONCLUSIONS Our results suggest that, when compared with PTCA, CABG is associated with a lower five-year mortality, less angina, and fewer revascularization procedures. For patients with multivessel disease, CABG provided a survival advantage at five to eight years, and for diabetics, a survival advantage at four years. The addition of stents reduced the need for repeat revascularization by about half. (J Am Coll Cardiol 2003;41:1293–304) © 2003 by the American College of Cardiology Foundation

An estimated 12.4 million adults in the U.S. are living with coronary heart disease, as manifest by angina or a history of myocardial infarction (MI). In 1999, there were an estimated 571,000 coronary artery bypass graft (CABG) surgeries and more than one million inpatient percutaneous transluminal coronary angioplasty (PTCA) procedures (1). Recent guidelines for the management of coronary artery disease include specific recommendations regarding revascularization strategy based on extensive literature review, qualitative analysis, consensus of expert opinion, and meta-analysis (2–4).

Previous meta-analyses compared one- to three-year outcomes of randomized trials comparing PTCA with CABG and found no significant difference in rates of death or MI (5,6). Since then, longer follow-up, additional randomized trials, and newer technologies such as stents have become available. Also, questions regarding benefits in subgroups such as diabetic patients have been raised. We performed a meta-analysis of 13 trials including 7,964 patients to examine the probabilities of death, nonfatal MI, angina, and revascularization for up to eight years following initial CABG or PTCA (7–19). In addition, we performed analyses to examine relative benefits in subgroups with isolated proximal left anterior descending (LAD), multivessel disease, diabetes, and trials with and without stents in the initial PTCA strategy.

METHODS

Literature search. We retrieved all articles with a MEDLINE search from 1966 through 2001, using the Medical Subject Heading terms "angioplasty, transluminal, percutaneous coronary," "coronary artery bypass," "randomized controlled trial," and "comparative study," which yielded 116 articles. Additional articles were identified from bibliographies of retrieved articles, including previous meta-analyses (5,6), personal files, and expert consultation. Since 2001, one additional trial was published and was included (18).

From the *Department of Medicine, Division of Clinical Decision Making, Informatics, and Telemedicine; and the †Division of Cardiology, Tufts-New England Medical Center, Boston, Massachusetts. Supported in part by grant LM07092-10 from the National Library of Medicine, Bethesda, Maryland, and by grant HS-06503 from the Agency for Healthcare Research and Quality, Rockville, Maryland. Dr. Wong was a co-investigator in the Patient Outcome Research Team grant for Ischemic Heart Disease from the then Agency for Health Care Policy and Research from 1990 to 1995 and is currently the content editor for Coronary Artery Disease for the nonprofit Foundation for Informed Medical Decision Making. In both of these cases he has complete independence from the funding source in study design, interpretation of data, report writing, and publication regardless of results.

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Abbreviations and Acronyms

AWESOME = Angina With Extremely Serious Operative Mortality Evaluation
CABG = coronary artery bypass graft surgery
LAD = left anterior descending coronary artery
MI = myocardial infarction
NNT = number needed to treat
PTCA = percutaneous transluminal coronary angioplasty
RD = risk difference

Eligible studies for the meta-analysis were limited to randomized controlled trials comparing the initial strategies of CABG and PTCA, in patients with multivessel (as defined by the study investigators) or proximal LAD disease who were candidates for either procedure. Studies that utilized stents as one of the initial interventions were included (15–18). Thirteen randomized trials met the above criteria for this meta-analysis (10,15–26). We excluded the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME) trial (27) because it enrolled patients with severe left ventricular dysfunction, ongoing or very recent MI, or prior heart surgery—clinical characteristics that would have excluded them from the other 13 trials.

Data abstraction. We captured prespecified data elements for each trial, including baseline characteristics, inclusion and exclusion criteria, and outcomes. We examined the following outcomes: 1) death; 2) cardiac death; 3) nonfatal MI; 4) subsequent revascularization (CABG or PTCA following initial strategy); 5) subsequent CABG; 6) subsequent PTCA; 7) combined end point of death, MI, or subsequent revascularization; and 8) angina. In our meta-analysis, follow-up data from years 2 to 3, 4 to 5, and 6 to 8 were combined where available and reported as three-, five-, and eight-year end points, respectively. For diabetic patients, we report outcomes where available at 4 and 6.5 years.

Two independent reviewers (S.N.H., J.A.T.) performed data extraction from text, tables, and figures, and consensus was obtained for all data. Discrepancies in data extraction from text or tables were arbitrated by a third party (J.B.W. or M.P.W.). Some studies reported revised data for the same end point in later publications. Hence, we gave priority to the most recent publication when there was a discrepancy. Survival curves and histograms were enlarged, digitally scanned, and then analyzed using CorelDRAW!4 (Corel Corp., Ottawa, Ontario, Canada), using a method similar to that described by Earle et al. (28).

Agreement between reviewers was analyzed using the kappa coefficient (kappa = 0.936 for agreement within 1%) using Excel 97 (Microsoft Corp., Redmond, Washington). We also calculated the intraclass correlation coefficient (29) ($r = 0.996$; median difference between reviewers = 0.2%; interquartile range = 0.1% to 0.6%) using SPSS 10.1 (SPSS Inc., Chicago, Illinois). Because details regarding dropouts were not uniformly available, our analysis was unable to account for censored observations in these analyses (28,30).

Statistical methods. The DerSimonian and Laird (31) random-effects model was used to obtain a summary estimate of risk difference and a 95% confidence interval (CI) for each end point. We chose the random-effects model because of its more conservative summary estimate, incorporating variance between and within studies.

All trials were randomized and analyzed based on the intention-to-treat principle and were reported in peer-reviewed journals, although the detail to which each study reported its methodology for randomization, censoring, handling of crossovers differed slightly. Given the nature of the treatments, blinding was not possible. Thus, application of a quality score such as the Jadad scale would likely be uninformative. In addition, weighting based on quality scores might introduce bias, and the use of such instruments is controversial (32). Statistical analysis of binary outcomes was performed using Meta-Analyst 0.989 (Joseph Lau, Boston, Massachusetts).

We performed the analysis using different metrics, including odds ratio, risk ratio, and risk difference (RD), each of which produced slightly different estimates of effect size and heterogeneity. We chose to report RD because it allows a straightforward calculation of the number needed to treat (NNT), a useful measure of clinical effectiveness (NNT = 1/RD). In this analysis, a positive RD indicates an advantage for CABG over PTCA. In contrast, a negative RD means that PTCA is favored over CABG. When the RD is statistically significant, we report NNT. For example, an RD of +0.02 would yield an NNT of +50, indicating that treating 50 patients with CABG would, on average, prevent one adverse outcome compared to the alternative of treating the same 50 patients with PTCA. Results using odds and risk ratios were similar to those reported here using RD and are available from the authors upon request.

Heterogeneity between studies was evaluated by the Q-statistic, considered significant for p values <0.10. To explore the source of heterogeneity, we sorted studies by event rate in the CABG arm and excluded one or more that contributed most to the Q-statistic. We performed separate analyses of prespecified subgroups with different trial characteristics including patients with single- or multivessel disease and use or nonuse of stents in the initial PTCA strategy.

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RESULTS

Study selection. Table 1 lists study characteristics for the 13 trials selected for inclusion with a total of 7,964 patients. Enrollment in these trials was from 1987 to 1999, including 2,764 patients from four trials that used stents in the initial PTCA strategy. The percentage of screened patients en-

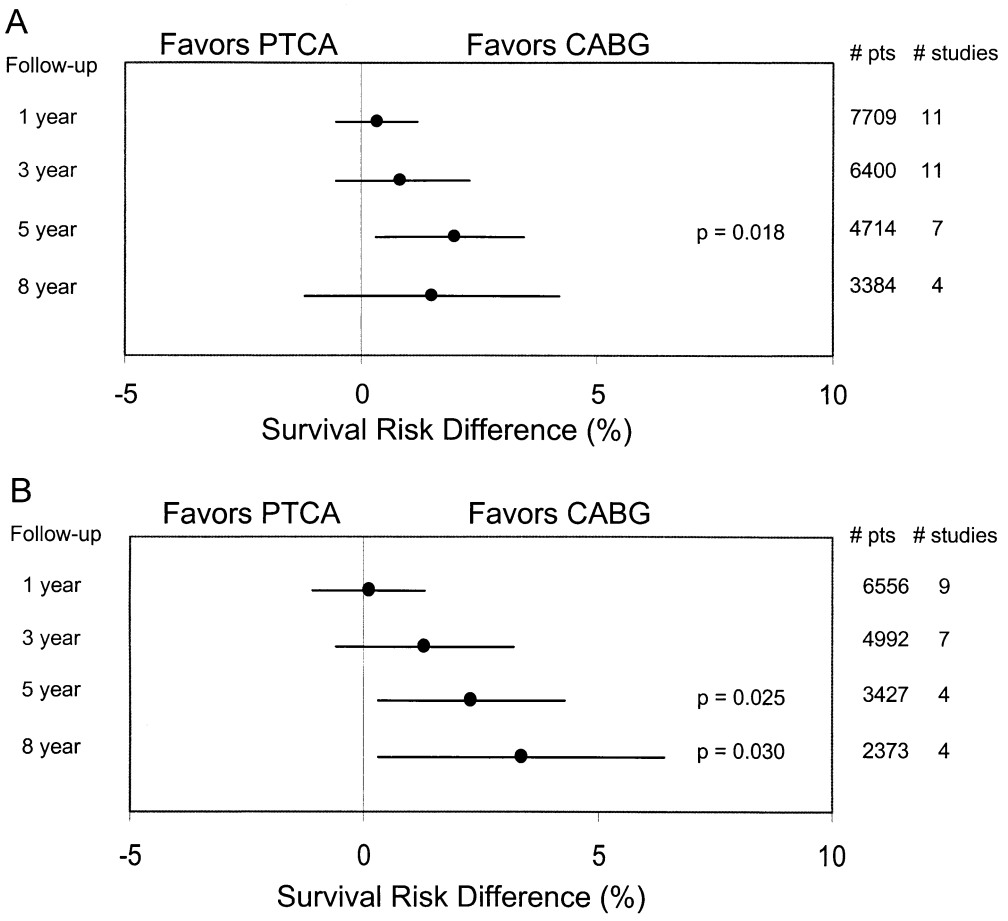

Figure 1. Risk difference for all-cause mortality for years 1, 3, 5, and 8 post-initial revascularization. All trials **(A)** and multivessel coronary artery disease **(B)**. The **lines** represent 95% confidence intervals. Event rates for the coronary bypass arm at one, three, five, and eight years for all trials **(A)** were 3.0%, 4.7%, 7.1%, and 13.7%; for multivessel trials **(B)** were 3.4%, 5.3%, 8.9%, and 15.8%. CABG = coronary artery bypass graft surgery; PTCA = percutaneous transluminal coronary angioplasty.

rolled in the trials ranged from 2% to 12%, except for the Medicine, Angioplasty, or Surgery Study (MASS) trial, which enrolled 69% of those screened. All trials included patients who were eligible for either CABG or PTCA. Ten studies explicitly excluded patients with prior revascularization (Table 1). Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in Patients with Multivessel Disease (ERACI-II) (16), permitted prior PTCA (>1 year) or left main disease amenable to stent therapy; analysis with and without this study did not change the overall results. Results of sensitivity analyses are available from the authors upon request.

Baseline characteristics were similar between patients randomized to PTCA and those randomized to CABG. One notable difference in inclusion criteria was the extent of anatomic disease present. Three studies (12,15,22) examined patients with single-vessel (proximal LAD) disease whereas nine examined patients with multivessel disease (9,10,16–19,21,24,26,33) and one, the Randomized Intervention Treatment of Angina (RITA) study (20), examined both types of patients. Two studies specified equivalent anatomic revascularization (10,19), and four specified equivalent functional revascularization (16,21,23,24). Most patients were men, with a high prevalence of hypertension, smoking, and angina. The proportion of patients with diabetes varied from 6% to 25% (Table 1).

Death, cardiac death, and nonfatal MI (all studies). We found no statistically significant risk difference for death or cardiac death between the two revascularization strategies, except at year 5 when there was a 1.9% to 2.0% RD favoring CABG over PTCA (CIs 0.33% to 3.4% for death and 0.29% to 3.7% for cardiac death, $p = 0.02$) (Fig. 1A), corresponding to NNTs of 53 for death and 51 for cardiac death favoring CABG. Although the magnitude of the difference in eight-year all-cause mortality was similar, fewer studies were available, and the results were not statistically significant. When compared with each other, neither CABG nor PTCA reduced nonfatal MI (Table 2).

Subsequent revascularization, combined end points, or angina (all studies). Risk of additional revascularization procedure (PTCA or CABG) was higher following PTCA at all time points (RDs 24% to 38%, $p < 0.001$), with most of the difference occurring in the first year. For the combined end point of death, MI, or any additional revascular-

Table 1. Demographic Data from Included Studies

	RITA	ERACI	Lausanne	GABI	EAST	CABRI	MASS*	BARI	Toulouse	SIMA†	ERACI II†	ARTS†	SoS†
Total patients	1011	127	134	359	392	1054	142	1829	152	121	450	1205	988
PTCA, n	510	63	68	182	198	541	72	915	76	62	225	600	488
CABG, n	501	64	66	177	194	513	70	914	76	59	225	605	500
Age (mean) (yrs)	57	57	56	< 75	62	60	56	61	67	59	62	61	61
PTCA	n/a	59	57	n/a	62	60	54	62	66	59	62	61	61
CABG	n/a	55	54	n/a	61	60	58	61	68	60	61	61	62
Male, n (%)													
PTCA	422 (83)	51 (81)	54 (79)	144 (79)	148 (75)	421 (78)	58 (81)	666 (73)	55 (72)	47 (76)	174 (77)	462 (77)	390 (80)
CABG	394 (79)	57 (89)	53 (80)	142 (80)	141 (73)	399 (78)	58 (83)	674 (74)	62 (82)	49 (83)	183 (81)	460 (76)	392 (78)
DM, n (%)													
PTCA	33 (6)	7 (11)	8 (12)	18 (10)	49 (25)	64 (12)	15 (21)	218 (24)	11 (14)	7 (11)	39 (17)	114 (19)	68 (14)
CABG	29 (6)	7 (11)	8 (12)	27 (15)	41 (21)	60 (12)	18 (26)	226 (25)	9 (12)	8 (14)	39 (17)	97 (16)	74 (15)
HTN, n (%)													
PTCA	n/a	33 (52)	31 (46)	76 (42)	106 (54)	190 (35)	34 (47)	449 (49)	31 (41)	28 (45)	160 (71)	270 (45)	212 (43)
CABG	n/a	37 (58)	27 (41)	69 (39)	100 (52)	188 (37)	30 (43)	447 (49)	33 (43)	28 (47)	159 (70)	272 (45)	235 (47)
Smokers, n (%)													
PTCA	n/a	39 (62)	40 (59)	127 (70)	38 (19)	79 (15)	36 (50)	238 (26)	39 (51)	35 (56)	122 (54)	168 (28)	77 (16)
CABG	n/a	45 (70)	34 (52)	119 (67)	41 (21)	66 (13)	37 (53)	219 (24)	41 (54)	30 (51)	111 (50)	157 (26)	72 (14)
Prior MI, n (%)													
PTCA	217 (43)	32 (51)	n/a	84 (46)	81 (41)	224 (41)	n/a	488 (53)	28 (37)	1 (2)	64 (28)	264 (44)	214 (44)
CABG	210 (42)	31 (48)	n/a	83 (47)	79 (41)	215 (42)	n/a	499 (55)	29 (38)	1 (2)	62 (28)	254 (42)	234 (47)
CCS class 0–2, n (%)													
PTCA	220 (43)	n/a	5 (7)	n/a	43 (22)	215 (40)	n/a	176 (19)	n/a	32 (52)	n/a	n/a	n/a
CABG	194 (39)	n/a	9 (14)	n/a	34 (18)	175 (34)	n/a	172 (19)	n/a	30 (51)	n/a	n/a	n/a
CCS class 3–4, n (%)													
PTCA	289 (57)	n/a	54 (79)	n/a	147 (74)	245 (45)	n/a	160 (17)	35 (46)	30 (48)	n/a	n/a	210 (43)
CABG	304 (61)	n/a	51 (77)	n/a	155 (80)	254 (50)	n/a	140 (15)	45 (59)	29 (49)	n/a	n/a	241 (48)
Unstable angina, n (%)													
PTCA	282 (55)	48 (76)	8 (12)	24 (13)	n/a	74 (14)	n/a	563 (62)	n/a	n/a	207 (92)	222 (37)	n/a
CABG	275 (55)	57 (89)	5 (8)	27 (15)	n/a	79 (15)	n/a	585 (64)	n/a	n/a	204 (91)	212 (35)	n/a
Mean cholesterol													
PTCA	n/a	n/a	n/a	n/a	218	237	213	217	n/a	217	n/a	n/a	n/a
CABG	n/a	n/a	n/a	n/a	224	223	230	220	n/a	220	n/a	n/a	n/a
Dyslipidemia, n (%)													
PTCA	n/a	35 (56)	n/a	109 (60)	n/a	n/a	n/a	412 (45)	n/a	38 (61)	141 (62)	348 (58)	258 (53)
CABG	n/a	39 (61)	n/a	108 (61)	n/a	n/a	n/a	393 (43)	n/a	32 (54)	135 (60)	135 (58)	251 (50)
Mean EF (%)													
PTCA	n/a	59	n/a	n/a	61	63	77	57	n/a	67	n/a	61	57
CABG	n/a	62	n/a	n/a	62	63	74	58	n/a	67	n/a	60	57
3VD, n (%)													
PTCA	63 (12)	27 (43)	0 (0)	27 (15)	79 (40)	216 (40)	n/a	378 (41)	21 (28)	n/a	123 (55)	180 (30)	183 (38)
CABG	61 (12)	30 (47)	0 (0)	39 (22)	77 (40)	222 (43)	n/a	376 (41)	23 (30)	n/a	130 (58)	200 (33)	236 (47)
2VD, n (%)													
PTCA	213 (42)	36 (57)	0 (0)	155 (85)	119 (60)	316 (58)	n/a	537 (59)	55 (72)	n/a	90 (40)	408 (68)	303 (62)
CABG	218 (44)	34 (53)	0 (0)	138 (78)	117 (60)	288 (56)	n/a	538 (59)	53 (70)	n/a	86 (38)	405 (67)	262 (52)

Continued on next page

Table 1 Continued

	RITA	ERACI	Lausanne	GABI	EAST	CABRI	MASS*	BARI	Toulouse	SIMA†	ERACI II†	ARTS†	SoS†
1VD, n (%)													
PTCA	234 (46)	n/a	68 (100)	0 (0)	0 (0)	9 (2)	72 (100)	0 (0)	0 (0)	62 (100)	n/a	12 (2)	n/a
CABG	222 (44)	n/a	66 (100)	0 (0)	0 (0)	3 (1)	70 (100)	0 (0)	0 (0)	59 (100)	n/a	0 (0)	n/a
Proximal LAD, n (%)													
PTCA	n/a	n/a	68 (100)	n/a	140 (71)	n/a	72 (100)	326 (36)	n/a	62 (100)	n/a	n/a	235 (48)
CABG	n/a	n/a	66 (100)	n/a	143 (74)	n/a	70 (100)	341 (37)	n/a	59 (100)	n/a	n/a	222 (44)
IMA, n (%)													
CABG	371 (74)	48 (75)	59 (100)‡	60 (37)		387 (75)	70 (100)	731 (80)	44 (58)	59 (100)	199 (88)	563 (93)	395 (81)
Primary outcomes (A–H)	A,B	A,B,C,D	E,B,C	F	A,B,G	A,D	A,B,C	A	F	A,B,C	A,B,C,H	A,C,H	C
Inclusion criteria (I–O)	I,J,K	I,J	I,K,L	I,J	I,J	I,J	I,K,L	I,J	I,J	I,K,M	I,J,M,N	I,J,O	I,J,M
Exclusion criteria (P–W)	P,Q,R	Q,R,S	P,T	P,Q,U,V,W	P,Q,R,V,W	P,Q,S,U,W	P,Q,T,V	P,Q,R	P,Q,R,V	T	S	P	P
Screened, n	27,975	1,407	5,119	8,981	5,118	42,580	313	15,000	5,964	n/a	5,619	n/a	n/a
%	3.6	9	2.6	4	3.8	2.5	69	12	2.5		2.2		
Reference	(20)	(21)	(22)	(19)	(23)	(24)	(25)	(26)	(10)	(15)	(16)	(17)	(18)

*Not including medical arm. †Stents used in PTCA arm. ‡On treatment.

1VD = one-vessel disease; 2VD = two-vessel disease; 3VD = three-vessel disease; CABG = coronary artery bypass graft; CCS Class = Canadian Cardiovascular Society angina class; DM = diabetes mellitus; EF = ejection fraction; HTN = hypertension; IMA = internal mammary artery; LAD = left anterior descending coronary artery; MI = myocardial infarction; n/a = data not available; PTCA = percutaneous transluminal coronary angioplasty; RITA = Randomised Intervention Treatment of Angina; ERACI = Argentine randomized trial of percutaneous transluminal coronary angioplasty versus coronary artery bypass surgery in multivessel disease; Lausanne = Goy JJ, et al. Coronary angioplasty versus left internal mammary artery grafting for isolated proximal left anterior descending artery stenosis. Lancet 1994;343:1449–53; GABI = German Angioplasty Bypass Surgery Investigation; EAST: Emory Angioplasty versus Surgery Trial; CABRI = Coronary Angioplasty versus Bypass Revascularization Investigation; MASS = Medicine, Angioplasty, or Surgery Study; BARI = Bypass Angioplasty Revascularization Investigation; Toulouse = French Monocentric Study; SIMA = Stenting vs. Internal Mammary Artery; ERACI II = Argentine randomized study: coronary angioplasty with stenting versus coronary bypass surgery in patients with multivessel disease; ARTS = Arterial Revascularization Therapies Study; SoS = Stent or Surgery trial.

A = death; B = nonfatal MI; C = revascularization; D = angina; E = cardiac death; F = angina CCS < II; G = large ischemic deficit on thallium scan; H = neurologic complication; I = Agreement that equivalent revascularization possible; J = multivessel disease; K = single-vessel (prox. LAD) disease; L = normal EF; M = ≥1 lesion amenable to stenting; N = severe angina; O = ≥2 lesions amenable to stenting; P = previous revascularization; Q = left main coronary disease; R = noncardiac disease limiting life expectancy; S = EF < 35%; T = previous MI; U = age >75; V = 100% occluded coronary artery; W = recent MI.

ization, the risk was always higher in the PTCA group (RDs 26% to 31%, $p < 0.001$). After one and three years, patients treated with CABG had a lower risk of angina than those receiving PTCA with a risk difference of ~10% ($p < 0.001$). After five years, this difference decreased to 5.3% and was no longer statistically significant (Table 2).

Trials with and without stents. Since the early trials of CABG versus PTCA, stents have become an important adjunct to balloon angioplasty. To assess this advance in technology, we performed subgroup analyses of trials with and without stents in the initial PTCA arm where data were available from at least two trials. For all-cause mortality, there was a trend favoring CABG over PTCA in pre-stent trials at three years (Table 3) (RD 1.1%, CI −0.1 to 2.3, $p = 0.08$) that was no longer present in trials with stents (Table 4). This trend favoring CABG disappeared despite a reduction in mortality in the CABG arm from 5.2% in trials without stents to 3.5% in the more recent trials with stents.

At three years, PTCA with stent provided a statistically significant reduction in nonfatal MI compared to CABG (RD −2.9%, CI −5.1 to −0.6%, $p = 0.01$) (Table 4). Although subsequent revascularization was still more frequent after PTCA with stent than after CABG, the risk difference for revascularization in trials with stents was about half that observed in trials without stents (Fig. 2). In trials without stents, however, neither CABG nor PTCA provided a significant advantage for preventing all-cause mortality or for preventing nonfatal MI at one or three years (Table 3).

Trials with multi- or single-vessel (proximal LAD) disease. We also performed meta-analyses of trials involving only multivessel or single-vessel (proximal LAD) disease. For patients with multivessel disease, risk of death was lower in the CABG-treated patients at five years (RD 2.3%, CI 0.29% to 4.3%, $p = 0.025$) and at eight years (RD 3.4%, CI 0.32% to 6.4%, $p = 0.03$) (Fig. 1B). Similarly, CABG lowered cardiac death at year 5 (RD 2.4%, CI 0.44% to 4.3%, $p = 0.016$). However, PTCA had a lower likelihood of nonfatal MI than CABG at three years (RD −3.3%, CI −5.5 to −1.1%, $p = 0.004$).

For those with single-vessel proximal LAD disease, the risk of death was lower in CABG-treated patients at year 5 (RD 5.6%, CI 0.19% to 11%, $p = 0.042$), but there was no statistically significant difference in all-cause mortality at year 3. Neither CABG nor PTCA was significantly favored for preventing cardiac death or nonfatal MI at years 3 or 5 (Tables 5 and 6). For single-vessel trials, data were insufficient for analysis at years 1 and 8.

Trials reporting outcomes in diabetic patients. We combined survival data from the four trials reporting on subgroups of patients with diabetes mellitus (9,20,34,35). At four years, we combined data from the Emory Angioplasty versus Surgery Trial (EAST), Coronary Angioplasty versus Bypass Revascularization Investigation (CABRI), and Bypass Angioplasty Revascularization Investigation (BARI) studies, and at 6.5 years, from the RITA, EAST, and BARI

Table 2. All Trials

Outcome	Pts (Trials)	Heterogeneity (p Value)	RD, % (95% CI)	p Value	NNT	References
Freedom from						
Death						
1 yr	7,709 (11)	13.6 (NS)	0.34 (−0.54 to 1.2)	0.45		(8–10,16–19,21,24–26)
3 yrs	6,400 (11)	15.6 (NS)	0.86 (−0.53 to 2.3)	0.23		(8–10,13–16,18,22,25,26)
5 yrs	4,714 (7)	3.7 (NS)	1.9 (0.33 to 3.4)	0.02	53	(8–13,26)
8 yrs	3,384 (4)	3.6 (NS)	1.5 (−1.2 to 4.2)	0.28		(7–10)
Cardiac death						
1 yr	780 (4)	2.6 (NS)	0.73 (−1.3 to 2.7)	0.47		(10,19,21,25)
3 yrs	3,067 (8)	2.9 (NS)	0.21 (−0.72 to 1.14)	0.65		(10,15,18,20–23,25)
5 yrs	2,649 (5)	1.5 (NS)	2.0 (0.29 to 3.7)	0.02	51	(9–12,33)
8 yrs	1,403 (2)	0.4 (NS)	−0.34 (−2.5 to 1.8)	0.76		(8,9)
Nonfatal MI						
1 yr	4,325 (7)	11.7 (<0.1)	−0.76 (−2.6 to 1.1)	0.43		(12,16–19,21,24)
3 yrs	3,365 (8)	13.9 (<0.1)	−0.48 (−3.0 to 2.0)	0.71		(9,14–16,18,20,22,23,25)
5 yrs	2,257 (4)	4.5 (NS)	1.4 (−2.5 to 5.3)	0.48		(10–12,26)
Subsequent revascularization (CABG or PTCA)						
1 yr	7,709 (11)	294 (<0.001)	24 (16 to 32)	< 0.001	4	(8–10,12,16–19,21,24,26)
3 yrs	6,258 (10)	170 (<0.001)	28 (20 to 36)	< 0.001	4	(8–10,13–16,18,22,26)
5 yrs	4,572 (6)	27 (<0.001)	37 (31 to 44)	< 0.001	3	(8–11,13,26)
8 yrs	3,384 (4)	18 (<0.001)	38 (30 to 46)	< 0.001	3	(7–10)
Subsequent CABG						
1 yr	7,259 (10)	183 (<0.001)	13 (8.0 to 18)	< 0.001	8	(8–10,12,17–19,21,24,26)
3 yrs	4,896 (9)	100 (<0.001)	17 (11 to 23)	< 0.001	6	(8–10,12,13,15,18,21,22,26)
5 yrs	3,660 (6)	27 (<0.001)	22 (16 to 27)	< 0.001	5	(8–12,26)
8 yrs	3,384 (4)	22 (<0.001)	26 (19 to 33)	< 0.001	4	(7–10)
Subsequent PTCA						
1 yr	7,259 (10)	124 (<0.001)	14 (9.1 to 19)	< 0.001	6	(8–10,12,17–19,21,24,26)
3 yrs	4,896 (9)	81 (<0.001)	16 (9.9 to 23)	< 0.001	6	(8–10,12,13,15,18,21,22,26)
5 yrs	3,660 (6)	32 (<0.001)	23 (16 to 30)	< 0.001	4	(8–12,26)
8 yrs	3,384 (4)	16 (<0.005)	20 (12 to 27)	< 0.001	5	(7–10)
Death, MI, or revascularization						
1 yr	1,280 (3)	3.6 (NS)	26 (18 to 33)	< 0.001	4	(12,20,21)
3 yrs	1,535 (5)	1.5 (NS)	26 (22 to 30)	< 0.001	4	(14,15,20,22,25)
5 yrs	276 (2)	0.02 (NS)	31 (21 to 41)	< 0.001	3	(11,12)
Angina						
1 yr	6,707 (8)	17 (<0.02)	11 (7.5 to 14)	< 0.001	9	(14,17–20,22,24,35)
3 yrs	5,260 (9)	24 (<0.005)	9.0 (5.0 to 13)	< 0.001	11	(13,15,16,20–23,25,35)
5 yrs	4,322 (6)	26 (<0.001)	5.3 (−0.82 to 11)	0.09		(8,10–13,35)

Risk difference (RD) = event rate for percutaneous transluminal coronary angioplasty (PTCA) group minus the event rate for coronary artery bypass graft surgery (CABG) group; NNT = 1/RD: number of patients needed to treat with CABG to prevent one adverse outcome in the same number of patients treated with PTCA, rounded to nearest integer and only reported if 95% confidence interval (CI) for RD does not cross zero; when RD is negative, a negative NNT is the number of patients needed to treat with PTCA to prevent one adverse outcome in the same number of patients treated with CABG; NS = nonsignificant p value. *8-year data not available.

studies. At 4 years, CABG was favored over PTCA for preventing all-cause death (RD 8.6%, CI 2.2% to 15%, $p < 0.01$), but after 6.5 years, CABG was no longer significantly favored (RD 3.9%, CI −17% to 25%, $p = 0.71$). For nondiabetic patients, there was no significant difference in survival at 4 or 6.5 years (Fig. 3, Table 7).

Analysis of heterogeneity. Heterogeneity was significant for survival in trials with stents and in the diabetic subgroup. Removing the Stent or Surgery (SoS) study (18) reduced heterogeneity to nonsignificant levels with a survival advantage for PTCA with stent at three years (RD −3.5%, CI −6.8% to −0.2%, $p = 0.04$). In the SoS study, there were eight cancer deaths in the stent arm and one in the CABG arm, which may explain the heterogeneity. Similarly, removing the RITA study from the diabetic data reduced heterogeneity to nonsignificant levels and resulted in a significant advantage for CABG at 6.5 years (RD 15.5%, CI 7% to 24%, $p < 0.001$). Notably, the RITA study had more deaths in the CABG than the PTCA arm among diabetic patients and was the only trial of these four that included diet-controlled diabetic patients in reporting this subgroup, which may explain the heterogeneity.

DISCUSSION

Our meta-analysis included 13 trials involving 7,964 eligible patients with CAD randomized to CABG or PTCA, followed for up to eight years. In the overall analysis, neither strategy provided a statistically significant survival advantage at one, three, or eight years. At five years, there was a statistically significant 1.9% RD advantage favoring CABG (Fig. 1A). Subgroup analysis of multivessel trials showed a similar survival advantage for CABG at years 5 and 8 (Fig.

Table 3. Trials Without Stents

Outcome	Pts (Trials)	Heterogeneity (p Value)	RD, % (95% CI)	p Value	NNT	References
Freedom from						
Death						
1 yr	5,066 (8)	3.9 (NS)	0.52 (−0.37 to 1.4)	0.26		(8–10,19,21,24–26)
3 yrs	4,841 (8)	4.9 (NS)	1.1 (−0.13 to 2.3)	0.08		(8–10,13,14,22,25,26)
Cardiac death						
3 yrs	1,958 (6)	0.6 (NS)	−0.4 (−1.7 to 0.85)	0.51		(10,20–23,25)
Nonfatal MI						
1 yr	1,682 (4)	3.5 (NS)	0.22 (−2.0 to 2.0)	0.84		(12,19,21,24)
3 yrs	1,806 (5)	5.6 (NS)	1.2 (−1.8 to 4.2)	0.42		(9,14,20,22,25)
Subsequent revascularization (CABG or PTCA)						
1 yr	5,066 (8)	239 (<0.001)	27 (17 to 38)	< 0.001	4	(8–10,12,19,21,24,26)
3 yrs	4,699 (7)	31 (<0.001)	34 (28 to 40)	< 0.001	3	(8–10,13,14,22,26)
Subsequent CABG						
1 yr	5,066 (8)	140 (<0.001)	15 (8.0 to 21)	< 0.001	7	(8–10,12,19,21,24,26)
3 yrs	3,787 (7)	23 (<0.001)	20 (15 to 24)	< 0.001	5	(8–10,12,21,22,26)
Subsequent PTCA						
1 yr	5,066 (8)	109 (<0.001)	15 (9.0 to 22)	< 0.001	7	(8–10,12,19,21,24,26)
3 yrs	3,787 (7)	50 (<0.001)	17 (10 to 24)	< 0.001	6	(8–10,12,21,22,26)
Death, MI, or revascularization						
3 yrs	1,414 (4)	1.3 (NS)	26 (22 to 31)	< 0.001	4	(14,20,22,25)
Angina						
1 yr	4,514 (6)	16 (<0.01)	10 (5 to 15)	< 0.001	10	(14,19,20,22,24,35)
3 yrs	4,689 (7)	24 (<0.001)	9.7 (4.6 to 15)	< 0.001	10	(13,20–23,25,35)

Note: Year 5–8 data identical to all trial data as in Table 2. Table 2 footnote applies to Tables 3 through 7.

1B). The long-term survival advantage for CABG is consistent with observational studies suggesting greater benefit from CABG over PTCA for patients with CAD (36,37).

However, it must be noted that all data at five and eight years are from earlier studies that did not employ stents in the initial revascularization procedure. The trend favoring CABG for survival at three years in pre-stent trials was no longer present in the stent era, despite a decrease in absolute mortality following CABG. Whether the introduction of stents and improvements in CABG will affect long-term results remains to be seen.

Our analysis of the diabetic subgroup reflects heterogeneity in outcomes reported in the literature. Coronary artery bypass graft surgery provided a statistically significant sur-

Table 4. Trials With Stents

Outcome	Pts (Trials)	Heterogeneity (p Value)	RD, % (95% CI)	p Value	NNT	References
Freedom from						
Death						
1 yr	2,643 (3)	9.6 (<0.01)	−0.6 (−3.4 to 2.2)	0.67		(16–18)
3 yrs	1,559 (3)	10.7 (<0.01)	−0.82 (−5.9 to 4.3)	0.75		(15,16,18)
Cardiac death						
3 yrs	1,109 (2)	0.21 (NS)	0.94 (−0.42 to 2.3)	0.17		(15,18)
Non-fatal MI						
1 yr	2,643 (3)	6.9 (<0.05)	−1.5 (−4.7 to 1.7)	0.35		(16–18)
3 yrs	1,559 (3)	1.8 (NS)	−2.9 (−5.1 to −0.6)	0.01	−35	(15,16,18)
Subsequent revascularization (CABG or PTCA)						
1 yr	2,643 (3)	2.9 (NS)	15 (12 to 18)	< 0.001	7	(16–18)
3 yrs	1,559 (3)	3.8 (NS)	15 (10 to 20)	< 0.001	7	(15,16,18)
Subsequent CABG						
1 yr	2,193 (2)	0.2 (NS)	6.3 (4.7 to 7.9)	< 0.001	16	(17,18)
3 yrs	1,109 (2)	0.5 (NS)	8.3 (5.8 to 11)	< 0.001	12	(15,18)
Subsequent PTCA						
1 yr	2,193 (2)	3.4 (<0.1)	10 (6.0 to 14)	< 0.001	10	(17,18)
3 yrs	1,109 (2)	3.3 (<0.1)	12 (2.6 to 21)	0.01	8	(15,18)
Angina						
1 yr	2,193 (2)	0.4 (NS)	11.4 (8.1 to 15)	< 0.001	9	(17,18)
3 yrs	571 (2)	~0 (NS)	7.7 (2.7 to 13)	0.0025	13	(15,16)

Table 2 footnote applies to Tables 3 through 7.

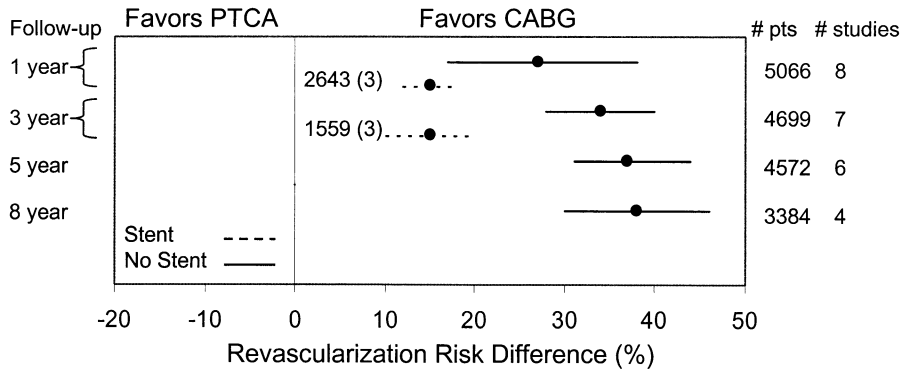

Figure 2. Risk difference for subsequent revascularization comparing coronary artery bypass graft surgery (CABG) to percutaneous transluminal coronary angioplasty (PTCA) (± stents) for years 1 and 3. The **lines** represent 95% confidence intervals. For trials with stents, numbers of patients and trials are adjacent to data at one and three years. Year 5 and 8 data were available only for CABG versus PTCA without stent.

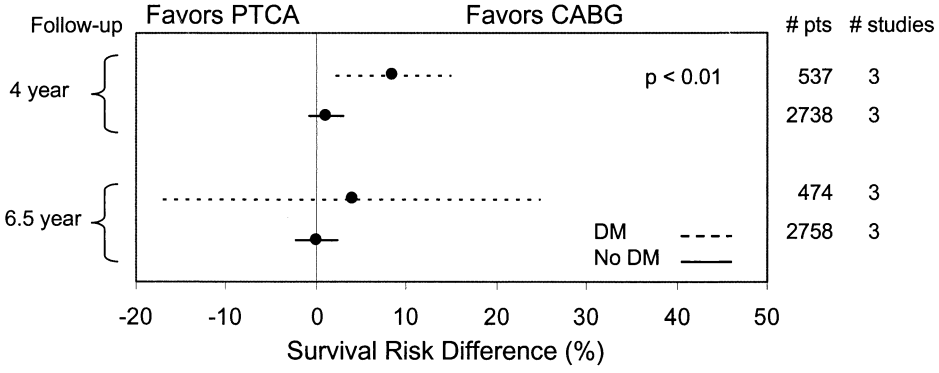

Figure 3. Risk difference for all-cause mortality for years 4 and 6.5 post-initial revascularization comparing coronary artery bypass graft surgery (CABG) to percutaneous transluminal coronary angioplasty (PTCA) for diabetic and non-diabetic patients. The **lines** represent 95% confidence interval.

Table 5. Trials of Single-Vessel (Proximal LAD) Disease Only

Outcome	Pts (Trials)	Heterogeneity (p Value)	RD, % (95% CI)	p Value	NNT	References
Freedom from						
Death						
3 yrs	397 (3)	1.4 (NS)	0.23 (−2.6 to 3.0)	0.87		(15,22,25)
5 yrs	276 (2)	~0 (NS)	5.6 (0.19 to 11)	0.042	18	(11,12)
Cardiac death						
3 yrs	397 (3)	0.32 (NS)	−0.6 (−3.0 to 1.8)	0.65		(15,22,25)
5 yrs	276 (2)	0.48 (NS)	0.73 (−2.8 to 4.2)	0.68		(11,12)
Nonfatal MI						
3 yrs	397 (3)	2.3 (NS)	2.8 (−1.2 to 6.7)	0.17		(15,22,25)
5 yrs	276 (2)	2.1 (NS)	5.0 (−3.6 to 14)	0.25		(11,12)
Subsequent revascularization (CABG or PTCA)						
3 yrs	255 (2)	0.22 (NS)	22 (14 to 30)	< 0.001	4	(15,22)
Subsequent CABG						
3 yrs	397 (3)	0.11 (NS)	12 (7.6 to 17)	< 0.001	8	(12,15,22)
5 yrs	276 (2)	1.1 (NS)	15 (8.9 to 22)	< 0.001	7	(11,12)
Subsequent PTCA						
3 yrs	397 (3)	9.4 (<0.01)	18 (5.5 to 30)	< 0.005	6	(12,15,22)
5 yrs	276 (2)	0.26 (NS)	27 (19 to 36)	< 0.001	4	(11,12)
Death, MI, or revascularization						
3 yrs	397 (3)	0.64 (NS)	24 (17 to 31)	< 0.001	4	(12,15,22)
5 yrs	276 (2)	0.02 (NS)	31 (21 to 41)	< 0.001	3	(11,12)
Angina						
3 yrs	397 (3)	1.6 (NS)	12 (6.2 to 18)	< 0.001	8	(12,15,22)
5 yrs	276 (2)	0.77 (NS)	2.4 (−8.5 to 13)	0.66		(11,12)

Table 2 footnote applies to Tables 3 through 7.

Table 6. Trials of Multivessel Disease

Outcome	Pts (Trials)	Heterogeneity (p Value)	RD, % (95% CI)	p Value	NNT	References
Freedom from						
Death						
1 yr	6,556 (9)	13 (NS)	0.12 (−1.1 to 1.3)	0.84		(9,10,16–19,21,24,26)
3 yrs	4,992 (7)	11 (<0.1)	1.3 (−0.6 to 3.2)	0.19		(9,10,16,18,21,24,26)
5 yrs	3,427 (4)	0.2 (NS)	2.3 (0.29 to 4.3)	0.025	44	(9,10,24,26)
8 yrs	2,373 (3)	0.02 (NS)	3.4 (0.32 to 6.4)	0.030	30	(7,9,10)
Cardiac death						
1 yr	638 (3)	2.4 (NS)	0.69 (−2.1 to 3.5)	0.63		(10,19,21)
3 yrs	1,659 (4)	0.7 (NS)	0.84 (−0.45 to 2.1)	0.20		(10,18,21,23)
5 yrs	2,373 (3)	0.4 (NS)	2.4 (0.44 to 4.3)	0.016	42	(9,10,33)
Nonfatal MI						
1 yr	4,183 (6)	11.7 (<0.05)	−0.92 (−3.1 to 1.3)	0.41		(16–19,21,24)
3 yrs	1,957 (4)	0.9 (NS)	−3.3 (−5.5 to −1.1)	0.004	−30	(14,16,18,23)
5 yrs	1,981 (2)	0.2 (NS)	−0.58 (−3.3 to 2.2)	0.68		(10,26)
Subsequent revascularization (CABG or PTCA)						
1 yr	6,556 (9)	164 (<0.001)	26 (18 to 34)	< 0.001	4	(9,10,16–19,21,24,26)
3 yrs	4,992 (7)	161 (<0.001)	28 (17 to 40)	< 0.001	4	(9,10,13,14,16,18,26)
5 yrs	3,427 (4)	23 (<0.001)	38 (30 to 47)	< 0.001	3	(9,10,13,26)
8 yrs	2,373 (3)	17 (<0.001)	36 (22 to 50)	< 0.001	3	(7–10)
Subsequent CABG						
1 yr	6,106 (8)	114 (<0.001)	14 (9.2 to 20)	< 0.001	7	(9,10,17–19,21,24,26)
3 yrs	3,488 (5)	92 (<0.001)	19 (9.1 to 29)	< 0.001	5	(9,10,18,21,26)
5 yrs	2,373 (3)	11 (<0.005)	24 (17 to 32)	< 0.001	4	(9,10,26)
8 yrs	2,373 (3)	17 (<0.001)	26 (16 to 36)	< 0.001	4	(7,9,10)
Subsequent PTCA						
1 yr	6,106 (8)	72 (<0.001)	16 (11 to 21)	< 0.001	6	(9,10,17–19,21,24,26)
3 yrs	3,488 (5)	70 (<0.001)	16 (5.2 to 26)	0.0033	6	(9,10,18,21,26)
5 yrs	2,373 (3)	14 (<0.001)	23 (12 to 34)	< 0.001	4	(9–11,26)
8 yrs	2,373 (3)	9.3 (<0.01)	21 (11 to 30)	< 0.001	5	(7,9,10)
Angina						
1 yr	5,562 (6)	17 (<0.01)	11 (6.4 to 15)	< 0.001	9	(14,17,19,24,35)
3 yrs	3,852 (5)	19 (<0.001)	7.7 (1.9 to 13)	0.009	13	(13,16,21,23,35)
5 yrs	3,035 (3)	16 (<0.005)	4.4 (−3.9 to 13)	0.30		(10,13,35)

Table 2 footnote applies to Tables 3 through 7.

vival advantage for diabetics over PTCA at 4 years but not at 6.5 years (Fig. 3), unless the RITA study is excluded. This advantage for CABG was not seen among nondiabetic patients, suggesting survival benefit only in diabetics. Registry data have also shown mixed results: some have suggested a survival advantage for CABG in diabetics (38) whereas others have not (39). Because the published diabetic randomized controlled trials data are all post-hoc analyses and not prespecified subgroups, they are subject to bias.

Angina and revascularization rates were higher following PTCA in the overall analysis and in all subgroups. For all trials, there was a 24% RD for repeat revascularization favoring CABG at one year increasing to 38% by eight years despite the expected need for revascularization in CABG patients due to failure of bypass grafts. With stents, however, the one- and three-year revascularization RD was reduced by one-half to 15%, perhaps because of reduced incidence of coronary restenosis (40). Drug-eluting stents may further reduce restenosis (41).

These revascularization results need to be interpreted with some caution because of the degree of heterogeneity found in reported outcomes. The decision for repeat revas-

Table 7. Trials of Diabetics and Nondiabetics

Outcome	Pts (Trials)	Heterogeneity (p Value)	RD, % (95% CI)	p Value	NNT	References
Freedom from						
Death (diabetic patients)						
4 yrs	537 (3)	1.3 (NS)	8.6 (2.2 to 15)	< 0.01	12	(9,34,35)
6.5 yrs	474 (3)	11.4 (<0.01)	3.9 (−17 to 25)	0.71		(8,9,35)
Death (nondiabetic patients)						
4 yrs	2,738 (3)	1.6 (NS)	1.1 (−0.83 to 3.1)	0.26		(9,34,35)
6.5 yrs	2,758 (3)	0.29 (NS)	0.09 (−2.2 to 2.3)	0.94		(8,9,35)

Table 2 footnote applies to Tables 3 through 7.

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cularization was not specified by the individual study protocols but was made by patients and their physicians and, therefore, was susceptible to differences in local practice patterns. Nonetheless, higher revascularization rates with PTCA might be explained in part by less complete revascularization with the initial PTCA (21,42), the lower likelihood of successful PTCA with bypass grafts in the CABG arm, the higher likelihood of operative mortality for repeat CABG, and the lower risk for angina with CABG. Additional sources of heterogeneity include variable definitions of outcomes such as postprocedure MI, the incidence of which may be biased by differences in surveillance and ascertainment.

There are several possible limitations to the present study. As in any meta-analysis, publication bias is always a concern (43). However, it is unlikely that a major randomized controlled trial escaped our search strategy and was also unknown to local experts. Our analysis only considered published rather than individual patient data; the latter would have permitted explicit examination of censored observations. To account in part for censoring, we elected to combine data for outcomes at specific time points. Because not all trials published the outcomes at the time points of interest, different studies contributed to the summary statistic at each time point.

For example, seven trials contributed to the overall analysis for five-year survival, but only four trials contributed at eight years (Fig. 1A, Table 2). While the point estimates for risk difference at five and eight years were similar (1.9% and 1.5%, respectively), the confidence interval was wider at eight years and the difference was no longer statistically significant, possibly due to reduced power. A new trial separate from this meta-analysis with 80% power to detect a 1.5% mortality difference at eight years would require about 8,700 patients. Note that such calculations of power to help explain a nonsignificant result after a trial has been completed, that is, "post-hoc power" analysis, may introduce problems with interpretation (44). A true reduction of the benefit from CABG or variation in included trials might also explain the lack of a significant survival advantage for CABG at eight years.

Multiple statistical comparisons were done over time for each clinical end point, raising the likelihood of seeing differences through chance alone. The use of Bonferroni's method for multiple comparisons in meta-analysis would be a conservative statistical correction but is controversial (29). When applied to our meta-analysis, neither PTCA nor CABG provided statistically significant benefit for the end points of death or cardiac death, except for cardiac death at five years for patients with multivessel disease, which continued to favor CABG.

Patients included in these trials are a carefully selected subgroup of coronary patients, typically 2% to 12% of those screened, so our results may not be generalizable to patients seen by community physicians. These results would appear to be most applicable to male smokers in their early 60s who are at low risk for cardiac death. Many sicker patients, such as those with heart failure, were ineligible for these trials. Recent trials, such as AWESOME (27), that include patients at high risk of cardiac death are addressing some of these questions.

Where comparable, the results of our overall meta-analysis showed no major differences from prior meta-analyses (5,6), for one- to three-year outcomes. Patients who underwent CABG had significantly fewer repeat revascularizations and less angina, and neither strategy had a clear advantage for preventing death or nonfatal MI at one to three years.

How then does one decide between CABG and PTCA? Certainly some patients may prefer having an initial PTCA to avoid the morbidity and short-term mortality incurred by having cardiac surgery (6,45–47). Other patients may prefer the lower risk for subsequent angina and the lower need for repeat revascularization after CABG. Still other patients, such as those with multivessel disease, may place greater emphasis on the potential long-term survival benefit with CABG. Although our analysis showed no significant survival advantage for PTCA with stent over CABG at one and three years, further studies and longer term data are needed, as only 35% of PTCA patients had stents in the initial revascularization.

Health technology assessment needs to be an ongoing process so physicians can be informed of the most efficacious technologies for providing health care (48). Our analysis contributes to this process by providing an assessment of currently available long-term data and recent trials, some of which include stents. Even though the technology has advanced and current treatments differ from earlier studies, our analysis can provide a benchmark against which future studies can be compared.

Overall, selected patients with coronary disease had a small survival advantage with CABG over PTCA at five years of follow-up, none of whom underwent initial stenting. The addition of stents and newer adjunctive therapies may improve outcomes from percutaneous interventions relative to CABG, but long-term data are not yet available. Repeat revascularization and angina were consistently lower with CABG compared to PTCA, although stents reduced the difference in repeat revascularization. Some patients may prefer to avoid the risk of surgical morbidity and mortality despite these potential long-term benefits. The decision to recommend CABG or PTCA will be guided by the results of randomized trials, technical improvements, local expertise, patient preferences, and periodic technology assessments, such as the meta-analysis presented here.

Reprint requests and correspondence: Dr. John B. Wong, Tufts-New England Medical Center, 750 Washington Street #302, Boston, Massachusetts 02111-1526. E-mail: jwong@tufts-nemc.org.

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