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Mortality after bypass surgery versus stenting for coronary artery disease: an individual patient-data pooled analysis of 11,518 patients from 11 randomized trials

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ABSTRACT

Background: Numerous randomized trials have compared coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for patients with multivessel (MVD) or left main (LM) coronary artery disease. No studies have been powered to detect a difference in mortality.

Methods: We performed a collaborative individual patient-data, pooled analysis of 11 randomized clinical trials comparing CABG with PCI using stents, in which a Heart Team selected patients with estimated clinical equipoise between CABG and PCI; ERACI II (n=450), ARTS (n=1205), MASS II (n=408), SoS (n=988), SYNTAX (n=1800), PRECOMBAT (n=600), FREEDOM (n=1900), VA CARDS (n=198), BEST (n=880), NOBLE (n=1184) and EXCEL (n=1905). Mortality rates up to 5 years were estimated using Kaplan-Meier curves, with comparisons between PCI and CABG performed in a random-effects Cox proportional hazards model stratified by trial. Consistency of treatment effect was explored in subgroup analyses according to baseline clinical and anatomical characteristics.

Findings: A total of 11,518 patients were randomly assigned to PCI (n=5753) or CABG (n=5765). Mean SYNTAX score was 26·0 ± 9·5, with 1798 patients (22·1%) having a SYNTAX score ≥33. Over a mean follow-up of 3·8 ± 1·4 years, 976 deaths occurred. Five-year all-cause mortality was 11·2% (539 deaths) after PCI and 9·2% (437 deaths) after CABG (HR=1·20, 95% CI 1·06-1·37; P=0·0038). All-cause mortality was significantly different in patients with MVD (PCI: 11·5% versus CABG: 8·9%; HR=1·28, 95% CI 1·09-1·49; P=0·0019) but not in patients with LM disease (PCI: 10·7% versus CABG: 10·5%; HR=1·07, 95% CI 0·87-1·33; P=0·52). In patients with MVD, mortality was significantly higher with PCI versus CABG in diabetics (15·5% versus 10·0%, P=0·0004) but not in non-diabetics

(8·7% versus 8·0%, P=0·49). Moreover, the difference between PCI and CABG in patients with MVD showed a stepwise increase from SYNTAX score 0-22 (P=0·59) to 23-32 (P=0·0129) to ≥33 (P=0·0094). In patients with LM disease, comparable outcomes were not significantly influenced by the presence of diabetes or increasing SYNTAX scores.

Interpretation: In this individual patient-data, pooled analysis of 11 randomized trials in which a Heart Team selected patients, five-year mortality was significantly higher after PCI than CABG in patients with MVD, specifically in those with diabetes and higher coronary complexity. There were no significant differences in 5-year mortality between PCI and CABG in patients with LM disease, regardless of diabetes and SYNTAX score. Longer follow-up is needed to better define mortality differences.

Keywords: Coronary artery bypass grafting; CABG; Percutaneous coronary intervention; PCI; Stenting; Left main; Multivessel; Survival; Mortality

INTRODUCTION

Numerous randomized trials have compared coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) using either balloon angioplasty, bare-metal stents (BMS) or drug-eluting stents (DES) for the treatment of multivessel (MVD) or left main (LM) coronary artery disease.[1-3] No individual trial has convincingly demonstrated a significant difference in all-cause mortality between the revascularization strategies. Hlatky and colleagues performed a pooled individual patient-data analysis of ten randomized trials including 7812 patients who underwent CABG with PCI using balloon angioplasty or BMS and reported five-year mortality to be 8·4% after CABG and 10·0% after PCI (P=0·12).[1] More contemporary trials comparing CABG versus PCI using DES have reported similar mortality rates. Despite the large number of clinical trials, all were underpowered to detect a difference in all-cause mortality. The objective of the present study was to overcome this limitation by pooling individual patient-data from all randomized trials comparing CABG with PCI using contemporary techniques (e.g. stents for PCI) to examine their comparative effects on long-term all-cause mortality in all patients, and separately in patients with MVD and LM disease.

METHODS

Reporting of this individual patient-data, pooled analysis concurs with specific PRISMA guidelines.[4] This study is not registered and no protocol has been published.

Study Selection and Data Collection

A literature search of the MEDLINE, EMBASE, and Cochrane databases was performed on July 19, 2017 using the following keywords: “coronary artery bypass

grafting", "percutaneous coronary intervention", "stent", and "random*". Two researchers (SJH and MM) independently identified randomized trials comparing CABG and PCI with the following characteristics: (i) patients were randomly assigned to undergo CABG or PCI treatment, (ii) patients had multivessel and/or left main coronary artery disease, (iii) patients did not present with an acute myocardial infarction (MI); (iv) PCI was performed using stents (BMS or DES) and not balloon angioplasty, and (v) more than one-year follow-up for all-cause mortality was available (Appendix 1). Abstracts from meetings were not considered, nor were unpublished trials. Reference lists from potentially relevant literature were checked to ensure no studies were missed.

From the 19 trials that were identified from the literature search, four trials were excluded because patients did not have multivessel or LM disease, one trial was excluded because only 54% of patients received a stent, and two trials were excluded because follow-up was only available up to one year (Appendix 1). Principal investigators of the remaining 12 trials were contacted to obtain individual patient data for a pooled analysis. One trial was unable to provide the data (n=105),[5] and investigators from the other 11 trials provided data in a standardized spreadsheet for the current pooled analysis: ERACI II[6], ARTS[7], MASS-II[8], SoS[9], SYNTAX[10], PRECOMBAT[11], FREEDOM[12], VA CARDS (Cooperative studies program [CSP] study #557)[13], BEST[14], NOBLE[15], and EXCEL[16]. Data were cross-checked against the publication of the primary endpoint and long-term follow-up publications. Several minor inconsistencies were resolved by contacting trial principal investigators. Baseline and procedural characteristics of individual trials are presented in the Appendix 2, with information of missing data for specific characteristics. Core laboratory assessed SYNTAX scores were available from 6 trials and a total of 8138 patients (CABG: n=4057, PCI: n=4081).

The quality of individual trials was assessed using the Cochrane Collaboration's tool for assessing risk of bias.[17] All trials were considered to have a high quality according to the criteria, despite not being able to blind investigators and patients (Appendix 3).

Local Medical Ethics Committees approved each trial at the time of study execution, and all patients provided written informed consent.

Outcomes and Follow-up

To allow a consistent definition of follow-up time among trials, the duration of follow-up was calculated from the procedure. If patients died before the procedure, the time from randomization 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 MVD and LM disease. Planned analyses were also performed for trials using BMS, all DES, and for first-generation DES and newer-generation DES. First-generation DES were paclitaxel-eluting stents or sirolimus-eluting stents. Newer-generation DES were everolimus-eluting stents, zotarolimus-eluting stents, and biolimus-eluting stents. The VA CARDS trial was excluded from the separate analysis of first-generation and newer-generation DES, because a mix of first-generation and newer-generation DES was used. We furthermore pre-specified subgroup analyses according to the following baseline characteristics: sex, age, body mass index, hypertension, hyperlipidemia, diabetes mellitus, peripheral vascular disease, previous MI, left ventricular ejection fraction, and lesion complexity as defined by the SYNTAX score. Post-hoc subgroup analyses were performed according to SYNTAX score tertiles in the overall groups of patients with or without diabetes.

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

Statistical Analysis

All analyses were performed according to intention-to-treat, with patients stratified according to the procedure assigned to by randomization. Individual patient baseline, procedural, and outcome data were pooled. Continuous variables were expressed as mean ± standard deviation and compared using t-tests, and discrete data were presented as frequencies and compared using chi-square tests. We pooled data from all 11 trials to provide unadjusted Kaplan-Meier estimates of all-cause mortality in overall and landmark analyses at 30 days, five years, and between 31 days and five years. Comparisons between PCI and CABG were performed using Cox proportional hazards models stratified by trial, using a gamma frailty term to account for heterogeneity between trials. In this model, each trial is considered as an individual study and the random-effects model establishes a single 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 among trials. The statistical significance of the variance parameter was assessed using the likelihood ratio test. The proportionality assumption was tested for the overall analysis and was not violated (P=0·12). Nevertheless, visual inspection of the Kaplan-Meier curves suggests a time-dependent variance in the HR of PCI versus CABG, and therefore time-dependent models were also performed. Subgroup analyses according to baseline clinical, procedural and anatomical characteristics were performed using the same Cox models. A two-sided $P<0.05$ was considered to indicate statistical significance; adjusting for multiplicity was not performed. All statistical analyses were performed using SPSS software version 21 (IBM Corporation, Armonk, NY, USA) or R software version 3.2.4 (Institute for Statistics and Mathematics of WU, Wien, Austria).

Role of Source Funding and Trial Sponsors

This current study was performed without funding, although individual trials were sponsored (see the end of the manuscript).

A team consisting of three epidemiologists and statisticians (M.M, E.B, and G.P) performed the statistical analyses. The decision to submit the manuscript for publication was made together by the principal investigators of the individual trials. Sponsors of the individual trials were involved with data collection in the individual trials, but uninvolved in performance of the analyses, interpretation of the data, or drafting of the manuscript.

RESULTS

Study Population and Procedures

The 11 trials randomly assigned 11,518 patients to CABG (n=5765) or PCI (n=5753). Four trials were performed with BMS (n=3051), four trials with first-generation DES (n=4498), and three trials with newer-generation DES (n=3969). PCI was performed with BMS in 26·6%, with first-generation DES in 39·2%, and with newer-generation DES in 34·2% of patients (Table 1). Data from individual trials are presented in the Appendix 2, including information on actual treatments performed (Appendix 4).

Patients had a mean age of 63·6 ± 9·8 years and 23·8% were female (Table 1). Diabetes was present in 38·1% of patients, and 12·4% were on insulin treatment. Unstable angina was present in 34·4% of patients and 27·7% had a prior MI, although only 1·0% had a left ventricular ejection fraction <30%. Three-vessel disease was present in 60·2% of patients, and 38·9% had significant LM disease. The mean SYNTAX score was 26·0 ± 9·5, with 1798 patients (22·1%) having a SYNTAX score ≥33.

Surgery was performed with a left internal mammary artery in 96·2% of patients, with bilateral internal mammary arteries in 18·7%. Procedures were performed off-pump in

27·5% of patients. In 73·4% of patients DES were used during PCI, with 53·4% of those being first-generation DES and 46·6% being newer-generation DES.

Patients were discharged with aspirin after CABG and PCI in 95·5% and 97·3%, respectively, and 44·0% and 95·1% with dual antiplatelet therapy, respectively (P<0·0001 for both analyses). Other secondary prevention was also higher at discharge after PCI than after CABG (Table 1).

The mean duration of follow-up was 3·8 ± 1·4 years.

Mortality in all patients

A total of 976 deaths occurred during follow-up. Five-year all-cause mortality was 11·2% (539 deaths) after PCI and 9·2% (437 deaths) after CABG (HR=1·20, 95% CI 1·06-1·37; P=0·0038) (Figure 1; Table 2). At 30-day follow-up, mortality occurred in 76 patients (1·3%) after PCI and in 78 patients (1·4%) after CABG (HR=0·97, 95% CI 0·71-1·33; P=0·84). In a landmark analysis, mortality between 31 days and 5 years occurred in 463 patients (10·0%) following PCI and in 359 patients (8·0%) following CABG (HR=1·26, 95% CI 1·09-1·44; P=0·0009). A time-dependent model showed that the hazard of mortality was comparable between PCI and CABG during the first year of follow-up (HR=0·97, 95% CI 0·80-1·19; P=0.80), but was in favour of CABG beyond one-year follow-up (HR=1·39, 95% CI 1·17-1·62; P<0·0001)(Appendix 5). The estimate of the frailty parameter for heterogeneity was significant (θ=0·39, P<0·0001).

Patients randomized in trials in which DES were used were significantly older, had more comorbidities, and more complex coronary disease than patients randomized in trials in which BMS were used (Table 3). Particularly, in DES versus BMS trials, diabetes was present in 45·4% versus 17·8%, respectively, LM disease was present in 52·5% versus 1·0%, respectively, and three-vessel disease in 70·6% versus 41·9% (P<0·0001 for all). Five-year mortality in BMS trials (n=3051) was 8·7% (131 deaths) after PCI and 8·2% (125 deaths) after CABG (HR=1·05, 95% CI 0·82-1·34; P=0·72). In DES trials (n=8467),

5-year mortality was 12·4% (408 deaths) after PCI with DES and 10·0% (312 deaths) after CABG (HR=1·27, 95% CI 1·09-1·47; P=0·0022). The interaction for CABG versus PCI with BMS or DES was not significant (P for interaction = 0·53). Although there were significant differences in clinical and anatomical characteristics between trials using first-generation DES and those using newer-generation DES (Table 3), the difference in 5-year mortality between PCI and CABG was consistent when analyzing the 4300 patients enrolled in trials using first-generation DES (PCI: 13·2% (254 deaths) versus CABG: 11·1% (201 deaths); P=0·0391) and the 3969 patients enrolled in trials using newer-generation DES (PCI: 10·3% (136 deaths) versus CABG: 7·9% (106 deaths); P=0·0684) (P for interaction = 0·78).

In subgroup analyses, the difference in mortality was consistent according to most baseline characteristics (Figure 2; Table 2). Diabetes was the only baseline characteristic for which a significant treatment interaction was present (P for interaction = 0·0077). In patients with diabetes there was a higher mortality with PCI compared with CABG (15·7% versus 10·7%, respectively; HR=1·44, 95% CI 1·20-1·74; P=0·0001), whereas mortality was comparable in patients without diabetes (PCI 8·7% versus CABG 8·4%; HR=1·02, 95% CI 0·86-1·21; P=0·81) (Figures 2 and 3B). Of note, although the interaction was not significant, the mortality benefit of CABG over PCI tended to be progressively greater with increasing SYNTAX scores (Table 2). Similar trends were found in subgroups of patients with or without diabetes (Appendix 6).

Multivessel disease

Among patients with multivessel disease randomized to PCI (n=3520) versus CABG (n=3520), there were 644 deaths during a mean of 4·1 ± 1·4 years follow-up. The 5-year rate of all-cause mortality was higher after PCI: 11·5% (365 deaths) versus 8·9% (279 deaths) after CABG (HR=1·28, 95% CI 1·09-1·49; P=0·0019) (Figure 3D; Table 2). Results of time-dependent models are provided in the Appendix 5; similar as for the

overall patient cohort, the benefit of CABG in MVD was particularly present with longer follow-up.

In patients with multivessel disease, mortality was 15·5% after PCI versus 10·0% after CABG, in the 3266 patients with diabetes (HR=1·48, 95% CI 1·19-1·84; P=0·0004), and 8·7% after PCI versus 8·0% after CABG, in the 3774 patients without diabetes (HR=1·08, 95% 0·86-1·36; P=0·49) (P for interaction = 0·0453) (Table 2).

The mortality benefit of CABG over PCI was greater with increasing SYNTAX scores in patients with multivessel disease. The respective mortality rates after PCI and CABG were 10·5% versus 8·4% in 1381 patients with a SYNTAX score of 0-22 (HR=1·11, 95% CI 0·77-1·62, P=0·57), 14·0% versus 9·5% in 1599 patients with a SYNTAX score of 23-32 (HR=1·50, 95% CI 1·09-2·08; P=0·0129), and 19·2% versus 11·2% in 820 patients with a SYNTAX score of ≥33 (HR=1·70, 95% CI 1·13-2·55; P=0·0094) (P for interaction = 0·32) (Table 2).

Left main disease

Among patients with LM disease randomized to PCI (n=2233) versus CABG (n=2245), there were 322 deaths during a mean of 3·4 ± 1·4 years follow-up. The 5-year rate of all-cause mortality was comparable with 10·7% (174 deaths) after PCI and 10·5% (158 deaths) after CABG (HR=1·07, 95% CI 0·87-1·33; P=0·52) (Figure 3C; Table 2). Results of time-dependent models are provided in the Appendix 5; in contrast to the overall cohort and MVD subgroup, the benefit of CABG was not seen with longer follow-up.

In subgroup analysis according to diabetes in patients with LM disease, there was no significant interaction in the treatment effect (P for interaction = 0·13). In 1120 patients with diabetes mortality was 16·5% after PCI versus 13·4% after CABG (HR=1·34, 95% CI 0·93-1·91; P=0·11) and 8·8% after PCI versus 9·6% after CABG in 3358 patients without diabetes (HR=0·94, 95% CI 0·72-1·23; P=0·65) (Table 2).

Analyses according to SYNTAX score in patients with LM disease revealed that there were no differences in mortality among PCI and CABG in any of the groups: 8·1% versus 8·3% among 1737 patients with a SYNTAX score of 0-22 (HR=0·91, 95% CI 0·60-1·36, P=0·64), 10·8% versus 12·7% among 1623 patients with a SYNTAX score of 23-32 (HR=0·92, 95% CI 0·65-1·30; P=0·65), and 15·0% versus 12·4% among 978 patients with a SYNTAX score of ≥33 (HR=1·39, 95% CI 0·94-2·06; P=0·1006) (P for interaction = 0·38) (Table 2).

DISCUSSION

This collaborative analysis of individual patient data from 11 randomized trials is the first large-scale analysis of data comparing CABG and PCI performed using stents. In a total of 11,518 randomly assigned patients, the 5-year mortality rate was significantly higher after PCI than after CABG. However, this difference was not consistent among subgroups. Specifically, the mortality benefit of CABG over PCI was seen only in patients with multivessel disease and diabetes. Conversely, there were no significant differences in mortality between CABG and PCI in patients without diabetes who had multivessel disease, or in all patients with left main disease (with or without diabetes). Coronary lesion complexity was an important effect modifier, particularly in patients with multivessel disease.

The difference between CABG and PCI using stents is a topic of debate that is fueled each time stent design is enhanced. Due to these improvements, randomized trials comparing CABG and PCI have increasingly included higher-risk patients with more complex disease, such as three-vessel or left main disease. This is also reflected in our data wherein 5-year all-cause mortality in both the CABG and PCI cohorts was higher in contemporary trials with DES versus earlier trials in which BMS were used.

It is important to acknowledge that in these trials, both an interventional cardiologist and a cardiac surgeon had to assume clinical equipoise between PCI and CABG for

patients to be randomized. Such a Heart Team concept has received more emphasis over the recent years to determine the best revascularization strategy for individual patients.[18] Some patients were not eligible for inclusion in the selected randomized trials due to coronary lesion complexity too severe to be treated by PCI or an operative risk deemed to high to undergo CABG.[19] The results of this analysis therefore do not correspond to the entire population of patients with coronary artery disease that require revascularization.

The mortality benefit of CABG versus PCI in the overall group was retained over a variety of patient baseline characteristics. However, the presence of diabetes remained as an important factor, as demonstrated in previous analyses.[1] The benefit of CABG in patients with diabetes may be attributed to more effective revascularization of diffuse, complex coronary disease. This is consistent with the findings of the subgroup analyses according to SYNTAX score. In the total cohort, there was a step-wise increase in the difference between CABG and PCI with higher SYNTAX scores. Other studies have identified sex as an effect modifier,[20] but we were unable to confirm a significant treatment-by-sex interaction for 5-year mortality.

Patients with multivessel disease have lower mortality with CABG, as shown in the SYNTAX trial that compared CABG with PCI with first-generation DES.[21,22] The BEST trial in which second-generation, everolimus-eluting stents were used to treat multivessel disease also found that CABG was associated with lower rates of major adverse cardiac or cerebrovascular events, driven by a reduced rate of MI and repeat revascularization.[14] However, both trials failed to show a survival benefit for either treatment. Large real-world registries that applied propensity matching of CABG versus PCI with DES for multivessel disease have attempted to find such differences with larger sample sizes.[23,24] The ASCERT study, the largest such analysis, reported an adjusted 4-year mortality of 16.4% for CABG and 20.8% for PCI among a cohort of patients aged 65 years or older, which was consistent in multiple subgroups.[24] Notably, a similar pattern

of the survival curves of CABG versus PCI is observed when comparing those of the real-world ASCERT study in which patients were treated with first-generation DES and that of the current analysis: PCI shows a benefit within the first year of follow-up but with longer follow-up there is a larger benefit with CABG. We were able to show that this reversal of the hazard resulted in a significant benefit of CABG over PCI at a mean of 4·1 years, which may potentially become larger with prolonged follow-up as the hazard ratio was more in favour of CABG at later follow-up in time-varying models.

Among patients with LM disease randomized in the SYNTAX trial, comparable 5-year mortality between CABG and paclitaxel-eluting, first-generation DES was noted.[25] Two major trials have since focused on finding the optimal revascularization strategy for LM disease and have recently reported conflicting outcomes of CABG versus PCI. The EXCEL trial reported non-inferiority of PCI versus CABG after 3 years, while the NOBLE trial did not demonstrate non-inferiority of PCI versus CABG at 5 years.[15,16] The differences in timing and composition of the primary endpoints make a comparison of these trials difficult and can presumably explain the apparent difference in results. Three-year individual endpoints in the NOBLE trial were later confirmed to be remarkably similar to EXCEL.[26] In the current pooled analysis of data from 4 different trials, mortality in patients with LM disease was similar after CABG and PCI at 5-year follow-up. The mortality comparison was consistent in a subgroup analysis according to diabetes, unlike the analysis of all patients and those with multivessel disease, although this may be due to smaller sample size in the diabetic subgroup of LM patients. Coronary complexity by SYNTAX score did not show to impact the mortality comparison, although patients with a high SYNTAX score were relatively underrepresented due to specific inclusion criteria (e.g. in the EXCEL trial) and a Heart Team preference for CABG.[19] Therefore, the degree of complexity should still be important to consider when proposing a specific treatment for individual patients with LM disease. Patients with a complex LM lesion and additional three-vessel disease with a high SYNTAX score may

still benefit from CABG in terms of mortality, as well as MI and repeat revascularization, while patients with a non-complex LM lesion and one or two-vessel disease may be excellent candidates for PCI. Clinical guidelines have not been revised since the release of the EXCEL and NOBLE trial data. Based on the current data of comparable mortality, the indication for PCI with contemporary DES may be broadened to patients with more complex LM disease (e.g. intermediate SYNTAX scores). However, since only 978 patients in the present LM cohort had high SYNTAX scores, additional data is required before PCI can be routinely recommended in patients with complex LM disease. Longer follow-up is essential to better define differences in survival between CABG and PCI, as landmark analyses from the EXCEL trial showed that the hazard of mortality after CABG and PCI was different according to the period of follow-up and may show a benefit of CABG with longer follow-up.[16]

The major strength of the current analysis is that we were able to find clinically relevant differences in all-cause mortality between CABG and PCI due to the collaboration of the principal investigators from 11 high-quality randomized trials, allowing pooled data to provide sufficient power to examine an outcome that occurs relatively infrequently. Indeed, all-cause mortality is considered to be the most clinically important and least biased endpoint, which is another strength of this analysis. Having individual patient data also facilitated formation of Kaplan-Meier curves so the temporal relationships of mortality could be examined, and analysis of outcomes in important subgroups, which in the present study were highly informative.

Nevertheless, several limitations should also be considered. First, all the included trials randomized patients with estimated 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 revascularization strategy based on the age, risk profile, or coronary complexity.[19] This resulted in a population with only 22·1% having a SYNTAX score ≥33. Second, these inclusion and exclusion criteria have

resulted in significant variance in the baseline characteristics of the patients from different trials, as shown by our assessment of frailty. Third, besides mortality, other outcome measures that impact morbidity and quality of life, such as MI, stroke, and repeat revascularization, are also important for the patient and should be taken into account by the Heart Team when deciding on the best revascularization option for each individual patient. In the current era of exponentially growing health care costs and the need to reduce expenses, the cost-effectiveness of PCI and CABG should furthermore be evaluated. Fourth, the mean patient age was 63.6 years, and the mean follow-up was 3·8 years. Considering the life expectancy of patients, this follow-up is still relatively short to determine the full impact of revascularization method on survival, especially considering the diverging or converging Kaplan-Meier curves in specific subgroups. Fifth, definitions of patient characteristics may have slightly differed between trials, which may have impacted the results of the subgroup analyses. Sixth, we were unable to include data from the LE MANS trial[5], although it is very unlikely that inclusion of these 105 patients with LM disease would significantly alter the results, and thus the outcomes of this study are robust with respect to the available evidence.

CONCLUSIONS

In this individual patient-data, pooled analysis from 11 trials in which a Heart Team randomized 11,518 patients with estimated clinical equipoise between PCI and CABG, 5-year mortality was significantly lower after CABG as compared with PCI. The benefit was demonstrated only in patients with multivessel disease and diabetes, but not in patients with multivessel disease without diabetes. Nor was there a benefit of CABG or PCI in patients with LM disease. Coronary lesion complexity is an important factor to consider when choosing the appropriate revascularization strategy, especially in patients with multivessel disease. Longer follow-up is needed to better define mortality

differences. These results may not be applicable to patients excluded from randomized trials for various reasons (e.g. coronary complexity or procedural risk).

RESEARCH IN CONTEXT

Evidence before this study

A literature search of the MEDLINE, EMBASE, and Cochrane databases was performed on July 19, 2017 to identify randomized clinical trials comparing coronary artery bypass grafting and percutaneous coronary intervention with stents using the following keywords: “coronary artery bypass grafting”, “percutaneous coronary intervention”, “stent”, and “random*”, with the following characteristics: (i) patients had multivessel and/or left main coronary artery disease, (ii) patients did not present with an acute myocardial infarction (MI); (iii) PCI was performed using stents (BMS or DES) and not balloon angioplasty, and (iv) more than one-year follow-up for all-cause mortality was available. We identified 12 high-quality trials, none of which found a significant difference in all-cause mortality between PCI and CABG at 3-10 year follow-up. Separate meta-analyses of randomized clinical trials that included patients with multivessel disease or with left main disease showed no significant differences in all-cause mortality between PCI and CABG. Meta-analyses did show that patients with diabetes have a benefit with CABG over PCI as opposed to patients without diabetes where no difference was found, although this has been contradicted in other pooled analyses.

Added value of this study

This study is the largest analysis of patients randomly assigned to PCI with stents or CABG. It shows for the first time, to the best of our knowledge, that all-cause mortality is significantly lower with CABG than with PCI in an overall randomized population of patients with multivessel or left main disease. However, because of the use of individual patient data, important subgroups are identified that have a survival benefit from CABG,

457 which are patients with multivessel disease and diabetes, and high coronary lesion
458 complexity. Patients with left main disease and lower coronary lesion complexity have
459 comparable survival with PCI and CABG.

460 **Implications of all the available evidence**

461 Some patients have specific indications for PCI or CABG because of too high coronary
462 complexity for PCI or too high operative risk for CABG. In patients with estimated
463 clinical equipoise as determined by a Heart Team, it is crucial to consider the presence
464 of multivessel or left main disease, the coronary complexity as determined by the
465 SYNTAX score, and the presence of diabetes, as these are important effect modifiers in
466 terms of PCI versus CABG and should impact the decisions for coronary
467 revascularization in daily practice. However, longer follow-up of randomized trials is
468 required to better define mortality differences in overall patients and specific
469 subgroups.

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Drafting of the manuscript: SJH

All authors provided a critical revision of the manuscript and approved the final version.

REFERENCES

1. Hlatky MA, Boothroyd DB, Bravata DM, et al. 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;373:1190-7.
2. Daemen J, Boersma E, Flather M, et al. Long-term safety and efficacy of percutaneous coronary intervention with stenting and coronary artery bypass surgery for multivessel coronary artery disease: a meta-analysis with 5-year patient-level data from the ARTS, ERACI-II, MASS-II, and SoS trials. Circulation 2008;118:1146-54.
3. Stefanini GG, Holmes DR, Jr. Drug-eluting coronary-artery stents. N Engl J Med 2013;368:254-65.
4. Stewart LA, Clarke M, Rovers M, et al. Preferred Reporting Items for Systematic Review and Meta-Analyses of individual participant data: the PRISMA-IPD Statement. JAMA 2015;313:1657-65.
5. Buszman PE, Buszman PP, Banasiewicz-Szkrobka I, et al. Left main stenting in comparison with surgical revascularization: 10-year outcomes of the (Left Main Coronary Artery Stenting) LE MANS trial. JACC Cardiovasc Interv 2016;9:318-27.
6. Rodriguez A, Bernardi V, Navia J, et al. Argentine Randomized Study: Coronary Angioplasty with Stenting versus Coronary Bypass Surgery in patients with Multiple-Vessel Disease (ERACI II): 30-day and one-year follow-up results. ERACI II Investigators. J Am Coll Cardiol 2001;37:51-8.
7. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. N Engl J Med 2001;344:1117-24.
8. Hueb W, Soares PR, Gersh BJ, et al. The medicine, angioplasty, or surgery study (MASS-II): a randomized, controlled clinical trial of three therapeutic strategies for multivessel coronary artery disease: one-year results. J Am Coll Cardiol 2004;43:1743-51.
9. SoS Investigators. Coronary artery bypass surgery versus percutaneous coronary intervention with stent implantation in patients with multivessel coronary artery disease (the Stent or Surgery trial): a randomised controlled trial. Lancet 2002;360:965-70.
10. Serruys PW, Morice MC, Kappetein AP, et al. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. N Engl J Med 2009;360:961-72.
11. Park SJ, Kim YH, Park DW, et al. Randomized trial of stents versus bypass surgery for left main coronary artery disease. N Engl J Med 2011;364:1718-27.
12. Farkouh ME, Domanski M, Sleeper LA, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med 2012;367:2375-84.
13. Kamalesh M, Sharp TG, Tang XC, et al. Percutaneous coronary intervention versus coronary bypass surgery in United States veterans with diabetes. J Am Coll Cardiol 2013;61:808-16.
14. Park SJ, Ahn JM, Kim YH, et al. Trial of everolimus-eluting stents or bypass surgery for coronary disease. N Engl J Med 2015;372:1204-12.
15. Makikallio T, Holm NR, Lindsay M, et al. Percutaneous coronary angioplasty versus coronary artery bypass grafting in treatment of unprotected left main stenosis (NOBLE): a prospective, randomised, open-label, non-inferiority trial. Lancet 2016;388:2743-52.
16. Stone GW, Sabik JF, Serruys PW, et al. Everolimus-eluting stents or bypass surgery for left main coronary artery disease. N Engl J Med 2016;375:2223-35.
17. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.
18. Head SJ, Kaul S, Mack MJ, et al. The rationale for Heart Team decision-making for patients with stable, complex coronary artery disease. Eur Heart J 2013;34:2510-8.

19. Head SJ, Holmes DR, Jr., Mack MJ, et al. Risk profile and 3-year outcomes from the SYNTAX percutaneous coronary intervention and coronary artery bypass grafting nested registries. JACC Cardiovasc Interv 2012;5:618-25.
20. Farooq V, van Klaveren D, Steyerberg EW, et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. Lancet 2013;381:639-50.
21. Mohr FW, Morice MC, Kappetein AP, et al. Coronary artery bypass graft surgery versus percutaneous coronary intervention in patients with three-vessel disease and left main coronary disease: 5-year follow-up of the randomised, clinical SYNTAX trial. Lancet 2013;381:629-38.
22. Head SJ, Davierwala PM, Serruys PW, et al. Coronary artery bypass grafting vs. percutaneous coronary intervention for patients with three-vessel disease: final five-year follow-up of the SYNTAX trial. Eur Heart J 2014;35:2821-30.
23. Bangalore S, Guo Y, Samadashvili Z, Blecker S, Xu J, Hannan EL. Everolimus-eluting stents or bypass surgery for multivessel coronary disease. N Engl J Med 2015;372:1213-22.
24. Weintraub WS, Grau-Sepulveda MV, Weiss JM, et al. Comparative effectiveness of revascularization strategies. N Engl J Med 2012;366:1467-76.
25. Morice MC, Serruys PW, Kappetein AP, et al. Five-year outcomes in patients with left main disease treated with either percutaneous coronary intervention or coronary artery bypass grafting in the synergy between percutaneous coronary intervention with taxus and cardiac surgery trial. Circulation 2014;129:2388-94.
26. Christiansen EH, Makikallio T, Holm NR. Everolimus-eluting stents or bypass surgery for left main coronary disease. N Engl J Med 2017;376:1088-9.

TABLES

Table 1. Baseline, procedural, and discharge data of randomized cohorts.

Characteristic	PCI (n=5753)	CABG (n=5765)	P value
Age	63·6 ± 9·8 (5753)	63·7 ± 9·9 (5765)	0·72
Female sex	23·9% (1373/5753)	23·8% (1371/5765)	0·91
BMI >30 kg/m^2	28·1% (1548/5506)	28·3% (1558/5511)	0·82
Smoking current	22·3% (1274/5701)	22·3% (1273/5703)	0·97
Diabetes	38·5% (2215/5753)	37·7% (2171/5765)	0·35
Insulin treated	12·9% (545/4234)	11·9% (504/4245)	0·16
Hypertension	67·6% (3880/5739)	68·1% (3913/5748)	0·59
Hypercholesterolemia	69·5% (3982/5726)	67·3% (3862/5735)	0·0112
Peripheral vascular disease	8·2% (424/5158)	8·5% (440/5164)	0·58
Carotid artery disease	7·8% (161/2072)	8·1% (168/2074)	0·69
Previous TIA or CVA	5·4% (218/4052)	6·2% (253/4054)	0·0977
Previous MI	28·0% (1438/5138)	27·5% (1417/5156)	0·57
Moderate LVEF (30-49%)	15·2% (807/5303)	14·3% (779/5430)	0·20
Poor LVEF (<30%)	0·9% (49/5303)	1·0 (54/5430)	0·71
Unstable angina pectoris	34·6% (1786/5158)	34·2% (1767/5160)	0·68
Three-vessel disease	58·6% (2460/4201)	61·8% (2594/4197)	0·0627
Left main disease	38·8% (2233/5753)	38·9% (2245/5765)	0·89
SYNTAX score	26·0 ± 9·3 (4081)	26·0 ± 9·8 (4057)	0·91
0-22	37·6 (1533/4081)	39·1 (1585/4057)	0·16
23-32	41·1 (1677/4081)	38·1 (1545/4057)	0·0053
≥33	21·3 (871/4081)	22·8 (927/4057)	0·10
PCI – stents*	100% (5610/5610)	-	-
BMS	26·6% (1490/5610)	-	-
DES	73·4% (4120/5610)	-	-
First-generation DES	39·2% (2199/5610)	-	-
Newer-generation DES	34·2% (1920/5610)	-	-
PCI – number of stents	3·1 ± 2·0 (4935)	-	-
CABG – LIMA use	-	96·2% (4574/4753)	-
CABG – BIMA use	-	18·7% (771/4122)	-
CABG – off-pump	-	27·5% (1085/3945)	-
Aspirin at discharge	97·3% (4487/4612)	95·5% (3814/3994)	<0·0001
Thienopyridine at discharge	96·7% (4479/4630)	45·1% (1815/4026)	<0·0001
DAPT at discharge	95·1% (4384/4612)	44·0% (1759/3994)	<0·0001
Statin at discharge	88·1% (3052/3464)	84·0% (2843/3384)	<0.0001
Beta-blocker at discharge	79·1% (2741/3464)	76·2% (2557/3356)	0.0040

ACEi or ARB at discharge	63·7% (2205/3464)	46·9% (1588/3383)	<0·0001
Calcium-channel blocker at discharge	27·7% (959/3463)	21·8% (736/3383)	<0·0001

*Data only for patients who were randomized to PCI and indeed underwent PCI. The type of DES used was not available for one patient enrolled in the VA CARDS trial.

Values are present as mean ± SD or n/N (%). PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; ACEi, angiotensin-converting enzyme inhibitor; ARD, angiotensin II receptor blocker; BMI, body mass index; BMS = bare-metal stent; TIA, transitory ischemic attack; CVA, cerebrovascular attack; MI, myocardial infarction; LVEF, left ventricular ejection fraction; DES, drug-eluting stents; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery; DAPT, dual antiplatelet therapy.

Table 2. Five-year mortality outcomes in all patients and according to multivessel or left main disease

	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**
Overall mortality	9·2% (437/5765)	11·2% (539/5753)	HR=1·20 [1·06-1·37] P=0·0038	ϑ=0·39 P<0·0001	8·9% (279/3520)	11·5% (365/3520)	HR=1·28 [1·09-1·49] P=0·0019	ϑ=0·40 P<0·0001	10·5% (158/2245)	10·7% (174/2233)	HR=1·07 [0·87-1·33] P=0·52	ϑ=0·0845 P<0·0001
Diabetes			P_{int} 0·008				P_{int} 0·0453				P_{int} 0·13	
Yes	10·7% (185/2171)	15·7% (278/2215)	HR=1·44 [1·20-1·74] P=0·0001	ϑ=0·11 P<0·0001	10·0% (134/1622)	15·5% (207/1644)	HR=1·48 [1·19-1·84] P=0·0004	ϑ=0·16 P<0·0001	13·4% (51/549)	16·5% (71/571)	HR=1·34 [0·93-1·91] P=0·11	ϑ=0·0536 P=0·0177
No	8·4% (252/3594)	8·7% (261/3538)	HR=1·02 [0·86-1·21] P=0·81	ϑ=0·0884 P<0·0001	8·0% (145/1898)	8·7% (158/1876)	HR=1·08 [0·86-1·36] P=0·49	ϑ=0·0992 P<0·0001	9·6% (107/1696)	8·8% (103/1662)	HR=0·94 [0·72-1·23] P=0·65	ϑ=0·0603 P=0·0027
SYNTAX score			P_{int} 0·21				P_{int} 0·32				P_{int} 0·38	
0-22	8·1% (100/1585)	8·8% (105/1533)	HR=1.02 [0.77-1.34] P=0.91	ϑ=0·0459 P=0·0092	8·4% (51/691)	10·5% (60/690)	HR=1·11 [0·77-1·62] P=0·57	ϑ=0·0523 P=0·0131	8·3% (49/894)	8·1% (45/843)	HR=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)	HR=1.20 [0.94-1.51] P=0.14	ϑ=0·0656 P=0·0031	9·5% (59/775)	14·0% (96/824)	HR=1·50 [1·09-2·08] P=0·0129	0·0621 P=0·0066	12·7% (63/770)	10·8% (67/853)	HR=0·92 [0·65-1·30] P=0·65	ϑ=0·0626 P=0·0093
≥33	11·6% (83/9276)	16·5% (117/871)	HR=1.52 [1.15-2.02] P=0.0029	ϑ=0·0189 P=0·0609	10·9% (38/423)	17·7% (61/397)	HR=1·70 [1·13-2·55] P=0·0094	ϑ=0·0252 P=0·0504	12·4% (45/504)	15·0% (56/474)	HR=1·39 [0·94-2·06] P=0·1006	ϑ=0·0217 P=0·0652

Percentages are from unadjusted Kaplan-Meier estimates; the number of events is provided between brackets. Hazard ratios with confidence intervals and p-values are from random-effects Cox proportional hazards models stratified by trial. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention; P_{int}= P for interaction

Table 3. Differences in patient characteristics among BMS and DES trials.

Characteristic	BMS (n=3051)	All DES (n=8467)	P-Value	First-generation DES (n=4300)	Newer-generation DES (n=3969)	P-Value
Age	60·8 ± 10·1 (3051)	64·7 ± 9·6 (8467)	<0·0001	63·8 ± 9·5 (4300)	65·7 ± 9·6 (3969)	<0·0001
Female sex	23·2% (707/3051)	24·1% (2037/8467)	0·32	25·3% (1087/4300)	23·9% (948/3969)	0·14
BMI >30 kg/m^2	22·3% (578/2593)	30·0% (8424/2528)	<0·0001	32·4% (1388/4290)	25·6% (1010/3939)	<0·0001
Smoking current	27·5% (843/3049)	20·4% (1704/8355)	<0·0001	19·6% (833/4260)	21·2% (827/3900)	0·0642
Diabetes	17·8% (543/3051)	45·4% (3843/8467)	<0·0001	59·2% (2544/4300)	27·7% (1101/3969)	<0·0001
Insulin treated	3·4% (48/1396)	14·1% (1001/7083)	<0·0001	19·0% (816/4299)	6·6% (185/2784)	<0·0001
Hypertension	51·1% (1558/3051)	73·9% (6235/8436)	<0·0001	76·5% (3278/4287)	70·1% (2770/3954)	<0·0001
Hypercholesterolemia	58·3% (1776/3047)	72·1% (6068/8414)	<0·0001	75·4% (3230/4285)	69·2% (2727/3938)	<0·0001
Peripheral vascular disease	7·6% (233)	8·7% (631/7271)	0·0813	9·2% (396/4300)	7·5% (208/2776)	0·0116
Carotid artery disease	5·6% (25/450)	8·2% (304/3696)	0·0479	8·2% (148/1800)	8·2% (156/1896)	0·99
Previous TIA or CVA	3·3% (47/1438)	6·4% (424/6668)	<0·0001	5·8% (215/3688)	6·8% (189/2782)	0·11
Previous MI	42·1% (1285/1766)	21·7% (1570/7243)	<0·0001	25·8% (1105/4280)	13·9% (384/2768)	<0·0001
Moderate LVEF (30-49%)	16·1% (442/2746)	14·3% (1144/7987)	0.0239	15·7% (668/4242)	11·9% (425/3568)	<0·0001
Poor LVEF (<30%)	0·1% (4/2746)	1·2% (99/7987)	<0·0001	1·6% (66/4242)	0·6% (21/3568)	<0·0001
Unstable angina pectoris	41·2% (850/2063)	32·7% (2703/8255)	<0·0001	31·8% (1369/4287)	33·7% (1334/3955)	0·0672
Three-vessel disease	41·9% (1280/3051)	70·6% (3774/5348)	<0·0001	69·4% (2976/4287)	77·2% (679/3969)	<0·0001
Left main disease	1·0% (29/3051)	52·5% (4449/8467)	<0·0001	30·5% (1313/4300)	79·0% (3136/3969)	<0·0001
Mean follow-up (years)	4·7 ± 1·0 (2795)	3·5 ± 1·4 (7726)	<0·0001	4·0 ± 1·4 (3830)	3·1 ± 1·2 (3723)	<0·0001

BMI, body mass index; BMS, bare-metal stents; TIA, transitory ischemic attack; CVA, cerebrovascular attack; MI, myocardial infarction; LVEF, left ventricular ejection fraction; DES, drug-eluting stents

FIGURE LEGENDS

Figure 1. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention during 5-year of follow-up. Kaplan-Meier estimates are from the overall pooled patient population. The hazard ratio (HR) with confidence intervals is derived from a Cox proportional hazards random-effects model stratified by trial. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

Figure 2. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention during 5-year follow-up in subgroup analyses according to baseline and procedural characteristics. Kaplan-Meier estimates are from the overall pooled patient population. Hazard ratios (HRs) with confidence intervals (CIs) are derived from Cox proportional hazards random-effects models stratified by trial. HR, hazard ratio; CI, confidence interval.

Figure 3. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention during 5-year follow-up of patients with and without diabetes mellitus (A and B), and with left main or multivessel disease (C and D). Kaplan-Meier estimates are from the overall pooled patient population. Hazard ratios (HRs) with confidence intervals (CIs) are derived from Cox proportional hazards random-effects models stratified by trial. CABG, coronary artery bypass grafting; DM, diabetes mellitus; LM, left main disease; MVD, multivessel disease; PCI, percutaneous coronary intervention.

FIGURES

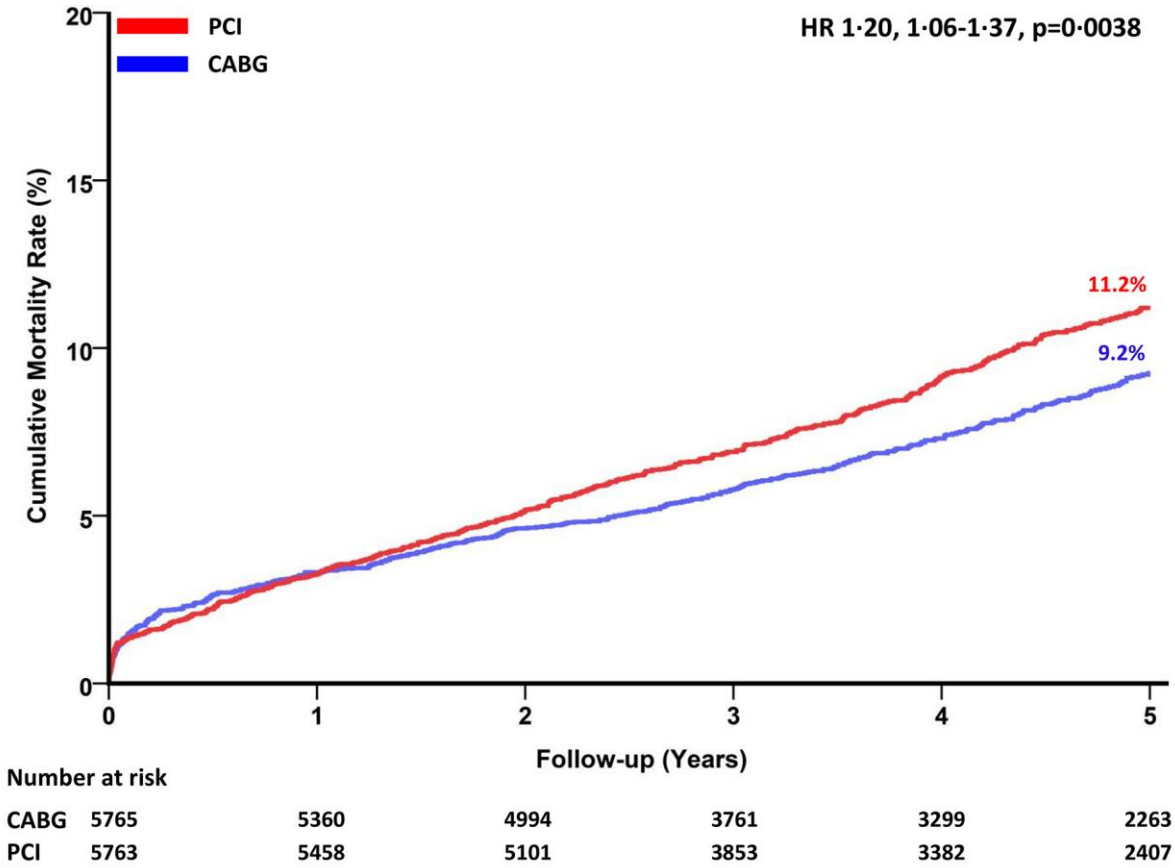
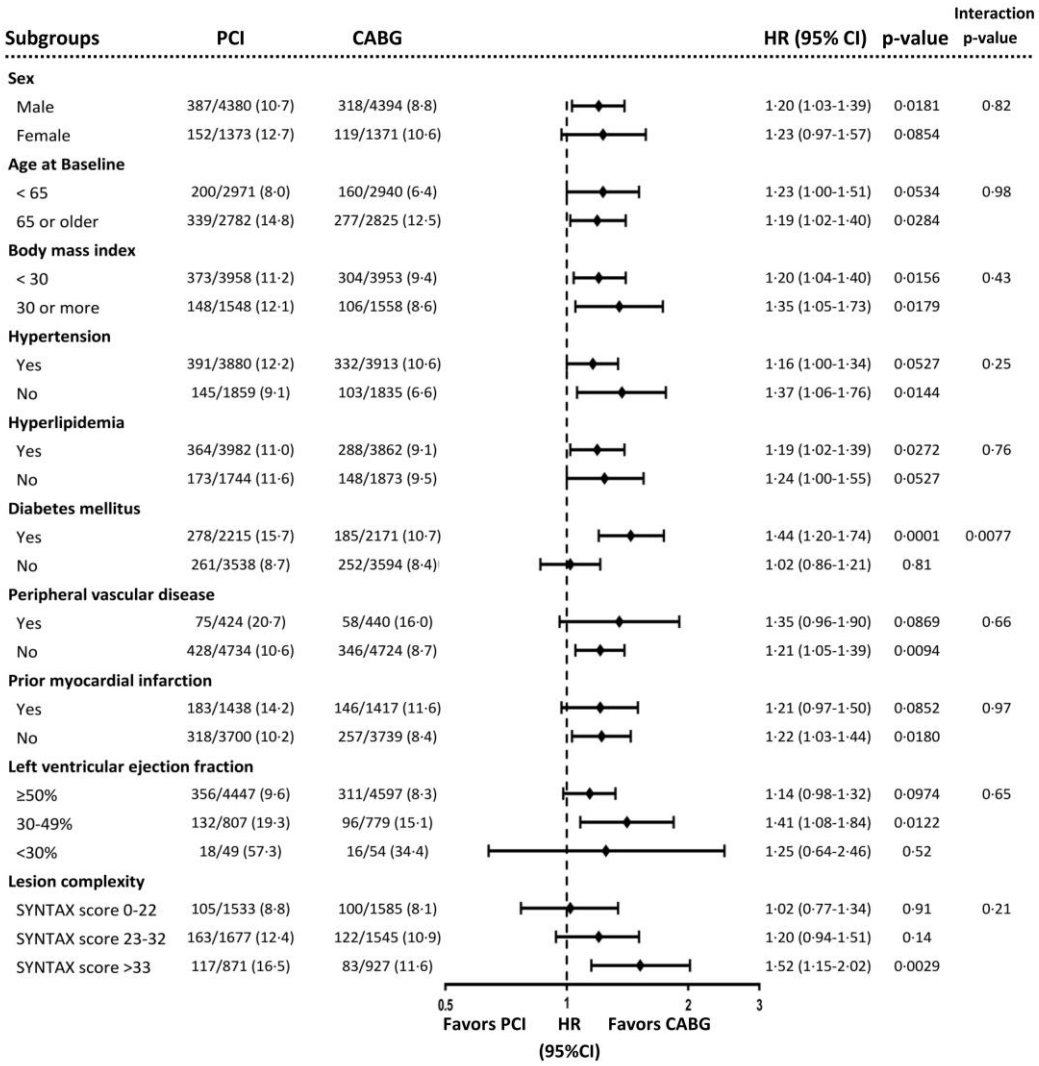


Figure 1. Mortality after coronary artery bypass grafting versus percutaneous coronary intervention during 5-year of follow-up. Kaplan-Meier estimates are from the overall pooled patient population. The hazard ratio (HR) with confidence intervals is derived from a Cox proportional hazards random-effects model stratified by trial. CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.



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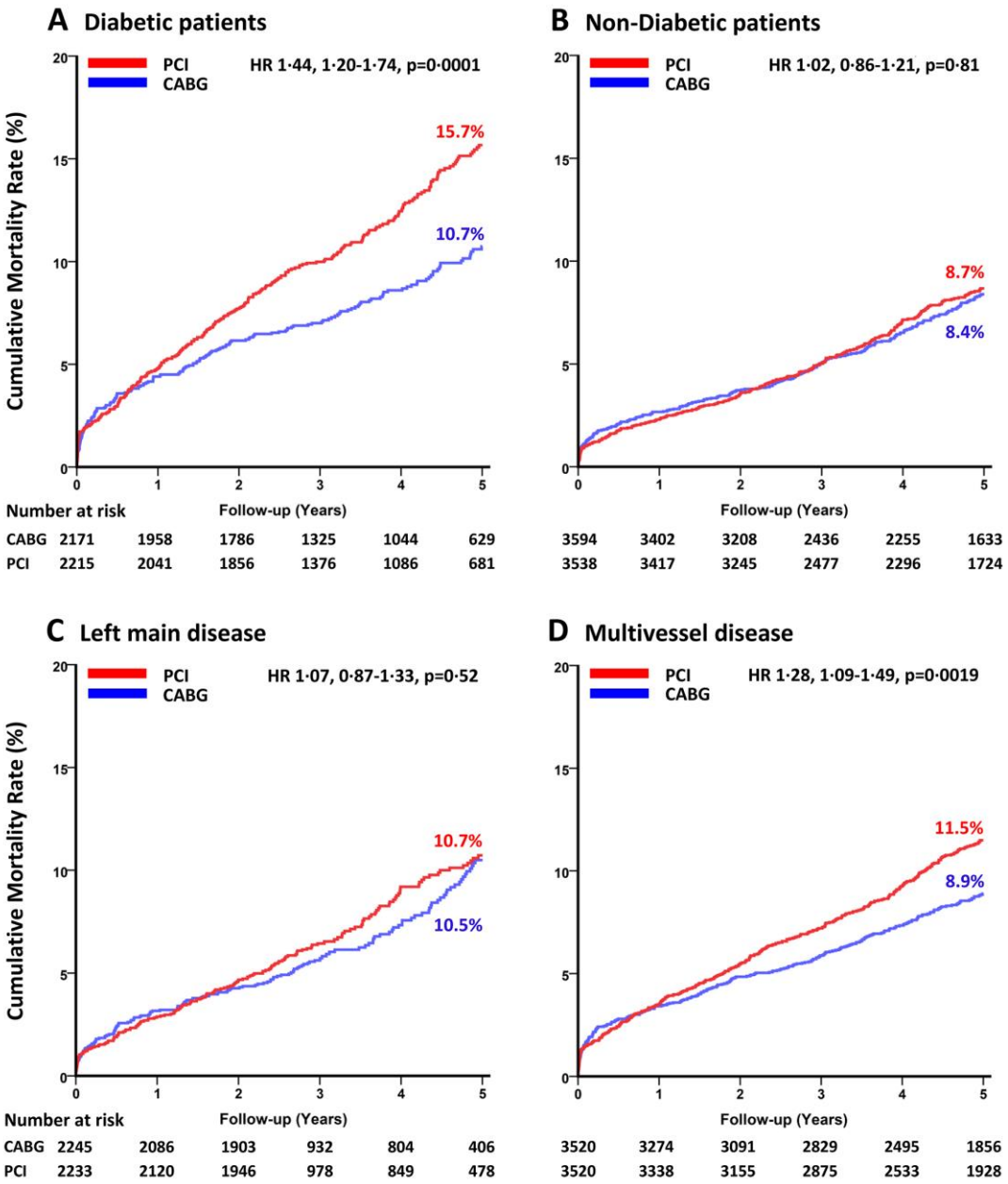

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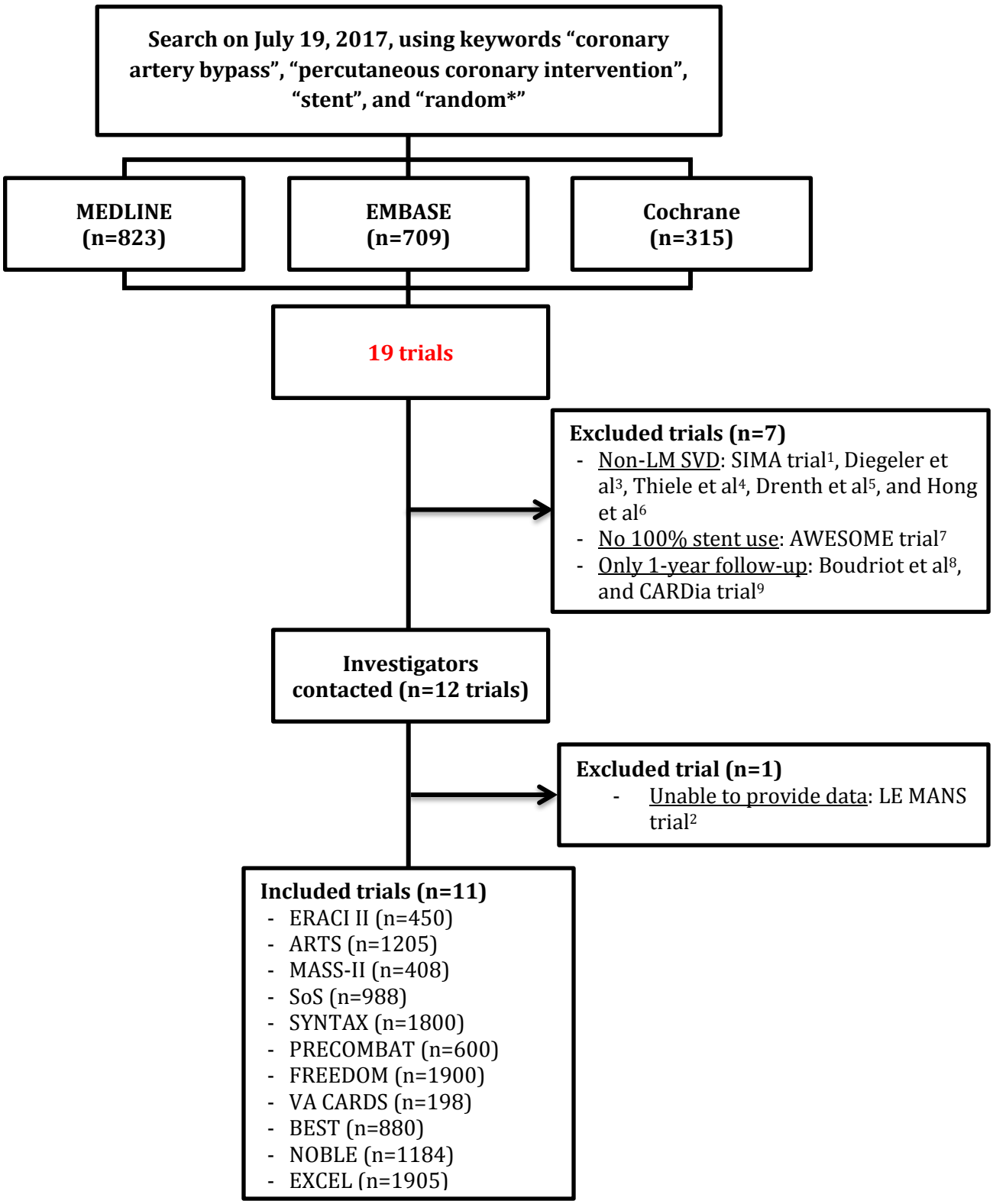
APPENDICES

APPENDIX 1. Study selection flow-chart



APPENDIX 2. Baseline and procedural characteristics in individual trials.

Characteristic	ERACI II (n=450)	ARTS (n=1205)	MASS-II (n=408)	SoS (n=988)	SYNTAX (n=1800)	PRECOMBAT (n=600)	FREEDOM (n=1900)	VA CARDS (n=198)	BEST (n=880)	NOBLE (n=1184)	EXCEL (n=1905)
Patient inclusion	1996-1998	1997-1998	1995-2000	1996-1999	2005-2007	2004-2009	2005-2010	2006-2010	2008-2013	2008-2015	2010-2014
Study location	Argentina	Europe, South America, Australasia	Brazil	Europe, Canada	Europe, US	Korea	North America, South America, Europe, India, Australasia	US	Asia	Europe	North America, South America, Europe, India, Australasia
Heart team composition	"Clinical cardiologist, interventionalist, cardiac surgeon"	"Interventional cardiologist and cardiac surgeon"	"Inter-ventionalist and surgeon"	"Inter-ventionalist and surgeon"	"Interventional cardiologist and cardiac surgeon"	"Physicians and surgeons"	Not explicitly reported	"Inter-ventional cardiologist and cardio-thoracic surgeon"	"Physicians and surgeons"	"Inter-ventional cardiologist and cardiac surgeon"	"Inter-ventional cardiologist and cardiac surgeon"
Age	60·7 ± 10·2	60·6 ± 10·8	59·8 ± 9·0	61·4 ± 9·3	65·1 ± 9·7	62·2 ± 9·7	62·1 ± 9·1	62·4 ± 7·2	64·5 ± 9·4	66·2 ± 9·7	65·9 ± 9·6
Female sex	21% (93/450)	23% (283/1205)	31% (125/408)	21% (206/988)	22% (402/1800)	24% (141/600)	29% (544/1900)	1% (2/198)	29% (251/880)	22% (256/1184)	23% (441/1905)
BMI >30 kg/m^2	NA	22% (260/1203)	25% (100/408)	22% (220/982)	32% (579/1799)	3% (20/595)	42% (789/1896)	68% (132/195)	4% (35/880)	29% (336/1155)	34% (639/1904)
Smoking current	52% (233/540)	27% (323/1203)	33% (134/408)	15% (149/988)	21% (363/1760)	29% (172/600)	16% (298/1900)	25% (48/195)	20% (177/880)	20% (235/1170)	22% (415/1850)
Diabetes	17% (78/450)	17% (208/1205)	28% (115/408)	14% (142/988)	25% (452/1800)	32% (192/600)	100% (1900/1900)	100% (198/198)	41% (363/880)	15% (184/1184)	29% (554/1905)
Insulin treated	NA	NA	5% (20/408)	3% (28/988)	10% (182/1800)	3% (19/600)	32% (615/1900)	NA	4% (38/880)	NA	8% (147/1905)
Hypertension	71% (318/450)	45% (540/1205)	62% (253/408)	45% (447/988)	75% (1349/1787)	53% (317/600)	85% (1612/1900)	96% (187/195)	67% (591/880)	66% (775/1182)	74% (1404/1892)
Hypercholesterolemia	61% (275/450)	58% (694/1201)	73% (298/408)	52% (509/988)	78% (1391/1785)	41% (247/600)	84% (1592/1900)	58% (111/191)	52% (461/880)	80% (946/1183)	70% (1320/1875)
Peripheral vascular disease	23% (103/450)	5% (64/1205)	0% (0/408)	7% (66/988)	10% (177/1800)	4% (22/600)	10% (197/1900)	14% (27/195)	3% (27/880)	NA	9% (181/1896)
Carotid artery	6% (25/450)	NA	NA	NA	8%	NA	NA	NA	NA	NA	8%

disease					(148/1800)						(156/1896)
Previous TIA/stroke	2% (10/450)	NA	NA	4% (37/988)	8% (150/1788)	NA	3% (65/1900)	10% (20/198)	8% (70/879)	NA	6% (119/1903)
Previous MI	28% (126/450)	43% (520/1205)	47% (191/408)	45% (448/988)	33% (585/1780)	6% (33/567)	26% (487/1900)	42% (81/195)	6% (54/880)	NA	17% (330/1888)
Moderate VEF (30-49%)	20% (88/446)	17% (189/1121)	4% (16/408)	19% (149/771)	17% (313/1800)	5% (26/542)	17% (329/1900)	29% (51/177)†	12% (90/744)	12% (120/1020)	12% (215/1804)
Poor LVEF (<30%)	0% (0/446)	0% (0/1121)	0% (0/408)	1% (4/771)	2% (34/1800)	1% (5/542)	1% (27/1900)	7% (12/177)	1% (5/744)	1% (5/1020)	1% (11/1804)
Unstable angina pectoris	92% (412/450)	36% (438/1205)	0% (0/408)	0% (0/988)	29% (513/1800)	45% (272/600)	31% (584/1900)	NA	44% (384/880)	17% (206/1183)	39% (744/1892)
Number of lesions	2·6 ± 0·6	2·8 ± 1·0	2·8 ± 0·8	2·8 ± 1·1	4·0 ± 1·7	3·0 ± 1·0	NA	3·6 ± 1·5	3·4 ± 1·2	1·7 ± 1·0	NA
Three-vessel disease	49% (220/450)	33% (403/1205)	58% (238/408)	42% (419/988)	61% (1095/1800)	51% (308/600)	83.4% (1573/1887)	66% (120/181)	77% (679/880)	NA	NA
Left main disease	5% (21/450)	0.1% (1/1205)	0% (0/408)	1% (7/988)	39% (705/1800)	100% (600/600)	0.4% (8/1900)	0% (0/198)	5% (47/880)	100% (1184/1184)	100% (1905/1905)
SYNTAX score	NA	NA	NA	NA	28·7 ± 11·4	25·1 ± 10·0	26·2 ± 8·6	NA	24·8 ± 7·7	22·4 ± 7·3	26·5 ± 9·3
PCI – DES used	0% (0/222)	0% (0/593)	0% (0/205)	0% (0/488)	100% (885/885)	100% (276/276)	100% (939/939)	99% (92/93)	100% (413/413)	100% (580/580)	100% (935/935)
DES type	-	-	-	-	Paclitaxel	Sirolimus	Paclitaxel and Sirolimus	Mixed paclitaxel, sirolimus, everolimus, zotarolimus	Everolimus	Majority Biolimus	Everolimus
PCI – number of stents	1.4 ± 0.6	NA	1.2 ± 0.9	2.6 ± 1.4	4.6 ± 2.3	2.7 ± 1.4	4.1 ± 1.9	NA	3.4 ± 1.4	2.2 ± 1.2	2.4 ± 1.5
CABG – LIMA use	95% (198/209)	NA	95% (188/198)	93% (450/485)	97% (827/854)	94% (233/248)	94% (843/893)	NA	100% (382/382)	96% (545/565)	99% (908/923)
CABG – BIMA use	0.5% (1/209)	NA	32% (65/203)	10% (50/485)	28% (236/854)	NA	12% (110/893)	NA	NA	8% (44/549)	29% (265/923)
CABG – off-pump	NA	NA	NA	NA	15% (128/854)	63% (155/248)	18% (165/893)	32% (26/82)	66% (252/382)	16% (88/564)	29% (271/923)
Complete revascularization	68% (303/448)	82% (992/1205)	57% (224/408)	70% (693/988)	60% (1043/1741)	69% (416/600)	90% (1701/1900)	NA	61% (518/855)	94% (543/577)*	NA
Aspirin at discharge	100% (450/450)	NA	98% (391/397)	NA	92% (1633/1766)	99% (593/600)	98% (1826/1867)	98% (172/176)	97% (852/880)	93% (539/580)*	98% (1823/1867)

Thienopyridine at discharge	53% (238/450)	NA	48% (194/408)	NA	59% (1037/1766)	94% (565/600)	62% (1158/1867)	55% (96/176)	93% (818/880)	97% (566/580)*	66% (1227/1867)
DAPT at discharge	53% (238/450)	NA	47% (187/397)	NA	56% (987/1766)	93% (560/600)	81% (1513/1867)	54% (94/176)	92% (806/880)	92% (532/580)*	65% (1204/1867)
Statin at discharge	NA	NA	NA	NA	80% (1425/1766)	73% (431/592)	88% (1566/1770)	NA	83% (733/880)	NA	95% (1740/1840)
Beta-blocker at discharge	NA	NA	NA	NA	80% (1412/1766)	51% (303/592)	83% (1477/1770)	NA	56% (489/880)	NA	89% (1617/1812)
ACEI or ARB at discharge	NA	NA	NA	NA	59% (1042/1766)	33% (198/592)	75% (1334/1770)	NA	35% (307/880)	NA	50% (912/1839)
Calcium-channel blocker at discharge	NA	NA	NA	NA	22% (391/1766)	54% (320/592)	23% (405/1770)	NA	52% (459/880)	NA	7% (120/1838)
Mean follow-up (years)	4·7 ± 1·1	4·8 ± 0·9	4·5 ± 1·3	4·7 ± 0·9	4·4 ± 1·4	4·7 ± 1·0	3·5 ± 1·4	1·4 ± 0·9	4·0 ± 1·3	3·2 ± 1·5	2·6 ± 0·7

*Data are available only for the PCI group.

†In the VA CARDS trial, the cut-off for a moderate LVEF was 35-55%.

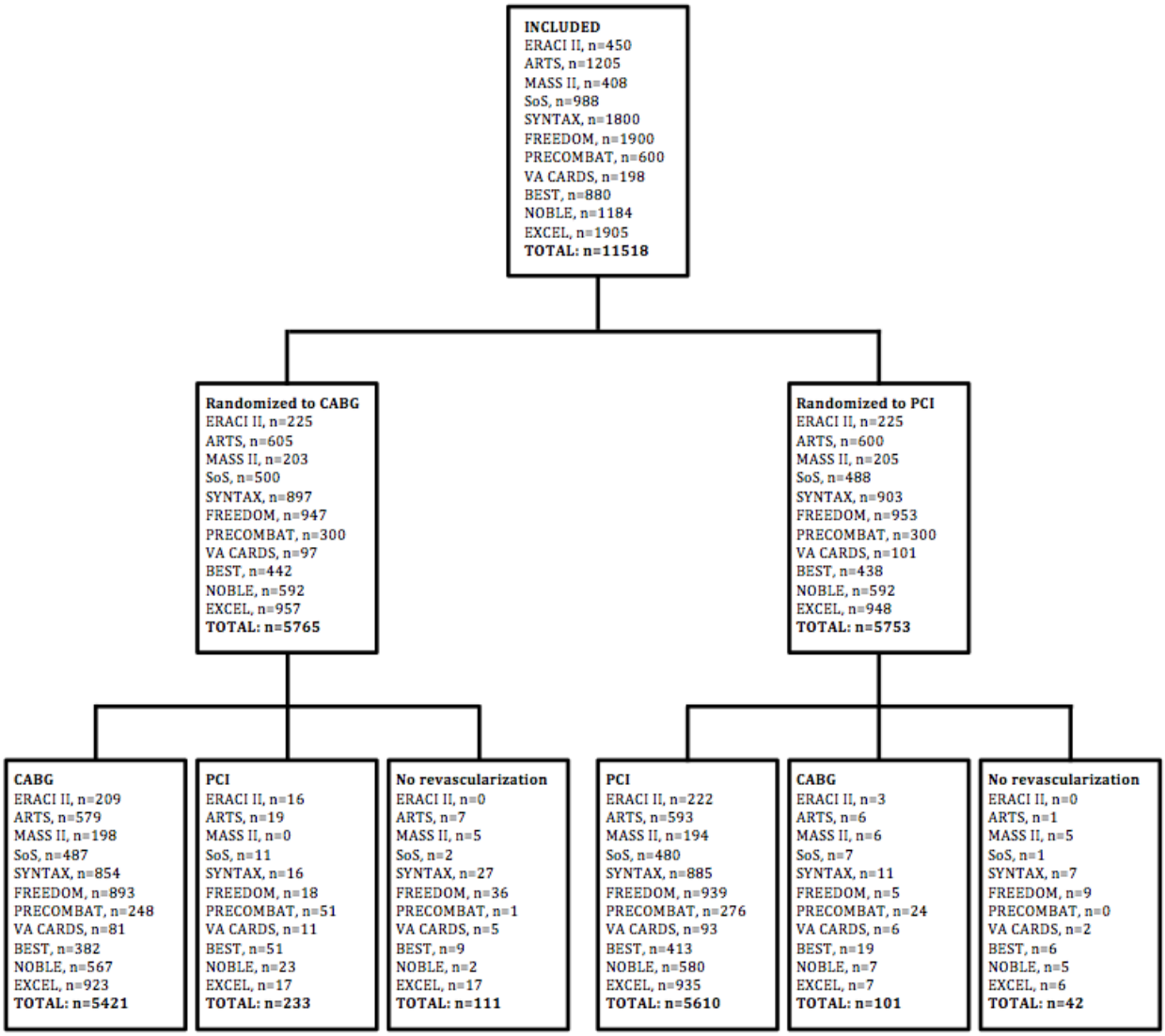
Values are present as mean ± SD or n/N (%). NA, not available; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; BMI, body mass index; TIA, transitory ischemic attack; CVA, cerebrovascular attack; MI, myocardial infarction; LVEF, left ventricular ejection fraction; DES, drug-eluting stents; LIMA, left internal mammary artery; BIMA, bilateral internal mammary artery; DAPT, dual antiplatelet therapy

APPENDIX 3. Assessment of risk of bias in individual trials.

Trial	Random sequence generation	Allocation concealment	Blinding patients and personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other Bias
ERACI II	+	-	-	+	+	+	+
ARTS	?	-	-	+	+	+	+
MASS-II	?	-	-	+	+	+	+
SoS	+	-	-	+	+	+	+
SYNTAX	+	-	-	+	-	+	+
PRECOMBAT	+	-	-	+	+	+	-
FREEDOM	+	-	-	+	+	+	+
VA CARDS	+	-	-	+	+	+	-
BEST	+	-	-	+	+	+	-
NOBLE	+	-	-	+	+	+	+
EXCEL	+	-	-	+	+	+	+

The assessment of "Random sequence generation" was rated "?" for the ARTS and MASS-II trials because it was not specified exactly how randomization took place. The assessment of "Allocation concealment" was rated standard as "-" for all trials because patients had to be informed on the allocated procedure, since these trials evaluate interventional procedures. The assessment of "Blinding of patients and personnel" was rated standard as "-" for all trials because the two interventional procedures evaluated are inherently different and patients cannot be blinded. The assessment of "Blinding of outcome assessment" was rated standard as "+" for all trials as no bias can be introduced for the endpoint of all-cause mortality, and thus blinding is irrelevant; yet still a clinical events committee reviewed all events. The assessment of "Incomplete outcome data" was "-" for the SYNTAX trial because >10% of patients after CABG were lost to follow-up, while this rate was only 3.5% after PCI. The assessment of "Selective reporting" was rated "+" for all trials because all trials reported all-cause mortality. The assessment of "Other bias" was rated as "-" in the RECOMBAT, VA CARDS, and BEST trials because a relatively high percentage (>10%) of patients did not receive the allocated treatment because of cross over or no interventional treatment.

APPENDIX 4. Information on randomization and actual treatments performed.



APPENDIX 5. Time-dependent models of PCI versus CABG

Patient group		First hazard		Second hazard		Frailty term (ϑ)	P for heterogeneity
		Time interval	HR [95% CI]	Time interval	HR [95% CI]		
Overall	**All**	0-365 days	0·97 [0·80-1·19]	365-1825 days	1·38 [1·17-1·62]	0·39	<0·0001
	Diabetes	0-280 days	1·05 [0·78-1·42]	280-1825 days	1·76 [1·38-2·24]	0·11	<0·0001
	No diabetes	0-280 days	0·84 [0·62-1·15]	280-1825 days	1·12 [0·90-1·37]	0·0880	<0·0001
	SYNTAX score 0-22	0-470 days	0·63 [0·41-0·99]	470-1825 days	1·40 [0·97-2·01]	0·0454	0·0094
	SYNTAX score 23-32	0-470 days	1·03 [0·72-1·46]	280-1825 days	1·36 [0·99-1.87]	0·0657	0·0031
	SYNTAX score ≥33	0-470 days	1·83 [1·18-2·82]	280-1825 days	1·34 [0·93-1·95]	0·0191	0·0602
	Bare-metal stent	0-730 days	0·90 [0·64-1·27]	730-1825 days	1·22 [0·86-1·73]	0·16	<0·0001
	Drug-eluting stent	0-500 days	1·08 [0·87-1·34]	500-1825 days	1·45 [1·18-1·77]	0·36	<0·0001
	First-generation drug-eluting stent	0-730 days	1·12 [0·87-1·45]	730-1825 days	1·31 [1·01-1·73]	0·23	<0·0001
	Newer-generation drug-eluting stent	0-180 days	0·68 [0·43-1·10]	180-1825 days	1·65 [1·21-2·25]	0·13	0·0020
MVD	**All**	0-280 days	0·99 [0·76-1·29]	280-1825 days	1·46 [1·20-1·77]	0·40	<0·0001

	Diabetes	0-280 days	1·11 [0·78-1·58]	280-1825 days	1·77 [1·34-2·34]	0·16	<0·0001
	No diabetes	0-370 days	0·94 [0·64-1·40]	370-1825 days	1·16 [0·88-1·53]	0·090	<0·0001
	SYNTAX score 0-22	0-600 days	0·65 [0·37-1·14]	600-1825 days	1·78 [1·05-3·01]	0·0935	0·0140
	SYNTAX score 23-32	0-600 days	1·43 [0·91-2·24]	600-1825 days	1·60 [1·00-2·55]	0·0720	0·0065
	SYNTAX score ≥33	0-600 days	1·72 [0·97-3·04]	600-1825 days	1·70 [0·95-3·01]	0·0252	0·0505
LM	**All**	0-730 days	1·09 [0·82-1·44]	730-1825 days	1·06 [0·76-1·48]	0·0845	<0·0001
	Diabetes	0-730 days	1·22 [0·79-1·86]	730-1825 days	1·70 [0·86-3·35]	0·0543	0·0172
	No diabetes	0-730 days	0·98 [0·67-1·43]	730-1825 days	0·90 [0·61-1·32]	0·0604	0·0027
	SYNTAX score 0-22	0-570 days	0·68 [0·37-1·25]	570-1825 days	1·12 [0·64-1·94]	<0·0001	0·0001
	SYNTAX score 23-32	0-570 days	0·79 [0·50-1·25]	570-1825 days	1·13 [0·70-1·90]	0·0626	0·0093
	SYNTAX score ≥33	0-570 days	1·70 [0·96-3·02]	570-1825 days	1·16 [0·67-1·99]	0·0222	0·0647
DM	**SYNTAX score 0-22**	0-730 days	0·60 [0·36-0·99]	730-1825 days	2·70 [1·40-5·21]	<0·0001	0·0001
	SYNTAX score 23-32	0-730 days	1·30 [0·90-1·89]	730-1825 days	1·35 [0·78-2·34]	0·0159	0·0713
	SYNTAX score ≥33	0-730 days	1·78 [1·06-2·97]	730-1825 days	1·75 [0·92-3·34]	<0·0001	0·0001

NO DM	**SYNTAX score 0-22**	0-730 days	0·91 [0·52-1·59]	730-1825 days	0·99 [0·55-1·79]	<0·0001	0·0193
	SYNTAX score 23-32	0-730 days	0·90 [0·54-1·48]	730-1825 days	1·19 [0·70-2·03]	0·0807	0·0096
	SYNTAX score ≥33	0-730 days	1·80 [1·00-3·23]	730-1825 days	1·00 [0·58-1·73]	0·0089	0·0884

Results of time-dependent models provide a hazard ratio for a first time interval and a second interval with the duration of this interval being dependent on when the hazard changes, which can be different according to the patient cohort. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio.

APPENDIX 6. Five-year outcomes within groups with and without diabetes according to SYNTAX score tertiles.

	Diabetes				No diabetes			
	PCI (n=1819)	**CABG (n=1782)**	**HR [95% CI] P-value**	**P for interaction**	**PCI (n=2262)**	**CABG (n=2275)**	**HR [95% CI] P-value**	**P for interaction**
SYNTAX score 0-22	13·0% (58/622)	9·8% (53/655)	1·09 [0·75-1·58] P=0·66	P_{int}=0·25	6·6% (47/911)	7·0% (47/930)	0·95 [0·63-1·42] P=0·80	P_{int}=0·66
SYNTAX score 23-32	15·1% (101/814)	12·5% (67/723)	1·32 [0·97-1·79] P=0·0817		9·9% (62/863)	9·4% (55/822)	1·03 [0·71-1·48] P=0·88	
SYNTAX score ≥33	20·0% (63/383)	12·3% (38/404)	1·77 [1·18-2·64] P=0·0056		13·6% (54/488)	11·1% (45/523)	1·32 [0·89-1·96] P=0·16	

Kaplan-Meier estimates are from the overall pooled patient population. Hazard ratios (HRs) with confidence intervals (CIs) are derived from Cox proportional hazards random-effects models stratified by trial.

APPENDIX 7. Supplementary references in the appendix.

1. Goy JJ, Kaufmann U, Goy-Eggenberger D, et al. A prospective randomized trial comparing stenting to internal mammary artery grafting for proximal, isolated de novo left anterior coronary artery stenosis: the SIMA trial. Stenting vs Internal Mammary Artery. Mayo Clin Proc 2000;75:1116-23.

2. Buszman PE, Kiesz SR, Bochenek A, et al. Acute and late outcomes of unprotected left main stenting in comparison with surgical revascularization. J Am Coll Cardiol 2008;51:538-45.

3. Diegeler A, Thiele H, Falk V, et al. Comparison of stenting with minimally invasive bypass surgery for stenosis of the left anterior descending coronary artery. N Engl J Med 2002;347:561-6.

4. Thiele H, Neumann-Schniedewind P, Jacobs S, et al. Randomized comparison of minimally invasive direct coronary artery bypass surgery versus sirolimus-eluting stenting in isolated proximal left anterior descending coronary artery stenosis. J Am Coll Cardiol 2009;53:2324-31.

5. Drenth DJ, Winter JB, Veeger NJ, et al. Minimally invasive coronary artery bypass grafting versus percutaneous transluminal coronary angioplasty with stenting in isolated high-grade stenosis of the proximal left anterior descending coronary artery: six months' angiographic and clinical follow-up of a prospective randomized study. J Thorac Cardiovasc Surg 2002;124:130-5.

6. Hong SJ, Lim DS, Seo HS, et al. Percutaneous coronary intervention with drug-eluting stent implantation vs. minimally invasive direct coronary artery bypass (MIDCAB) in patients with left anterior descending coronary artery stenosis. Catheter Cardiovasc Interv 2005;64:75-81.

7. Morrison DA, Sethi G, Sacks J, et al. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial

ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. Investigators of the Department of Veterans Affairs Cooperative Study #385, the Angina With Extremely Serious Operative Mortality Evaluation (AWESOME). J Am Coll Cardiol 2001;38:143-9.

8. Boudriot E, Thiele H, Walther T, et al. Randomized comparison of percutaneous coronary intervention with sirolimus-eluting stents versus coronary artery bypass grafting in unprotected left main stem stenosis. J Am Coll Cardiol 2011;57:538-45.

9. Kapur A, Hall RJ, Malik IS, et al. Randomized comparison of percutaneous coronary intervention with coronary artery bypass grafting in diabetic patients. 1-year results of the CARDia (Coronary Artery Revascularization in Diabetes) trial. J Am Coll Cardiol 2010;55:432-40.