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# 10-Year All-Cause Mortality Following Percutaneous or Surgical Revascularization in Patients With Heavy Calcification

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## ABSTRACT

**OBJECTIVES** The aim of this study was to assess 10-year all-cause mortality in patients with heavily calcified lesions (HCLs) undergoing percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).

**BACKGROUND** Limited data are available on very long term outcomes in patients with HCLs according to the mode of revascularization.

**METHODS** This substudy of the SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) study assessed 10-year all-cause mortality according to the presence of HCLs within lesions with >50% diameter stenosis and identified during the calculation of the anatomical SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) score among 1,800 patients with the 3-vessel disease and/or left main disease randomized to PCI or CABG in the SYNTAX trial. Patients with HCLs were further stratified according to disease type (3-vessel disease or left main disease) and assigned treatment (PCI or CABG).

**RESULTS** The 532 patients with ≥1 HCL had a higher crude mortality rate at 10 years than those without (36.4% vs 22.3%; HR: 1.79; 95% CI: 1.49-2.16; $P < 0.001$). After adjustment, an HCL remained an independent predictor of 10-year mortality (HR: 1.36; 95% CI: 1.09-1.69; $P = 0.006$). There was a significant interaction in mortality between treatment effect (PCI and CABG) and the presence or absence of HCLs ($P_{interaction} = 0.005$). In patients without HCLs, mortality was significantly higher after PCI than after CABG (26.0% vs 18.8%; HR: 1.44; 95% CI: 0.97-1.41; $P = 0.003$), whereas in those with HCLs, there was no significant difference (34.0% vs 39.0%; HR: 0.85; 95% CI: 0.64-1.13; $P = 0.264$).

**CONCLUSIONS** At 10 years, the presence of an HCL was an independent predictor of mortality, with a similar prognosis following PCI or CABG. Whether HCLs require special consideration when deciding the mode of revascularization beyond their current contribution to the anatomical SYNTAX score deserves further evaluation. (Synergy Between PCI With TAXUS and Cardiac Surgery: SYNTAX Extended Survival [SYNTAXES], NCT03417050; SYNTAX Study: TAXUS Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries [SYNTAX], NCT00114972) (J Am Coll Cardiol Intv 2022;15:193–204) © 2022 by the American College of Cardiology Foundation.

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**ABBREVIATIONS AND ACRONYMS**

**3VD** = 3-vessel disease

**CABG** = coronary artery bypass grafting

**CAD** = coronary artery disease

**HCL** = heavily calcified lesion

**LM** = left main

**PCI** = percutaneous coronary intervention

**RA** = rotational atherectomy

Severe coronary calcification has been associated with worse clinical outcomes in patients undergoing revascularization. In current registries and meta-analyses, the prevalence of moderate and severe calcific coronary stenoses has ranged from 18% to 26% (1-3). Their presence is frequently associated with advanced age, systemic hypertension, dyslipidemia, diabetes, and chronic kidney disease. As a consequence of an aging population and the increased prevalence of these comorbidities, the number of patients with heavily calcified lesions (HCLs) presenting for revascularization is anticipated to rise. Unfortunately, despite recent procedural and instrumental advancements, percutaneous coronary intervention (PCI) for HCLs remains challenging. It is associated with lower procedural success and higher complication rates compared with PCI for non-HCLs (4,5). Severe lesion calcification is also associated with increased mortality in patients undergoing coronary artery bypass grafting (CABG), as shown in 5-year outcome data from the SYNTAX (Synergy Between PCI With Taxus and Cardiac Surgery) trial and SYNTAX registry (6). However, currently, there are no data on very long term outcomes after revascularization in patients with HCLs and complex coronary artery disease (CAD).

The SYNTAXES (Synergy Between PCI With Taxus and Cardiac Surgery Extended Survival) study obtained vital status out to 10 years in patients with the 3-vessel disease (3VD) and/or left main (LM) disease randomized in the SYNTAX trial (7). The aim of the present subanalysis of the SYNTAXES study was to investigate 10-year all-cause mortality in patients with HCLs and complex CAD undergoing PCI or CABG.

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## METHODS

**STUDY DESIGN AND PATIENT POPULATION.** The present study was a post hoc subgroup analysis of the SYNTAXES study (NCT03417050) (7), which was an investigator-driven extended 10-year follow-up of the SYNTAX trial (NCT00114972) beyond its initially planned final follow-up at 5 years. In brief, the SYNTAX trial was a multicenter, randomized controlled trial performed at 85 hospitals across 18 North American and European countries, which adopted an "all-comers" design with minimum exclusion criteria (8). A total of 1,800 patients with de novo 3VD and/or LM disease, who were deemed eligible for both PCI and CABG on the basis of clinical judgment and the consensus of a heart team, were enrolled and randomized in a 1:1 fashion to undergo either PCI (n = 903) with the default use of paclitaxel-eluting stents (Taxus Express, Boston Scientific) or CABG (n = 897). Lesions that were deemed amenable to CABG only were excluded from the SYNTAX trial and included in the SYNTAX registry. Therefore, by default, all HCLs that were not amenable to PCI were already excluded from the present study. The main result of the SYNTAXES study in terms of vital status up to 10 years has been previously reported and the (re)development of the SYNTAX score II 2020 (7,9). The ethics committee at each investigating center approved the SYNTAX and SYNTAXES trials, and all patients provided written informed consent before participation in the SYNTAX trial. Follow-up was performed under local law and the regulations of each participating institution and complied with the Declaration of Helsinki.

**OUTCOMES.** The primary endpoint of this study was all-cause mortality at 10 years. All analyses were performed according to the intention-to-treat principle. Vital status was confirmed by (electronic) health care record review and national death registries. Patients with missing vital status were included in the analysis and censored at the last date of contact or observation (7). Two hospitals, which included 5 patients in total, decided not to participate in the SYNTAXES study (7). The LM disease subgroup consisted of patients with any LM disease, either isolated or in combination with single-vessel, 2-vessel, or 3-vessel CAD. The 3VD subgroup consisted of patients with 3VD in the absence of LM disease (7,10).

**SYNTAX SCORE AND HEAVY CALCIFICATION.** The presence of heavy calcification was evaluated during the calculation of the anatomical SYNTAX score, which was performed retrospectively in all patients in the SYNTAX trial by an independent core laboratory blinded to treatment assignment (11). Two trained analysts reviewed the angiographic films. While calculating the anatomical SYNTAX score,

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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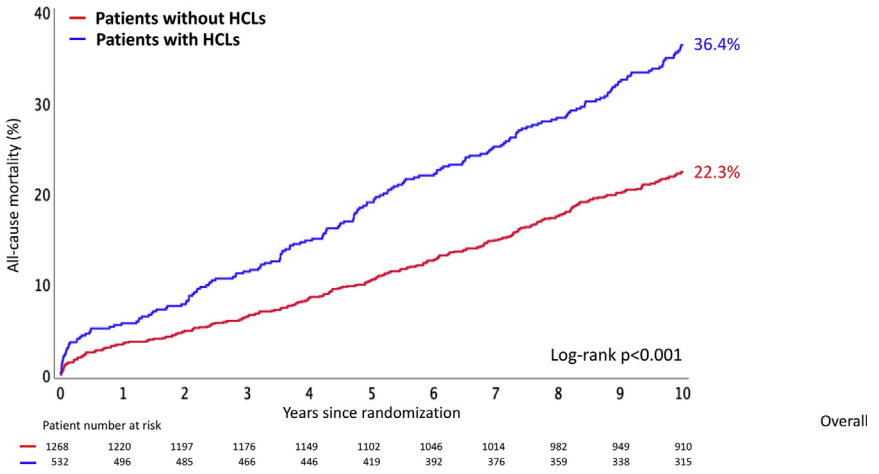
**TABLE 1 Baseline and Postprocedural Characteristics and Medical Therapy at Discharge in Patients With or Without HCLs**

| | Overall | | | PCI | | | CABG | | |
|---|---|---|---|---|---|---|---|---|---|
| | Patients Without HCLs (n = 1,268) | Patients With HCLs (n = 532) | *P* Value | Patients Without HCLs (n = 627) | Patients With HCLs (n = 276) | *P* Value | Patients Without HCLs (n = 641) | Patients With HCLs (n = 256) | *P* Value |
| Age (y) | 64.1 ± 9.8 | 67.5 ± 9.0 | <0.001 | 64.3 ± 10.0 | 67.4 ± 8.5 | <0.001 | 63.9 ± 9.7 | 67.6 ± 9.5 | <0.001 |
| Body mass index (kg/m$^2$) | 28.2 ± 4.7 | 27.6 ± 4.5 | 0.017 | 28.3 ± 4.8 | 27.7 ± 4.7 | 0.080 | 28.1 ± 4.6 | 27.5 ± 4.4 | 0.098 |
| Male | 980 (77.3) | 418 (78.6) | 0.551 | 475 (75.8) | 215 (77.9) | 0.485 | 505 (78.8) | 203 (79.3) | 0.865 |
| Diabetes | 297 (23.4) | 155 (29.1) | 0.011 | 147 (23.4) | 84 (30.4) | 0.027 | 150 (23.4) | 71 (27.7) | 0.174 |
| On insulin | 116 (9.1) | 66 (12.4) | 0.036 | 56 (8.9) | 33 (12.0) | 0.160 | 60 (9.4) | 33 (12.9) | 0.117 |
| Hypertension | 823 (64.9) | 373 (70.1) | 0.033 | 419 (66.8) | 203 (73.6) | 0.044 | 404 (63.0) | 170 (66.4) | 0.341 |
| Dyslipidemia | 994 (79.1) | 397 (75.2) | 0.071 | 498 (79.8) | 207 (76.1) | 0.213 | 496 (78.4) | 190 (74.2) | 0.183 |
| Current smoking | 267 (21.1) | 96 (18.1) | 0.153 | 127 (20.3) | 40 (14.5) | 0.040 | 140 (22.0) | 56 (22.1) | 0.960 |
| Previous myocardial infarction | 418 (33.3) | 167 (31.9) | 0.564 | 204 (32.9) | 81 (29.7) | 0.340 | 214 (33.6) | 86 (34.3) | 0.862 |
| Previous cerebrovascular disease | 161 (12.7) | 92 (17.4) | 0.010 | 77 (42) | 42 (15.3) | 0.225 | 84 (13.2) | 50 (19.8) | 0.013 |
| Previous stroke | 52 (4.1) | 26 (4.9) | 0.436 | 23 (3.7) | 12 (4.4) | 0.607 | 29 (4.6) | 14 (5.5) | 0.538 |
| Previous transient ischemic attack | 56 (4.4) | 28 (5.3) | 0.418 | 27 (4.3) | 12 (4.4) | 0.960 | 29 (4.6) | 16 (6.3) | 0.273 |
| Previous carotid artery disease | 82 (6.5) | 66 (12.4) | <0.001 | 42 (6.7) | 31 (11.2) | 0.021 | 40 (6.2) | 35 (13.7) | <0.001 |
| Peripheral vascular disease | 106 (8.4) | 71 (13.3) | 0.001 | 49 (7.8) | 33 (12.0) | 0.046 | 57 (8.9) | 38 (14.8) | 0.009 |
| Chronic obstructive pulmonary disease | 93 (7.3) | 61 (11.5) | 0.004 | 39 (6.2) | 32 (11.6) | 0.006 | 54 (8.4) | 29 (11.3) | 0.175 |
| Active malignancy | 6 (0.5) | 2 (0.4) | 0.563 | 2 (0.3) | 0 (0.0) | 0.482 | 4 (0.6) | 2 (0.8) | 0.548 |
| Chronic kidney disease | 206 (17.7) | 110 (23.2) | 0.010 | 103 (17.3) | 64 (24.8) | 0.012 | 103 (18.1) | 46 (21.3) | 0.303 |
| Creatinine clearance (mL/min) | 88.0 ± 32.7 | 81.5 ± 32.4 | <0.001 | 89.1 ± 35.9 | 81.1 ± 34.2 | 0.002 | 86.9 ± 29.1 | 82.0 ± 30.1 | 0.037 |
| Left ventricular ejection fraction (%) | 59.1 ± 12.9 | 57.5 ± 13.3 | 0.053 | 59.6 ± 13.0 | 57.9 ± 12.7 | 0.155 | 58.7 ± 12.8 | 57.1 ± 13.9 | 0.184 |
| Congestive heart failure | 48 (3.8) | 35 (6.7) | 0.009 | 25 (4.0) | 11 (4.0) | 0.993 | 23 (3.6) | 24 (9.7) | <0.001 |
| Clinical presentation | | | <0.001 | | | 0.002 | | | 0.005 |
| Silent ischemia | 161 (12.7) | 99 (18.6) | | 81 (12.9) | 46 (16.7) | | 80 (12.5) | 53 (20.7) | |
| Stable angina | 714 (56.3) | 313 (58.8) | | 342 (54.5) | 172 (62.3) | | 372 (58.0) | 141 (55.1) | |
| Unstable angina | 393 (31.0) | 120 (22.6) | | 204 (32.5) | 58 (21.0) | | 189 (29.5) | 62 (24.2) | |
| EuroSCORE | 3.6 ± 2.5 | 4.2 ± 2.9 | <0.001 | 3.6 ± 2.5 | 4.0 ± 2.8 | 0.044 | 3.6 ± 2.5 | 4.4 ± 3.0 | <0.001 |
| Parsonnet score | 7.9 ± 6.5 | 9.9 ± 7.6 | <0.001 | 8.1 ± 6.7 | 9.5 ± 7.4 | 0.004 | 7.7 ± 6.2 | 10.3 ± 7.8 | <0.001 |
| Disease type | | | 0.570 | | | 0.073 | | | 0.311 |
| 3-vessel disease | 766 (60.4) | 329 (61.8) | | 367 (58.5) | 179 (64.9) | | 399 (62.2) | 150 (58.6) | |
| Left main disease | 502 (39.6) | 203 (38.2) | | 260 (41.5) | 97 (35.1) | | 242 (37.8) | 106 (41.4) | |
| Number of lesions | 4.3 ± 1.8 | 4.6 ± 1.6 | <0.001 | 4.2 ± 1.8 | 4.7 ± 1.7 | <0.001 | 4.3 ± 1.9 | 4.5 ± 1.6 | 0.121 |
| Anatomical SYNTAX score | 22.4 ± 8.9 | 30.8 ± 10.7 | <0.001 | 22.7 ± 9.0 | 30.5 ± 11.8 | <0.001 | 22.1 ± 8.9 | 31.2 ± 9.4 | <0.001 |
| Predictive 10-y all-cause mortality according to SYNTAX score II 2020 (%) | | | | | | | | | |
| PCI | 25.0 ± 17.5 | 35.5 ± 22.5 | <0.001 | 25.0 ± 17.0 | 34.4 ± 21.8 | <0.001 | 25.0 ± 17.9 | 36.7 ± 23.2 | <0.001 |
| CABG | 22.7 ± 16.5 | 29.4 ± 20.2 | <0.001 | 22.7 ± 16.0 | 28.2 ± 19.2 | <0.001 | 22.6 ± 16.9 | 30.8 ± 21.3 | <0.001 |
| Any bifurcation | 884 (70.4) | 416 (78.3) | 0.001 | 431 (69.4) | 218 (79.0) | 0.003 | 182 (28.7) | 57 (22.4) | 0.055 |
| Number of bifurcations | 1.1 ± 1.0 | 1.3 ± 1.0 | <0.001 | 1.1 ± 1.0 | 1.3 ± 0.9 | 0.003 | 1.2 ± 1.0 | 1.3 ± 1.1 | 0.021 |
| Total occlusions | 290 (22.9) | 170 (32.0) | <0.001 | 145 (23.1) | 92 (33.3) | 0.001 | 145 (22.6) | 78 (30.5) | 0.014 |
| Total number of graft conduits | | | | | | | 2.7 ± 0.7 | 2.8 ± 0.8 | 0.359 |
| Number of artery graft conduits | | | | | | | 1.4 ± 0.7 | 1.4 ± 0.7 | 0.934 |
| Left internal mammary artery used | | | | | | | 534 (85.7) | 210 (86.8) | 0.686 |
| Number of vein graft conduits | | | | | | | 1.4 ± 0.9 | 1.4 ± 1.0 | 0.507 |
| Randomized treatment | | | 0.346 | | | – | | | – |
| PCI | 627 (49.4) | 276 (51.9) | | – | – | | – | – | |
| CABG | 641 (50.6) | 256 (48.1) | | – | – | | – | – | |
| Completeness of revascularization | 788 (63.2) | 270 (52.0) | <0.001 | 384 (61.8) | 124 (45.1) | <0.001 | 404 (64.5) | 146 (59.8) | 0.196 |

Values are mean ± SD or n (%).

CABG = coronary artery bypass grafting; EuroSCORE = European System for Cardiac Operative Risk Evaluation; HCL = heavily calcified lesion; PCI = percutaneous coronary intervention; SYNTAX = Synergy Between PCI With Taxus and Cardiac Surgery.

**FIGURE 1 Kaplan-Meier Curves of All-Cause Mortality at 10 Years According to the Presence of at Least 1 HCL (N = 1,800)**




Patients without heavily calcified lesions (HCLs) **(red line)** versus patients with at least 1 HCL **(blue line)**.

using a previously described methodology, they identified the presence of heavy calcification, defined as radiopacities noted without cardiac motion before contrast injection, generally compromising both sides of the arterial lumen, in vessels ≥1.5 mm in diameter with >50% diameter stenosis (11). In cases of disagreement, the opinion of a third expert analyst was requested, and the final decision was obtained by consensus. At the time of the angiographic analysis, reviewers were blinded to the patients' demographic characteristics and clinical outcomes. In our analysis, randomized patients were stratified according to the presence or absence of an HCL, and those with HCLs were further stratified according to disease type (3VD or LM disease) and randomized treatment (PCI or CABG). Patients with HCLs were further stratified according to their proximal or distal topography and according to the number of HCLs.

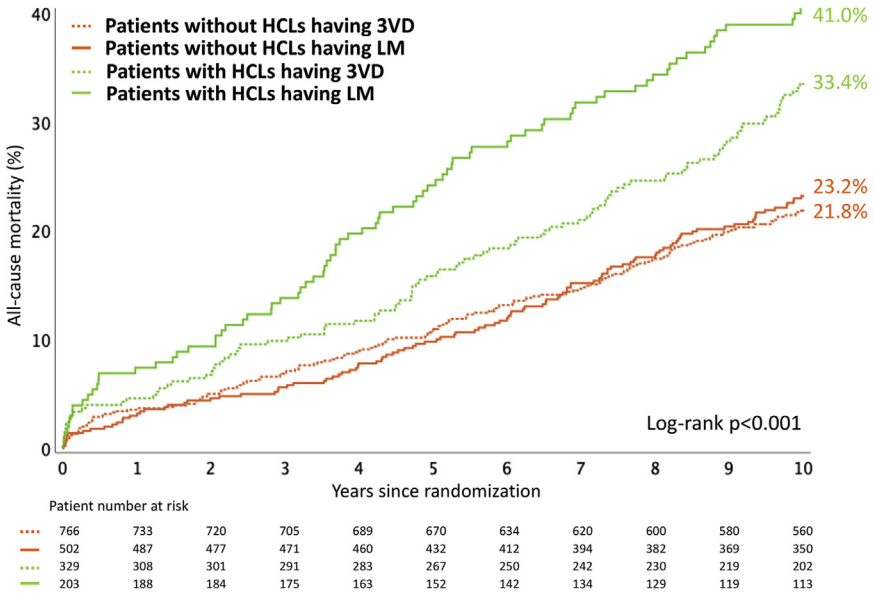
Patients with at least 1 HCL were stratified as HCLs only located in the proximal-mid coronary vasculature (LM trunk [segment 5], proximal and mid vessels [segments 1-2, 6-7, 11, and 13]) or in the distal coronary vasculature or side branch (segments 3, 4, 16, 16a, 16b, 16c, 8, 9, 9a, 10, 10a, 12, 12a, 12b, 14, 14a, 14b, and 15) according to the anatomical description of the segment numbers in the SYNTAX score (11,12). In addition, patients with at least 1 HCL were stratified according to the number of HCLs (1 or ≥2 HCLs).

**STATISTICAL ANALYSIS.** The mean ± SD for continuous variables was compared using Student's *t*-test. Categorical variables are reported as counts and/or percentages and were compared using the chi-square or Fisher exact test as appropriate. The cumulative incidence of all-cause mortality up to 10 years was assessed using the Kaplan-Meier method and compared using the log-rank test. Between 5 and 10 years after PCI or CABG, the landmark analyses according to the presence of at least 1 HCL and the randomized treatment were performed. HRs with 95% CIs were evaluated using Cox proportional regression models. To investigate whether the presence of at least 1 HCL is an independent predictor of 10-year all-cause mortality, the variables included in the SYNTAX score II 2020 (9), hypertension, assigned treatment, and the presence of at least 1 HCL were entered into a multivariable Cox regression model as follows: age, medically treated diabetes, current smoking, peripheral vascular disease, chronic obstructive pulmonary disease, creatinine clearance, left ventricular ejection fraction, disease type (3VD or LM disease), anatomical SYNTAX score, hypertension, randomized revascularization mode (PCI or CABG), and the presence of at least 1 HCL. Furthermore, the association between randomized treatment and mortality according to the presence of at least 1 HCL was compared using unadjusted and adjusted Cox regression hazards models. A *P* value <0.05 was considered to indicate statistical significance. All data were processed using SPSS version 26.0 (IBM).

## RESULTS

**PATIENT CHARACTERISTICS.** The median duration of follow-up was 11.2 years (IQR: 7.7-12.1 years)

**FIGURE 2** **Kaplan-Meier Curves of All-Cause Mortality at 10 Years Stratified According to the Presence of at Least 1 HCL and Disease Type (3VD or LM Disease) (N = 1,800)**




Patients without heavily calcified lesions (HCLs) with 3-vessel disease (3VD) **(orange dotted line)** versus patients without HCLs with left main (LM) disease **(orange solid line)** versus patients with HCLs with 3VD **(green dotted line)** versus patients with HCLs with LM disease **(green solid line)**.

overall and 11.9 years (IQR: 11.2-12.3 years) in survivors. Among 1,800 randomized patients, 532 (29.6%) had at least 1 HCL, and 1,268 (70.4%) did not have any HCLs (Table 1). Baseline and postprocedural characteristics are shown in Table 1.

At baseline, compared with those without, patients with HCLs were older and had lower body mass index and higher rates of insulin-treated diabetes, hypertension, previous cerebrovascular disease, peripheral vascular disease, chronic obstructive pulmonary disease, chronic kidney disease, and congestive heart failure. The European System for Cardiac Operative Risk Evaluation score, Parsonnet score, number of lesions, anatomical SYNTAX score (30.8 ± 10.7 vs 22.4 ± 8.9; $P < 0.001$), and predicted 10-year all-cause mortality according to the SYNTAX score II 2020 following PCI (35.5% ± 22.5% vs 25.0% ± 17.5%; $P < 0.001$) or CABG (29.4% ± 20.2% vs 22.7% ± 16.5%; $P < 0.001$) were higher in patients with HCLs. Furthermore, patients with HCLs had more bifurcation lesions and total occlusions.

Overall, the completeness of revascularization was significantly lower in patients with HCLs, which was driven primarily by the significantly lower rate in patients undergoing PCI (overall, 52.0% vs 63.2% [$P < 0.001$]; PCI, 45.1% vs 61.8% [$P < 0.001$]; CABG, 59.8% vs 64.5% [$P = 0.196$]).

Medication status at discharge, 1 and 6 months, and 1, 3, and 5 years according to assigned treatment in patients with or without HCLs is shown in Supplemental Table 1.

**COMPARISONS OF MORTALITY UP TO 10 YEARS BETWEEN PATIENTS WITH AND WITHOUT HCLs.** All-cause mortality estimates up to 10 years according to the presence of at least 1 HCL are shown in Figure 1. Patients with HCLs had higher mortality compared with those without HCLs (36.4% vs 22.3%; HR: 1.79; 95% CI: 1.49-2.16; $P < 0.001$).

All-cause mortality estimates up to 10 years stratified according to the presence of at least 1 HCL and disease type (3VD or LM disease) are shown in Figure 2. Irrespective of the type of disease (3VD or LM disease), patients with HCLs had higher mortality than those without (3VD, 33.4% vs 21.8% [HR: 1.62; 95% CI: 1.27-2.07; $P < 0.001$]; LM disease, 41.0% vs 23.2% [HR: 2.07; 95% CI: 1.56-2.77; $P < 0.001$]).

**INDEPENDENT PREDICTORS OF 10-YEAR ALL-CAUSE MORTALITY.** In both the univariate and multivariate analyses, the presence of at least 1 HCL was an independent predictor of all-cause mortality at 10 years (adjusted HR: 1.36; 95% CI: 1.09-1.69; $P = 0.006$) (Table 2). Furthermore, age (per 1-year increase), medically treated diabetes, peripheral vascular

**TABLE 2 Predictors of All-Cause Mortality at 10 Years**

| | Unadjusted HR (95% CI) | *P* Value | Adjusted HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Peripheral vascular disease | 2.72 (2.16-3.43) | <0.001 | 2.13 (1.67-2.75) | <0.001 |
| Chronic obstructive pulmonary disease | 2.03 (1.56-2.65) | <0.001 | 1.65 (1.24-2.19) | 0.001 |
| Presence of at least 1 heavily calcified lesion | 1.79 (1.49-2.16) | <0.001 | 1.36 (1.09-1.69) | 0.006 |
| Medically treated diabetes | 1.61 (1.32-1.95) | <0.001 | 1.53 (1.24-1.88) | <0.001 |
| Randomized treatment (PCI over CABG) | 1.17 (0.97-1.41) | 0.092 | | |
| Current smoking | 1.17 (0.94-1.46) | 0.154 | | |
| Left main coronary artery disease | 1.15 (0.95-1.38) | 0.149 | | |
| Age (per 1-y increase) | 1.07 (1.06-1.08) | <0.001 | 1.08 (1.06-1.09) | <0.001 |
| Hypertension | 1.06 (0.87-1.29) | 0.564 | | |
| Anatomical SYNTAX score (per 1-point increase) | 1.02 (1.01-1.03) | <0.001 | | |
| Creatinine clearance (per 1 mL/min increase) | 0.99 (0.98-0.99) | <0.001 | | |
| Left ventricular ejection fraction (per 1% increase) | 0.98 (0.97-0.99) | <0.001 | 0.99 (0.98-0.99) | <0.001 |

Abbreviations as in Table 1.

disease, chronic obstructive pulmonary disease, and left ventricular ejection fraction (per 1% decrease) were also independent predictors of 10-year mortality (Table 2).

**COMPARISONS OF MORTALITY UP TO 10 YEARS BETWEEN PATIENTS UNDERGOING PCI AND CABG.** All-cause mortality estimates up to 10 years according to the presence of at least 1 HCL and randomized treatment (PCI or CABG) are shown in the Central Illustration. The association between randomized treatment and all-cause mortality according to the presence of at least 1 HCL is presented in Table 3. There was a significant interaction on 10-year all-cause mortality between the mode of revascularization and the presence or absence of HCLs ($P_{\text{interaction}} = 0.005$). In patients without HCLs, PCI was associated with poorer survival compared with CABG (26.0% vs 18.8%; HR: 1.44; 95% CI: 1.14-1.83; $P = 0.003$), whereas in those with HCLs, there was no significant difference between the 2 treatments (34.0% vs 39.0%; HR: 0.85; 95% CI: 0.64-1.13; $P = 0.264$). In the multivariate analyses, those findings were consistent with those of the univariate analyses (Supplemental Table 2).

**COMPARISONS OF MORTALITY UP TO 10 YEARS BETWEEN PATIENTS UNDERGOING PCI AND CABG ACCORDING TO THE LOCATION OF HCLs.** Irrespective of the location of the HCL (proximal or distal coronary vasculature, LM trunk or other vessels, LM trunk and/or left anterior descending coronary artery or other vessels, right coronary artery or other vessels, and left circumflex coronary artery or other vessels), there were no significant differences in all-cause mortality at 10 years between PCI and CABG (Table 4).

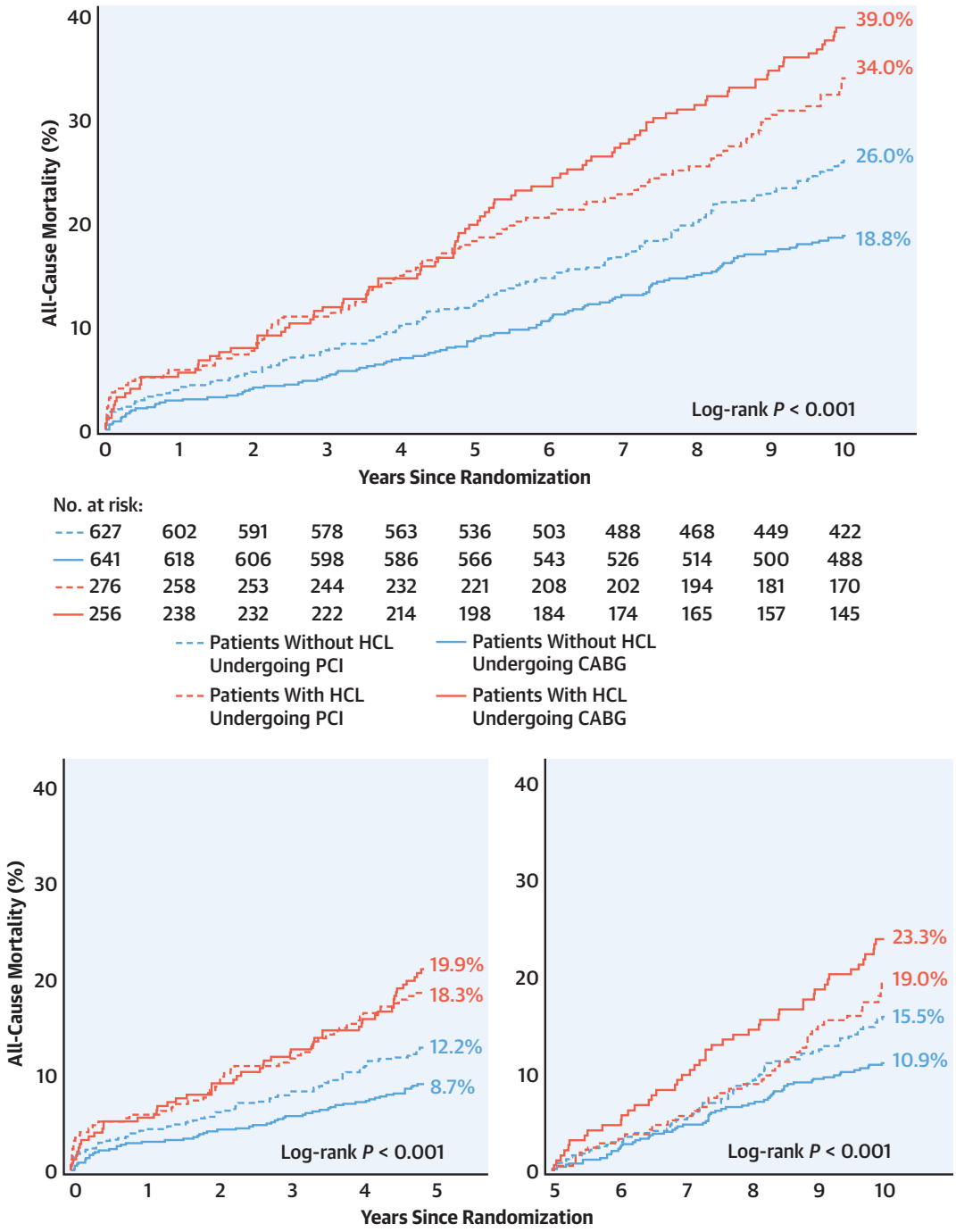
**COMPARISONS OF MORTALITY UP TO 10 YEARS BETWEEN PATIENTS WITH 1 AND ≥2 HCLs.** All-cause mortality estimates up to 10 years according to the number of HCLs and randomized treatment are shown in Figure 3. In the CABG arm, patients with ≥2 HCLs had higher 10-year all-cause mortality compared with those with 1 HCL (44.1% vs 31.6%; HR: 1.59; 95% CI: 1.04-2.43; $P = 0.033$), whereas in the PCI arm, there was no significant difference between patients with 1 and ≥2 HCLs (Figure 3).

## DISCUSSION

The main findings of this study in patients with de novo 3VD and/or LM CAD can be summarized as follows: 1) patients with HCLs had higher 10-year all-cause mortality compared with those without HCLs; 2) the presence of HCLs was an independent predictor of 10-year mortality; 3) in patients without HCLs, CABG had a mortality benefit compared with PCI, whereas in those with HCLs, mortality was similar between the 2 modes of revascularization; 4) the location of the HCL did not have any impact on 10-year mortality, regardless of the assigned treatment; and 5) in the CABG arm, patients with ≥2 HCLs had higher mortality than those with 1 HCL, whereas in the PCI arm, there was no significant difference between patients with 1 or ≥2 HCLs.

In our analysis, the presence of at least 1 HCL was an independent predictor of 10-year all-cause mortality (Table 2). This finding may be attributed to calcium's effects on coronary plaque and the success of revascularization procedures. On a macroscopic level, calcification has been linked with total plaque burden, plaque (in)stability, and delayed healing

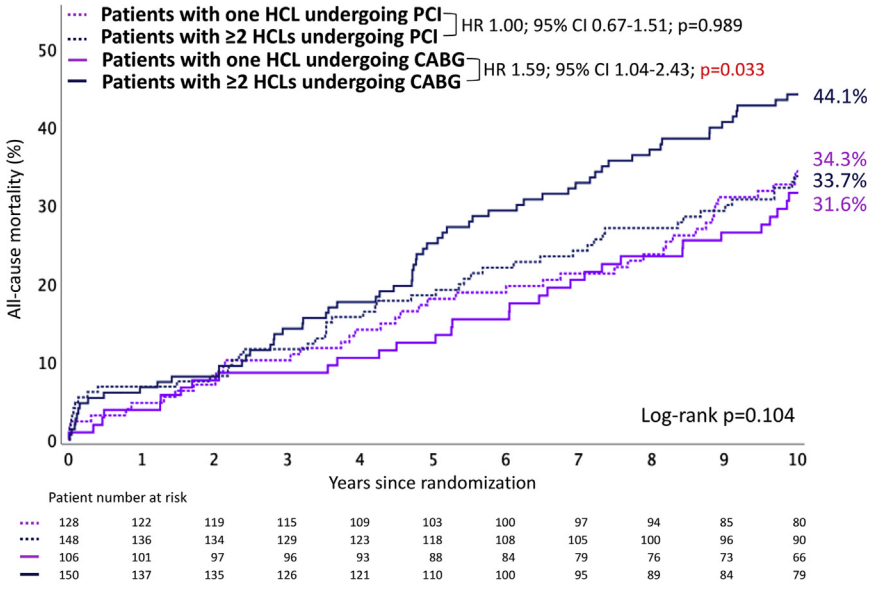
**CENTRAL ILLUSTRATION** **Kaplan-Meier Curves of All-Cause Mortality According to the Presence of at Least 1 Heavily Calcified Lesion and Randomized Treatment With PCI or CABG (N = 1,800)**




**Kawashima, H. et al. J Am Coll Cardiol Intv. 2022;15(2):193–204.**

Patients without heavily calcified lesions (HCLs) undergoing percutaneous coronary intervention (PCI) **(blue dotted line)** versus patients without HCLs undergoing coronary artery bypass grafting (CABG) **(blue solid line)** versus patients with HCLs undergoing PCI **(red dotted line)** versus patients with HCLs undergoing CABG **(red solid line)**.

**FIGURE 3 Kaplan-Meier Curves of All-Cause Mortality at 10 Years According to the Number of Heavily Calcified Lesions and Randomized Treatment With PCI or CABG (N = 532)**




Patients with 1 heavily calcified lesion (HCL) undergoing percutaneous coronary intervention (PCI) **(purple dotted line)** versus patients with ≥2 HCLs undergoing PCI **(dark blue dotted line)** versus patients with 1 HCL undergoing coronary artery bypass grafting (CABG) **(purple solid line)** versus patients with ≥2 HCLs undergoing CABG **(dark blue solid line)**.

after revascularization. Serial intravascular ultrasound and multislice computed tomographic studies have shown that heavy calcification correlates with overall plaque burden, whereas spotty calcification predicts plaque instability (13-15). Calcification progresses with plaque type, as well as with the degree of luminal narrowing (16). In MESA (Multi-Ethnic Study of Atherosclerosis), coronary artery calcification volume was associated with increased cardiovascular risk, although at any level of calcification volume, calcification density was inversely related to risk (17). In addition, heavy calcification delays healing after the implantation of a drug-eluting stent. Torii et al (18) analyzed 46 autopsies with severe calcification and concluded that severe calcification, especially surface calcified area, was an independent predictor of uncovered struts and delayed healing, which are important predictors of late stent thrombosis after implantation of drug-eluting stents.

On a procedural level, during PCI, coronary artery calcification hampers lesion crossing with stents and other devices, as well as limiting the optimal dilation of coronary stenoses with standard balloons, which often results in stent underexpansion and procedural complications such as slow flow or no reflow, dissection, and/or perforation (19). Techniques to treat calcified stenoses, including the use of support wires, buddy wires, guide extensions, low-profile scoring and cutting balloons, high-pressure post-dilatation balloons, and anchoring the guide catheter with inflation of a second balloon in a side branch or distal vessel, have been refined in contemporary practice, further improving success rates (20,21). Furthermore, when successful treatment cannot be achieved using these techniques, dedicated devices, such as rotational atherectomy (RA), orbital atherectomy, intravascular lithotripsy, and lasers, can be used for adequate lesion preparation (22). RA is a useful adjunct for treating coronary stenoses and can effectively ablate calcified plaque, thereby facilitating stent delivery and expansion (5,23,24). The American College of Cardiology and American Heart Association guidelines give RA a Class 2a recommendation in HCLs, which may be difficult to cross or dilate (25). Disappointingly, in the SYNTAX trial, RA was performed in only 27 cases (3.0% of the PCI population), while in the more contemporary randomized EXCEL (Evaluation of XIENCE Versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial, which enrolled patients with unprotected LM disease, it was performed in only 6.0% (26). These findings may reflect that in actual clinical practice, RA is grossly underused, possibly because of cost but also because of the

**TABLE 3 Association Between Randomized Treatment With PCI or CABG and All-Cause Mortality According to the Presence of at Least 1 HCL (N = 1,800)**

| | PCI (n = 903) | CABG (n = 897) | HR (95% CI) | *P* Value | *P* Value for Interaction |
|---|---|---|---|---|---|
| 0-10 y | | | | | |
| Overall | 244 (27.0) | 211 (23.5) | 1.17 (0.97-1.41) | 0.092 | – |
| Patients without HCLs (n = 1,268) | 157 (26.0) | 116 (18.8) | 1.44 (1.14-1.83) | 0.003 | 0.005 |
| Patients with HCLs (n = 532) | 91 (34.0) | 96 (39.0) | 0.85 (0.64-1.13) | 0.264 | |
| 0-5 y | | | | | |
| Overall | 126 (14.0) | 105 (11.9) | 1.20 (0.93-1.56) | 0.167 | – |
| Patients without HCLs (n = 1,268) | 76 (12.2) | 55 (8.7) | 1.43 (1.01-2.02) | 0.045 | 0.103 |
| Patients with HCLs (n = 532) | 50 (18.3) | 50 (19.9) | 0.92 (0.62-1.37) | 0.691 | |
| 5-10 y | | | | | |
| Overall | 122 (16.5) | 107 (14.1) | 1.18 (0.91-1.52) | 0.224 | – |
| Patients without HCLs (n = 1,268) | 81 (15.5) | 61 (10.9) | 1.46 (1.05-2.03) | 0.026 | 0.020 |
| Patients with HCLs (n = 532) | 41 (19.0) | 46 (23.3) | 0.77 (0.51-1.17) | 0.225 | |

The number of deaths (values are percentages based on Kaplan-Meier estimates). The HR shows the risk for all-cause death in patients after PCI vs CABG.
Abbreviations as in Tables 1 and 2.

perceived greater procedural risk in the hands of inexperienced operators.

The poorer survival of patients with HCLs undergoing CABG may be more related to the increased risk associated with total plaque burden and suboptimal site characteristics for graft implantation than to impaired healing after revascularization. Notably, those patients with HCLs had more comorbidities and greater coronary artery complexity compared with those without. In the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial, severe lesion calcification was shown to be an independent predictor of 1-year mortality and major adverse cardiovascular events among 755 patients with acute coronary syndrome who underwent CABG (27). Similarly, data from 1,545 patients treated with CABG in the SYNTAX trial and SYNTAX CABG registry showed that those with severely calcified coronaries had increased mortality at 5-year follow-up (6). Our findings at 10-year follow-up are in keeping with these results.

The present study highlights the interaction between the treatment effect (PCI and CABG) and heavy calcification in terms of all-cause mortality at 10 years. This study also demonstrated that CABG had a mortality benefit compared with PCI in patients without HCLs (Table 3), which is consistent with the main result of the SYNTAXES study (7). In contrast, although not statistically significant, the 10-year

**TABLE 4 Association Between Randomized Treatment With PCI or CABG and All-Cause Mortality at 10 Years in Patients With HCLs (N = 532)**

| | PCI (n = 276) | CABG (n = 256) | HR (95% CI) | *P* Value |
|---|---|---|---|---|
| Patients with HCLs | 91 (34.0) | 96 (39.0) | 0.85 (0.64-1.13) | 0.264 |
| Patients with HCLs and 3VD (n = 329) | 56 (32.6) | 49 (34.5) | 0.96 (0.65-1.41) | 0.827 |
| Patients with HCLs LM disease (n = 203) | 35 (36.6) | 47 (45.0) | 0.75 (0.48-1.16) | 0.193 |
| Patients with HCLs only in proximal-mid coronary vasculature[a] (n = 385) | 67 (34.1) | 67 (37.6) | 0.90 (0.64-1.26) | 0.532 |
| Patients with HCLs in distal coronary vasculature or side branch[b] (n = 147) | 24 (33.8) | 29 (42.4) | 0.74 (0.43-1.27) | 0.275 |
| Patients with HCLs except in left main trunk (n = 413) | 71 (33.8) | 70 (37.2) | 0.91 (0.65-1.26) | 0.568 |
| Patients with HCLs in left main trunk (n = 119) | 20 (34.5) | 26 (44.7) | 0.69 (0.39-1.24) | 0.213 |
| Patients with HCLs except in left main trunk and/or LAD (n = 84) | 12 (26.7) | 11 (29.7) | 0.92 (0.41-2.08) | 0.838 |
| Patients with HCLs in left main trunk and/or LAD (n = 448) | 79 (35.5) | 85 (40.6) | 0.85 (0.62-1.15) | 0.283 |
| Patients with HCLs except in RCA (n = 312) | 52 (33.7) | 51 (34.8) | 0.96 (0.65-1.41) | 0.825 |
| Patients with HCLs in RCA (n = 220) | 39 (34.3) | 45 (45.1) | 0.73 (0.47-1.12) | 0.147 |
| Patients with HCLs except in LCx (n = 310) | 49 (31.2) | 54 (37.6) | 0.80 (0.55-1.18) | 0.264 |
| Patients with HCLs in LCx (n = 222) | 42 (38.0) | 42 (40.8) | 0.91 (0.60-1.40) | 0.673 |

The number of deaths (values are percentages based on Kaplan-Meier estimates). The HR shows the risk for all-cause death in patients after PCI vs CABG. [a]Patients had HCLs only in the left main trunk (segment 5), proximal, or mid coronary vasculature (segments 1-2, 6-7, 11, and 13) (11). [b]Patients had HCLs in distal coronary vasculature or side branch (segments 3, 4, 16, 16a, 16b, 16c, 8, 9, 9a, 10, 10a, 12, 12a, 12b, 14, 14a, 14b, and 15) (11).
3VD = 3-vessel disease; LAD = left anterior descending coronary artery; LCx = left circumflex coronary artery; LM = left main; RCA = right coronary artery; other abbreviations as in Tables 1 and 2.

mortality in patients with HCLs undergoing PCI (34.0%) was numerically lower than that observed after CABG (39.0%) (**Central Illustration, Table 3**). In addition, there were no significant interactions of the mode of revascularization (PCI or CABG) and the presence or absence of HCLs on clinical outcomes at 5 years (major adverse cardiac and cerebrovascular events [defined as death, documented myocardial infarction, any stroke, or any repeat revascularization], all-cause mortality, cardiac mortality, myocardial infarction, any stroke, or any repeat revascularization) (Supplemental Table 3).

There was an apparent lack of benefit at very long term follow-up with CABG versus PCI in the presence of HCLs. The main reason for this observation is that the HCLs affected long-term mortality in patients undergoing CABG up to 10 years, and subsequently, mortality after CABG became similar to that in patients undergoing PCI. As HCLs, the final status of atherosclerosis and inflammation, reflect the aging process, the complexity and extensiveness of CAD, and comorbidity (28-30), it is possible that the currently available revascularization methods do not provide benefit in the prevention of long-term mortality. Therefore, this study highlights the need for further research on this topic focusing on this specific population with HCLs, representing 30% (n = 532) of patients with 3VD and/or LM disease in the SYNTAXES study (n = 1,800).

In general, for short- and mid-term outcomes, CABG is preferred to PCI in patients with HCLs because of the higher rate of complete revascularization and less need for repeat revascularization. However, there is only scarce research on long-term mortality between PCI and CABG up to 10 years. As shown here, the treatment effect of PCI versus CABG on all-cause mortality varies over time (**Central Illustration**). The benefit of CABG over PCI is time dependent, especially for all-cause mortality. For example, in another SYNTAXES subgroup analysis of the elderly population (age >70 years), at 10 years, there was no significant difference in all-cause mortality between PCI and CABG (44.0% vs 41.5%; HR: 1.08; 95% CI: 0.84-1.40; $P = 0.530$), whereas in non-elderly patients (age ≤70 years), PCI was associated with numerically higher mortality compared with CABG (21.1% vs 16.6%; HR: 1.30; 95% CI: 1.00-1.69; $P = 0.052$) (31). Furthermore, a previous study demonstrated that mortality after PCI and CABG converged between 15- and 40-year follow-up (32). In our analysis, patients with HCLs were significantly older than those without (**Table 1**). This could imply that the mortality difference between patients with HCLs undergoing PCI and CABG may converge after 10 years. Therefore, we believe that our findings at 10 years are in line with the general findings preferring CABG in the mid and long term, whereas the benefit of very long term follow-up might be more complex to capture and comprehend.

**STUDY LIMITATIONS.** First, the present study was a post hoc analysis and should be considered only as hypothesis generating. Second, the characterization of lesion calcification was performed on the basis of the angiographic images and relied on the visual estimations of experts. To increase interobserver and intraobserver agreement, we decided to categorize lesion calcium in a binary fashion (severe vs non-severe calcification) according to the anatomical SYNTAX score, as it has been shown that this classification is more reproducible than the scheme of none or mild, moderate, and severe proposed in other studies (33,34). In addition, we classified patients on the basis of the presence of heavy calcification at the lesion site. We did not consider the presence of heavy calcification in segments with nonobstructive (<50% diameter stenosis) CAD, which may, however, have been the landing zone for graft anastomoses and have compromised the medium-term success of the procedure.

Third, the SYNTAX trial was conducted between 2005 and 2007, with a predominant use of first-generation paclitaxel-eluting stents for treatment with PCI, limiting the generalizability of our findings to current practice. However, it is unavoidable that the findings stemming from long-term follow-up data are based on partially outdated technology. Evidence for contemporary technology can be derived from studies with only short-term follow-up.

Finally, the endpoint in the SYNTAXES study was all-cause mortality alone. However, the SYNTAXES study provides randomized data that were meticulously collected and achieved a high follow-up rate of 93.8% for 10-year vital status (1,689 of 1,800 enrolled patients) (7).

## CONCLUSIONS

At 10-year follow-up, the presence of heavy calcification was an independent predictor of mortality, with a similar prognosis following PCI or CABG. Whether HCLs require special consideration when deciding the mode of revascularization beyond their current contribution to the anatomical SYNTAX score deserves further evaluation.

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## PERSPECTIVES

**WHAT IS KNOWN?** Heavy coronary calcification has been associated with worse clinical outcomes in patients undergoing PCI and CABG. However, no previous trial has provided clinical outcomes at 10 years or compared outcomes between PCI and CABG or between patients with 3VD and/or LM disease.

**WHAT IS NEW?** At 10-year follow-up, the presence of heavy calcification was an independent predictor of mortality, with a similar prognosis following PCI or CABG.

**WHAT IS NEXT?** Whether HCLs require special consideration when deciding the mode of revascularization beyond their contribution to the SYNTAX score deserves further evaluation.

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**KEY WORDS** calcification, coronary artery bypass grafting, long-term mortality, percutaneous coronary intervention, SYNTAX

**APPENDIX** For supplemental tables and references, please see the online version of this paper.