# Comparative determinants of 5-year cardiovascular event rates in patients with unprotected left main coronary artery disease

Cheol Hyun Lee[a,*], Jung-Min Ahn[a,*], Pil Hyung Lee[a], Minkyu Han[b], Se Hun Kang[a], Soo-Jin Kang[a], Seung-Whan Lee[a], Young-Hak Kim[a], Cheol Whan Lee[a], Seong-Wook Park[a], Duk-Woo Park[a] and Seung-Jung Park[a]

***Background*** **Diabetes mellitus (DM), low ejection fraction (EF), and the extent of coronary artery disease (CAD) have all been identified as predictors of cardiovascular events in multivessel disease, but their comparative contributions to future risk remain unclear in patients with unprotected left main coronary artery (ULMCA) disease. Through this study we aimed to categorize the risk for cardiovascular events in patients with ULMCA disease using simple clinical descriptors.**

***Patients and methods*** **Our study included a total of 5975 patients with ULMCA disease from the Interventional Research Incorporation Society-Left MAIN Revascularization registry who were treated with percutaneous coronary intervention ($n = 2850$), coronary artery bypass grafting ($n = 2337$), or medical therapy alone ($n = 608$). We categorized the risk for cardiovascular events using simple clinical descriptors (DM, low EF, and the extent of CAD). The primary outcome was a major adverse cardiac or cerebrovascular event (MACCE) (i.e. death from any cause, stroke, myocardial infarction, or repeat revascularization).**

***Results*** **Overall, the 5-year rate of MACCE was highest in the medical group, lower in the percutaneous coronary intervention group, and lowest in the coronary artery bypass grafting group (42.5, 25.7, and 19.9%, respectively; $P < 0.001$). In multivariable modeling, the presence of DM [hazard ratio (HR): 1.25; 95% confidence interval (CI): 1.12–1.40; $P < 0.001$], low EF of 40% or less (HR: 1.83; 95% CI: 1.56–2.15; $P < 0.001$), and the extent of CAD (HR: 1.14; 95% CI: 1.08–1.21; $P < 0.001$) were independent predictors of MACCE; in addition, these factors were consistently associated with a significantly higher risk for MACCE, regardless of index treatment strategies.**

***Conclusion*** **Simple clinical descriptors can assist clinicians in identifying high-risk patients and in predicting future cardiovascular events within the broad range of risk factors for ULMCA disease.** *Coron Artery Dis* **28:387–394**


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[a]Department of Cardiology and [b]Division of Biostatistics, Center for Medical Research and Information, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

Correspondence to Duk-Woo Park, MD, PhD, Department of Cardiology, Asan Medical Center, University of Ulsan College of Medicine, 88, Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: + 82 230 103 995; fax: + 82 247 56898; e-mail: dwpark@amc.seoul.kr

*Cheol Hyun Lee and Jung-Min Ahn contributed equally to the writing of this article.

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## Introduction

Patients with unprotected left main coronary artery (ULMCA) are at highest risk for cardiovascular events among the various categories of patients with obstructive coronary artery disease (CAD) but, depending on their specific clinical and anatomic characteristics, may have varying degrees of future cardiovascular events. Previous studies have reported that diverse clinical and anatomical scores [i.e. European system for cardiac operative risk evaluation, Parsonnet score, Synergy between PCI with Taxus and Cardiac Surgery (SYNTAX) score, clinical SYNTAX score, logistic clinical SYNTAX score, residual SYNTAX score, SYNTAX Score II, or New Risk Stratification Score] are useful for risk stratification, and some scores are important instruments for making decisions pertaining to optimum revascularization in patients with complex CAD (with or without ULMCA involvement) [1–10]. However, no studies have shown that patients managed using these scores do better than those who are not. Despite much focus on personalized medicine (i.e. individualized decision making) using complex clinical or anatomical assessment tools, many existing risk-scoring algorithms have limited reproducibility and clinical performance and are difficult to apply easily in real practice because of their complexity [11–18].

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For clinicians, the ability to rapidly identify the major determinants of risk in patients with ULMCA disease will help them triage more aggressive management toward those at the higher end of the risk spectrum and guide them in deciding the best treatment methods. We therefore aimed to identify major clinical determinants using the large, multinational, all-comers registry of the Interventional Research Incorporation Society-Left MAIN Revascularization (IRIS-MAIN) study, comprising patients with ULMCA disease, spanning from those treated medically to those who underwent percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). This contemporary data set would be potentially useful to evaluate the performance of simple clinical descriptors and to establish the risk for future cardiovascular events in the 'real-world' setting.

## Patients and methods

### Study population and procedures

The IRIS-MAIN registry comprised consecutive patients with significant ULMCA disease (defined as stenosis > 50%) registered between January 1995 and December 2013 (*http://www.clinicaltrials.gov* unique identifier: NCT01341327). This registry is a nonrandomized, multinational, multicenter observational study; the study population was recruited from 50 academic and community hospitals in Asia (China, India, Indonesia, Japan, Malaysia, South Korea, Taiwan, and Thailand). The study had an 'all-comers' design involving the consecutive enrollment of patients with ULMCA disease who were treated with medical therapy alone, or with PCI, or with CABG, and was designed to evaluate 'real-world' outcomes according to treatment modalities. Patients who had undergone prior CABG and those who had undergone concomitant valvular or aortic surgery were excluded. The registry was supported by the CardioVascular Research Foundation, Seoul, Korea, and there was no industry involvement in the design, conduct, or analysis of the study. The study protocol was approved by the Institutional Review Board of each center, and written informed consent was provided by all patients.

Selection of treatment was at the discretion of the attending physician. Several clinical (age, comorbidity, hemodynamic condition, clinical presentation, left ventricular function, prior history of PCI, and patient preference) and angiographic (coronary anatomy, disease extent, and procedural complexity) factors were considered as possibly influencing the selection of the revascularization method. Medical therapy was performed in accordance with accepted guidelines and standards. All PCI procedures were performed according to standard guidelines [19]. The application of predilation, intravascular ultrasound, and intra-aortic balloon pumps and the selection of a specific type of implanted stent were at the discretion of the treating physicians. All patients undergoing PCI received a loading dose of aspirin and adenosine diphosphate receptor antagonists before or during the procedure. After PCI, aspirin was continued indefinitely. Patients treated with bare-metal stents were prescribed clopidogrel or ticlopidine for at least 1 month, and those treated with drug-eluting stents were prescribed clopidogrel for at least 12 months. The decision to prolong the duration of dual-antiplatelet therapy beyond 12 months or to add another antiplatelet or anticoagulant was made at the attending physician's discretion. CABG was performed using standard bypass techniques. The selection of graft was made by the attending surgeon. Whenever possible, the internal thoracic artery was used preferentially for revascularization of the left anterior descending artery. On-pump or off-pump surgery was performed at the discretion of the surgeon.

### Outcomes, definitions, and follow-up

The primary outcome of the study was a major adverse cardiac or cerebrovascular event (MACCE), defined as a composite of all-cause death, myocardial infarction (MI), stroke, or repeat revascularization. The secondary outcomes included each component of primary outcome, serious composite outcome (death, MI, or stroke), or repeat revascularization. All events were based on clinical diagnoses assigned by the patient's physician and were centrally adjudicated by an independent group of clinicians. The cause of death was considered cardiac unless an unequivocal noncardiac cause could be established. MI was defined as follows: (a) if occurring within 48 h following index treatment, an increase in the creatine kinase–myocardial band concentration more than five times the upper reference limit, with either new pathological Q waves or new bundle branch block, or new graft or new native coronary occlusion documented on angiography, or new regional wall motion abnormality, or loss of viable myocardium on imaging studies; (b) if occurring 48 h after index treatment, an increase in the creatine kinase–myocardial band level above the upper reference limit with ischemic symptoms or signs [20]. Stroke, as indicated by neurological deficits, was confirmed by a neurologist on the basis of imaging modalities. Repeat revascularization included any percutaneous or surgical revascularization procedure, regardless of the presence of target or nontarget lesions.

Patient demographics, cardiovascular risk factors, clinical manifestations, hemodynamic status, left ventricular function, extent of CAD, details of the procedures, and outcomes during follow-up were collected from each center and were recorded in the prespecified, web-based, standardized case report form by independent research personnel. Clinical follow-up was performed at 1 month, 6 months, and 1 year, and then annually thereafter through an office visit or through telephonic contact.

### Statistical analysis

The baseline characteristics of patients were compared according to the index treatment methods (medication, PCI, or CABG). Continuous variables are expressed as mean ± SD, and categorical variables are expressed as

frequencies (percentages). Comparisons between groups were performed using the Kruskal–Wallis test for continuous variables and by means of the $\chi^2$-test or Fisher's exact test for categorical variables, as appropriate. Cumulative event rates and incidence curves for clinical outcomes were generated using the Kaplan–Meier method and compared using the log-rank test.

Multivariable analysis was performed to determine predictors of 5-year clinical outcomes; the candidate variables listed in Table 1 were entered in the Cox model. No method was used to impute missing values or to adjust the model for the presence of missing data. For the purposes of comparing event rates, patients were also classified on the basis of (a) whether they had diabetes mellitus (DM), (b) the presence of low ejection fraction (EF), or (c) the extent of CAD. For the current analyses, these simple clinical descriptors were selected a priori on the basis of clinical and medical knowledge, being well established in previous literature [21–24]. DM was defined as any history of diabetes or current diabetes (diagnosed by at least two fasting blood glucose measures > 126 mg/dl) treated with medication, lifestyle, or both. Low EF was defined as left ventricular EF less than 40%. The extent of CAD was classified as isolated ULMCA disease, or ULMCA with one-vessel, LM with two-vessel, or LM with three-vessel disease, according to extra-ULMCA CAD. Cumulative incidence rates of clinical outcomes are reported for each subgroup according to clinical descriptors.

In addition, unadjusted and adjusted Cox proportional hazard models were used to compare clinical events of PCI and CABG in the overall population and in each major subgroup by key clinical descriptors. To compensate for the nonrandomized design of observational studies and to reduce the effect of potential confounding factors on outcomes, we used a propensity score method. We fitted weighted Cox proportional hazard models using the inverse probability of treatment weighting [25]. A full nonparsimonious model was developed that included all variables shown in Table 1. All reported *P* values are two sided. A *P* value of less than 0.05 was considered statistically significant. Analyses were performed using R software, version 3.1.2.

**Table 1 Baseline characteristics of the patients according to index treatment strategies**

| Variables | Overall (*N* = 5795) | PCI (*N* = 2850) | CABG (*N* = 2337) | Medication (*N* = 608) | *P*-value |
|---|---|---|---|---|---|
| Age (years) | 63.4 ± 10.4 | 62.7 ± 11.0 | 63.5 ± 9.4 | 66.7 ± 10.6 | < 0.001 |
| Sex (male) | 4328 (74.7) | 2128 (74.7) | 1779 (76.1) | 421 (69.2) | 0.002 |
| BMI (kg/m$^2$) | 24.5 ± 3.0 | 24.5 ± 3.0 | 24.5 ± 2.9 | 24.4 ± 3.2 | 0.65 |
| Medically treated diabetes | | | | | |
| Any | 2024 (34.9) | 922 (32.4) | 879 (37.6) | 223 (36.7) | < 0.001 |
| Requiring insulin | 430 (7.4) | 174 (6.1) | 204 (8.7) | 52 (8.6) | 0.001 |
| Hypertension | 3353 (57.9) | 1626 (57.1) | 1337 (57.2) | 390 (64.1) | 0.004 |
| Hyperlipidemia | 2367 (40.8) | 1199 (42.1) | 910 (38.9) | 258 (42.4) | 0.05 |
| Current smoker | 1551 (26.8) | 718 (25.2) | 666 (28.5) | 167 (27.5) | 0.03 |
| Previous myocardial infarction | 607 (10.5) | 230 (8.1) | 316 (13.5) | 61 (10.0) | < 0.001 |
| Previous PCI | 871 (15.0) | 489 (17.2) | 285 (12.2) | 97 (16.0) | < 0.001 |
| Previous stroke | 455 (7.9) | 214 (7.5) | 180 (7.7) | 61 (10.0) | 0.10 |
| Previous congestive heart failure | 205 (3.5) | 71 (2.5) | 101 (4.3) | 33 (5.4) | < 0.001 |
| Chronic lung disease | 160 (2.8) | 67 (2.4) | 70 (3.0) | 23 (3.8) | 0.099 |
| Chronic renal failure | 206 (3.6) | 98 (3.4) | 78 (3.3) | 30 (4.9) | 0.15 |
| Peripheral vascular disease | 356 (6.1) | 92 (3.2) | 216 (9.2) | 48 (7.9) | < 0.001 |
| Atrial fibrillation | 152 (2.6) | 71 (2.5) | 57 (2.4) | 24 (3.9) | 0.096 |
| Clinical presentation | | | | | < 0.001 |
| Stable angina | 2075 (35.8) | 1170 (41.1) | 652 (27.9) | 253 (41.6) | |
| Unstable angina | 2999 (51.8) | 1288 (45.2) | 1461 (62.5) | 250 (41.1) | |
| Myocardial infarction | 721 (12.4) | 392 (13.8) | 224 (9.6) | 105 (17.3) | |
| Left ventricular function | | | | | |
| Mean ejection fraction | 58.0 ± 10.8 | 59.7 ± 9.8 | 56.7 ± 11.3 | 55.4 ± 11.6 | < 0.001 |
| Ejection fraction (< 40%) | 435 (7.5) | 141 (4.9) | 230 (9.8) | 64 (10.5) | < 0.001 |
| Disease extent of CAD | | | | | < 0.001 |
| Isolated LM | 629 (10.8) | 463 (16.2) | 105 (4.5) | 60 (9.9) | |
| LM + 1 vessel | 993 (17.1) | 695 (24.4) | 209 (8.9) | 89 (14.6) | |
| LM + 2 vessel | 1589 (27.4) | 922 (32.4) | 524 (22.4) | 143 (23.5) | |
| LM + 3 vessel | 2584 (44.6) | 770 (27.0) | 1498 (64.1) | 316 (52.0) | |
| LM involved location | | | | | < 0.001 |
| Ostium and mid-shaft | 2208 (38.1) | 1177 (41.3) | 758 (32.4) | 273 (44.9) | |
| Distal bifurcation | 3587 (61.9) | 1673 (58.7) | 1579 (67.6) | 335 (55.1) | |
| Discharge medications | | | | | |
| Aspirin | 5515 (95.2) | 2775 (97.4) | 2221 (95.0) | 519 (85.4) | < 0.001 |
| Clopidogrel | 5249 (90.6) | 2713 (95.2) | 1928 (82.5) | 608 (100.0) | < 0.001 |
| β-Blocker | 2955 (51.0) | 1546 (54.2) | 1120 (47.9) | 289 (47.5) | < 0.001 |
| Calcium channel blocker | 2593 (44.7) | 1241 (43.5) | 1100 (47.1) | 252 (41.4) | 0.009 |
| ACE inhibitor or ARB | 1923 (33.2) | 1103 (38.7) | 635 (27.2) | 185 (30.4) | < 0.001 |
| Statin | 2365 (51.4) | 1059 (54.4) | 1104 (50.4) | 202 (43.7) | < 0.001 |

Data are shown as mean ± SD for continuous variables and absolute *n* (%) for dichotomous variables.
ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor antagonist; CABG, coronary artery bypass graft surgery; CAD, coronary artery disease; LM, left main; PCI, percutaneous coronary intervention.

### Ethical approval

The local ethics committee at each hospital approved the use of clinical data for this study, and all patients provided written informed consent.

## Results

### Patient characteristics

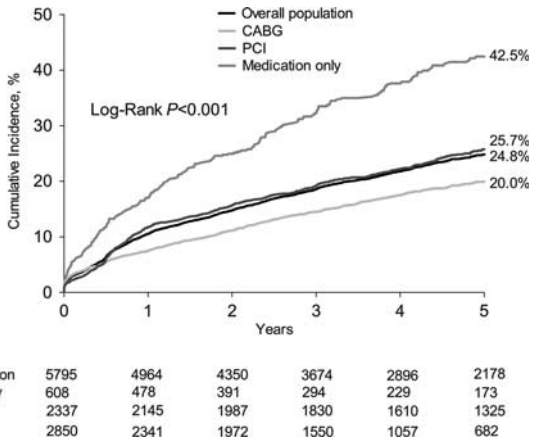
Of 5975 patients with significant ULMCA disease enrolled in the IRIS-MAIN Registry, 2850 received PCI, 2337 received CABG, and 608 received medical therapy alone as the index treatment. The baseline clinical and anatomic characteristics of the overall population and each group according to treatment modality are shown in Table 1. The mean age was 63 years, and 75% were men. DM was present in approximately one-third of patients. The mean EF was 58.0, and 7.5% of patients had low EF (< 40%). A majority had extra-ULMCA CAD; 17% had additional one-vessel, 27% had two-vessel, and 45% had three-vessel disease. Compared with patients who underwent coronary revascularization, those who were treated with medical therapy alone were significantly older and had a higher prevalence of comorbidities. Among patients who underwent revascularization, those treated with CABG were older, had a higher prevalence of DM, previous MI, previous heart failure, peripheral vascular disease, had a lower EF, and had a more severe extent of CAD compared with those who underwent PCI. Procedural and surgical characteristics of patients who underwent ULMCA revascularization are summarized in Supplementary Appendix Table 1, Supplemental digital content 1, *http://links.lww.com/MCA/A143*.

### Predictors and outcomes

The mean overall follow-up was 5.2 (interquartile range: 2.7–7.3) years. During the follow-up period, 1245 patients had at least 1 MACCE event, including 713 with all-cause death, 75 with MI, 101 with stroke, and 483 with repeat revascularization. As shown in Fig. 1 and Table 2, the 5-year rates of MACE were highest in patients treated with medical therapy alone, intermediate in those treated with PCI, and lowest in those treated with CABG (42.5, 25.7, and 19.9%, respectively; $P < 0.001$). The risks for death and a composite of serious outcomes (death, MI, or stroke) were substantially higher in the medical group compared with those in the revascularization group; these rates were similar in the PCI and CABG groups.

Table 3 lists the multivariable predictors of MACCE (death, MI, stroke, or repeat revascularization) in the entire population. The c statistic for this model was 0.64 (95% confidence interval: 0.62–0.65). The prespecified, simple clinical descriptors (DM, low EF, and extent of CAD) were included in the final model and were independently associated with a higher risk for MACCE. Figure 2 and Table 4 show the 5-year rates of MACCE according to baseline risk category stratified by three simple clinical descriptors (DM, low EF, and the extent of CAD) in all patients and in those treated with PCI, CABG, or medication alone. Regardless of index treatment strategy, such key clinical factors apparently categorize the risk for MACCE in patients with significant ULMCA disease. From the lowest-risk to the highest-risk subgroup, the primary outcome rates ranged from 8.7 to 24.9%. Differential rates of all-cause mortality and serious composite outcome (death, MI, or stroke) according to three key clinical determinants are shown in Supplementary Appendix Table 2, Supplemental digital content 1, *http://links.lww.com/MCA/A143*; these factors were also significantly associated with higher risks for events, regardless of the index treatment strategies.

**Fig. 1**




Kaplan–Meier cumulative incidence curves for major adverse cardiac or cerebrovascular events according to treatment strategy. Major adverse cardiac or cerebrovascular events was defined as a composite of death, myocardial infarction, stroke, or repeat revascularization. *P* value was calculated by the log-rank test. CABG, coronary artery bypass graft surgery; PCI, percutaneous coronary intervention.

### Relative effect of percutaneous coronary intervention versus coronary-artery bypass grafting according to key clinical descriptors

The 5-year event rates and unadjusted/adjusted risks for MACCE for PCI and CABG in each subgroup according to three key risk factors are shown in Table 5. In each subgroup stratified by DM, low EF, or the extent of CAD, CABG was consistently associated with a lower risk for MACCE, as compared with PCI. These findings were unchanged after multivariable adjustment for differences in baseline characteristics. Similar analyses were also performed for the risk for all-cause mortality and serious composite outcome (death, MI, or stroke) (Supplementary Appendix Table 3, Supplemental digital content 1, *http://links.lww.com/MCA/A143*). Overall, after baseline risk adjustment, the risks for all-cause mortality and serious composite outcome were similar between PCI and CABG in each risk subgroup.

**Table 2 Five-year event rates of primary and secondary outcomes according to index treatment strategies**

| Outcomes | Overall ($N=5795$) | PCI ($N=2850$) | CABG ($N=2337$) | Medication ($N=608$) | *P*-value |
|---|---|---|---|---|---|
| Primary composite outcome | | | | | |
| MACCE | 24.8 (1245) | 25.7 (591) | 20.0 (437) | 42.5 (217) | <0.001 |
| Secondary outcomes | | | | | |
| Death | 14.6 (713) | 11.3 (246) | 14.1 (306) | 32.0 (161) | <0.001 |
| MI | 2.1 (75) | 2.2 (34) | 1.5 (22) | 4.5 (19) | <0.001 |
| Stroke | 2.8 (101) | 2.0 (33) | 3.7 (56) | 2.9 (12) | 0.023 |
| Composite of death, MI, or stroke | 10.8 (841) | 13.5 (299) | 16.6 (363) | 35.5 (179) | <0.001 |
| Repeat revascularization | 10.0 (483) | 15.0 (340) | 4.4 (90) | 12.0 (53) | <0.001 |

Event rates are shown as Kaplan–Meier estimates [*n* (%)].
MACCE was defined as a composite of all-cause death, MI, stroke, and repeat revascularization.
CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

**Table 3 Multivariable predictors of primary clinical outcome from the Cox regression model**

| Variables | HR (95% CI) | Estimate | *P*-value |
|---|---|---|---|
| Chronic renal failure (yes vs. no) | 2.53 (2.05–3.13) | 0.93 | <0.001 |
| Low ejection fraction (LVEF <40%) (yes vs. no) | 1.83 (1.56–2.15) | 0.60 | <0.001 |
| Chronic lung disease (yes vs. no) | 1.76 (1.37–2.28) | 0.57 | <0.001 |
| Atrial fibrillation (yes vs. no) | 1.54 (1.18–2.00) | 0.43 | 0.001 |
| Peripheral vessel disease (yes vs. no) | 1.43 (1.21–1.69) | 0.36 | <0.001 |
| Previous stroke (yes vs. no) | 1.31 (1.11–1.55) | 0.27 | 0.001 |
| Diabetes mellitus (yes vs. no) | 1.25 (1.12–1.40) | 0.23 | <0.001 |
| Disease extent of CAD, per one-vessel increase | 1.14 (1.08–1.21) | 0.13 | <0.001 |
| Statin use (yes vs. no) | 0.86 (0.77–0.96) | −0.16 | 0.006 |
| Aspirin use (yes vs. no) | 0.36 (0.30–0.43) | −1.03 | <0.001 |

The primary clinical outcome was an MACCE, defined as a composite of death, MI, stroke, or repeat revascularization.
CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac or cerebrovascular event; MI, myocardial infarction.

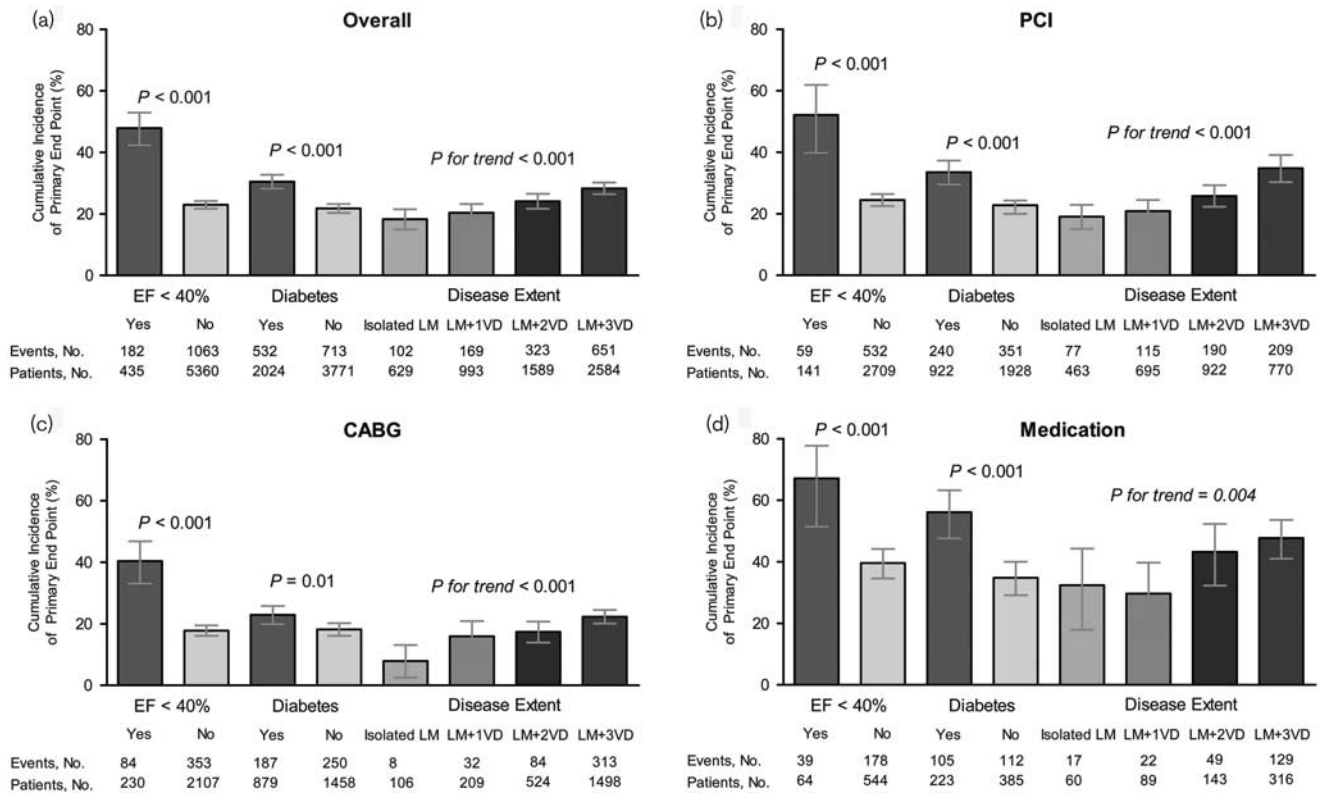
## Discussion

This analysis of a large international registry of ULMCA disease demonstrates that there exist easily applicable simple clinical descriptors of future cardiovascular events in patients at various stages along the treatment continuum. Over the course of 5 years, easily demarcated subgroups of patients stratified by simple clinical descriptors (DM, low EF, and the extent of CAD) showed widely varying risk for MACCE. These findings might provide clinicians with improved estimates of cardiovascular risk, and thus enable more effective identification of higher-risk patients in daily clinical practice who should be targeted for more intensive therapy and follow-up.

Similar to previous reports of complex multivessel or ULMCA disease treated with percutaneous or surgical revascularization [24,26,27], our study found that the presence of DM was the major determinant of major cardiovascular events, irrespective of the index treatment modalities. Because patients with diabetes are prone to a diffuse and rapidly progressive form of atherosclerosis, the deleterious impact of DM on cardiovascular prognosis was already established. With regard to the choice of optimal revascularization methods for patients with complex CAD according to the presence or absence of diabetic status, the threshold for CABG has generally been lower for diabetic individuals than for nondiabetic individuals. However, in our study, we found that the relative treatment effect of PCI and CABG was not modified by diabetic status. These results are similar to those of previous reports [6,28]. Such findings suggest that the presence of DM in itself is not important for deciding between PCI and CABG. Although the exact reasons are still unclear, improved PCI outcomes with advances in stent technology, procedural techniques, and adjunctive pharmacotherapy might narrow the gap in treatment effect between PCI and CABG in diabetic patients. These changes might attenuate the interaction effect of DM on long-term outcomes. From a clinical viewpoint, although aggressive preventive measures against cardiovascular events, adequate blood glucose control, and additional cardiovascular risk factor management remain cornerstones of therapy, the decision to proceed to optimal revascularization in diabetic individuals should be based on the extent of CAD, ischemic burden, ventricular function, and combined comorbidities.

In our study, the presence of left ventricular dysfunction was significantly associated with higher risk for cardiovascular events in patients with ULMCA disease, irrespective of initial treatment strategies. Until recently, optimal therapy for patients with multivessel CAD with left ventricular dysfunction has been controversial. The long-term (10-year) results of the Surgical Treatment for Ischemic Heart Failure trial showed that the rates of death from any cause or from cardiovascular causes were significantly lower in the CABG group than in the medical therapy group, in patients with low EF and CAD [29]. However, because patients with severe left ventricular dysfunction were mostly excluded (or included in small proportions) from recent clinical trials comparing PCI and CABG for complex or ULMCA disease [3,30,31], the relative benefit of CABG over PCI has not been fully determined. Moreover, several observational studies showed conflicting results with regard to the treatment effect of CABG and PCI in patients with low EF [32,33]. Because previous reports were limited by a small number of patients, by subgroup analyses, and by inherent limitations of the study design, further clinical studies are required to guide

**Fig. 2**




Risk for major adverse cardiac or cerebrovascular events in the subsequent 5 years of follow-up in patients according to key clinical descriptors. Major adverse cardiac or cerebrovascular events was defined as a composite of death, myocardial infarction, stroke, or repeat revascularization. Cumulative incidences were estimated from the Kaplan–Meier curves at 5 years and are not simple proportions. CABG, coronary artery bypass graft surgery; EF, ejection fraction; LM, left main; PCI, percutaneous coronary intervention; VD, vessel disease.

**Table 4 Five-year rates of primary clinical outcome according to key clinical descriptors**

| Outcomes | Overall ($N=5795$) | PCI ($N=2850$) | CABG ($N=2337$) | Medication ($N=608$) | $P$-value* |
|---|---|---|---|---|---|
| Diabetes | | | | | |
| Present ($n=2024$) | 30.5 (532) | 33.5 (240) | 18.2 (532) | 56.1 (105) | < 0.001 |
| Absent ($n=3771$) | 21.8 (713) | 22.2 (351) | 22.9 (713) | 34.8 (112) | < 0.001 |
| $P$-value† | < 0.001 | < 0.001 | 0.010 | < 0.001 | |
| Low ejection fraction | | | | | |
| Present ($n=435$) | 47.9 (182) | 52.1 (59) | 40.4 (182) | 67.1 (39) | < 0.001 |
| Absent ($n=5360$) | 23.0 (1063) | 24.5 (532) | 17.8 (1063) | 39.6 (178) | < 0.001 |
| $P$-value† | < 0.001 | < 0.001 | < 0.001 | < 0.001 | |
| Disease extent of CAD | | | | | |
| Isolated LM ($n=629$) | 18.2 (102) | 19.1 (77) | 7.9 (102) | 32.4 (17) | 0.04 |
| LM + 1 vessel ($n=993$) | 20.4 (169) | 20.9 (115) | 15.9 (169) | 29.7 (22) | 0.18 |
| LM + 2 vessel ($n=1589$) | 24.1 (323) | 25.8 (190) | 17.4 (323) | 43.2 (49) | < 0.001 |
| LM + 3 vessel ($n=2584$) | 28.3 (651) | 34.8 (209) | 22.3 (651) | 47.7 (129) | < 0.001 |
| $P$-value for trend† | < 0.001 | < 0.001 | < 0.001 | < 0.001 | |

Event rates are shown as Kaplan–Meier estimates [$n$ (%)].
The primary clinical outcome was a major adverse cardiac or cerebrovascular event, defined as a composite of death, myocardial infarction, stroke, or repeat revascularization.
CABG, coronary artery bypass grafting; CAD, coronary artery disease; LM, left main; PCI, percutaneous coronary intervention.
*$P$ value for comparison between treatment groups.
†$P$ value for comparison between risk factor-group.

decision-making between CABG, PCI, or medical therapy for patients with complex CAD and heart failure.

The anatomic complexity of the lesions is associated with clinical outcomes in patients with complex CAD, and also influences the relative benefit of CABG and PCI. Similarly to previous reports evaluating the clinical impact of CAD [7,34,35], we found that there was an incremental association between the anatomic extent of CAD and higher risk for clinical events in patients with

**Table 5 Five-year event rates and unadjusted and adjusted hazard ratios for primary clinical outcome between coronary artery bypass grafting and percutaneous coronary intervention, according to key clinical descriptors**

| | 5-Year event rate [*n* (%)] | | Unadjusted | | Adjusted by IPTW | |
|---|---|---|---|---|---|---|
| Outcomes | CABG | PCI | HR (95% CI)[a] | *P*-value | HR (95% CI)[a] | *P*-value |
| Overall population | 20.0 (437/2337) | 25.9 (591/2850) | 0.82 (0.74–0.92) | <0.001 | 0.62 (0.56–0.70) | <0.001 |
| Diabetes | | | | | | |
| Present (*n* = 1801) | 23.0 (187/879) | 33.5 (240/922) | 0.72 (0.61–0.86) | <0.001 | 0.58 (0.49–0.69) | <0.001 |
| Absent (*n* = 3386) | 18.2 (250/1458) | 22.2 (356/1928) | 0.86 (0.75–0.99) | 0.035 | 0.64 (0.56–0.74) | <0.001 |
| Low ejection fraction | | | | | | |
| Present (*n* = 371) | 40.4 (84/230) | 52.1 (62/141) | 0.72 (0.53–0.97) | 0.047 | 0.76 (0.56–1.03) | 0.079 |
| Absent (*n* = 4816) | 17.8 (353/2107) | 24.5 (536/2709) | 0.78 (0.69–0.87) | <0.001 | 0.61 (0.54–0.69) | <0.001 |
| Disease extent of CAD | | | | | | |
| Isolated LM (*n* = 569) | 8.0 (8/106) | 19.1 (77/463) | 0.73 (0.45–1.19) | 0.21 | 0.62 (0.38–1.03) | 0.066 |
| LM + 1 vessel (*n* = 904) | 15.9 (32/209) | 20.9 (115/695) | 0.81 (0.59–1.12) | 0.21 | 0.74 (0.54–1.01) | 0.057 |
| LM + 2 vessel (*n* = 1446) | 17.4 (84/524) | 25.8 (190/922) | 0.64 (0.51–0.81) | <0.001 | 0.59 (0.47–0.74) | <0.001 |
| LM + 3 vessel (*n* = 2268) | 22.4 (313/1498) | 34.8 (145/770) | 0.64 (0.54–0.75) | <0.001 | 0.54 (0.47–0.64) | <0.001 |

The primary clinical outcome was a major adverse cardiac or cerebrovascular event, defined as a composite of death, myocardial infarction, stroke, or repeat revascularization.

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio ; IPTW, inverse probability of treatment weighting; LM, left main; PCI, percutaneous coronary intervention.

[a]Hazard ratios are for the CABG group, as compared with the PCI group (referent).

ULMCA disease who were treated with PCI, CABG, or even with medical therapy alone. On the basis of prior evidence showing differential treatment effects of PCI and CABG according to the anatomic complexity of concomitant CAD [3,4], current revascularization guidelines provide a class II indication for PCI in patients with low-to-intermediate anatomical complexity (class IIa for relatively simple and class IIb for intermediate complexity), and a class III indication for PCI in those with highly complex disease [36,37]. It is likely that any future changes in recommendations for ULMCA disease will strongly depend on the results of the EXCEL (NCT01205776) and the NOBLE (NCT01496651) trial.

Our study had a number of limitations. First, we used observational registry data with inherent methodological limitations [38]. Therefore, overall findings should be considered hypothetical and hypotheses-generating only. Second, the choice of treatment was left to the physician and/or patient; thus, our findings are subject to selection bias. Particularly, in the medical therapy group, the status of frailty, short life expectancy, and other severe comorbidities, which were not exactly reflected in our study variables, influenced the worst clinical outcomes. Third, a fair comparison between CABG and PCI in each subgroup according to key clinical descriptors was not possible. Despite appropriate statistical adjustments, comparative findings might be influenced by unmeasured variables known to affect clinical outcomes. Finally, this study was exclusively performed in an Asian population, and it is uncertain whether these findings can be applied to other ethnicities. Moreover, the particulars of clinical practice in the institutions in our study, as well as the specific expertise of the interventional cardiologists and cardiac surgeons who performed the procedures, may differ from those of other institutions and practitioners, potentially limiting the reproducibility of these results in other settings.

### Conclusion

In this largest, multinational registry involving patients with ULMCA disease who underwent medical, percutaneous, or surgical treatment, we found that easily ascertainable and simple clinical descriptors (DM, low EF, or the extent of CAD) were significantly associated with an increased risk for cardiovascular events, regardless of the index treatment strategy. Such key clinical descriptors can simply and rapidly assist clinicians in identifying high-risk subsets within the broad range of risk factors for patients with ULMCA stenosis. Further studies are required to guide decision-making for optimal revascularization strategies in key subgroups according to these clinical descriptors.

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Clinical trial registration: *http://ClinicalTrials.gov* (identifier; NCT01341327).

### Conflicts of interest

There are no conflicts of interest.

## References

1 Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). *Eur J Cardiothorac Surg* 1999; **16**:9–13.

2 Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. *Circulation* 1990; **82**:1078.

3 Serruys PW, Morice MC, Kappetein AP, Colombo A, Holmes DR, Mack MJ, *et al*. Percutaneous coronary intervention versus coronary-artery bypass grafting for severe coronary artery disease. *N Engl J Med* 2009; **360**:961–972.

4 Morice MC, Serruys PW, Kappetein AP, Feldman TE, Stahle E, Colombo A, *et al*. Outcomes in patients with de novo left main disease treated with either percutaneous coronary intervention using paclitaxel-eluting stents or coronary artery bypass graft treatment in the Synergy Between

Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial. *Circulation* 2010; **121**:2645–2653.
5 Garg S, Sarno G, Garcia-Garcia HM, Girasis C, Wykrzykowska J, Dawkins KD, *et al*. A new tool for the risk stratification of patients with complex coronary artery disease: the clinical SYNTAX score. *Circ Cardiovasc Interv* 2010; **3**:317–326.
6 Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A, *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**:639–650.
7 Park DW, Kim YH, Yun SC, Song HG, Ahn JM, Oh JH, *et al*. Complexity of atherosclerotic coronary artery disease and long-term outcomes in patients with unprotected left main disease treated with drug-eluting stents or coronary artery bypass grafting. *J Am Coll Cardiol* 2011; **57**:2152–2159.
8 Farooq V, Vergouwe Y, Raber L, Vranckx P, Garcia-Garcia H, Diletti R, *et al*. Combined anatomical and clinical factors for the long-term risk stratification of patients undergoing percutaneous coronary intervention: the logistic clinical SYNTAX score. *Eur Heart J* 2012; **33**:3098–3104.
9 Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, *et al*. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation* 2013; **128**:141–151.
10 Chen SL, Chen JP, Mintz G, Xu B, Kan J, Ye F, *et al*. Comparison between the NERS (New Risk Stratification) score and the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score in outcome prediction for unprotected left main stenting. *JACC Cardiovasc Interv* 2010; **3**:632–641.
11 Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, *et al*. Strategies for multivessel revascularization in patients with diabetes. *N Engl J Med* 2012; **367**:2375–2384.
12 Ranucci M, Di Dedda U, Castelvecchio S, La Rovere MT, Menicanti L. In search of the ideal risk-scoring system for very high-risk cardiac surgical patients: a two-stage approach. *J Cardiothorac Surg* 2016; **11**:13.
13 Genereux P, Palmerini T, Caixeta A, Cristea E, Mehran R, Sanchez R, *et al*. SYNTAX score reproducibility and variability between interventional cardiologists, core laboratory technicians, and quantitative coronary measurements. *Circ Cardiovasc Interv* 2011; **4**:553–561.
14 Arnaiz-Garcia ME, Gonzalez-Santos JM, Lopez-Rodriguez J, Dalmau-Sorli MJ, Bueno-Codoner M, Arevalo-Abascal A. Survival after major cardiac surgery: performance and comparison of predictive ability of EuroSCORE II and logistic EuroSCORE in a sample of Mediterranean population. *Thorac Cardiovasc Surg* 2014; **62**:298–306. [discussion 306–297].
15 Poullis M, Pullan M, Chalmers J, Mediratta N. The validity of the original EuroSCORE and EuroSCORE II in patients over the age of seventy. *Interact Cardiovasc Thorac Surg* 2015; **20**:172–177.
16 Guida P, Mastro F, Scrascia G, Whitlock R, Paparella D. Performance of the European System for Cardiac Operative Risk Evaluation II: a meta-analysis of 22 studies involving 145,592 cardiac surgery procedures. *J Thorac Cardiovasc Surg* 2014; **148**:3049–3057.e1.
17 Serruys PW, Farooq V, Vranckx P, Girasis C, Brugaletta S, Garcia-Garcia HM, *et al*. A global risk approach to identify patients with left main or 3-vessel disease who could safely and efficaciously be treated with percutaneous coronary intervention: the SYNTAX Trial at 3 years. *JACC Cardiovasc Interv* 2012; **5**:606–617.
18 Capodanno D, Miano M, Cincotta G, Caggegi A, Ruperto C, Bucalo R, *et al*. EuroSCORE refines the predictive ability of SYNTAX score in patients undergoing left main percutaneous coronary intervention. *Am Heart J* 2010; **159**:103–109.
19 Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, *et al*. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines and the Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv* 2012; **79**:453–495.
20 Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, *et al*. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 2013; **62**:1563–1570.
21 Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, *et al*. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. *Lancet* 1994; **344**:563–570.
22 BARI Investigators. Seven-year outcome in the Bypass Angioplasty Revascularization Investigation (BARI) by treatment and diabetic status. *J Am Coll Cardiol* 2000; **35**:1122–1129.
23 Brener SJ, Lytle BW, Casserly IP, Schneider JP, Topol EJ, Lauer MS. Propensity analysis of long-term survival after surgical or percutaneous revascularization in patients with multivessel coronary artery disease and high-risk features. *Circulation* 2004; **109**:2290–2295.
24 Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, *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**:1190–1197.
25 Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000; **11**:550–560.
26 Roffi M, Angiolillo DJ, Kappetein AP. Current concepts on coronary revascularization in diabetic patients. *Eur Heart J* 2011; **32**:2748–2757.
27 Banning AP, Westaby S, Morice MC, Kappetein AP, Mohr FW, Berti S, *et al*. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with cardiac surgery and paclitaxel-eluting stents. *J Am Coll Cardiol* 2010; **55**:1067–1075.
28 Park DW, Kim YH, Song HG, Ahn JM, Kim WJ, Lee JY, *et al*. Long-term outcome of stents versus bypass surgery in diabetic and nondiabetic patients with multivessel or left main coronary artery disease: a pooled analysis of 5775 individual patient data. *Circ Cardiovasc Interv* 2012; **5**:467–475.
29 Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, *et al*. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016; **374**:1511–1520.
30 Park SJ, Kim YH, Park DW, Yun SC, Ahn JM, Song HG, *et al*. Randomized trial of stents versus bypass surgery for left main coronary artery disease. *N Engl J Med* 2011; **364**:1718–1727.
31 Park SJ, Ahn JM, Kim YH, Park DW, Yun SC, Lee JY, *et al*. Trial of everolimus-eluting stents or bypass surgery for coronary disease. *N Engl J Med* 2015; **372**:1204–1212.
32 Hannan EL, Wu C, Walford G, Culliford AT, Gold JP, Smith CR, *et al*. Drug-eluting stents vs. coronary-artery bypass grafting in multivessel coronary disease. *N Engl J Med* 2008; **358**:331–341.
33 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**:1213–1222.
34 Kim YH, Park DW, Kim WJ, Lee JY, Yun SC, Kang SJ, *et al*. Impact of the extent of coronary artery disease on outcomes after revascularization for unprotected left main coronary artery stenosis. *J Am Coll Cardiol* 2010; **55**:2544–2552.
35 Koskinas KC, Siontis GC, Piccolo R, Franzone A, Haynes A, Rat-Wirtzler J, *et al*. Impact of diabetic status on outcomes after revascularization with drug-eluting stents in relation to coronary artery disease complexity: patient-level pooled analysis of 6081 patients. *Circ Cardiovasc Interv* 2016; **9**:e003255.
36 Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, Falk V, *et al*. 2014 ESC/EACTS guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS) Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). *Eur Heart J* 2014; **35**:2541–2619.
37 Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, *et al*. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol* 2014; **64**:1929–1949.
38 Bhatt DL. Advancing the care of cardiac patients using registry data: going where randomized clinical trials dare not. *JAMA* 2010; **303**:2188–2189.