Comparative Effectiveness Review

Number 9 Addendum

Addendum to:

Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease

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This report is based on research conducted by the Stanford-UCSF Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0017). The findings and conclusions in this document are those of the authors, who are responsible for its contents, and do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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www.ahrq.gov

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Prepared by:
Stanford-UCSF Evidence-based Practice Center

Investigators
Mark A. Hlatky, M.D.
Derek B. Boothroyd, Ph.D.
Dena M. Bravata, M.D., M.S.
Kathryn M. McDonald, M.M.
Douglas K. Owens, M.D., M.S.

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Collaborators

Eric Boersma, Ph.D., and Patrick Serruys, M.D., Erasmus University, Rotterdam, The Netherlands

Jean Booth, M.S., and Marcus Flather, M.B.B.S., FRCP, Royal Brompton & Harefield NHS Trust, London, United Kingdom

Maria M. Brooks, Ph.D., and Sheryl F. Kelsey, Ph.D., University of Pittsburgh, Pittsburgh, PA

Didier Carrié, M.D., Ph.D., Rangueil Hospital, Toulouse, France

Tim C. Clayton, M.S., and Stuart J. Pocock, Ph.D., London School of Hygiene and Tropical Medicine, London, United Kingdom

Nicolas Danchin, M.D., Hôpital Georges Pompidou, Paris, France

Christian W. Hamm, M.D., Kerckhoff Klinik, Bad Nauheim, Germany

Whady A. Hueb, M.D., and Neuza Lopes, M.D., Instituto do Coracäo, Säo Paulo, Brazil

Jan Kahler, M.D., Universitäres Herzzentrum, Hamburg, Germany

Spencer B. King, M.D., Saint Joseph's Heart and Vascular Institute, Atlanta, GA

Andrzej S. Kosinski, Ph.D., Duke Clinical Research Institute, Durham, NC

Alfredo Rodriguez, M.D., Sanatario Otamendi, Buenos Aires, Argentina

Ulrich Sigwart, M.D., Université de Genevè, Geneva, Switzerland

Rodney H. Stables, M.D., Cardiothoracic Centre Liverpool, Liverpool, United Kingdom

Role of Collaborators

The individual patient data were collected and prepared for analysis by the investigators representing the 10 participating trials. All authors reviewed and revised a manuscript version of this report and approved the companion paper: Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, Carrié D, Clayton TC, Danchin N, Flather M, Hamm CW, Hueb WA, Kähler J, Kelsey SF, King SB, Kosinski AS, Lopes N, McDonald KM, Rodriguez A, Serruys P, Sigwart U, Stables RH, Owens DK, Pocock SJ. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet 2009 Apr 4;373(9670):1190-1197.

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the State Children's Health Insurance Program (SCHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting Comparative Effectiveness Reviews of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://effectivehealthcare.ahrq.gov/reference/purpose.cfm.

AHRQ expects that Comparative Effectiveness Reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

AHRQ Contact

Beth A. Collins-Sharp, Ph.D., R.N.
Director
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality
Rockville, MD

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Abstract

Background. Coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) are alternative treatments for multivessel coronary disease. Although the procedures have been compared in several randomized trials, their long-term effects on mortality in key clinical subgroups are uncertain. We undertook a collaborative analysis of data from randomized trials to assess whether the effects of the procedures on mortality are modified by patient characteristics.

Methods. Details of the search strategy that was used to identify relevant trials for inclusion in this collaborative analysis have been reported in a previous report developed for AHRQ (Bravata DM, McDonald KM, Gienger AL, Sundaram V, Perez MV, Varghese R, Kapoor JR, Ardehali R, McKinnon MC, Stave CD, Owens DK, Hlatky MA. Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease. Comparative Effectiveness Review No. 9. (Prepared by Stanford-UCSF Evidence-based Practice Center under Contract No. 290-02-0017.) Rockville, MD: Agency for Healthcare Research and Quality. October 2007.). In this addendum study, we pooled individual patient data from ten randomized trials to compare the effectiveness of CABG with PCI according to patients' baseline clinical characteristics. We used stratified, random effects Cox proportional hazards models to test the effect on all-cause mortality of randomized treatment assignment and its interaction with clinical characteristics. All analyses were by intention to treat.

Findings. Ten participating trials provided data on 7812 patients. PCI was done with balloon angioplasty in six trials and with bare-metal stents in four trials. Over a median follow-up of 5.9 years (Interquartile range [IQR] 5.0-10.0), 575 (15%) of 3889 patients assigned to CABG died compared with 628 (16%) of 3923 patients assigned to PCI (hazard ratio [HR] 0.91, 95% CI 0.82-1.02, p=0.12). In patients with diabetes (CABG, n=615; PCI, n=618), mortality was substantially lower in the CABG group than in the PCI group (HR 0.70, 0.56-0.87); however, mortality was similar between groups in patients without diabetes (HR 0.98, 0.86-1.12; p=0.014 for interaction). Patient age modified the effect of treatment on mortality, with hazard ratios of 1.25 (0.94-1.66) in patients younger than 55 years, 0.90 (0.75-1.09) in patients 55-64 years, and 0.82 (0.70-0.97) in patients 65 years and older (p=0.002 for interaction). Treatment effect was not modified by the number of diseased vessels or other baseline characteristics.

Interpretation. Data for long-term mortality are similar after CABG and PCI in most patient subgoups with multivessel coronary artery disease, so choice of treatment may incorporate patient preferences for other outcomes. Results also showed lower mortality for two subgroups receiving CABG: patients with diabetes and patients aged 65 years or older.

Conclusion. Pooling individual patient data from randomized trials to assess treatment has advantages over the more common technique of meta-analysis of published aggregate data. Pooling of individual patient data permits analysis in key subgroups of interest and also allows use of more sensitive statistical methods, including analysis of survival times, use of multivariable models, and tests for treatment-by-covariate interactions.

Introduction

Coronary artery bypass graft (CABG) and percutaneous coronary intervention (PCI) are alternative revascularization procedures for patients with multivessel coronary artery disease. The effects of these two procedures on patient outcomes (mortality, myocardial infarction, angina symptoms, repeat procedures) have been compared in several randomized clinical trials[1-12] and in analyses of large clinical registries,[13-17] and in meta-analyses of the published trial results.[18-20] However, the outcomes of the procedures might vary according to patient characteristics, such as the presence of diabetes or the number of diseased vessels. This possibility has been difficult to assess because no randomized trial has been large enough to provide adequate statistical power, meta-analyses in patient subgroups have been limited by inconsistent reporting in published trials,[20] and observational studies have been confounded by treatment selection biases.

Pooling of individual patient data from randomized trials substantially increases the number of patients within clinical subgroups of interest and provides a more precise assessment of the effects of treatment.[21-24] Previous collaborations among clinical trial groups have provided information about variation in the efficacy of other cardiovascular treatments according to baseline clinical characteristics.[25,26] We undertook a collaborative analysis of data from randomized trials of patients with multivessel coronary artery disease to assess whether the effects of CABG and PCI on mortality are modified by patient characteristics.

Methods

Patients and Procedures

Details of the search strategy that was used to identify relevant trials for inclusion in this collaborative analysis have been reported in a previous report developed for AHRQ (www.effectivehealthcare.ahrq.gov; Comparative Effectiveness of Percutaneous Coronary Interventions and Coronary Artery Bypass Grafting for Coronary Artery Disease). Briefly, we searched Medline, Embase, and Cochrane databases for studies published between January, 1966 and August, 2006, by use of terms including “angioplasty,” “coronary,” and “coronary artery bypass surgery.” We also reviewed the reference lists of retrieved articles, conference abstracts, and the bibliographies of expert advisers. We did not limit the searches to the English language. Clinical trials that randomly assigned patients with multivessel coronary artery disease to either CABG or PCI and that reported at least three years of follow-up were eligible for inclusion. We excluded trials that compared either method alone with medical therapy, those that compared two forms of PCI, and those that compared two forms of CABG. All included trials were reviewed and approved by ethics committees.

We identified 12 eligible trials; the principal investigators of these studies were invited to participate in this collaborative analysis. Investigators from ten of the trials[1-10] provided individual patient data on a set of core clinical variables consisting of demographics (age, sex, and ethnicity), cardiac risk factors (diabetes, smoking, hypertension, and hypercholesterolemia), clinical manifestations (stable or unstable symptoms, history of myocardial infarction, heart failure, prior PCI, and prior CABG, and peripheral vascular disease), angiographic factors (abnormal left ventricular function, number of diseased vessels, and disease of the proximal left anterior descending coronary artery), randomized treatment assignment, and outcomes in follow-

up (death, myocardial infarction, stroke, repeat revascularization, last follow-up contact, and angina). We recoded data from each trial in a uniform format after resolution of data queries and checked data summaries from individual trials against the associated publications for accuracy.

The primary outcome measure of this study was all-cause mortality over all available follow-up, and the principal research question was whether comparative survival after random assignment to CABG or PCI was modified by patients' baseline clinical characteristics.

Statistical Analysis

All analyses followed the intention-to-treat principle. For descriptive analyses, we pooled individual patient data from all ten trials and created unadjusted Kaplan-Meier survival curves. For statistical analyses of mortality, we used Cox proportional hazards models stratified by trial[24] that included a gamma frailty term to assess random effects across the ten contributing trials.[27] We tested for interactions of assigned treatment with baseline characteristics by use of multivariable, stratified Cox models that included treatment assignment, the baseline characteristic of interest, and their interaction. We also tested the significance of these interactions after including other baseline characteristics in the model.

We undertook several analyses to test the sensitivity of results to various assumptions and model specifications. Since length of follow-up varied among the trials, we tested for any differences in the hazard ratio [HR] for CABG versus PCI as a function of follow-up time (0-3, 3-6, 6-9, and >9 years) in a stratified Cox model. Additionally, we checked for any violation of the proportional hazards assumption by testing for a correlation with follow-up time of scaled Schoenfeld residuals. We tested the effect of diabetes on mortality with and without inclusion of the trial that had previously shown an effect of diabetes survival in patients randomized to CABG and PCI.[28] We also assessed whether the method of PCI used in the trial (i.e., balloon angioplasty or bare-metal coronary stents) had an effect on treatment outcome. Statistical analyses were performed using SAS Version 9.1 and R Version 2.4.0.

Results

The ten participating trials provided data on 7,812 individual patients. The median age of the study population was 61 years (interquartile range [IQR] 53-67), with 389 patients aged 75 years or older (only 19 patients were aged 80 years or older). Table 1 shows the baseline characteristics of patients included in the trials. Median follow-up time in surviving patients was 5.9 years and varied among trials from 3.0 years to 13.0 years (Table 1).

Most patients receive the assigned treatment within 60 days of randomization. Within 90 days of randomization, 75 (2%) of 3889 patients assigned to CABG died, compared with 74 (2%) of 3923 patients assigned to PCI (p=0.89). The composite endpoint of death or myocardial infarction within 90 days, which could be assessed in nine trials (1-3, 5-10) occurred in 240 (6%) of 3695 patients in the CABG group and 201 (5%) of 3725 patients in the PCI group (p=0.045). Data on stroke within 90 days of randomization were available from seven trials:[1,5-10] 26 (1%) of 2268 patients assigned to CABG had a stroke compared with 12 (0.5%) of 2269 patients assigned to PCI (p=0.02).

Overall mortality was similar between treatment groups (Figure 1); 575 (15%) of 3,889 patients died in the CABG group compared with 628 (16%) of 3,923 patients in the PCI group [HR for mortality 0.91, 95% CI 0.82-1.02; p=0.12; Table 2). There was no evidence of a treatment-time interaction—i.e., the proportional hazards assumption was not violated.

Several secondary endpoints could be assessed in most, but not all trials (Table 2). The composite endpoint of death or myocardial infarction was not significantly different between treatment groups (Figure 1). The composite outcome of death or repeat revascularization was significantly lower ($p<0.0001$) in patients assigned to CABG than in patients assigned to PCI (Table 2). Angina at 1 year of follow-up was significantly less frequent ($p<0.0001$) in the CABG group (439 [14%] of 3228 patients) than in the PCI group (856 [26%] of 3240 patients; difference 13%, 95% CI 11-15).

Treatment effect was not modified by clinical characteristics, apart from diabetes and age (Figure 2). Of the 1233 patients with diabetes, 143 (23%) of 615 patients assigned to CABG died, compared with 179 (29%) of 618 patients assigned to PCI (Figure 3). By contrast, of the 6561 patients without diabetes, 432 (13%) of 3263 patients and 448 (14%) of 3298 patients died, respectively ($p=0.014$ for interaction). The interaction of diabetes with treatment remained after adjustment for age, sex, smoking, hypertension, and three-vessel disease ($p=0.008$), and also after exclusion of patients enrolled in the Bypass Angioplasty Revascularization Investigation (BARI) trial[28] (HR 0.68, 0.47-0.95, in patients with diabetes; HR 1.01, 0.85-1.20, in patients without diabetes; $p=0.048$ for interaction; Figure 3).

Patient age had a graded effect on mortality after CABG or PCI ($p=0.002$ for interaction with age as a continuous variable; Figure 2 and Figure 4). 107 (10%) of 1063 patients younger than 55 years who were assigned to CABG died compared with 88 (8%) of the 1122 patients assigned to PCI. 201 (14%) of 1477 patients aged 55-64 years in the CABG group died compared with 220 (15%) of 1456 patients in the PCI group. In patients aged 65 years and older, mortality was 20% (267 of 1347 patients) for CABG and 24% (319 of 1341 patients) for PCI. The interaction between age and treatment effect remained after adjustment for sex, diabetes, smoking, hypertension, history of myocardial infarction, heart failure, and three-vessel disease ($p=0.002$).

In the six earliest trials[2-4,6,8,10] PCI was done with balloon angioplasty, whereas in the four more recent trials, the procedure was done with bare-metal stents.[1,5,7,9] Most baseline clinical characteristics differed significantly ($p<0.0001$) between patients in the two types of trials (Table 3). There was no significant difference in survival between CABG and PCI groups according to the use of bare metal stent or balloon angioplasty (Figure 2). In the six balloon angioplasty trials, 436 (19%) of 2356 patients died in the CABG group compared with 481 (20%) of 2405 patients in the PCI group, whereas in the bare metal stent trials 139 (9%) of 1,533 patients and 147 (10%) of 1,518 patients died, respectively (Figure 2). In a multivariate analysis of pooled data that adjusted for baseline patient characteristics and restricted length of follow-up to a maximum of five years, there was no significant effect of trial use of bare-metal stents on the treatment comparison of CABG and PCI ($p=0.19$ for interaction). The interactions of diabetes and age with treatment assignment that were present in the overall population were evident in both balloon angioplasty and bare-metal stent trials (data not shown).

Discussion

Randomized clinical trials provide the reference standard for comparing the effectiveness of treatments for a given clinical condition. The effectiveness of treatments might vary importantly among patients included in randomized trials, but this possibility can not be tested adequately in a single study because of limited statistical power. Combining individual patient data from several randomized trials helps to overcome this limitation by increasing the number of patients available for analysis in clinical subgroups, and hence enhancing statistical power.

Combined analysis of individual patient data from ten randomized trials suggests that diabetes and age modify the effect of CABG compared with PCI on the survival of patients with multivessel coronary disease. Treatment effect was not altered by other patient characteristics, including the number of diseased coronary vessels, despite observational data strongly suggesting that this factor would modify the effectiveness of coronary revascularization.[13,14,16] The pooled data provide more precise estimates of the overall effect of CABG and PCI on long-term survival, both overall and within clinical subgroups.

The BARI trial[28] was the first to report that patients with diabetes had substantially better survival after CABG than after PCI. This result was not universally accepted, since analyses of large clinical registries did not confirm this effect,[29-30] similarly, other, smaller randomized clinical trials were unable to replicate the BARI trial findings.[4,6,8,31] Our analysis is based on pooled data from 1,233 randomized patients with diabetes and provides strong evidence that survival is substantially higher after CABG than PCI for the treatment of multivessel disease. This finding is not a result of the inclusion of the BARI trial,[2] since a significant interaction of diabetes with treatment assignment remained after exclusion of that trial. Nor is our result explained by the adverse clinical risk profile of patients with diabetes, because it remained significant after adjustment for other baseline clinical characteristics. Despite the strength of our finding, it is important to note that coronary revascularization and background medical treatment have continued to advance since the trials in this study were done. Further evidence in this long-running debate will be provided by the results of current trials of procedures in patients with diabetes.[32,33]

Our finding that patient age modifies the relative effectiveness of CABG and PCI on survival has not been previously reported by individual randomized trials. The interaction of age with assigned treatment might be mediated by the more favorable clinical characteristics in younger patients; however, we found that the effects persisted after multivariable adjustment for such characteristics. One potential interpretation of this finding is that younger patients might benefit more from initial PCI than from CABG because the latter treatment could be done at a more appropriate time in the course of their disease. Another potential interpretation is that older age might be a marker for more severe disease that was otherwise unmeasured and that might respond better to CABG. It is important to emphasize that few patients in this study were 75 years or older, and the older patients randomized in these trials might have been more highly selected.

Observational comparisons of CABG with PCI suggest a strong relation between the extent of coronary disease and the relative effectiveness of these procedures on survival.[13,14,16] In particular, clinical registry studies have reported that patients with the least extensive coronary disease have better survival with PCI, whereas patients with the most extensive disease have better survival with CABG.[13] Contrary to these observational data and to our previous hypothesis, we found no significant interaction between the number of diseased vessels and treatment effect. An association might have been found if we had been able to analyze a more detailed measure of extent of disease such as the Duke[13] or SYNTAX[34] scores. However, a count of diseased vessels was the only measure available from all ten trials. The extent of disease in patients eligible for randomization might also have fallen into a narrow range in which CABG and PCI yield equivalent results.[13] Additionally, the results of observational studies might represent the residual effects of selection bias rather than a true variation in clinical effectiveness, since the extent of coronary disease is the strongest clinical factor affecting the choice between CABG or PCI for coronary revascularization.[17]

The techniques of the procedures investigated here continue to be refined over time, and coronary stents in particular have been widely adopted for PCI. Six of the trials included in this analysis were conducted before the introduction of coronary stents,[2-4,6,8,10] whereas the remaining four studies[1,5,7,9] were done after bare-metal stents became available. We attempted to assess whether the results of the earlier trials differed from those of the subsequent trials. This analysis was difficult because stent use was completely confounded with patient enrollment in specific trials. There were also many other differences between these trials, including important differences in baseline clinical characteristics (Table 3). We found that the effect of CABG compared with PCI on survival did not differ between balloon angioplasty and bare-metal stent trials. This result is consistent with the findings from meta-analyses of randomized trials that showed no significant reductions in survival, despite significant reductions in the rate of repeat revascularization procedures or between balloon angioplasty PCI and bare metal stents,[35] or between bare-metal stents and drug eluting stents.[36]

Our study shows that pooling individual patient data from randomized trials to assess treatment has advantages over the more common technique of meta-analysis of published aggregate data. Most clinical trials do not publish results in key subgroups of interest,[20] and even when they do, the data are typically presented in different ways and are difficult to combine in a meta-analysis. Pooling of individual patient data overcomes these limitations and also allows use of more sensitive statistical methods, including analysis of survival times, use of multivariable models, and tests for treatment-by-covariate interactions. However, this technique poses logistical challenges and requires collaboration among trial groups and support from funding agencies; thus it has not been used as often as meta-analysis of published data. Our experience suggests that collaborative analysis could be used more often, especially to assess subgroup effects that are difficult to address in one trial.

Our study has several limitations. We were not able to obtain data from two smaller trials of CABG and PCI that enrolled 359 patients with multivessel disease,[11,12] but we did analyze data from 95% of all randomized patients, and believe our results would be unlikely to change if these smaller trials were included. We have no data on concomitant drug treatment or on control of coronary risk factors during follow-up.

Our analysis shares the underlying limitations of the ten participating trials, which excluded some patients of interest (e.g., those with prior CABG or PCI), and did not have adequate representation of others (e.g., patients aged 75 years and older or patients with reduced left ventricular function). The participating studies each selected patients in whom either treatment would be technically feasible and for whom either would be a reasonable clinical option. Consequently, patients with extensive three-vessel disease or left main disease were generally excluded because CABG would be the most appropriate treatment, and patients with limited single-vessel disease were excluded because PCI would be most appropriate. Therefore, our findings should not be extrapolated to all patients with coronary disease; they apply only to patients for whom either CABG or PCI is a reasonable therapeutic option and to patients similar to those enrolled in the contributing trials.

None of the ten trials included in this study used drug-eluting stents for PCI. Although clinical trials have shown equivalent rates of mortality and myocardial infarction after randomization to either bare-metal stents or drug-eluting stents,[36] trials that compare CABG with PCI by use of drug-eluting stents are still in progress.[33,37] The recently reported 1-year follow-up from the SYNTAX trial,[32] which showed no significant difference in the combined endpoint of

death, myocardial infarction, or stroke between patients randomly assigned to CABG or to PCI with drug-eluting stents, are generally consistent with the result of our combined analysis.

Thus, pooled data from ten long-term randomized trials of patients with multivessel coronary disease suitable for either CABG or PCI suggest that patients with diabetes, and older patients, might have a significant survival advantage if treated with CABG.

It should also be noted that the CABG:PCI hazard ratio did not differ significantly over follow-up ($p > 0.31$) and the proportional hazards assumption was not violated ($p=0.15$), so we analyzed mortality over the entire follow-up period using the stratified Cox model.

The interactions of diabetes with treatment, and age with treatment remained significant when both were included in the model.

The hazard ratio (confidence limits) for the interaction term of CABG with diabetes was 0.72 (0.56 to 0.94) overall, 0.75 (0.56 to 1.00) in the "balloon era trials," and 0.62 (0.35 to 1.08) in the "bare metal stent era" trials. Similarly, in the analysis of age as a continuous variable, the treatment interaction term with CABG was 0.98 (0.97 to 0.99) overall, 0.98 (0.96 to 0.99) in the "balloon era trials", and 0.98 (0.96 to 1.01) in the "bare metal stent era" trials.

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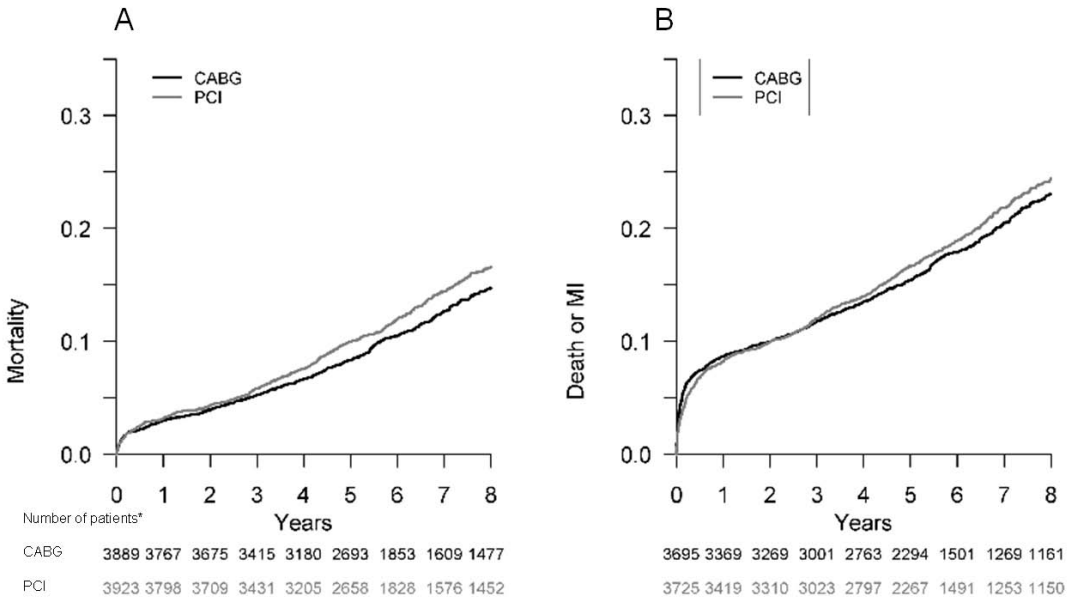
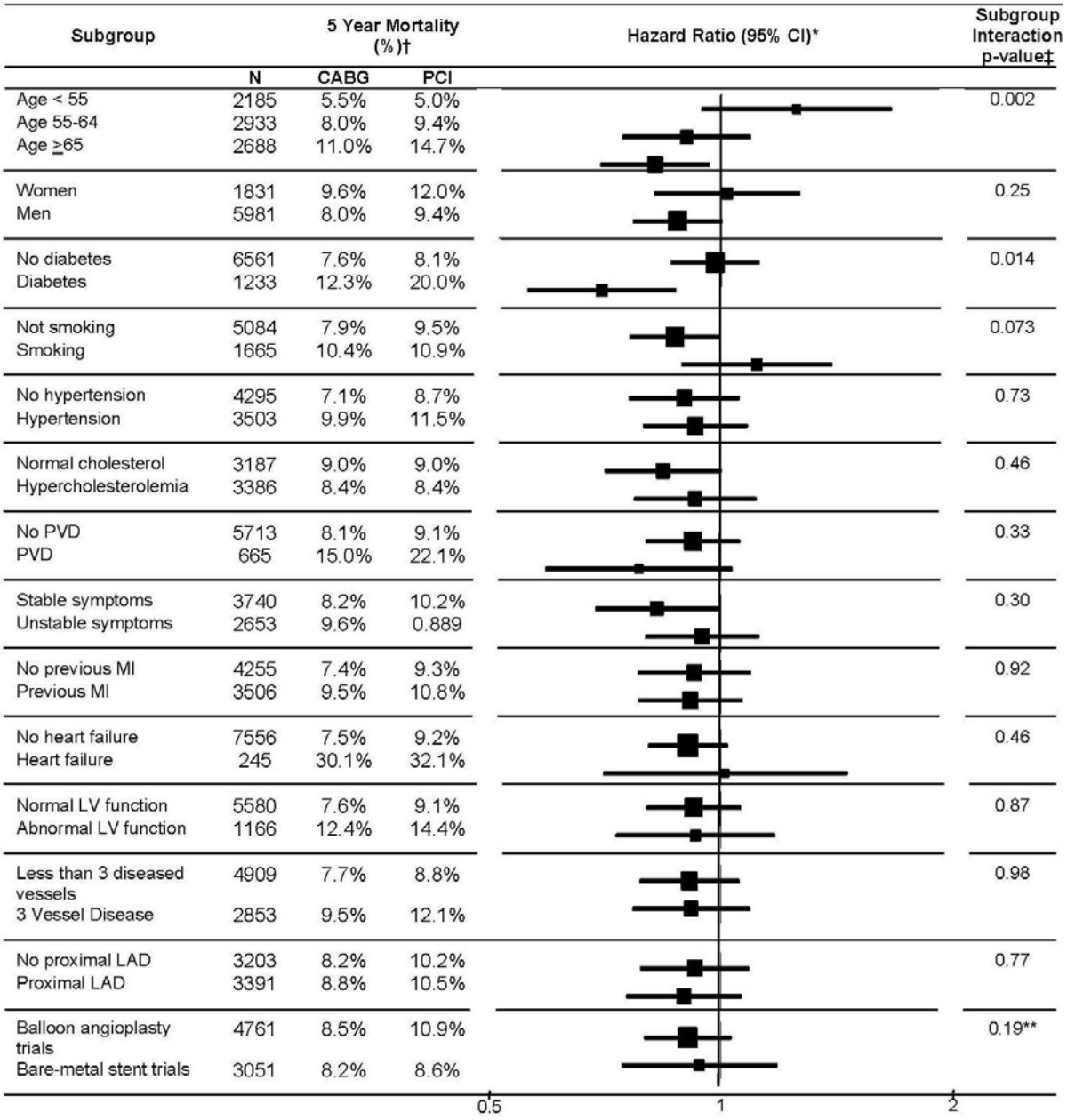
Figures

Figure 1. Outcomes of treatment with coronary artery bypass graft or percutaneous coronary intervention



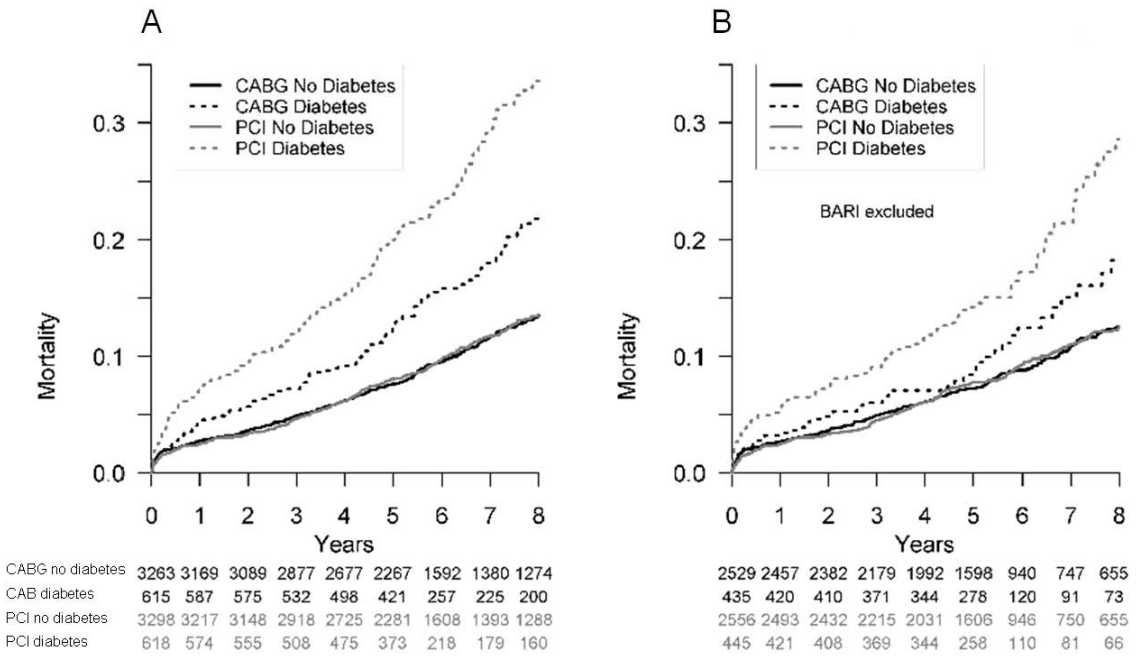
CABG = coronary artery bypass graft. PCI = percutaneous coronary intervention. *Number of patients available for follow-up. Data show overall unadjusted mortality (A) and composite endpoint of death or myocardial infarction (B) after randomization to CABG or PCI. Data on death with myocardial infarction were not available from the Emory Angioplasty versus Surgery Trial.[4]

Figure 2. Subgroup analyses for mortality after treatment with coronary artery bypass graft or percutaneous coronary intervention.



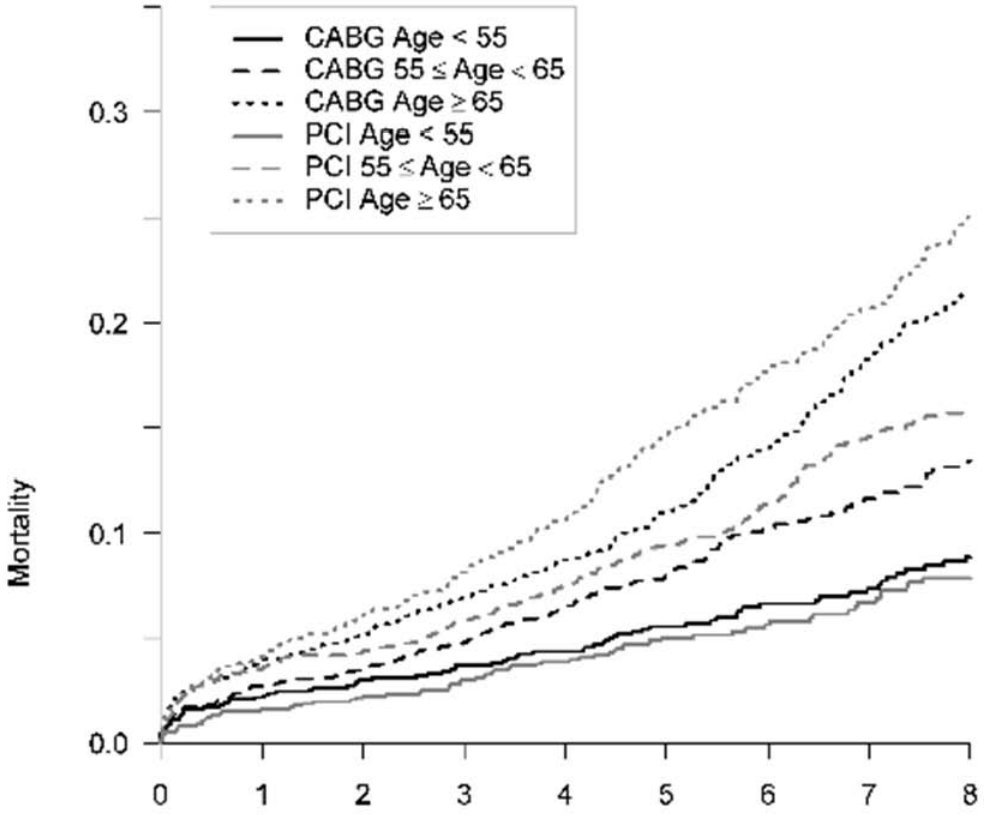
The CABG = coronary artery bypass graft. LAD = left anterior descending artery. LV = left ventricular. MI= myocardial infarction. PCI = percutaneous coronary intervention. PVD = peripheral vascular disease. The vertical line indicates a hazard ratio of 1.0, equivalent to no difference between treatment subgroups. *Based on the full duration of follow-up in all trials. †Pooled unadjusted 5-year Kaplan-Meier survival rates. ‡p value for the treatment covariate interaction. **The analysis that compares patients enrolled in balloon angioplasty trials[2,4,6,8,10] and bare-metal stent trials[1,5,7,9] is pooled and not stratified by study.

Figure 3. Mortality in patients assigned to coronary artery bypass graft or percutaneous coronary intervention by diabetes status.



CABG or CAB = coronary artery bypass graft. PCI = percutaneous coronary intervention. Number of patients available for follow-up reported below graphs. Data show overall unadjusted mortality rates for patients with diabetes and without diabetes. Panel A includes patients from all ten trials. Panel B excludes patients from the Bypass Angioplasty Revascularization Investigation trial.[2]

Figure 4 Mortality in patients assigned to coronary artery bypass graft or percutaneous coronary intervention by age.



Number of patients*									
CABG <65 years	1063	1039	1016	938	891	774	556	507	468
CABG 55-64 years	1477	1434	1400	1306	1205	1017	711	634	585
CABG > 65 years	1347	1292	1257	1167	1082	902	586	468	424
PCI < 55 years	1122	1104	1087	1013	955	817	561	500	466
PCI 55-65 years	1456	1404	1371	1262	1177	989	705	614	576
PCI > 65 years	1341	1286	1247	1154	1072	852	562	462	408

CABG = coronary artery bypass graft. PCI = percutaneous coronary intervention. *Number of patients available for follow-up. Data show overall unadjusted mortality rates for patients aged less than 55 years, 55 to 64 years, and 65 years or older.