Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data

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Summary

Background Numerous randomised trials have compared coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) for patients with coronary artery disease. However, no studies have been powered to detect a difference in mortality between the revascularisation strategies.

Methods We did a systematic review up to July 19, 2017, to identify randomised clinical trials comparing CABG with PCI using stents. Eligible studies included patients with multivessel or left main coronary artery disease who did not present with acute myocardial infarction, did PCI with stents (bare-metal or drug-eluting), and had more than 1 year of follow-up for all-cause mortality. In a collaborative, pooled analysis of individual patient data from the identified trials, we estimated all-cause mortality up to 5 years using Kaplan-Meier analyses and compared PCI with CABG using a random-effects Cox proportional-hazards model stratified by trial. Consistency of treatment effect was explored in subgroup analyses, with subgroups defined according to baseline clinical and anatomical characteristics.

Findings We included 11 randomised trials involving 11 518 patients selected by heart teams who were assigned to PCI (n=5753) or to CABG (n=5765). 976 patients died over a mean follow-up of 3·8 years (SD 1·4). Mean Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score was 26·0 (SD 9·5), with 1798 (22·1%) of 8138 patients having a SYNTAX score of 33 or higher. 5 year all-cause mortality was 11·2% after PCI and 9·2% after CABG (hazard ratio [HR] 1·20, 95% CI 1·06–1·37; p=0·0038). 5 year all-cause mortality was significantly different between the interventions in patients with multivessel disease (11·5% after PCI *vs* 8·9% after CABG; HR 1·28, 95% CI 1·09–1·49; p=0·0019), including in those with diabetes (15·5% *vs* 10·0%; 1·48, 1·19–1·84; p=0·0004), but not in those without diabetes (8·7% *vs* 8·0%; 1·08, 0·86–1·36; p=0·49). SYNTAX score had a significant effect on the difference between the interventions in multivessel disease. 5 year all-cause mortality was similar between the interventions in patients with left main disease (10·7% after PCI *vs* 10·5% after CABG; 1·07, 0·87–1·33; p=0·52), regardless of diabetes status and SYNTAX score.

Interpretation CABG had a mortality benefit over PCI in patients with multivessel disease, particularly those with diabetes and higher coronary complexity. No benefit for CABG over PCI was seen in patients with left main disease. Longer follow-up is needed to better define mortality differences between the revascularisation strategies.

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Introduction

Numerous randomised trials[1–3] have compared coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) with balloon angioplasty, bare-metal stents, or drug-eluting stents for the treatment of multivessel or left main coronary artery disease. In 2009, Hlatky and colleagues[1] reported the results of a pooled analysis of individual patient data from ten randomised trials involving 7812 patients assigned to CABG or PCI with balloon angioplasty or bare-metal stents. In that study, 5 year mortality was 8·4% after CABG and 10·0% after PCI (p=0·12). More recent trials[4–10] comparing CABG with PCI with drug-eluting stents have found similar mortality for the revascularisation strategies. However, to date, no clinical trial has been sufficiently powered to detect a difference in all-cause mortality between CABG and PCI using stents.

To overcome this limitation, we did a pooled analysis of individual-patient data from randomised trials comparing CABG with PCI using stents to examine the comparative effects of these interventions on long-term all-cause mortality in all patients with coronary artery disease and separately in patients with multivessel or left main disease.

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Research in context

Evidence before this study

We searched MEDLINE, Embase, and the Cochrane Library up to July 19, 2017, to identify randomised clinical trials comparing coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) using stents. We used the search terms "coronary artery bypass grafting", "percutaneous coronary intervention", "stent", and "random*". Studies were included if the patients had multivessel or left main coronary artery disease and did not present with acute myocardial infarction, PCI was done with bare-metal or drug-eluting stents and not balloon angioplasty, and more than 1 years' follow-up for all-cause mortality was available. We identified 12 high-quality trials. One trial found a survival benefit of CABG over PCI with bare-metal stents for multivessel disease at 6 years' follow-up. Another trial found better survival at 5 years' follow-up with CABG than with PCI using first-generation drug-eluting stents in patients with multivessel disease and diabetes. However, these results have not been reproduced in other individual trials with 3–10 years' follow-up, except in underpowered and hypothesis-generating subgroup analyses. Two pooled analyses of CABG versus PCI with balloon angioplasty or bare-metal stents for multivessel disease found conflicting results, and what the survival differences are between CABG and PCI remains largely unclear.

Added value of this study

This study is the largest analysis of patients randomly assigned to PCI using stents or to CABG. To our knowledge, this study shows for the first time that all-cause mortality is significantly lower with CABG than with PCI in an overall randomised population of patients with multivessel or left main coronary artery disease. Additionally, the use of individual patient data allowed identification of important subgroups that have a survival benefit from CABG. These subgroups include patients with multivessel disease and diabetes and those with higher coronary lesion complexity (established with the Synergy between PCI with Taxus and Cardiac Surgery [SYNTAX] score). Patients with left main disease had similar survival with PCI and CABG, regardless of diabetes and SYNTAX score.

Implications of all the available evidence

Some patients have specific indications for PCI or CABG, such as coronary complexity too high for PCI or operative risk too high for CABG. In patients with estimated clinical equipoise, as determined by heart teams, consideration of disease type (multivessel or left main), coronary complexity, and diabetes status is crucial because these are important treatment effect modifiers of favourable mortality after CABG versus PCI and should affect decisions on coronary revascularisation in daily practice. However, longer follow-up of randomised trials is needed to better define mortality differences in overall patients and specific subgroups.

Methods

Study selection and data collection

We searched MEDLINE, Embase, and the Cochrane Library up to July 19, 2017, using the search terms "coronary artery bypass grafting", "percutaneous coronary intervention", "stent", and "random*". Two researchers (SJH and MM) independently identified randomised trials comparing CABG with PCI in which patients had multivessel or left main coronary artery disease and did not present with acute myocardial infarction, PCI was done with stents (bare-metal or drug-eluting) and not balloon angioplasty, and more than 1 year follow-up for all-cause mortality was available (appendix). Abstracts from meetings were not considered, nor were unpublished trials. Reference lists from potentially relevant articles were checked to ensure no studies were missed.

See Online for appendix

We contacted the principal investigators of the eligible trials to obtain individual patient data for pooled analyses; data were provided in a standardised spreadsheet. Data were cross-checked against the publication of the primary endpoint and long-term follow-up publications. Several minor inconsistencies were resolved through consensus with trial principal investigators. Baseline and procedural characteristics of individual trials are presented in the appendix with information about missing data for certain characteristics.

We assessed the quality of individual trials using the Cochrane Collaboration's tool for assessing risk of bias.[11] Each trial was approved by its local medical ethics committee, and all patients provided written informed consent.

Outcomes and follow-up

To allow a consistent definition of follow-up among trials, the duration of follow-up was calculated from the day of the procedure. If patients died before the procedure, the time from randomisation to death was used to calculate the duration of follow-up.

All-cause mortality was the primary endpoint of this study, with analyses planned in all patients and separately in patients with multivessel disease or left main disease. The multivessel disease group consisted of patients with multivessel disease without left main disease, whereas the left main disease group consisted of patients with any left main disease, irrespective of the number of diseased vessels.

We also planned separate analyses for trials that used bare-metal stents, those that used drug-eluting stents, those that used first-generation drug-eluting stents, and those that used newer-generation drug-eluting stents. First-generation drug-eluting stents released paclitaxel or sirolimus. Newer-generation drug-eluting stents released

everolimus, zotarolimus, or biolimus. The VA CARDS trial[7] (Cooperative Studies Program study number 557) was excluded from the separate analyses of first-generation and newer-generation drug-eluting stents because a mixture of these stents was used.

We prespecified subgroups for analyses according to the baseline characteristics sex, age, body-mass index, hypertension, hypercholesterolaemia, diabetes, peripheral vascular disease, previous myocardial infarction, left-ventricular ejection fraction, and core laboratory-assessed Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score (as a measure of lesion complexity).[12] Post-hoc subgroup analyses were done according to SYNTAX score tertiles in the groups of patients with or without diabetes.

In all trials, a Clinical Events Committee adjudicated the events.

Statistical analysis

A team consisting of three epidemiologists and statisticians (MM, EB, and GP) did the statistical analyses. All analyses were done by intention to treat. Baseline, procedural, and outcome data for individual patients were pooled. Continuous variables are presented as mean (SD) and were compared with *t* tests; discrete data are presented as frequencies and were compared with χ^2 tests.

We pooled data from all trials to provide unadjusted Kaplan-Meier estimates of all-cause mortality at 5 years follow-up and for landmark analyses at 30 days and between 31 days and 5 years. Subgroup analyses were done with follow-up data at 5 years only. PCI and CABG were compared with random-effects Cox proportional-hazards models stratified by trial and with inclusion of a γ frailty term to account for heterogeneity between trials. Trial heterogeneity is captured in random-intercept frailty terms, which quantify trial-specific deviation from the average hazard ratio (HR). Frailties are unobserved factors, distributed as γ random variables with a mean of 1 and variance (θ). Hence, the variance of the frailty terms represents heterogeneity in baseline risk between trials. The significance of the variance parameter was assessed with the likelihood ratio test. The proportional hazards assumption in the Cox model for the overall group was assessed by visual inspection of the scaled Schoenfeld residuals over a Kaplan-Meier transform of time, as well as with the corresponding test for the correlation of the Schoenfeld residuals with time, and was not violated ($p=0·12$). Nevertheless, visual inspection of the Kaplan-Meier curves suggested a time-dependent variance in the HR of PCI versus CABG and, therefore, models that allowed for a time-varying HR were also done. For these models, we assumed a single cutoff point, allowing the HR to have different values before and after the cutoff. The cutoff was selected on the basis of visual inspection of the scaled Schoenfeld residuals. Subgroup analyses according to baseline clinical, procedural, and anatomical characteristics were also done with the Cox models.

	PCI (n=5753)	CABG (n=5765)	p value
Age (years)	63·6 (9·8; 5753)	63·7 (9·9; 5765)	p=0·72
Sex			
Female	23·9% (1373/5753)	23·8% (1371/5765)	p=0·91
Male	76·1% (4380/5753)	76·2% (4394/5765)	p=0·91
Body-mass index >30 kg/m²	28·1% (1548/5506)	28·3% (1558/5511)	p=0·82
Current smoker	22·3% (1274/5701)	22·3% (1273/5703)	p=0·97
Diabetes	38·5% (2215/5753)	37·7% (2171/5765)	p=0·35
Insulin treated	12·9% (545/4234)	11·9% (504/4245)	p=0·16
Hypertension	67·6% (3880/5739)	68·1% (3913/5748)	p=0·59
Hypercholesterolaemia	69·5% (3982/5726)	67·3% (3862/5735)	p=0·0112
Peripheral vascular disease	8·2% (424/5158)	8·5% (440/5164)	p=0·58
Carotid artery disease	7·8% (161/2072)	8·1% (168/2074)	p=0·69
Previous TIA or CVA	5·4% (218/4052)	6·2% (253/4054)	p=0·098
Previous myocardial infarction	28·0% (1438/5138)	27·5% (1417/5156)	p=0·57
Left-ventricular ejection fraction			
Moderate (30–49%)	15·2% (807/5303)	14·3% (779/5430)	p=0·20
Poor (<30%)	0·9% (49/5303)	1·0 (54/5430)	p=0·71
Unstable angina pectoris	34·6% (1786/5158)	34·2% (1767/5160)	p=0·68
Three-vessel disease*	58·6% (2460/4201)	61·8% (2594/4197)	p=0·063
Left main disease	38·8% (2233/5753)	38·9% (2245/5765)	p=0·89
SYNTAX score	26·0% (9·3; 4081)	26·0% (9·8; 4057)	p=0·91
0–22	37·6% (1533/4081)	39·1% (1585/4057)	p=0·16
23–32	41·1% (1677/4081)	38·1% (1545/4057)	p=0·0053
≥33	21·3% (871/4081)	22·8% (927/4057)	p=0·10
Type of stent used in PCI†			
Bare-metal stent	26·6% (1490/5610)	..	..
Drug-eluting stent	73·4% (4120/5610)	..	..
First-generation	39·2% (2199/5610)	..	..
Newer-generation	34·2% (1920/5610)	..	..
Number of stents used in PCI	3·1 (2·0; 4935)	..	..
CABG procedure			
Left internal mammary artery	..	96·2% (4574/4753)	..
Bilateral internal mammary artery	..	18·7% (771/4122)	..
Off-pump	..	27·5% (1085/3945)	..
Medication at discharge			
Aspirin	97·3% (4487/4612)	95·5% (3814/3994)	p<0·0001
Thienopyridine	96·7% (4479/4630)	45·1% (1815/4026)	p<0·0001
Dual antiplatelet therapy	95·1% (4384/4612)	44·0% (1759/3994)	p<0·0001
Statin	88·1% (3052/3464)	84·0% (2843/3384)	p<0·0001
β blocker	79·1% (2741/3464)	76·2% (2557/3356)	p=0·0040
ACE inhibitor or ARB	63·7% (2205/3464)	46·9% (1588/3383)	p<0·0001
Calcium-channel blocker	27·7% (959/3463)	21·8% (736/3383)	p<0·0001

Data are mean (SD; n) or % (n/N). PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. TIA=transient ischaemic attack. CVA=cerebrovascular attack. SYNTAX=Synergy between PCI with Taxus and Cardiac Surgery. ACE=angiotensin-converting enzyme. ARB=angiotensin II receptor blocker. *Of the group of patients with multivessel disease. †Data are only for patients who underwent PCI; the type of drug-eluting stent used was not available for one patient enrolled in the VA CARDS trial.[7]

Table 1: **Baseline, procedural, and discharge data of randomised cohorts**

A two-sided p value of less than 0·05 was considered to indicate statistical significance; we did not adjust for multiplicity. All statistical analyses were done with SPSS software, version 21, or R software, version 3.2.4.

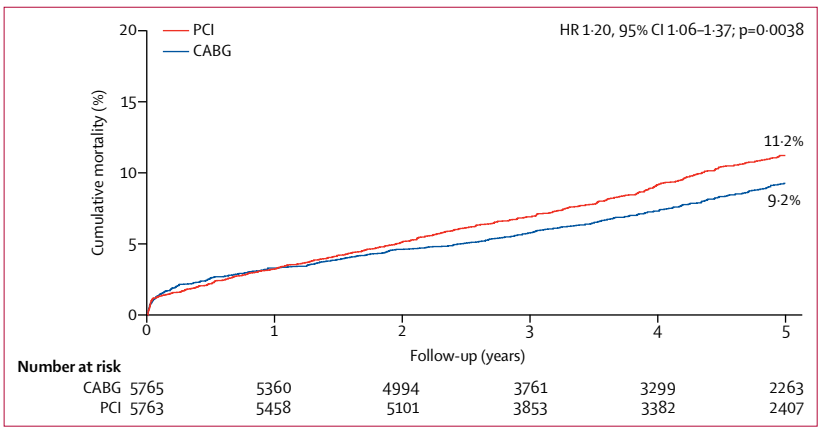

Figure 1: **Mortality after CABG versus after PCI during 5 years' follow-up**
Kaplan-Meier estimates are from the overall pooled patient population. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. HR=hazard ratio.

Reporting of this individual patient-data, pooled analysis concurs with specific PRISMA guidelines.[13] This study is not registered and no protocol has been published.

Role of the funding source
This study was done without funding, although individual trials were sponsored. The decision to submit the manuscript for publication was made by consensus among the principal investigators of the individual trials. Sponsors of the individual trials were involved in data collection in the trials, but were not involved in data analyses, data interpretation, or drafting of this manuscript.

Results
We identified 19 relevant trials in the literature search, of which seven were excluded because patients did not have multivessel or left main disease (n=4), only 54% of PCI procedures were done with a stent (n=1), or follow-up was only available up to 1 year (n=2; appendix). The principal investigators of the remaining 12 trials[4–10,14–18] were contacted to obtain individual patient data for a pooled analysis; one trial[14] involving 105 patients was unable to provide data. All trials were considered to be of high quality according to criteria, despite being unable to mask investigators and patients to treatment allocation (appendix).

In the 11 trials that provided data, 11 518 patients selected by heart teams were randomly assigned to CABG (n=5765) or to PCI (n=5753). PCI was done with bare-metal stents in 1490 patients in four trials (n=3051), with first-generation drug-eluting stents in 2199 patients in four trials (n=4498), and with newer-generation drug-eluting stents in 1920 patients in three trials (n=3969; table 1). CABG was done with a left internal mammary artery in 4574 patients in nine trials (n=4753), with a bilateral internal mammary artery in 771 patients in seven trials (n=4122), and off-pump in 1085 patients in seven trials (n=3945). SYNTAX scores were available from six trials and for 8138 patients (CABG: n=4057; PCI: n=4081). The mean SYNTAX score was 26·0 (SD 9·5), with 1798 (22·1%) patients having a SYNTAX score of 33 or higher. Baseline, procedural, and discharge data for the patients are shown in table 1, and data for each trial and treatment crossovers are shown in the appendix.

976 patients died during a mean follow-up of 3·8 years (SD 1·4). 5 year all-cause mortality was 11·2% (539 events) after PCI and 9·2% (437 events) after CABG (HR 1·20, 95% CI 1·06–1·37; p=0·0038; figure 1, table 2). At 30 days' follow-up, all-cause mortality was 1·3% (76 events) after PCI and 1·4% (78 events) after CABG (0·97, 0·71–1·33; p=0·84). Between 31 days' and 5 years' follow-up, all-cause mortality was 10·0% (463 events) after PCI and 8·0% (359 events) after CABG (1·26, 1·09–1·44; p=0·0009). A time-dependent model showed that the risk of mortality was similar for PCI and CABG during the first year of follow-up (0·97, 0·80–1·19; p=0·80), but in favour of CABG beyond 1 year (1·39, 1·17–1·62; p<0·0001; appendix). The estimate of the frailty parameter for heterogeneity was significant (θ=0·39, p<0·0001).

Patients in trials in which drug-eluting stents were used were older, had more comorbidities, and were more likely to have diabetes, left main disease, and three-vessel disease than patients in trials in which bare-metal stents were used (table 3). 5 year all-cause mortality was 8·7% (131 events) after PCI and 8·2% (125 events) after CABG (HR 1·05, 95% CI 0·82–1·34; p=0·72) in trials that did PCI with bare-metal stents (including 3051 patients), and 12·4% (408 events) after PCI and 10·0% (312 events) after CABG (1·27, 1·09–1·47; p=0·0017) in trials that did PCI with drug-eluting stents (including 8467 patients). The type of stent used (bare-metal *vs* drug-eluting) did not interact with the treatment effect ($p_{interaction}$=0·53).

Although there were significant differences in clinical and anatomical characteristics between the trials using first-generation drug-eluting stents and those using newer-generation drug-eluting stents (table 3), the difference in 5 year mortality between PCI and CABG was consistent when analysing the 4300 patients in the trials using first-generation drug-eluting stents (13·2% [254 events] after PCI *vs* 11·1% [201 events] after CABG; HR 1·21, 95% CI 1·01–1·46; p=0·0415) and the 3969 patients in the trials using newer-generation drug-eluting stents (10·3% [136 events] after PCI *vs* 7·9% [106 events] after CABG; 1·27, 0·98–1·64; p=0·0658; $p_{interaction}$=0·78).

In subgroup analyses, diabetes was the only baseline characteristic with a significant treatment interaction ($p_{interaction}$=0·0077). In patients with diabetes, PCI was associated with higher 5 year all-cause mortality than was CABG (15·7% [278 events] *vs* 10·7% [185 events]; HR 1·44, 95% CI 1·20–1·74; p=0·0001), whereas mortality did not differ between the interventions in patients without diabetes (8·7% [261 events] after PCI *vs* 8·4% [252 events] after CABG; 1·02, 0·86–1·21; p=0·81; table 2, figures 2, 3). Although the interaction was not significant ($p_{interaction}$=0·21), the mortality benefit of CABG over PCI

tended to increase with increasing SYNTAX scores (table 2). A similar trend was found in subgroups of patients with or without diabetes (appendix).

644 of 7040 patients with multivessel disease assigned to PCI (n=3520) or to CABG (n=3520) died during a mean follow-up of 4·1 years (SD 1·4). 5 year all-cause mortality in patients with multivessel disease was higher after PCI than after CABG (11·5% [365 events] *vs* 8·9% [279 events]; HR 1·28, 95% CI 1·09–1·49; p=0·0019; figure 3, table 2). As observed for the overall patient cohort, the mortality benefit of CABG over PCI in patients with multivessel disease increased with duration of follow-up in time-dependent models (appendix). 5 year all-cause mortality was 15·5% (207 events) after PCI versus 10·0% (134 events) after CABG in the subgroup of patients with multivessel disease who had diabetes (HR 1·48, 95% CI 1·19–1·84; p=0·00037), and 8·7% (158 events) after PCI versus 8·0% (145 events) after CABG in the subgroup of those patients without diabetes (1·08, 0·86–1·36; p=0·49; $p_{interaction}$=0·0453; table 2). The mortality benefit of CABG over PCI increased with increasing SYNTAX scores in patients with multivessel disease (table 2).

322 of 4478 patients with left main disease assigned to PCI (n=2233) or to CABG (n=2245) died during a mean follow-up of 3·4 years (SD 1·4). 5 year all-cause mortality for patients with left main disease was 10·7% (174 events) after PCI and 10·5% (158 events) after CABG (HR 1·07, 95% CI 0·87–1·33; p=0·52; figure 3, table 2). By contrast with the overall cohort and multivessel disease subgroup, a benefit for CABG over PCI was not seen with longer follow-up in time-dependent models (appendix). Diabetes status did not interact with the treatment effect in patients with left main disease ($p_{interaction}$=0·13). 5 year all-cause mortality was 16·5% (71 events) after PCI versus 13·4% (51 events) after CABG (HR 1·34, 95% CI 0·93–1·91; p=0·11) in the subgroup of patients with left main disease who had diabetes, and 8·8% (103 events) after PCI versus 9·6% (107 events) after CABG (0·94, 0·72–1·23; p=0·65) in the subgroup of those patients without diabetes (table 2). Subgroup analyses according to SYNTAX score in patients with left main disease showed that mortality from PCI and CABG did not differ according to score (table 2).

Discussion

This collaborative analysis of individual patient data from 11 randomised trials is the first large-scale study to compare CABG with PCI with stents. We found that 5 year all-cause mortality was higher after PCI than after CABG in 11 518 patients. In subgroup analyses, CABG only had a mortality benefit over PCI in patients with multivessel disease and diabetes; no difference was seen in patients with multivessel disease without diabetes, nor in patients with left main disease (with or without diabetes). Coronary lesion complexity, assessed with the SYNTAX score, was an important effect

	All patients			Multivessel disease				Left main disease			
	CABG (n=5765)	PCI (n=5753)	HR (95% CI; p value)	Heterogeneity	CABG (n=3520)	PCI (n=3520)	HR (95% CI; p value)	Heterogeneity	CABG (n=2245)	PCI (n=2233)	HR (95% CI; p value)	Heterogeneity
All	9·2% (437/5765)	11·2% (539/5753)	1·20 (1·06–1·37; p=0·0038)	ϑ=0·39; p<0·0001	8·9% (279/3520)	11·5% (365/3520)	1·28 (1·09–1·49; p=0·0019)	ϑ=0·40; p<0·0001	10·5% (158/2245)	10·7% (174/2233)	1·07 (0·87–1·33; p=0·52)	ϑ=0·0845; p<0·0001
Diabetes	..	..	$p_{interaction}$=0·0077	..	..	..	$p_{interaction}$=0·0453	..	..	..	$p_{interaction}$=0·13	..
Yes	10·7% (185/2171)	15·7% (278/2215)	1·44 (1·20–1·74; p=0·0001)	ϑ=0·11; p<0·0001	10·0% (134/1622)	15·5% (207/1644)	1·48 (1·19–1·84; p=0·00037)	ϑ=0·16; p<0·0001	13·4% (51/549)	16·5% (71/571)	1·34 (0·93–1·91; p=0·11)	ϑ=0·0536; p=0·0177
No	8·4% (252/3594)	8·7% (261/3538)	1·02 (0·86–1·21; p=0·81)	ϑ=0·0884; p<0·0001	8·0% (145/1898)	8·7% (158/1876)	1·08 (0·86–1·36; p=0·49)	ϑ=0·0992; p<0·0001	9·6% (107/1696)	8·8% (103/1662)	0·94 (0·72–1·23; p=0·65)	ϑ=0·0603; p=0·0027
SYNTAX score	..	..	$p_{interaction}$=0·21	..	..	..	$p_{interaction}$=0·32	..	..	..	$p_{interaction}$=0·38	..
0–22	8·1% (100/1585)	8·8% (105/1533)	1·02 (0·77–1·34; p=0·91)	ϑ=0·0459; p=0·0092	8·4% (51/691)	10·5% (60/690)	1·11 (0·77–1·62; p=0·57)	ϑ=0·0523; p=0·0131	8·3% (49/894)	8·1% (45/843)	0·91 (0·60–1·36; p=0·64)	ϑ<0·0001; p=0·0001
23–32	10·9% (122/1545)	12·4% (163/1677)	1·20 (0·94–1·51; p=0·14)	ϑ=0·0656; p=0·0031	9·5% (59/775)	14·0% (96/824)	1·50 (1·09–2·08; p=0·0129)	ϑ=0·0621; p=0·0066	12·7% (63/770)	10·8% (67/853)	0·92 (0·65–1·30; p=0·65)	ϑ=0·0626; p=0·0093
≥33	11·6% (83/9276)	16·5% (117/871)	1·52 (1·15–2·02; p=0·0029)	ϑ=0·0189; p=0·061	10·9% (38/423)	17·7% (61/397)	1·70 (1·13–2·55; p=0·0094)	ϑ=0·0252; p=0·050	12·4% (45/504)	15·0% (56/474)	1·39 (0·94–2·06; p=0·10)	ϑ=0·0217; p=0·065

Data are percentages from unadjusted Kaplan-Meier analyses (number of events/total number of patients), unless otherwise specified. CABG=coronary artery bypass grafting. PCI=percutaneous coronary intervention. HR=hazard ratio. ϑ=variance. SYNTAX=Synergy between PCI with Taxus and Cardiac Surgery.

Table 2: **5 year all-cause mortality in all patients and according to disease type**

	Trials with bare-metal stents (n=3051)	Trials with drug-eluting stents (n=8467)	p value	Trials with first-generation drug-eluting stents (n=4300)*	Trials with newer-generation drug-eluting stents (n=3969)*	p value
Age (years)	60·8 (10·1; 3051)	64·7 (9·6; 8467)	p<0·0001	63·8 (9·5; 4300)	65·7 (9·6; 3969)	p<0·0001
Sex						
Female	23·2% (707/3051)	24·1% (2037/8467)	p=0·32	25·3% (1087/4300)	23·9% (948/3969)	p=0·14
Male	76·8% (2344/3051)	75·9% (6430/8467)	p=0·32	74·7% (3213/4300)	76·1% (3021/3969)	p=0·14
Body-mass index >30 kg/m^2	22·3% (578/2593)	30·0% (2528/8424)	p<0·0001	32·4% (1388/4290)	25·6% (1010/3939)	p<0·0001
Current smoker	27·5% (843/3049)	20·4% (1704/8355)	p<0·0001	19·6% (833/4260)	21·2% (827/3900)	p=0·064
Diabetes	17·8% (543/3051)	45·4% (3843/8467)	p<0·0001	59·2% (2544/4300)	27·7% (1101/3969)	p<0·0001
Insulin treated	3·4% (48/1396)	14·1% (1001/7083)	p<0·0001	19·0% (816/4299)	6·6% (185/2784)	p<0·0001
Hypertension	51·1% (1558/3051)	73·9% (6235/8436)	p<0·0001	76·5% (3278/4287)	70·1% (2770/3954)	p<0·0001
Hypercholesterolaemia	58·3% (1776/3047)	72·1% (6068/8414)	p<0·0001	75·4% (3230/4285)	69·2% (2727/3938)	p<0·0001
Peripheral vascular disease	7·6% (233/3051)	8·7% (631/7271)	p=0·081	9·2% (396/4300)	7·5% (208/2776)	p=0·0116
Carotid artery disease	5·6% (25/450)	8·2% (304/3696)	p=0·0479	8·2% (148/1800)	8·2% (156/1896)	p=0·99
Previous TIA or CVA	3·3% (47/1438)	6·4% (424/6668)	p<0·0001	5·8% (215/3688)	6·8% (189/2782)	p=0·11
Previous myocardial infarction	42·1% (1285/1766)	21·7% (1570/7243)	p<0·0001	25·8% (1105/4280)	13·9% (384/2768)	p<0·0001
Left-ventricular ejection fraction						
Moderate (30–49%)	16·1% (442/2746)	14·3% (1144/7987)	p=0·0239	15·7% (668/4242)	11·9% (425/3568)	p<0·0001
Poor (<30%)	0·1% (4/2746)	1·2% (99/7987)	p<0·0001	1·6% (66/4242)	0·6% (21/3568)	p<0·0001
Unstable angina pectoris	41·2% (850/2063)	32·7% (2703/8255)	p<0·0001	31·8% (1369/4287)	33·7% (1334/3955)	p=0·067
Three-vessel disease†	41·9% (1280/3051)	70·6% (3774/5348)	p<0·0001	69·4% (2976/4287)	77·2% (679/3969)	p<0·0001
Left main disease	1·0% (29/3051)	52·5% (4449/8467)	p<0·0001	30·5% (1313/4300)	79·0% (3136/3969)	p<0·0001
Follow-up (years)	4·7 (1·0; 2795)	3·5 (1·4; 7726)	p<0·0001	4·0 (1·4; 3830)	3·1 (1·2; 3723)	p<0·0001

Data are mean (SD; n) or % (n/N). TIA=transient ischaemic attack. CVA=cerebrovascular attack. PCI=percutaneous coronary intervention. *The VA CARDS trial[7] was excluded from the analysis of first-generation and newer-generation drug-eluting stents because a mixture of these stents was used. †Of the group of patients with multivessel disease.

Table 3: **Differences in patient characteristics according to whether trials did PCI with bare-metal or drug-eluting stents**

modifier in patients with multivessel disease, but did not appear to modify treatment effect in those with left main disease.

The relative benefits of CABG versus PCI with stents in terms of outcomes are highly debated, particularly each time stent design is enhanced. Improvements in stent design have led to inclusion of higher-risk patients with more complex disease, such as three-vessel or left main disease, in randomised trials. This higher-risk profile is also reflected in our data, wherein 5 year all-cause mortality in both the CABG and PCI cohorts was higher in more recent trials with drug-eluting stents than in earlier trials with bare-metal stents, but a larger relative benefit of CABG over PCI was most likely due to more complex coronary artery disease.

In all of the included trials, both an interventional cardiologist and a cardiac surgeon had to assume clinical equipoise between PCI and CABG for patients to be randomised. Some patients were not eligible for inclusion in the selected trials because of having coronary lesion complexity too severe to be treated with PCI or operative risk deemed too high for CABG.[19] The results of this analysis are not generalisable to the entire population of patients with coronary artery disease that require revascularisation. Therefore, heart team decision making is crucial to recommend the best revascularisation strategy for an individual patient.[20]

The mortality benefit of CABG over PCI in the overall group was retained over a variety of patient baseline characteristics. However, the presence of diabetes was an important modifier, as shown in previous analyses.[1] The benefit of CABG in patients with diabetes might be attributed to more effective revascularisation of diffuse, complex coronary disease. This hypothesis is consistent with the findings of the subgroup analysis according to SYNTAX score. In the total cohort, a step-wise increase in the difference between CABG and PCI was observed with increasing SYNTAX scores. Other studies[21] have also identified sex as an effect modifier, but we did not find a significant treatment-by-sex interaction for 5 year mortality.

Patients with multivessel disease had lower mortality with CABG than with PCI, consistent with the SYNTAX trial that compared CABG with PCI using first-generation drug-eluting stents.[22,23] The BEST trial,[8] in which second-generation everolimus-eluting stents were used to treat multivessel disease, also found that CABG was associated with a lower incidence of major adverse cardiac or cerebrovascular events, driven by a reduced incidence of myocardial infarction and repeat revascularisation. Large real-world registries have applied propensity score

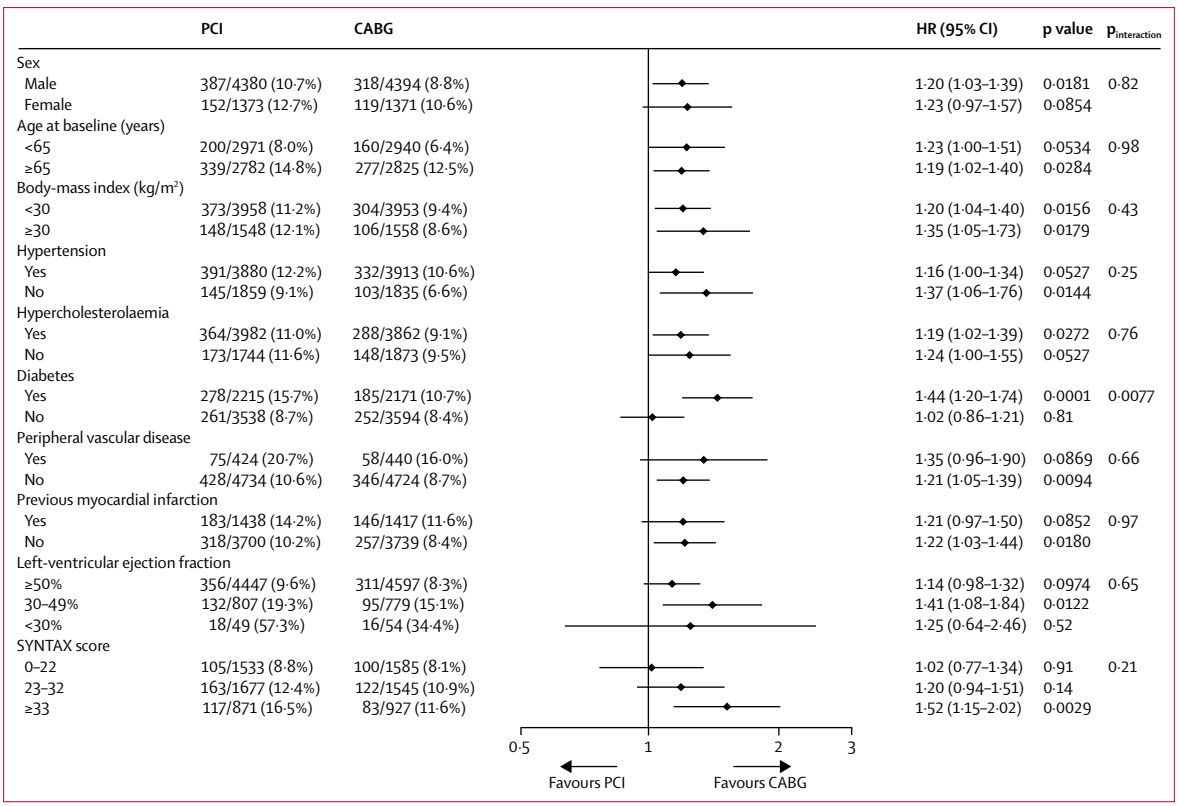

Figure 2: **Mortality after CABG versus after PCI during 5 years' follow-up, by subgroup**
Kaplan-Meier estimates are from the overall pooled patient population. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. HR=hazard ratio. SYNTAX=Synergy between PCI with Taxus and Cardiac Surgery.

matching to compare CABG with PCI using drug-eluting stents for multivessel disease to find differences in survival with larger sample sizes.[24,25] The ASCERT study,[25] the largest of such analyses, reported an adjusted 4 year mortality of 16·4% for CABG and 20·8% for PCI with first-generation drug-eluting stents in a cohort of patients aged 65 years or older; mortality was consistent across multiple subgroups. Notably, the survival curves of CABG and PCI in this study are similar to those of the ASCERT study: PCI shows a benefit within the first year of follow-up, but a larger benefit is seen with CABG than with PCI with longer follow-up. We showed that this reversal of risk resulted in a benefit for CABG over PCI at a mean follow-up of 4·1 years, which might become larger with longer follow-up given that the HR favoured CABG at later follow-up in time-varying models.

In the SYNTAX trial,[26] 5 year mortality was similar for CABG and PCI with paclitaxel-eluting, first-generation drug-eluting stents in patients with left main disease. Two major trials[9,10] have since focused on finding the optimal revascularisation strategy for left main disease and have reported conflicting outcomes of CABG versus PCI. The EXCEL trial[10] reported that PCI was non-inferior to CABG after 3 years, whereas the NOBLE trial[9] did not show non-inferiority for PCI versus CABG at 5 years. The differences in timing and composition of the primary endpoints make comparing these trials difficult and presumably explain the apparent difference in results. 3 year individual endpoints in the NOBLE trial were later confirmed to be similar to those in the EXCEL trial.[27] In our pooled analysis of data for patients with left main disease from four different trials, mortality was similar after CABG and PCI at 5 years' follow-up. Unlike for patients with multivessel disease, the similarity in mortality in patients with left main disease was consistent in a subgroup analysis according to diabetes status, although this difference might be due to the smaller sample size in the diabetic subgroup of patients with left main disease. Coronary complexity did not affect mortality in patients with left main disease, although patients with a high SYNTAX score were relatively under-represented because of specific inclusion criteria (eg, in the EXCEL trial) and a preference of heart teams for CABG.[19] Therefore, the degree of complexity should still be considered when proposing a specific treatment for individual patients with left main disease. Patients with a complex left main lesion and three-vessel disease with a high SYNTAX score might still benefit from CABG in terms of mortality, as well as incidence of myocardial infarction and repeat revascularisation, whereas patients with a non-complex lesion and one-vessel or two-vessel disease might be excellent candidates for PCI. Clinical guidelines have not

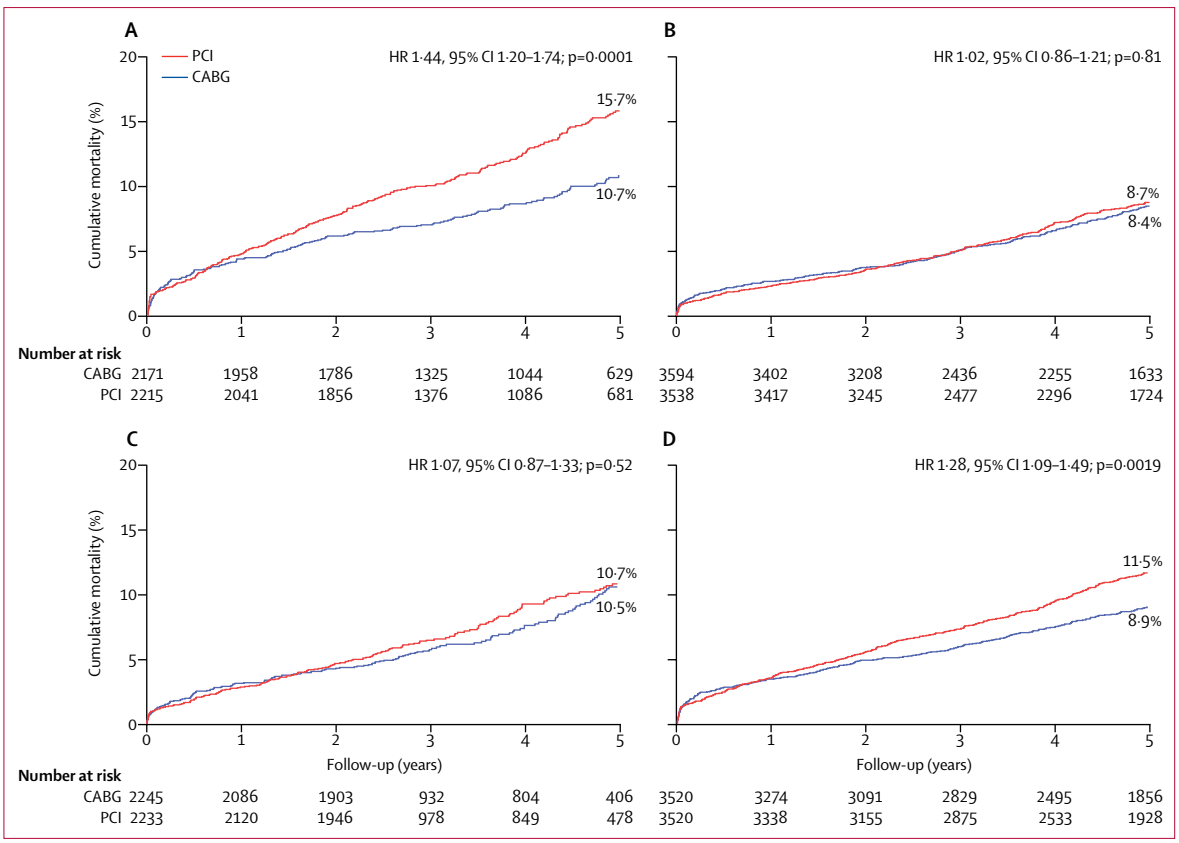

Figure 3: **Mortality after CABG versus after PCI during 5 years' follow-up of patients with (A) or without (B) diabetes and with left main disease (C) or multivessel disease (D)**

Kaplan-Meier estimates are from the overall pooled patient population. PCI=percutaneous coronary intervention. CABG=coronary artery bypass grafting. HR=hazard ratio.

been revised since the release of data from the EXCEL and NOBLE trials. Based on existing data of similar mortality with the two interventions, the indication for PCI with contemporary drug-eluting stents might be broadened to patients with more complex left main disease (eg, intermediate SYNTAX scores). However, given that only 978 patients with left main disease in our cohort had high SYNTAX scores, additional data are required before PCI can be routinely recommended in patients with complex left main disease. Longer follow-up is essential to better define differences in survival between CABG and PCI, because landmark analyses from the EXCEL trial[10] showed that the risk of mortality after CABG and PCI was different according to follow-up duration and might show a benefit for CABG with longer follow-up.

The main strength of this study is that we were able to identify clinically relevant differences in all-cause mortality between CABG and PCI because of collaboration with the principal investigators of 11 high-quality randomised trials. This collaboration allowed data to be pooled to provide sufficient power to examine an outcome that occurs reasonably infrequently. Indeed, all-cause mortality is considered to be the most clinically important and least biased endpoint, which is another strength of this analysis. Access to individual patient data facilitated analysis of outcomes in important subgroups and construction of Kaplan-Meier curves so that temporal associations between the interventions and mortality could be examined.

Nevertheless, this study has several limitations. First, all the included trials assumed clinical equipoise between CABG and PCI. These trials had specific inclusion and exclusion criteria, and many patients were excluded because CABG or PCI was thought to be the preferred revascularisation strategy based on the age, risk profile, or coronary complexity of the individual.[19] These criteria and the selection of patients resulted in only 22·1% of patients having a SYNTAX score of 33 or higher. Second, the inclusion and exclusion criteria led to significant heterogeneity in the baseline characteristics of patients from different trials, as shown by our assessment of frailty. Third, besides mortality, other outcomes that affect morbidity and quality of life, such as myocardial infarction, stroke, and repeat revascularisation, are important for the patient and should be considered by heart teams when deciding on the best revascularisation option for each patient. In an era of exponentially growing health-care costs, with a need to reduce expenses, the cost-effectiveness of PCI and CABG should also be evaluated. Fourth, the mean

patient age was about 64 years, and the mean follow-up was 3·8 years. In view of the reasonably long life expectancy of patients with coronary artery disease, this follow-up is still too short to establish the full effect of the revascularisation method on survival, particularly considering the diverging or converging Kaplan-Meier curves in specific subgroups. Fifth, definitions and reporting of patient characteristics might have slightly differed between trials, which could have affected the results of the subgroup analyses and meant that we were unable to do a subgroup analysis according to renal function. Sixth, we could not include data from the LE MANS trial,[14] although it is very unlikely that inclusion of these 105 patients with left main disease would have substantially altered the results, and thus the outcomes of this study are robust with respect to the available evidence.

In conclusion, we showed that 5 year mortality was significantly lower after CABG than after PCI. In particular, the benefit of CABG over PCI was shown in patients with multivessel disease and diabetes, but not in patients with multivessel disease without diabetes. Nor was there a benefit for CABG or PCI in patients with left main disease. Consideration of coronary lesion complexity is important when choosing the appropriate revascularisation strategy. Longer follow-up is needed to better define mortality differences between the interventions.

Contributors

SJH, MM, JD, MF, MAH, GWS, PWS, and APK designed the study. SJH and MM did the literature search. SJH, JD, J-MA, EHC, MJD, MEF, VF, NRH, WAH, MK, Y-HK, TM, FWM, S-JP, AER, JFS 3rd, RHS, GWS, PWS, and APK contributed to the data collection. SJH, MM, GP, and EB did the data analysis. MM constructed the figures. SJH, MM, JD, MF, MAH, EB, GWS, and APK interpreted the data. SJH wrote the first draft of the manuscript. All authors critically reviewed the manuscript and approved the final version.

Declaration of interests

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