Intravascular Ultrasound Guidance Is Associated With Better Outcome in Patients Undergoing Unprotected Left Main Coronary Artery Stenting Compared With Angiography Guidance Alone

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Background—Small observational studies have indicated better outcome with intravascular ultrasound (IVUS) guidance when performing unprotected left main coronary artery (LMCA) percutaneous coronary intervention (PCI), but the overall picture remains inconclusive and warrants further investigation. We studied the impact of IVUS guidance on outcome in patients undergoing unprotected LMCA PCI in a Swedish nationwide observational study.

Methods and Results—Patients who underwent unprotected LMCA PCI between 2005 and 2014 because of stable coronary artery disease or acute coronary syndrome were included from the nationwide SCAAR (Swedish Coronary Angiography and Angioplasty Registry). Of 2468 patients, IVUS guidance was used in 621 (25.2%). The IVUS group was younger (median age, 70 versus 75 years) and had fewer comorbidities but more complex lesions. IVUS was associated with larger stent diameters (median, 4 mm versus 3.5 mm). After adjusting for potential confounders, IVUS was associated with significantly lower occurrence of the primary composite end point of all-cause mortality, restenosis, or definite stent thrombosis (hazard ratio, 0.65; 95% confidence interval, 0.50–0.84) and all-cause mortality alone (hazard ratio, 0.62; 95% confidence interval, 0.47–0.82). In 340 propensity score–matched pairs, IVUS was also associated with significantly lower occurrence of the primary end point (hazard ratio, 0.54; 95% confidence interval, 0.37–0.80).

Conclusions—IVUS was associated with an independent and significant outcome benefit when performing unprotected LMCA PCI. Potential mediators of this benefit include larger and more appropriately sized stents, perhaps translating into lower risk of subsequent stent thrombosis. Although residual confounding cannot be ruled out, our findings indicate a possible hazard when performing unprotected LMCA PCI without IVUS guidance. (***Circ Cardiovasc Interv*. 2017;10:e004813. DOI: 10.1161/CIRCINTERVENTIONS.116.004813.**)

Key Words: acute coronary syndrome ■ angioplasty ■ comorbidity ■ percutaneous coronary intervention ■ thrombosis

Coronary artery bypass surgery (CABG) has been the traditional revascularization procedure for patients with unprotected left main coronary artery (LMCA) disease. The implementation of percutaneous coronary intervention (PCI) in LMCA disease has risen, however, in part because of research citing comparable outcomes to CABG, especially in uncomplicated cases.[1–3] Two recently published randomized trials demonstrated conflicting results. The first showed that LMCA PCI was noninferior to CABG in patients with a low or intermediate SYNTAX score (Synergy Between PCI With Taxus and Cardiac Surgery) in terms of outcome at 3 years,[4] whereas the other study found CABG to be superior.[5] Today, the guidelines accept LMCA PCI in patients with stable coronary artery disease (CAD) with high surgical risk and a SYNTAX score ≤22.[6,7]

See Editorial by Park and Park

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WHAT IS KNOWN

- Previous studies indicate better outcome with intravascular ultrasound (IVUS) guidance when performing percutaneous coronary intervention of unprotected left main coronary artery.
- These studies have inherent limitations; some are small or single center, and none has appropriately investigated underlying causative mechanisms of benefit with IVUS.

WHAT THE STUDY ADDS

- We present the largest study sample to date and the first nationwide population-based inclusion.
- Unlike previous studies, we show that IVUS use was independently associated with larger stent diameters that in turn was independently associated with improved outcome, providing potential evidence that IVUS confers a clinical benefit through the implantation of larger stents.

Even though PCI techniques have evolved rapidly, LMCA PCI remains a challenging procedure. Stent thrombosis (ST) may be caused by stent underexpansion and is often a fatal complication.[8–11] Intravascular ultrasound (IVUS) is an adjunct imaging modality that can provide valuable information including lesion quantification and luminal dimensions.[12] IVUS is acknowledged as a valuable complement to conventional angiography. It aids the operator's stent selection pre-PCI and provides information on stent apposition and coverage post-PCI.[13,14] In a recent randomized trial of IVUS-guided versus angiography-guided stent implantation, IVUS significantly reduced major adverse cardiac events at 1 year; this reduction was primarily driven by a reduction in target lesion revascularization.[15] Several observational studies on LMCA PCI have indicated clinical benefits of IVUS guidance,[16–18] and it currently has a class 2A recommendation in international guidelines.[6,7]

Although available studies indicate better outcome with IVUS guidance in LMCA PCI, some of these are small or single-center studies with inherent limitations and inconsistent results.[16–20] We sought to investigate the clinical impact of IVUS guidance on a composite end point of all-cause mortality, restenosis, or definite ST in patients undergoing unprotected LMCA PCI in a nationwide population-based observational study using the SCAAR registry (Swedish Coronary Angiography and Angioplasty Registry).

Methods

National Registries

Patients were selected from the SCAAR, a component of the nationwide Swedish web-system for enhancement and development of evidence-based care in heart disease evaluated according to recommended therapies cardiovascular healthcare quality registry.[21] SCAAR is used in all catheterization laboratories (29 during the study period) in Sweden, and all consecutive patients undergoing coronary angiography and PCI are entered into the registry. On enrollment, data are collected prospectively on background characteristics (eg, age, comorbidities, smoking status, and body mass index) and in-hospital and procedural characteristics (eg, indication, Killip class during the procedure, pharmacotherapies, and stent characteristics). Rehospitalizations because of restenosis and ST leading to a new procedure are also gathered prospectively and linked to the prior PCI, providing follow-up for specific coronary segments. Information on comorbidities was enriched from the National Patient Registry that includes International Classification of Disease diagnosis codes from previous inpatient and specialized outpatient hospitalizations.[22] Information on vital status and date of death was obtained from the National Cause of Death Registry. Data from the various registries were merged using the personal identification number unique to every Swedish citizen. Anonymity was protected by replacing the identification number with a serial number. The Regional Ethical Review board at Lund University, Sweden, approved this study.

Study Population and End Points

Patients were included if they underwent PCI and stent implantation in the LMCA because of stable CAD or acute coronary syndrome (ie, ST-segment–elevation myocardial infarction [STEMI], non-STEMI, and unstable angina) between January 1, 2005, and October 31, 2014 (Figure 1). Exclusion criteria were previous CABG, Killip class III–IV during the procedure, complications or deaths in the catheterization laboratory, and stent diameter <3 mm. The primary end point was a composite of all-cause mortality, restenosis, or definite ST, both angiographically verified. Secondary end points were the individual components of the primary end point and probable ST, defined as any unexplained death (ie, any death not explained by noncardiovascular causes) within 30 days, similar to the ARC criteria (Academic Research Consortium).[23] The follow-up time was the maximum available (≈10 years for patients included in 2005).

Statistical Analyses

Continuous variables are expressed as medians and 25th to 75th percentiles. Categorical variables are expressed as counts and percentages. Differences in non-normally distributed continuous variables between the 2 groups were assessed with the Mann–Whitney *U* test. Differences between categorical variables were assessed with the χ^2 test. Predictors of IVUS guidance were calculated using mixed-effects logistic regression, with PCI center entered as a random effect and all other covariates (shown below) as fixed effects. End point event rates were calculated with the Kaplan–Meier estimator, and differences between the 2 groups were calculated with the log-rank test. Univariable and multivariable hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated with the Cox proportional hazards model. For the multivariable models, we identified confounders using a combined approach of (1) reasoning establishing the covariates as plausible confounders based on previous literature and clinical experience and (2) marked differences in variables between the IVUS and the non-IVUS groups (defined as $P<0.25$). Confounders included in the multivariable models were age (3-knot restricted cubic spline), sex, diabetes mellitus, heart failure, previous myocardial infarction, previous stroke, previous PCI, chronic kidney disease (CKD) stage (calculated with the CKD-EPI formula (Chronic Kidney Disease Epidemiology Collaboration) and defined as 3 categories: CKD I–II, III, and IV–V), inclusion time (3 categories: early [2005–2008], mid [2009–2011], and late [2012–2014]), indication (3 categories: stable CAD, non-STEMI, and STEMI), time of day (office hours versus on-call hours), urgency (3 categories: elective, subacute, and emergency), upstream dual antiplatelet therapy, aspirin, ticagrelor, bivalirudin, low-molecular-weight heparin, GP IIb/IIIa inhibitor, other concomitantly diseased coronary vessels (4 categories: none, 1, 2, and 3), American College of Cardiology/American Heart Association lesion classification (3 categories: type A, type B, and type B/C with bifurcation), drug-eluting stent versus bare-metal stent, number of implanted stents in the total procedure (4 categories: 1, 2, 3, and ≥4), number of stented segments during the entire procedure (4 categories: 1, 2, 3, and ≥4), and complete revascularization. PCI center was entered as a random effect to account for center-specific effects.

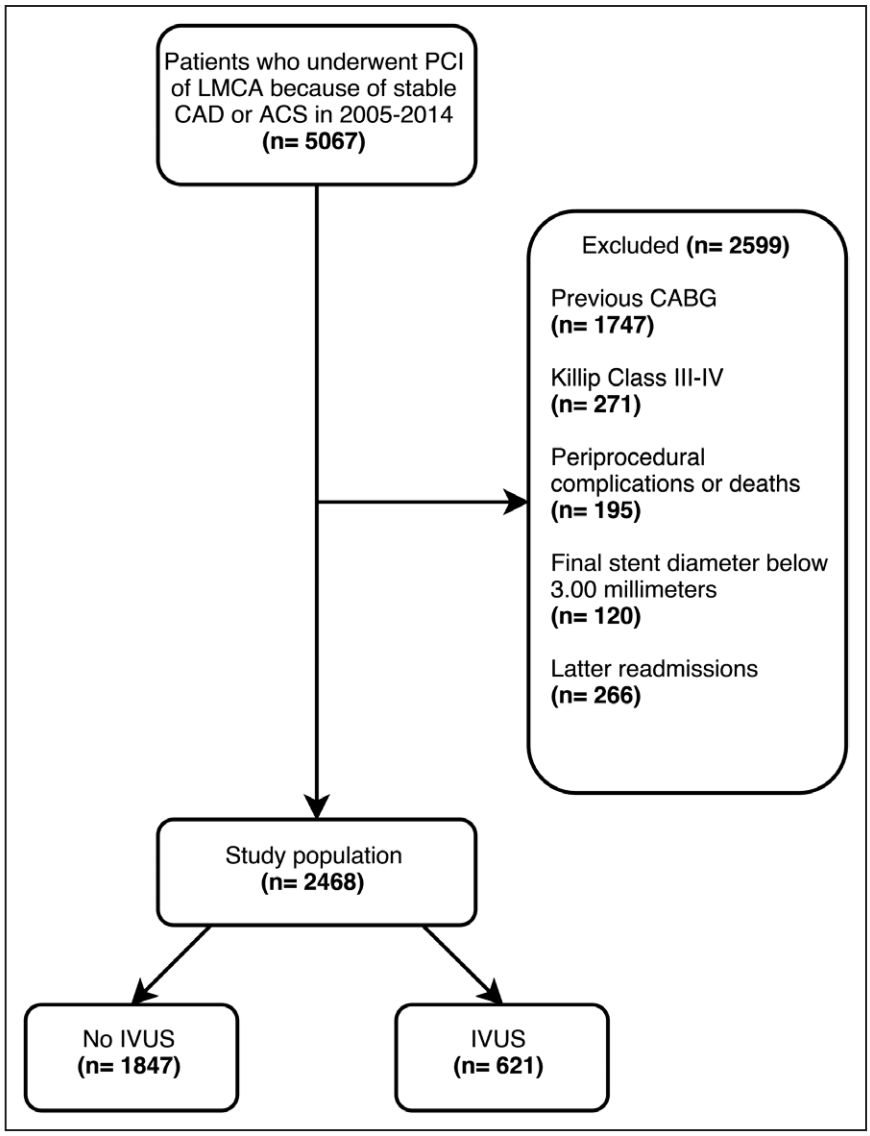

Figure 1. Study flowchart. ACS indicates acute coronary syndrome; CABG, coronary artery bypass grafting; CAD, coronary artery disease; IVUS, intravascular ultrasound; LMCA, left main coronary artery; and PCI, percutaneous coronary intervention.

Missing data were multiply imputed 5× with the chained equation method. All above covariates and outcome variables were used to impute values in covariates with missing data (time of day [1.9%], urgency [1.9%], CKD stage [22.8%], concomitantly diseased vessels [0.3%], American College of Cardiology/American Heart Association lesion classification [0.1%], and number of stents in total procedure [n=1, 0%]).

Propensity score (PS) matching was performed using the aforementioned covariates. First, for each case, a PS between 0 and 1 was calculated using a mixed-effects logistic regression, with PCI center entered as a random effect and all other covariates entered as fixed effects with IVUS guidance as the dependent variable. A higher score indicates a higher predicted probability of undergoing IVUS guidance. Second, we matched cases and controls using the caliper method, set to 0.01 with 1 control per case. We then calculated event rates with the Kaplan–Meier estimator and HRs with the univariable Cox proportional hazards model. The PS matching analysis was restricted to complete cases (only patients with complete data on all covariates).

We also analyzed whether IVUS guidance was independently associated with larger stent diameters (ie, final stent diameter including subsequent postdilatation when performed). Note that reference vessel size was not available in the registry. For this analysis, the unit of observation was implanted stents (n=2734) and not restricted to 1 per individual. We then investigated the association between stent diameter and the primary end point using the same multivariable Cox proportional hazards model as described above with stent diameter as the exposure instead of IVUS guidance. This was done in 2 approaches, the first used stent diameter as a categorical variable divided into 4 groups and the second input as a continuous variable, stratified by IVUS guidance with interaction *P* values reported.

Sensitivity and Subgroup Analyses

Several sensitivity analyses were performed. First, a complete case analysis using only cases with no missing values. Second, we performed 2 landmark analyses of 30 days and 1 year, where cases were excluded if they died from day 0 to 30 and day 0 to 365, respectively. Third, we gathered information from death certificates in the Swedish Cause of Death Registry and estimated cardiovascular mortality (caution is advised when interpreting the findings because of inherent limitations, ie, <50% agreement with last known main diagnosis and cause of death in the death certificate).[24] Finally, we investigated the effect of IVUS in an unrelated end point of bleeding (defined as a rehospitalization because of bleeding). It is highly unlikely that periprocedural IVUS guidance would have any effect on rehospitalizations for bleeding, but differences in patient characteristics could bias the results in favor of IVUS even in unrelated end points, indicating remaining residual confounding.

We also explored the primary end point analysis in several subgroups: male versus female, age ≤75 versus >75 years, stable CAD

Table 1. Patient Characteristics

	Total Study Population			PS-Matched Population		
	No IVUS (n=1847)	IVUS (n=621)	*P* Value	No IVUS (n=340)	IVUS (n=340)	*P* Value
Demographics						
Age, y	75 (67–82)	70 (62–77)	<0.001	71 (63–79)	72 (64–78)	0.750
Age >75	920 (49.8)	183 (29.5)	<0.001	120 (35.3)	125 (36.8)	0.690
Male	1283 (69.5)	463 (74.6)	0.016	244 (71.8)	248 (72.9)	0.732
Body mass index	26.0 (23.8–28.7) [17.0]	25.9 (24.1–28.7) [7.3]	0.430	26.2 (24.0–29.2)	25.8 (24.0–28.4)	0.395
Current smoker	236 (12.8)	85 (13.7)	0.560	51 (15.0)	41 (12.1)	0.262
Comorbidities						
Diabetes mellitus	428 (23.2)	160 (25.8)	0.190	78 (22.9)	89 (26.2)	0.327
Hypertension	1316 (71.3)	432 (69.6)	0.424	253 (74.4)	247 (72.6)	0.602
Heart failure	208 (11.3)	50 (8.1)	0.024	28 (8.2)	33 (9.7)	0.502
Previous MI	714 (38.7)	204 (32.9)	0.010	119 (35.0)	117 (34.4)	0.872
Previous stroke	199 (10.8)	47 (7.6)	0.021	36 (10.6)	32 (9.4)	0.609
Previous PCI	493 (26.7)	195 (31.4)	0.024	110 (32.4)	116 (34.1)	0.625
Peripheral artery disease	134 (7.3)	44 (7.1)	0.888	22 (6.5)	22 (6.5)	1.000
COPD	127 (6.9)	38 (6.1)	0.514	24 (7.1)	22 (6.5)	0.760
Cancer within 3 y	75 (4.1)	21 (3.4)	0.449	9 (2.6)	13 (3.8)	0.386
Estimated GFR	70.6 (53.7–85.2) [25.3]	75.8 (62.6–90.6) [15.3]	<0.001	75.1 (59.2–89.4)	74.5 (61.3–89.2)	0.649
Chronic kidney disease stage			<0.001			0.444
Stage I–II	895 (64.9) [25.3]	416 (79.1) [15.3]		251 (73.8)	264 (77.6)	
Stage III	423 (30.7)	93 (17.7)		76 (22.4)	67 (19.7)	
Stage IV–V	61 (4.4)	17 (3.2)		13 (3.8)	9 (2.6)	
In-hospital characteristics						
Inclusion time			<0.001			0.904
Early (2005–2008)	406 (22.0)	81 (13.0)		42 (12.4)	44 (12.9)	
Mid (2009–2011)	505 (27.3)	200 (32.2)		96 (28.2)	91 (26.8)	
Late (2012–2014)	936 (50.7)	340 (54.8)		202 (59.4)	205 (60.3)	
High-volume PCI center	1114 (60.3)	516 (83.1)	<0.001	275 (80.9)	274 (80.6)	0.923
Indication			<0.001			0.827
Stable CAD	463 (25.1)	222 (35.7)		121 (35.6)	119 (35.0)	
UA/NSTEMI	1106 (59.9)	349 (56.2)		208 (61.2)	207 (60.9)	
STEMI	278 (15.1)	50 (8.1)		11 (3.2)	14 (4.1)	
Time of day			0.001			0.614
Office hours	1480 (82.0) [2.3]	542 (87.8) [0.6]		303 (89.1)	307 (90.3)	
On-call hours	325 (18.0)	75 (12.2)		37 (10.9)	33 (9.7)	
Urgency			<0.001			0.949
Elective	640 (35.5) [2.3]	274 (44.4) [0.6]		150 (44.1)	14 (42.9)	
Subacute	651 (36.1)	257 (41.7)		155 (45.6)	159 (46.8)	
Emergency	514 (28.5)	86 (13.9)		35 (10.3)	35 (10.3)	
Killip class at presentation			0.822			0.155
I	1104 (93.7) [36.2]	440 (93.4)		258 (97.7)	254 (95.5)	
II	74 (6.3)	31 (6.6)		6 (2.3)	12 (4.5)	

(*Continued*)

Table 1. Continued

	Total Study Population			PS-Matched Population		
	No IVUS (n=1847)	IVUS (n=621)	*P* Value	No IVUS (n=340)	IVUS (n=340)	*P* Value
Medical treatments						
Upstream DAPT	1569 (84.9)	557 (89.7)	0.003	302 (88.8)	297 (87.4)	0.554
Aspirin	1801 (97.5)	612 (98.6)	0.128	333 (97.9)	333 (97.9)	1.000
Clopidogrel	1359 (73.6)	444 (71.5)	0.312	248 (72.9)	247 (72.6)	0.931
Prasugrel	54 (2.9)	18 (2.9)	0.974	4 (1.2)	10 (2.9)	0.105
Ticagrelor	420 (22.7)	172 (27.7)	0.012	92 (27.1)	87 (25.6)	0.663
Heparin	1533 (83.0)	522 (84.1)	0.541	280 (82.4)	292 (85.9)	0.208
Bivalirudin	399 (21.6)	161 (25.9)	0.026	63 (18.5)	65 (19.1)	0.844
LMWH	233 (12.6)	57 (9.2)	0.021	33 (9.7)	30 (8.8)	0.692
Fondaparinux	382 (20.7)	142 (22.9)	0.250	76 (22.4)	88 (25.9)	0.282
GP IIb/IIIa inhibitor	256 (13.9)	47 (7.6)	<0.001	31 (9.1)	27 (7.9)	0.583
Procedure characteristics						
Vascular approach			0.825			0.227
Femoral	688 (37.3) [0.1]	228 (36.8) [0.2]		111 (32.6)	126 (37.1)	
Other	1158 (62.7)	392 (63.2)		229 (67.4)	214 (62.9)	
Aortic balloon pump	143 (7.7)	45 (7.2)	0.687	15 (4.4)	18 (5.3)	0.592
Concomitantly diseased vessels			0.002			0.942
None	177 (9.6) [0.3]	81 (13.1) [0.2]		34 (10.0)	32 (9.4)	
1	532 (28.9)	210 (33.9)		123 (36.2)	119 (35.0)	
2	626 (34.5)	193 (31.1)		118 (34.7)	118 (34.7)	
3	496 (26.9)	136 (21.9)		65 (19.1)	71 (20.9)	
ACC/AHA lesion classification			<0.001			0.965
Type A	67 (3.6) [0.2]	15 (2.4)		8 (2.4)	7 (2.1)	
Type B1–B2	766 (41.5)	168 (27.1)		97 (28.5)	98 (28.8)	
Type C or B1–B2 with bifurcation	1011 (54.8)	428 (70.5)		235 (69.1)	235 (69.1)	
Thrombus aspiration	66 (3.6)	18 (2.9)	0.422	4 (1.2)	3 (0.9)	0.704
Direct stent vs balloon and stent			0.531			0.393
Direct stent	503 (27.2)	179 (28.8)		100 (29.4)	90 (26.5)	
Balloon and stent	1344 (72.8)	442 (71.2)		240 (70.6)	250 (73.5)	
Drug-eluting stent	1482 (80.2)	554 (89.2)	<0.001	309 (90.9)	30 (90.3)	0.793
Stent length, mm	16 (12–20)	16 (12–23)	<0.001	18 (12–23)	16 (12–23)	0.764
Stent diameter, mm	3.50 (3.50–4.00)	4.00 (4.00–4.50)	<0.001	4.00 (3.50–4.00)	4.00 (4.00–4.50)	<0.001
Stent diameter categories			<0.001			<0.001
3.00 to <3.50	306 (16.6)	21 (3.4)		30 (8.8)	11 (3.2)	
3.50 to <4.00	689 (37.3)	118 (19.0)		121 (35.6)	64 (18.8)	
4.00 to <4.50	579 (31.3)	251 (40.4)		117 (34.4)	142 (41.8)	
>4.50	273 (14.8)	231 (37.2)		72 (21.2)	123 (36.2)	
Max pressure in balloon (atm)	20 (18–21)	20 (18–20)	0.545	20 (18–20)	20 (18–20)	0.498
Postdilatation	1007 (65.6) [16.8]	503 (87.9) [7.9]	<0.001	259 (83.3)	280 (88.6)	0.055

(*Continued*)

Table 1. Continued

	Total Study Population			PS-Matched Population		
	No IVUS (n=1847)	IVUS (n=621)	*P* Value	No IVUS (n=340)	IVUS (n=340)	*P* Value
Fluoroscopy time, min	17 (11–25) [0.1]	21 (14–30) [0.1]	<0.001	19 (13–29)	22 (14–31)	0.048
Contrast volume, mL	180 (130–250) [0.1]	200 (150–280) [0.1]	<0.001	195 (150–270)	200 (150–280)	0.152
Distal end of stent placement			0.003			0.893
LMCA	596 (38.8) [16.8]	172 (30.1) [7.9]		97 (31.2)	103 (32.6)	
LAD	790 (51.4)	341 (59.6)		179 (57.6)	180 (57.0)	
LCx	143 (9.3)	57 (10.0)		34 (10.9)	31 (9.8)	
Other	87 (0.5)	2 (0.3)		1 (0.3)	2 (0.6)	
No. of implanted stents in total procedure			<0.001			0.922
1	667 (36.1)	185 (29.8) [0.2]		101 (29.7)	106 (31.2)	
2	598 (32.4)	194 (31.3)		109 (32.1)	110 (32.4)	
3	319 (17.3)	109 (17.6)		57 (16.8)	58 (17.1)	
>4	263 (14.2)	132 (21.3)		73 (21.5)	66 (19.4)	
No. of stented segments in total procedure			0.003			0.919
1	580 (31.4)	171 (27.5)		96 (28.2)	100 (29.4)	
2	629 (34.1)	192 (30.9)		99 (29.1)	104 (30.6)	
3	404 (21.9)	146 (23.5)		86 (25.3)	80 (23.5)	
>4	234 (12.7)	112 (18.0)		59 (17.4)	56 (16.5)	
Complete revascularization	1077 (58.3)	452 (72.8)	<0.001	246 (72.4)	236 (69.4)	0.399

Continuous variables are expressed as medians and 25th to 75th percentiles. Categorical variables are expressed as counts and percentages. Brackets denote percentage of cases with missing values. ACC/AHA indicates American College of Cardiology/American Heart Association; atm, standard atmosphere; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; DAPT, dual antiplatelet therapy; GFR, glomerular filtration rate; IVUS, intravascular ultrasound; LAD, left anterior descending; LCx, left circumflex artery; LMCA, left main coronary artery; LMWH, low-molecular-weight heparin; MI, myocardial infarction; NSTEMI, non–ST-segment–elevation myocardial infarction; PCI, percutaneous coronary intervention; PS, propensity score; STEMI, ST-segment–elevation myocardial infarction; and UA, unstable angina.

versus acute coronary syndrome, CKD stage I–II versus III–V, high-volume PCI center (defined as at least 100 cases undergoing LMCA PCI during the study period [9 of 29 centers]) versus low-volume PCI center and early (2005–2009) versus late (2010–2014) inclusion period with HRs, 95% CIs and interaction *P* values reported.

All statistical analyses were performed in STATA (version 14.1; StataCorp, TX) except the matching part of the PS matching which was performed in R with the package matchit (version 3.2.3; The R Foundation for Statistical Computing, Vienna, Austria). A 2-sided *P*=0.05 was considered statistically significant.

Results

Patient Characteristics

After application of inclusion and exclusion criteria (Figure 1), the total study population consisted of 2468 patients, where IVUS guidance was used in 621 (25.2%) cases. Compared with the non-IVUS group, the IVUS group was younger (median age, 70 versus 75 years); was more often men (74.6% versus 69.5%); less often had a history of heart failure, previous myocardial infarction, or stroke (Table 1); and had better renal function. Patients in the IVUS group more often underwent PCI because of stable CAD than those in the non-IVUS group (35.7% versus 25.1%), and procedures were more often elective (44.4% versus 35.5%). The IVUS group was more often treated with upstream (before PCI) dual antiplatelet therapy (89.7% versus 84.9%) and ticagrelor (27.7% versus 22.7%). Patients in the IVUS group had less extensive CAD with fewer concomitantly diseased vessels. Stent diameter was higher in the IVUS group (median, 4 versus 3.50 mm), as were stent length and number of implanted stents during the procedure. Fluoroscopy time and contrast volume were higher in the IVUS group, which was more often completely revascularized during the procedure (72.8% versus 58.3%).

Predictors of IVUS Guidance

Increasing age, previous myocardial infarction, STEMI, emergencies during on-call hours, decreasing renal function, and more extensive CAD were all independently negatively associated with IVUS guidance (Table I in the Data Supplement). Diabetes mellitus, later inclusion period, ticagrelor treatment, ≥4 procedural stents, and complete revascularization were independent factors positively associated with IVUS guidance.

PS Matching

The mean calculated PSs differed significantly before matching between the groups (Figure I in the Data Supplement). Matching generated 340 pairs of IVUS and non-IVUS cases and neutralized the difference in mean PSs. After matching, there were no significant differences in patient characteristics except stent diameter, which was still significantly increased in the IVUS group (Table 1).

End Points

In the total study population, the primary composite end point of mortality, restenosis or definite ST occurred significantly less in the IVUS group (Table 2). After adjustment for confounders, the primary end point still occurred significantly less in the IVUS group (HR, 0.65; 95% confidence interval [CI], 0.50–0.84; *P*=0.001). The secondary end point of mortality was also significantly lower in the IVUS group after adjustment for confounders (HR, 0.62; 95% CI, 0.47–0.82; *P*=0.001). There were numerically fewer restenoses and ST in the IVUS group. In the PS-matched population, the primary end point also occurred less in the IVUS group (Kaplan–Meier event rates: 31.8% versus 53.2%; HR, 0.54; 95% CI, 0.37–0.80; *P*=0.002; Table 2 and Figure 2A). Mortality was also lower in the IVUS group in the PS-matched population (Figure 2B).

Stent Diameter and Outcome

IVUS guidance was independently positively associated with larger stent diameters (Table II in the Data Supplement), and the proportion of large stents (>4.50 mm) was more than doubled in the IVUS group (37.2% versus 14.8%; Table 1). Large stent diameters were independently associated with lower occurrence of the primary end point after adjustment for the same confounders as in the primary end point analysis. The beneficial effect of increasing stent diameter was nominally more pronounced in the IVUS group although without significant interactions (Table 3).

Sensitivity and Subgroup Analyses

The complete case outcome analysis using only cases with no missing values yielded similar results about the primary end point (IVUS versus no IVUS HR, 0.64; 95% CI, 0.48–0.86; *P*=0.003). The 30-day landmark analysis of the primary end point showed a slightly higher but still significant HR (0.74; 95% CI, 0.56–0.97; *P*=0.030), whereas the 1-year landmark analysis showed nominally lower occurrence of the primary end point (HR, 0.79; 95% CI, 0.58–1.08; *P*=0.142) without statistical significance. Cardiovascular mortality in the PS-matched population was significantly lower in the IVUS group (Figure II in the Data Supplement). There was no difference in rehospitalization because of bleeding between the groups (HR, 1.02; 95% CI, 0.68–1.53; *P*=0.927).

The subgroup analyses were in line with the main outcome analysis on the primary end point, and there were no significant IVUS-by-subgroup interactions (Figure 3).

Discussion

The main finding in this nationwide population-based study was that IVUS guidance, compared with angiography guidance alone, was associated with improved outcome when performing unprotected LMCA PCI. The improvement in outcome was primarily driven by a marked and significant reduction of all-cause mortality. Stent diameters were significantly larger in patients who underwent IVUS guidance, and larger stents were independently associated with improved outcome, providing a potential mechanism that could explain our findings. To our knowledge, this is the largest and only nationwide study to date investigating IVUS guidance in unprotected LMCA PCI.

An underexpanded stent is a known risk factor for ST, an often fatal event if it occurs in the unprotected LMCA.[8,10] In our study, the IVUS group had significantly larger stent

Table 2. End Points

End Point	No IVUS	IVUS	Univariable HR (95% CI)	Multivariable HR (95% CI)
Total study population				
Primary composite end point	541/1847 (62.5)	86/621 (33.5)	0.47 (0.37–0.58)*	0.65 (0.50–0.84)*
Mortality	509/1847 (62.1)	75/621 (32.5)	0.44 (0.34–0.56)*	0.62 (0.47–0.82)*
Restenosis	54/1847 (4.3)	14/621 (2.9)	0.72 (0.40–1.29)	NA
Definite stent thrombosis	8/1847 (1.7)	0/1847 (0.0)	NA	NA
Probable stent thrombosis	90/1847 (4.9)	6/621 (1.0)	0.19 (0.09–0.44)*	NA
PS-matched population				
Primary composite end point	68/340 (53.2)	41/340 (31.8)	0.54 (0.37–0.80)†	NA
Mortality	63/340 (56.6)	37/340 (33.7)	0.54 (0.36–0.81)†	NA
Restenosis	10/340 (5.3)	6/340 (2.4)	0.55 (0.20–1.52)	NA
Definite stent thrombosis	1/340 (1.9)	0/340 (0.0)	NA	NA
Probable stent thrombosis	6/340 (1.8)	3/640 (0.9)	0.50 (0.12–1.98)	NA

Number/total number (Kaplan–Meier event rates) for maximum available follow-up time (nearly 10 years). Multivariable model adjusted for age, sex, diabetes mellitus, heart failure, previous myocardial infarction, stroke and PCI, chronic kidney disease stage, inclusion time, indication, time of day, urgency, upstream dual antiplatelet therapy, aspirin, ticagrelor, bivalirudin, low-molecular-weight heparin, GPIIbIIIa inhibitor, other concomitantly diseased coronary vessels, ACC/AHA lesion classification, drug-eluting stent vs bare-metal stent, number of implanted stents in the total procedure, number of stented segments in the total procedure, and complete revascularization. PCI center was entered as a random effect. Propensity score was calculated using the same covariates. HR for IVUS vs No IVUS. CI indicates confidence interval; HR, hazard ratio; IVUS, intravascular ultrasound; NA, not applicable (to too few events or irrelevant model); and PS, propensity score.

*$P \leq 0.001$, †$P < 0.01$.

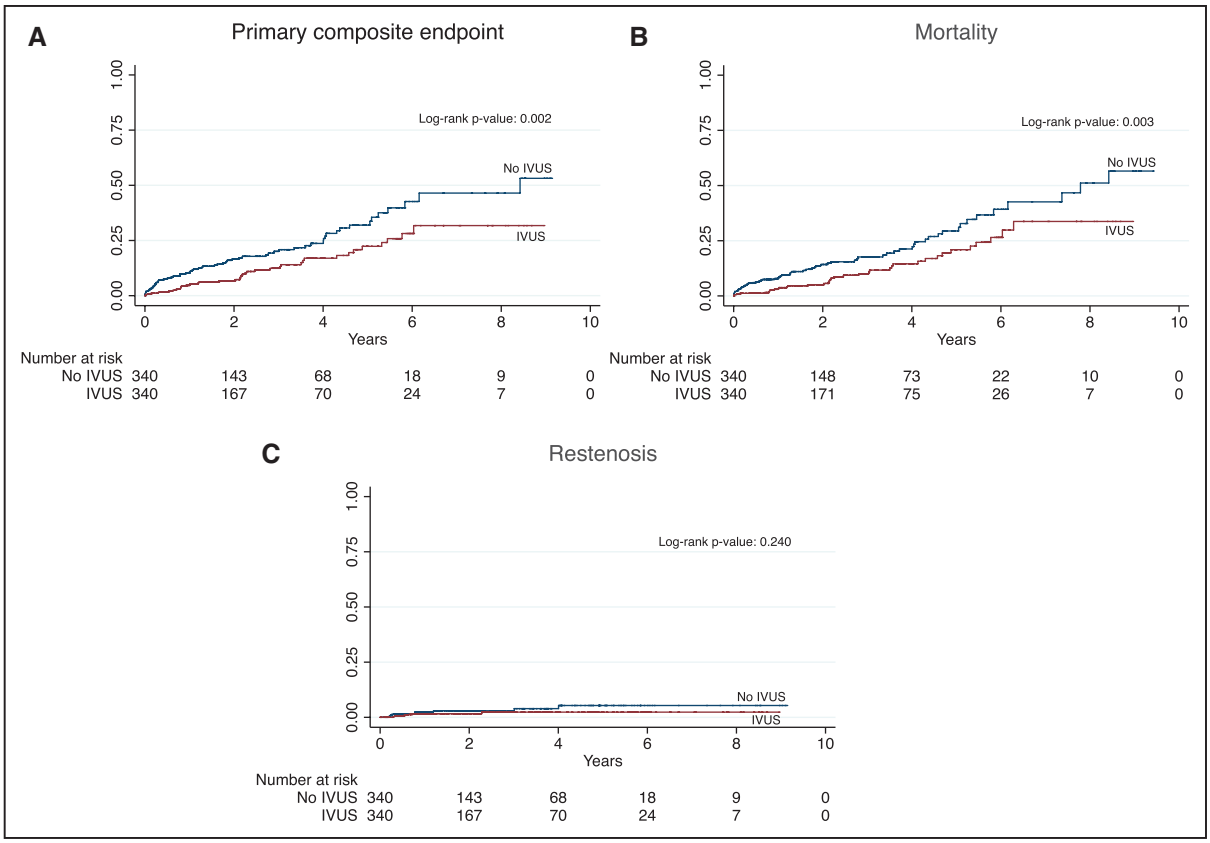

Figure 2. A–C, End points in the propensity score-matched population. Cumulative Kaplan–Meier estimates of end points in the propensity score-matched population. The intravascular ultrasound group had significantly lower occurrence of the primary composite end point and mortality.

diameters, possibly a result of better pre-PCI lesion and lumen characterization, but likely also because of post-PCI IVUS evaluations with subsequent postdilatation, which was more frequent in the IVUS group. Other studies have similarly shown IVUS guidance to be associated with larger stent diameters.[16,17] Because underexpanded stents may cause ST, it is reasonable to think that implantation of a larger and more appropriately sized stent could be a key mechanism behind the IVUS-derived benefit seen in our study. The outcome analysis in relation to stent diameter supports this hypothesis.

Although there are many observational studies showing beneficial effects of IVUS guidance, the randomized clinical trials performed on this topic have failed to show consistent favorable results in hard clinical end points.[25] There are several possible explanations to this inconsistency; the rather small randomized trials performed have investigated IVUS guidance in different lesion locations, of varying lengths and complexities, not necessarily comparable to each other, thus diluting a potential positive effect.[25] Currently, there is only 1 small single-center study that investigated IVUS guidance in relation to LMCA PCI in elderly patients, where IVUS was associated with lower occurrence of target lesion revascularization.[20]

Most of the events in our study were deaths while observed restenosis, and definite ST were uncommon. We used a strict definition of angiographically verified definite ST that likely resulted in an underestimation of ST because of its potential presentation as acute circulatory collapse and sudden death, likely explaining why identified definite ST were so few. These patients rarely make it to the catheterization laboratory and ST could only have been confirmed by postmortem

Table 3. Stent Diameter and Outcome

	No IVUS HR (95% CI)	IVUS HR (95% CI)	Interaction *P* Value
Stent size categories			
3.00 to <3.50	Ref	Ref	
3.50 to <4.00	0.93 (0.73–1.19)	0.59 (0.22–1.59)	0.199
4.00 to <4.50	0.92 (0.71–1.18)	0.51 (0.18–1.34)	0.127
>4.50	0.73 (0.52–1.01)	0.25 (0.09–0.73)	0.078
Continuous variable			
Per 1-mm increase	0.86 (0.72–1.04)	0.60 (0.37–0.99)	NA

Association between stent diameter and the primary composite end point of mortality or restenosis in non-IVUS and IVUS groups. Illustrated both as categorical and continuous variables. Hazard ratios calculated with the Cox proportional hazards model. Multivariable model included the same variables as the primary end point analysis. CI indicates confidence interval; HR, hazard ratio; NA, not applicable; and REF, reference category.

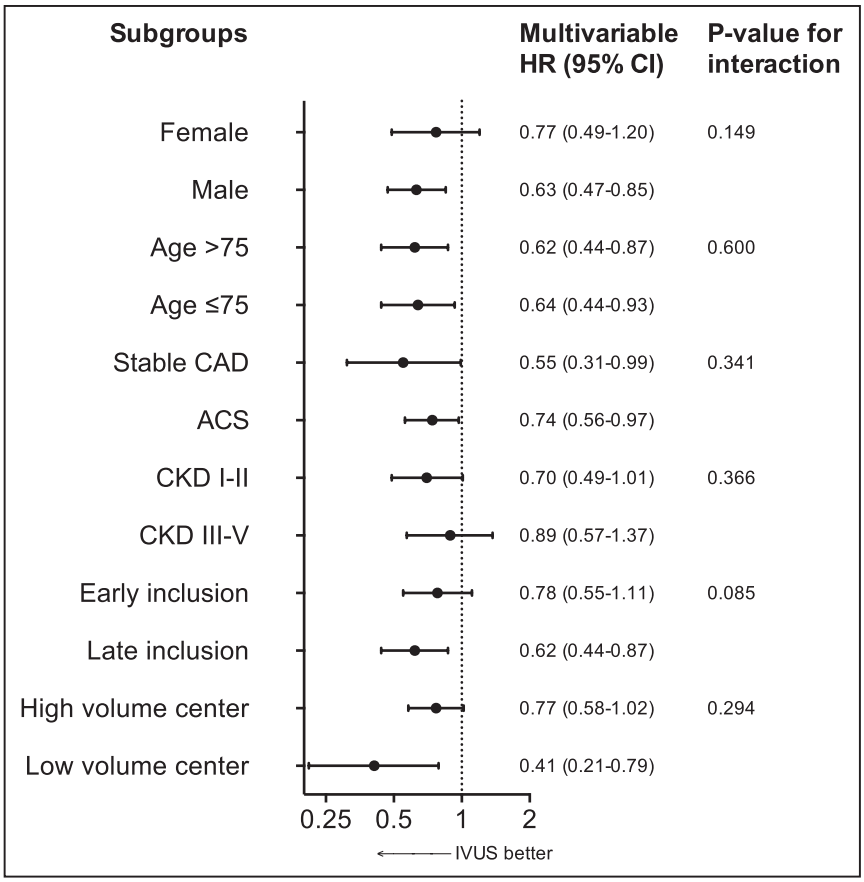

Figure 3. Subgroup analyses. Hazard ratios (HR) for intravascular ultrasound (IVUS) vs no IVUS for the primary composite end point of mortality or restenosis. There were no significant interactions. ACS indicates acute coronary syndrome; CAD, coronary artery disease; and CKD, chronic kidney disease stage.

examinations, on which we regrettably did not have data. More events were classified as probable ST, indicating a potentially much higher rate of undetected ST. Regardless of the type of end point studied, our findings are in accord with previous studies that indicate a clinical benefit of IVUS guidance in LMCA PCI.[16,17,20]

To try to combat residual confounding and selection bias, we applied a strict set of inclusion and exclusion criteria. The rationale behind these were that the scope of this study was to specifically investigate IVUS guidance when stenting the unprotected LMCA; therefore, we excluded patients who had previously underwent CABG. We also excluded unstable patients (Killip class III–IV) to reduce selection bias where unstable patients or complications during the procedure make IVUS guidance unlikely, which could create a strong reverse causal link between not using IVUS and poor outcome that could have confounded the results. Additionally, we excluded patients where the stent diameter was small, indicating a narrow and perhaps tortuous vessel where IVUS guidance was highly unlikely (only 0.4% in the IVUS group compared with 4.8% in the non-IVUS group had stent sizes <3 mm). We also performed PS matching that eliminated statistically significant known baseline differences between the groups, and the results of the PS-matched outcome analysis was in line with the primary analysis.

Limitations

There are several limitations to this study that merit consideration. First, even though we adjusted for known confounders with Cox regression and PS-matched models, residual confounding and in particular unknown confounders may still have biased the results in favor of IVUS. Second, we were not able to account for individual skill differences of different PCI operators, as it is reasonable to believe that those who perform IVUS may be more ambitious and meticulous in their approach, which in part may explain the beneficial effect of IVUS. Third, noncardiac comorbidities in the generally older non-IVUS group could furthermore affect the investigated outcome of all-cause mortality in favor of IVUS. Fourth, SCAAR does not include baseline reference vessel size pre-PCI and difference between the groups may also have influence on stent sizes. Lastly, the register does not provide information whether IVUS was used pre-PCI, post-PCI, or both.

Conclusions

IVUS guidance was associated with an independent and significant outcome benefit when performing unprotected LMCA PCI. Potential mediators of this benefit include larger and more appropriately sized stents, perhaps translating into lower risk of subsequent ST. Although residual confounding cannot be ruled out, our findings indicate a possible hazard when performing unprotected LMCA PCI without IVUS guidance.

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