JAMA Internal Medicine | Original Investigation

# Overall and Cause-Specific Mortality in Randomized Clinical Trials Comparing Percutaneous Interventions With Coronary Bypass Surgery
## A Meta-analysis

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**IMPORTANCE** Mortality is a common outcome in trials comparing percutaneous coronary intervention (PCI) with coronary artery bypass grafting (CABG). Controversy exists regarding whether all-cause mortality or cardiac mortality is preferred as a study end point, because noncardiac mortality should be unrelated to the treatment.

**OBJECTIVE** To evaluate the difference in all-cause and cause-specific mortality in randomized clinical trials (RCTs) comparing PCI with CABG for the treatment of patients with coronary artery disease.

**DATA SOURCES** MEDLINE (1946 to the present), Embase (1974 to the present), and the Cochrane Library (1992 to the present) databases were searched on November 24, 2019. Reference lists of included articles were also searched, and additional studies were included if appropriate.

**STUDY SELECTION** Articles were considered for inclusion if they were in English, were RCTs comparing PCI with drug-eluting or bare-metal stents and CABG for the treatment of coronary artery disease, and reported mortality and/or cause-specific mortality. Trials of PCI involving angioplasty without stenting were excluded. For each included trial, the publication with the longest follow-up duration for each outcome was selected.

**DATA EXTRACTION AND SYNTHESIS** For data extraction, all studies were reviewed by 2 independent investigators, and disagreements were resolved by a third investigator in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline. Data were pooled using fixed- and random-effects models.

**MAIN OUTCOMES AND MEASURES** The primary outcomes were all-cause and cause-specific (cardiac vs noncardiac) mortality. Subgroup analyses were performed for PCI trials using drug-eluting vs bare-metal stents and for trials involving patients with left main disease.

**RESULTS** Twenty-three unique trials were included involving 13 620 unique patients (6829 undergoing PCI and 6791 undergoing CABG; men, 39.9%-99.0% of study populations; mean age range, 60.0-71.0 years). The weighted mean (SD) follow-up was 5.3 (3.6) years. Compared with CABG, PCI was associated with a higher rate of all-cause (incidence rate ratio, 1.17; 95% CI, 1.05-1.29) and cardiac (incidence rate ratio, 1.24; 95% CI, 1.05-1.45) mortality but also noncardiac mortality (incidence rate ratio, 1.19; 95% CI, 1.00-1.41).

**CONCLUSIONS AND RELEVANCE** Percutaneous coronary intervention was associated with higher all-cause, cardiac, and noncardiac mortality compared with CABG at 5 years. The significantly higher noncardiac mortality associated with PCI suggests that even noncardiac deaths after PCI may be procedure related and supports the use of all-cause mortality as the end point for myocardial revascularization trials.

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Supplemental content

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During the course of the last 3 decades, several randomized clinical trials (RCTs)[1-5] have compared the results of percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) in patients with stable ischemic heart disease and recent acute coronary syndromes. The individual trials were underpowered to detect differences in mortality, and all used a composite of major adverse cardiac or cardiovascular events as the primary outcome. Although mortality was included in the primary composite outcome of all the trials, some used all-cause mortality and others used cardiac mortality.

The use of all-cause mortality reduces the risk of adjudication bias due to incomplete, skewed, or inadequate supporting evidence,[6] but it has the potential to dilute the treatment effect due to the inclusion of events unrelated to interventions for the coronary circulation.[7] On the other hand, the use of cause-specific mortality reduces the event rate, is subject to bias, and can lead to underpowered comparisons.[8]

The controversy has been ignited by the recent publication of the 5-year results of the Evaluation of XIENCE vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization (EXCEL) trial.[1] In the EXCEL trial at 5 years, PCI was associated with significantly higher all-cause mortality, but the difference between the 2 groups was not observed when considering cardiac mortality alone.[1] To date, no systematic evaluation of cause-specific mortality in PCI vs CABG trials has been published. In this meta-analysis, we evaluate the difference in all-cause and cause-specific mortality in the RCTs that have compared PCI and CABG for the treatment of patients with coronary artery disease.

### Key Points

**Question** What is the difference in all-cause and cause-specific mortality in the randomized clinical trials that have compared percutaneous coronary intervention (PCI) with coronary artery bypass grafting?

**Findings** In a pooled meta-analysis of 23 randomized clinical trials (13 260 unique patients) comparing PCI vs coronary artery bypass grafting, PCI was associated with a significantly higher rate of cardiac mortality, noncardiac mortality, and all-cause mortality.

**Meaning** The significantly higher noncardiac mortality associated with PCI suggests that even noncardiac deaths after PCI may be procedure related and supports the use of all-cause mortality as the end point for myocardial revascularization trials.

## Methods

### Search Strategy

Because no individual patient data are involved in the analysis, there was no need for ethical approval or individual patient consent according to the Weill Cornell Institutional Review Board. A medical librarian (M.D.) performed comprehensive searches to identify all RCTs comparing PCI vs CABG. Searches were run on November 24, 2019, on the following databases: Ovid MEDLINE (1946 to the present), Ovid Embase (1974 to the present), and the Cochrane Library (Wiley; 1992 to the present). The full search strategy for Ovid MEDLINE is available in eTable 1 in the Supplement. This review was registered with the PROSPERO register of systematic reviews (CRD42020165349) and followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.

### Study Selection and Data Extraction

Searches retrieved 4916 results. After deduplication, 2 reviewers (I.H. and M. Rahouma) independently screened a total of 4411 citations. Discrepancies were resolved by a third author (M.G.). Titles and abstracts were reviewed against predefined inclusion and exclusion criteria. Articles were considered for inclusion if they were in English and were RCTs comparing PCI with bare-metal or drug-eluting stents and CABG for the treatment of coronary artery disease and reported mortality and/or cause-specific mortality. Trials of PCI involving angioplasty without stenting were excluded. For each included trial, the publication with the longest follow-up duration for each outcome was selected. Animal studies, case reports, conference presentations, editorials, expert opinions, and observational studies were excluded.

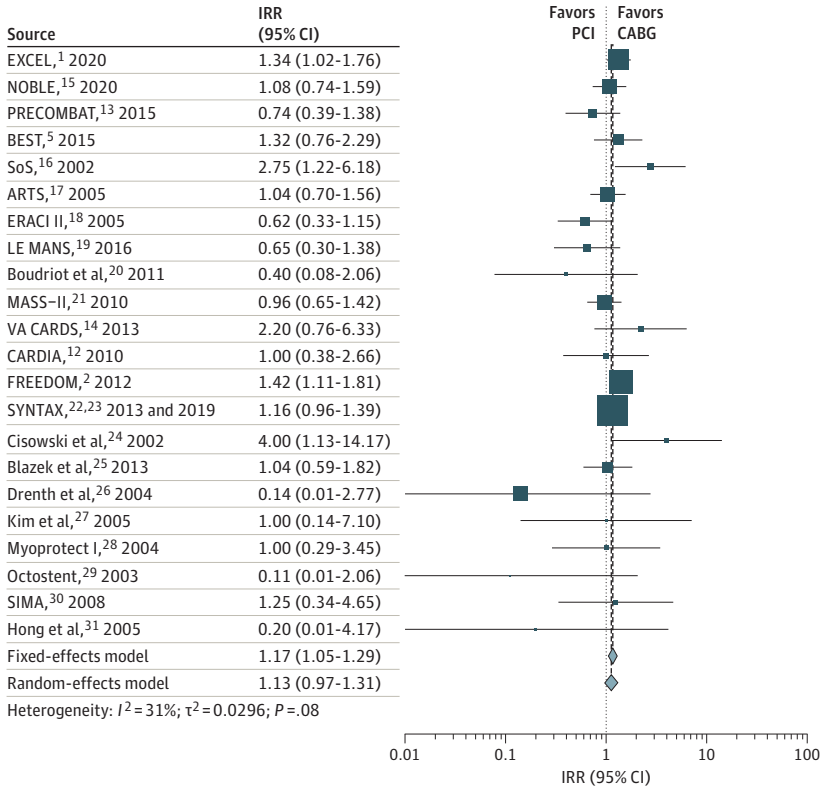
The full text was pulled for the selected studies for a second round of eligibility screening. Reference lists of articles were also searched to identify other relevant trials.

Two investigators (I.H. and M. Rahouma) performed data extraction independently, and the extracted data were verified by a third investigator (M.G.) for accuracy. The following variables were extracted: trial data, including number of enrolling centers, location, study period, number of patients randomized, and mean length of follow-up; patient demographics, including age, sex, body mass index, New York Heart Association Class, EuroSCORE (European System for Cardiac Operative Risk Evaluation), SYNTAX (Synergy Between PCI with Taxus and Cardiac Surgery) score, and comorbidities and/or past treatment (diabetes, insulin therapy, statin therapy, smoking, hypertension, hypercholesterolemia/hyperlipidemia, peripheral vascular disease, carotid artery disease, stroke, myocardial infarction, heart failure, previous PCI/CABG, stable or unstable angina pectoris, acute coronary syndrome); procedure-related factors, including number of stents, type of stent, total stent length, stent diameter, left main bifurcation stent technique, intravascular ultrasonongraphy, use of left or bilateral internal mammary arteries, off-pump CABG, number of arterial and venous grafts, use of epiaortic or transesophageal ultrasonography, and completeness of revascularization; details of medical therapy; and all-cause and cause-specific mortality in the CABG and PCI arms. The quality of the included studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias, version 2, in randomized trials.[9]

### Outcomes and Effect Summary

The primary outcomes were all-cause and cause-specific (cardiac vs noncardiac) mortality. Subgroup analyses were performed for trials comparing PCI using bare-metal or drug-eluting stents vs CABG and for trials comparing PCI with CABG in patients with left main disease.

Figure 1. Pooled Incidence Rate Ratio (IRR) for All-Cause Mortality




ARTS indicates Arterial Revascularization Therapies Study; BEST, Randomized Comparison of Coronary Artery Bypass Surgery and Everolimus-Eluting Stent Implantation in the Treatment of Patients With Multivessel Coronary Artery Disease; CABG, coronary artery bypass grafting; CARDIA, Coronary Artery Revascularization in Diabetes; ERACI II, Coronary Angioplasty With Stenting vs Coronary Bypass Surgery in Patients With Multiple-Vessel Disease; EXCEL, Evaluation of XIENCE vs Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization; FREEDOM, Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease; LE MANS, Left Main Stenting Trial; MASS-II, Medicine, Angioplasty, or Surgery Study; NOBLE, Nordic–Baltic–British Left Main Revascularisation Study; PCI, percutaneous coronary intervention; PRECOMBAT, Premier of Randomized Comparison of Bypass Surgery vs Angioplasty Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; SIMA, Stenting vs Internal Mammary Artery Grafting; SoS, Stent or Surgery; SYNTAX, Synergy Between PCI With Taxus and Cardiac Surgery; and VA CARDS, Veterans Affairs Coronary Artery Revascularization in Diabetes. Different size markers indicate 95% CIs.

### Meta-analysis

The generic inverse variance method was used to pool outcomes as natural logarithms of the incident rate ratios (IRRs) across studies to account for potentially different follow-up durations between the groups. Fixed- and random-effects inverse variance meta-analyses were performed using the metafor and meta packages[10] in R, version 3.3.3 (R Project for Statistical Computing). Publication bias was assessed by funnel plot (using the trim and fill method)[11] and Egger test. Heterogeneity was reported as low ($I^2$ = 0%-25%), moderate ($I^2$ = 26%-50%), or high ($I^2$>50%). Because the $I^2$ value was less than 50% in all primary comparisons, the fixed effect was considered as the primary model and the random effect as a sensitivity analysis. To better infer the predictive accuracy of the point estimates and minimize the selection bias, a cross-validation leave-one-out analysis was performed for the primary outcome. $P$ value for interaction was used to ascertain subgroup differences. Statistical significance was set at the 2-tailed $P$ = .05 level, without multiplicity adjustments.

## Results

A total of 425 citations were evaluated, of which 23 trials in 24 studies[1,2,5,12-32] met the eligibility criteria and were included in the final meta-analysis, the details of which are included in eTables 2 to 5 in the Supplement. Eighteen trials used all-cause mortality in their composite primary end point (eTable 6 in the Supplement). The details of the methods used for adjudication of the cause of death for each trial are summarized in eTable 7 in the Supplement. The full PRISMA flow diagram outlining the study selection process is available in eFigure 1 in the Supplement.[33]

A total of 13 620 patients were included (6829 undergoing PCI and 6791 undergoing CABG). The number of patients in the individual trials ranged from 44 to 1905. The mean follow-up duration of the individual studies was 4.5 years (range, 0.5-11.4 years). The mean age of patients ranged from 60.0 to 71.0 years. Women constituted 1.0% to 40.0% of the study populations (PCI, 1.0%-40.0%; CABG, 1.0%-

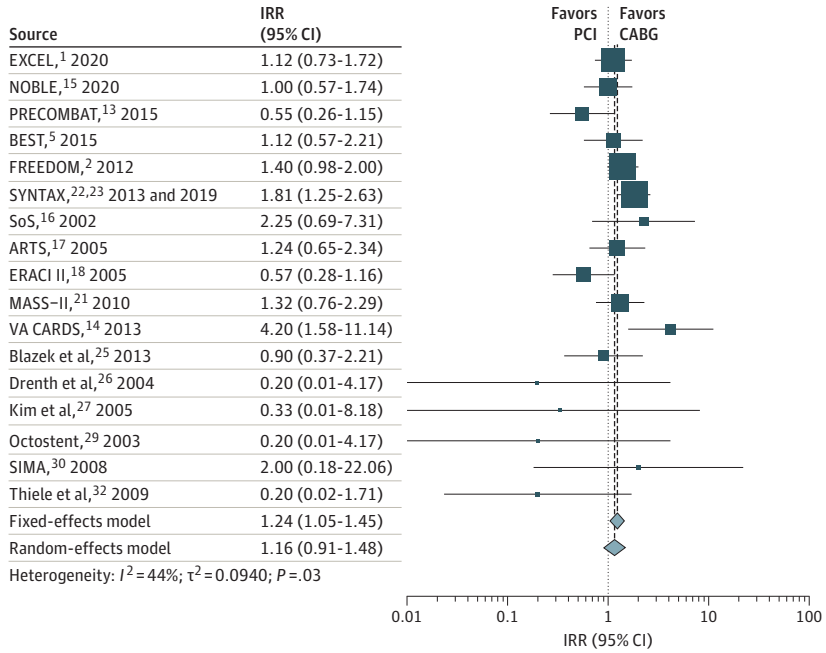
Table. Summary of Outcomes for the Main Analysis Comparing PCI vs CABG and for the Subgroup Analyses[a]

| Outcomes | No. of studies | No. of patients | Fixed-effect model | | | Random-effects model | | | Heterogeneity | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | IRR (95% CI) | *P* value | *P* value for interaction | IRR (95% CI) | *P* value | *P* value for interaction | $I^2$, % | *P* value |
| All-cause mortality | 22 | 13 490 | 1.17 (1.05-1.29) | .003 | NA | 1.13 (0.97-1.31) | .12 | NA | 31.2 | .08 |
| PCI with drug-eluting stents | 9 | 8857 | 1.22 (1.09-1.38) | <.001 | .19 | 1.22 (1.06-1.41) | .006 | .51 | 15.8 | .30 |
| PCI with bare-metal stents | 11 | 4018 | 1.04 (0.84-1.29) | .70 | .19 | 1.08 (0.78-1.50) | .63 | .51 | 40.6 | .08 |
| Left main disease | 5 | 3995 | 1.11 (0.91-1.35) | .32 | .56 | 0.99 (0.73-1.36) | .97 | .37 | 41.5 | .15 |
| Other vessel disease | 17 | 9495 | 1.19 (1.06-1.33) | .004 | .56 | 1.17 (0.98-1.40) | .09 | .37 | 31.4 | .11 |
| Cardiac mortality | 17 | 12 471 | 1.24 (1.05-1.45) | .009 | NA | 1.16 (0.91-1.48) | .24 | NA | 43.8 | .03 |
| PCI with drug-eluting stents | 8 | 8597 | 1.31 (1.09-1.58) | .004 | .21 | 1.24 (0.89-1.73) | .21 | .46 | 62.1 | .01 |
| PCI with bare-metal stents | 9 | 3874 | 1.04 (0.76-1.43) | .79 | .21 | 1.04 (0.74-1.45) | .84 | .46 | 5.9 | .39 |
| Left main disease | 3 | 3689 | 0.96 (0.70-1.30) | .78 | .06 | 0.93 (0.64-1.35) | .71 | .20 | 27.4 | .25 |
| Other vessel disease | 14 | 8782 | 1.36 (1.13-1.64) | .001 | .06 | 1.27 (0.95-1.70) | .11 | .20 | 41.1 | .06 |
| Noncardiac mortality | 16 | 12 341 | 1.19 (1.00-1.41) | .046 | NA | 1.19 (1.00-1.42) | .05 | NA | 3.0 | .42 |
| PCI with drug-eluting stents | 7 | 8467 | 1.28 (1.04-1.57) | .02 | .22 | 1.30 (1.00-1.69) | .05 | .23 | 27.1 | .22 |
| PCI with bare-metal stents | 9 | 3874 | 1.02 (0.75-1.38) | .91 | .22 | 1.02 (0.75-1.38) | .91 | .23 | 0.0 | .68 |
| Left main disease | 3 | 3689 | 1.41 (1.05-1.89) | .02 | .15 | 1.41 (1.05-1.89) | .02 | .17 | 0.0 | .64 |
| Other vessel disease | 13 | 8652 | 1.09 (0.88-1.34) | .43 | .15 | 1.10 (0.88-1.36) | .42 | .17 | 4.2 | .40 |

Abbreviations: CABG, coronary artery bypass grafting; IRR, incidence rate ratio; NA, not applicable; PCI, percutaneous coronary intervention.

[a] In all subgroup analyses, the reference is CABG. Differences were calculated using *P* for interaction.

Figure 2. Pooled Incidence Rate Ratio (IRR) for Cardiac Mortality

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30.5%); men, 39.9% to 99.0% (PCI, 60.0%-99.0%; CABG, 57.0%-99.0%). The prevalence of diabetes ranged from 6.0% to 100.0% (PCI, 8.0%-100.0%; CABG, 6.0%-100.0%). The details of patient characteristics are summarized in eTable 3 in the Supplement. The assessment of the quality of the individual studies and of the evidence is reported using the Cochrane risk of bias tool in the eMethods in the Supplement.

The weighted mean (SD) follow-up was 5.3 (3.6) years. Compared with CABG, PCI was associated with a higher rate of all-cause mortality (IRR, 1.17; 95% CI, 1.05-1.29) (**Figure 1** and **Table**), cardiac mortality (IRR, 1.24; 95% CI, 1.05-1.45) (**Figure 2** and Table), and noncardiac mortality (IRR, 1.19; 95% CI, 1.00-1.41) (**Figure 3** and Table). Sensitivity analyses confirmed the solidity of the primary analysis (eFigures 2-7 in the Supplement). The causes of noncardiac mortality in each study are summarized in eTable 8 in the Supplement.

## Subgroup Analysis

The pooled IRR for all-cause mortality was 1.22 (95% CI, 1.09-1.38) for studies including drug-eluting stents vs 1.04 (95% CI, 0.84-1.29) for studies including bare-metal stents (*P* = .19 for subgroups) (**Figure 4**A). In the analysis by anatomical extent of coronary disease, the IRR was 1.11 (95% CI, 0.91-1.35) for studies including patients with left main disease vs 1.19 (95% CI, 1.06-1.33) for the others (*P* = .56 for subgroups) (Table and eFigure 8 in the Supplement).

The pooled IRR for cardiac mortality was 1.31 (95% CI, 1.09-1.58) for studies including drug-eluting stents vs 1.04 (95% CI, 0.76-1.43) for studies including bare-metal stents (*P* = .21 for subgroups) (Figure 4B). The pooled IRR was 0.96 (95% CI, 0.70-1.30) for studies including patients with left main disease vs 1.36 (95% CI, 1.13-1.64) for the others (*P* = .06 for subgroups) (Table and eFigure 9 in the Supplement).

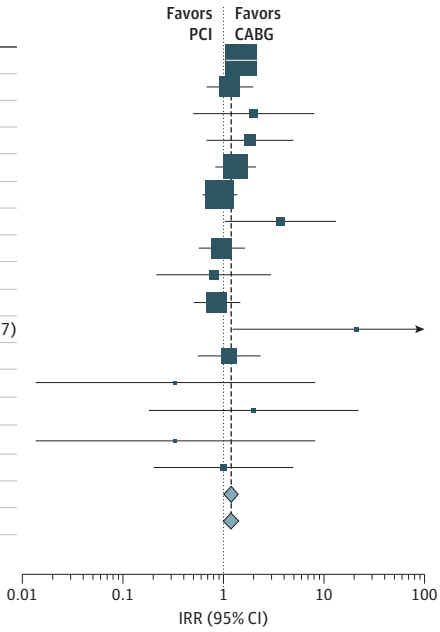
The pooled IRR for noncardiac mortality was 1.28 (95% CI, 1.04-1.57) for studies including drug-eluting stents vs 1.02 (95% CI, 0.75-1.38) for studies including bare-metal stents (*P* = .22 for subgroups) (Figure 4C). The pooled IRR was 1.41 (95% CI, 1.05-1.89) for studies including patients with left main disease vs 1.09 (95% CI, 0.88-1.34) for the others (*P* = .15 for subgroups) (Table and eFigure 10 in the Supplement).

## Discussion

The outcomes of PCI and CABG have been extensively evaluated, but comparative data on the cause of mortality after these revascularization procedures are limited. Our meta-analysis of 23 RCTs (13 620 patients) is the first, to our knowledge, to compare all-cause and cause-specific mortality between the

Figure 3. Pooled Incidence Rate Ratio (IRR) for Noncardiac Mortality

| Source | IRR (95% CI) |
|---|---|
| EXCEL,[1] 2020 | 1.51 (1.05-2.17) |
| NOBLE,[15] 2020 | 1.16 (0.68-1.98) |
| PRECOMBAT,[13] 2015 | 2.00 (0.50-8.00) |
| BEST,[5] 2015 | 1.83 (0.68-4.96) |
| FREEDOM,[2] 2012 | 1.32 (0.83-2.11) |
| SYNTAX,[22,23] 2013 and 2019 | 0.92 (0.62-1.37) |
| SoS,[16] 2002 | 3.67 (1.02-13.14) |
| ARTS,[17] 2005 | 0.96 (0.57-1.64) |
| ERACI II,[18] 2005 | 0.80 (0.21-2.98) |
| MASS–II,[21] 2010 | 0.86 (0.50-1.47) |
| VA CARDS,[14] 2013 | 21.00 (1.23-358.37) |
| Blazek et al,[25] 2013 | 1.14 (0.56-2.34) |
| Drenth et al,[26] 2004 | 0.33 (0.01-8.18) |
| Kim et al,[27] 2005 | 2.00 (0.18-22.06) |
| Octostent,[29] 2003 | 0.33 (0.01-8.18) |
| SIMA,[30] 2008 | 1.00 (0.20-4.95) |
| Fixed-effects model | 1.19 (1.00-1.41) |
| Random-effects model | 1.19 (1.00-1.42) |
| Heterogeneity: $I^2 = 3\%$; $\tau^2 = 0.0040$; $P = .42$ | |

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2 revascularization modalities. Among the included patients, compared with CABG, PCI was associated with higher all-cause, cardiac, and noncardiac mortality at a mean follow-up of 5.3 years. On subgroup analysis, PCI with drug-eluting stents was associated with higher all-cause, cardiac, and noncardiac mortality compared with bare-metal stents, although the test for interaction did not reach statistical significance.

Observational evidence shows that the causes of mortality after PCI and CABG are predominantly cardiac in the first year after the procedure and noncardiac in the following years.[12,34-37] The common causes of cardiac mortality include cardiogenic shock, heart failure, stent thrombosis, bleeding, coronary dissection, malignant arrhythmia, and sudden death,[12,34,38] whereas cancer, sepsis, bleeding, and vascular, pulmonary, and/or renal disease are among the most frequent causes of noncardiac mortality.[12,34,36,37]

Our finding of higher all-cause mortality with PCI is consistent with the most recent individual patient data meta-analysis of 11 RCTs and 11 518 patients.[39] Compared with PCI, CABG offers additional protection against the evolution of lesions that were non-flow limiting at the time of the procedure, and this has been proposed as a potential mechanism for the observed survival benefit in the surgical arm.[40]

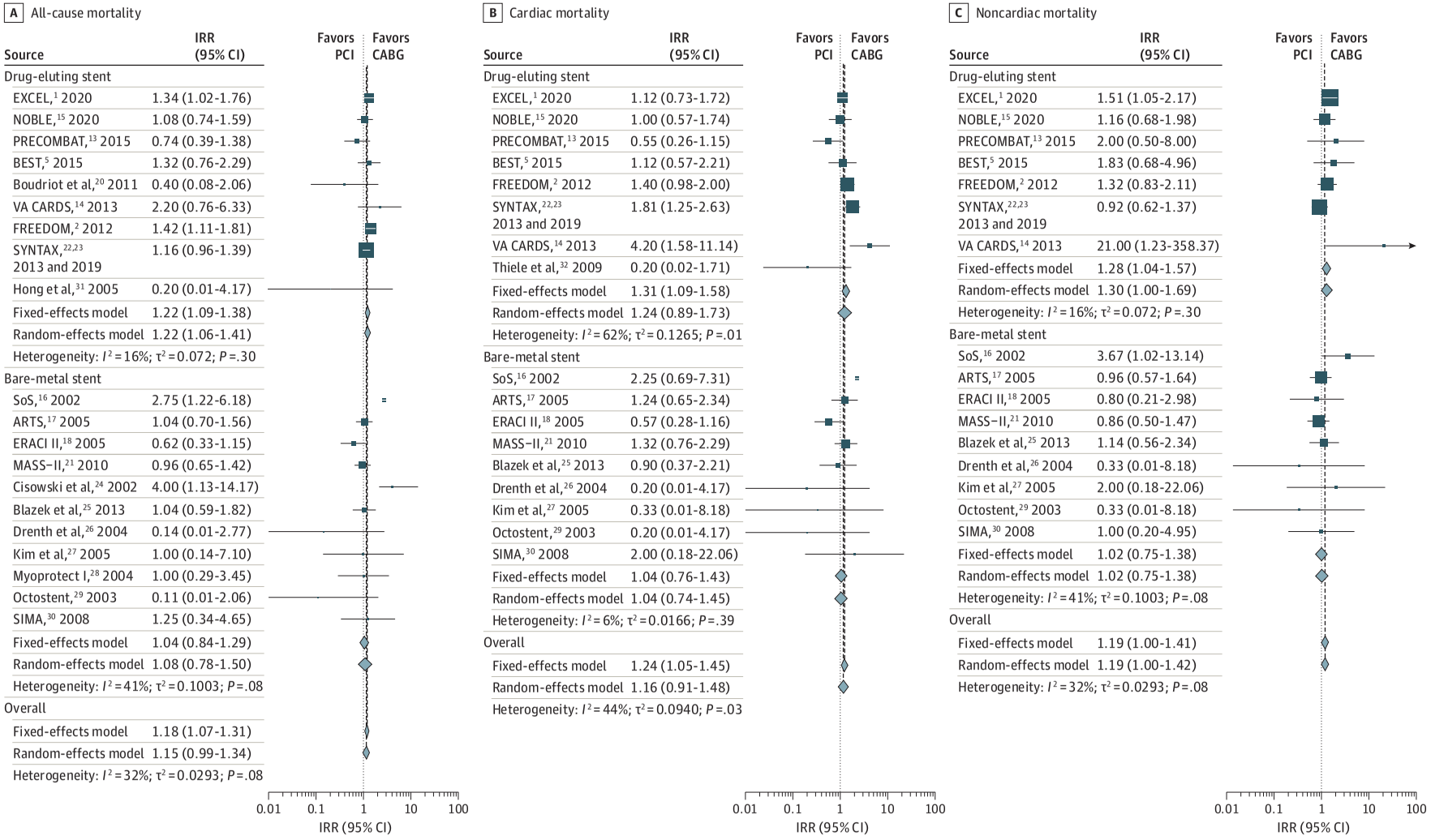
We found PCI to be also associated with significantly higher noncardiac mortality compared with CABG. All 6 revascularization RCTs during the last decade have shown PCI to be associated with an increase in the rate of noncardiac mortality compared with CABG.[1-3,5,13,14] Large observational studies have shown an increased risk of noncardiac mortality in the late post-PCI period and independent of patients' characteristics.[41-43]

This finding may have several explanations. Dual antiplatelet therapy has been linked to non-cardiac-related deaths in a large trial,[44] but not in an individual data meta-analysis.[45] Evidence suggests that longer duration of dual antiplatelet therapy is associated with an increased risk of noncardiac mortality.[46] The reasons for these associations are not fully understood, but may include deaths due to major bleeding events (that are often coded as noncardiac) or a higher bleeding-related mortality in case of trauma or other acute events in patients receiving dual antiplatelet therapy.

Another explanation—perhaps the most likely—is that cardiac deaths were coded as noncardiac owing to bias or errors. The risk that insufficient or inadequate supporting data and/or assessors bias may lead to misclassification in the adjudication of cause-specific mortality is well known and has been described in detail previously.[47,48] This may be particularly true in case of sudden cardiac death, a particularly frequent cause of death in patients who presented with acute coronary syndromes.[38]

In our analysis, PCI with drug-eluting stents was associated with higher all-cause and noncardiac mortality relative to CABG compared with PCI with bare-metal stents, although

## Figure 4. Subgroup Analysis for All-Cause Mortality, Cardiac Mortality, and Noncardiac Mortality for Trials Using Drug-Eluting vs Bare-Metal Stents

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the difference did not reach statistical significance. This result is consistent with a previous meta-analysis of 17 RCTs (8221 patients)[49] comparing first-generation drug-eluting vs bare-metal stents in which the use of sirolimus-eluting stents was significantly associated with higher noncardiac and, in particular, cancer-related mortality. Although the reasons for this association are unclear, it is most likely related to the differences in baseline characteristics and risk profile between patients with PCI in the era of bare-metal vs drug-eluting stents.

We also found that in patients with left main disease, the benefit of CABG over PCI for cardiac mortality was reduced, and the difference between the 2 revascularization modalities was mostly based on a higher rate of noncardiac deaths in the PCI arm. This finding is likely related to the reduced power of the left main disease subgroup analysis, to heterogeneity in the population with left main disease, or to differences in baseline characteristics between patients with left main disease compared with other types of coronary disease.

Our findings have implications for future RCTs comparing the 2 revascularization modalities. The use of all-cause mortality in myocardial revascularization trials remains controversial,[6] as recently highlighted by the difference in all-cause, but not cause-specific, mortality in the EXCEL trial[1] and from the fact that 5 of the 23 trials included in our analysis used cause-specific rather than all-cause mortality in their primary composite outcome. Based on our results, the use of cardiac mortality may exclude deaths that are in fact related to the procedure, either through noncardiac mechanisms or because of misclassification.

### Limitations

Our results must be viewed in light of the limitations of this analysis. Differences in procedural aspects, postprocedural management, and follow-up protocol may have existed between the included trials. In addition, the exact causes of noncardiac mortality were not reported by several trials and could not be independently compared between PCI and CABG.

## Conclusions

This meta-analysis found that percutaneous coronary intervention is associated with higher all-cause, cardiac, and noncardiac mortality compared with CABG. The significantly higher noncardiac mortality associated with PCI suggests that even noncardiac deaths after PCI may in fact be related to the procedure and/or subsequent management, and our data strongly support the use of all-cause mortality as the most comprehensive and unbiased end point for myocardial revascularization trials.

ARTICLE INFORMATION

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