Increased late mortality with percutaneous stenting for unprotected left main coronary artery stenosis relative to coronary artery bypass grafting: A meta-analysis of observational studies

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A recent meta-analysis by Naik and associates¹ of 3733 patients in 2 randomized trials and 8 observational studies revealed no difference in mortality for as long as 3 years between percutaneous coronary stenting (PCS) and coronary artery bypass grafting (CABG) for the treatment of unprotected left main coronary artery (ULMCA) stenosis. Naik and associates¹ extracted and combined not adjusted but unadjusted odds ratios (ORs) for mortality at each of years 1, 2, and 3 after treatment. It is usually appropriate for non-randomized studies to analyze adjusted rather than unadjusted effect estimates, however, and the most appropriate way of summarizing time-to-event data is to use methods of survival analysis and express the intervention effect as a hazard ratio (HR).² We performed a meta-analysis of com-

parative studies of PCS versus CABG for prevention of late mortality (≥ 1 year) in ULMCA stenosis that combined adjusted HRs.

METHODS

All comparative studies of PCS versus CABG enrolling patients with ULMCA stenosis were selected with a 2-level search strategy. First, public domain databases including MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (current through December 2009) were searched with internet-based search engines (PubMed, OVID). Second, relevant studies were culled through a manual search of secondary sources, including references of initially identified articles and a search of reviews and commentaries. Studies considered for inclusion met the following criteria (Tables 1 and 2): the design was a comparative study; the study population consisted of patients with ULMCA stenosis; patients were assigned to PCS versus CABG; and main outcomes included adjusted HR for mortality with at least 1-year follow-up. Study-specific estimates were combined with inverse variance-weighted averages of logarithmic HRs in both fixed- and random-effects models. Where no significant statistical heterogeneity was found, the fixed-effects estimate was used preferentially as the summary measure. Publication bias was assessed mathematically with an adjusted rank correlation test. Metaregression analyses of summary statistics were conducted to investigate the effects of percentages of patients receiving drug-eluting stents and those undergoing off-pump CABG on logarithmic HRs for mortality in an unrestricted maximum likelihood model. All analyses were conducted with Review Manager version 5.0 (Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-Analysis version 2 (Biostat, Englewood, NJ).

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TABLE 1. Studies included in the meta-analysis

First author	Reference	Adjustment method	Follow-up (y)	PCS		CABG	
				N	DES	N	OPCAB
Brener	<i>Am J Cardiol.</i> 2008;101:169-72	Matching on age, EF, history of myocardial infarction, presence of diabetes mellitus, and procedure date	3	97	57%	190	0%
Mäkikallio	<i>Ann Med.</i> 2008;40:437-43	Cox proportional hazard regression adjusted for medication, EF, and acute coronary syndrome	2	49	100%	238	52%
Palmerini 2006 (Bologna Registry)	<i>Am J Cardiol.</i> 2006;98:54-9	Cox proportional hazard regression with propensity score	2	157	60%	154	10%
Palmerini 2007	<i>Eur Heart J.</i> 2007;28:2714-9	Cox proportional hazard regression with propensity score	2	98	100%	161	21
Seung	<i>N Engl J Med.</i> 2008;358:1781-92	Cox proportional hazard regression after propensity score matching	3	542	75%	542	NR
White	<i>JACC Cardiovasc Interv.</i> 2008;1:236-45	Cox proportional hazard regression with propensity score	2.5	120	100%	223	0%
Wu	<i>Ann Thorac Surg.</i> 2008;86:1153-9	Cox proportional hazard regression after propensity score matching	2	135	41%	135	NR
Total				1198		1643	

PCS, Percutaneous coronary stenting; CABG, coronary artery bypass grafting; DES, drug-eluting stents; OPCAB, off-pump coronary artery bypass; EF, ejection fraction; NR, not reported.

TABLE 2. Studies excluded from the meta-analysis

First author	Reference	Reasons for exclusion
Buszman	<i>J Am Coll Cardiol.</i> 2008;51:538-45	No HR could be abstracted
Chieffo	<i>Circulation.</i> 2006;113:2542-7	No adjusted HR (only adjusted odds ratio) could be abstracted
Hsu	<i>Int Heart J.</i> 2008;49:355-70	No adjusted risk estimates could be abstracted
Lee	<i>J Am Coll Cardiol.</i> 2006;47:864-70	No adjusted risk estimates could be abstracted
Rodés-Cabau	<i>Circulation.</i> 2008;118:2374-81	No adjusted risk estimates could be abstracted
Sanmartín	<i>Am J Cardiol.</i> 2007;100:970-3	No adjusted risk estimates could be abstracted
Serruys (SYNTAX)	<i>N Engl J Med.</i> 2009;360:961-72	No HR could be abstracted; only 39% of patients had unprotected left main coronary artery stenosis

HR, Hazard ratio; SYNTAX, Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

RESULTS

Our search selected 7 qualifying nonrandomized studies of PCS versus CABG that enrolled patients with ULMCA stenosis (Table 1). In total, our meta-analysis included data on 2841 patients with ULMCA stenosis assigned to undergo PCS or CABG.

Pooled analysis of the 7 studies demonstrated a statistically significant 35% increase in HR for mortality with PCS relative to CABG (fixed-effects HR, 1.35; 95% confidence interval [CI], 1.04–1.75; effect $P = .02$; heterogeneity $P = .11$; Figure 1, A). There was no evidence of significant

publication bias ($P = .88062$). Metaregression analyses revealed that the percentage of patients receiving DES was statistically nonsignificantly associated with improved PCS treatment estimates ($P = .05908$; Figure 1, B), whereas that of those undergoing off-pump CABG was statistically significantly associated with impaired CABG treatment estimates ($P = .02157$; Figure 1, C).

DISCUSSION

The results of our analysis of real-world clinical practice (observational studies) suggest that PCS may increase late

FIGURE 1. A, Late mortality among patients assigned to percutaneous coronary stenting (PCS) versus coronary artery bypass grafting (CABG). SE, Standard error; IV, inverse variance; CI, confidence interval. Studies are listed by first author; publication data are given in Table 1. B, Regression of percentages of patients receiving drug-eluting stents (DES) on log hazard ratio for late mortality. C, Regression of percentages of patients undergoing off-pump coronary artery bypass grafting (OPCAB) on log hazard ratio for late mortality.

(2- to 4-year) mortality by 35% relative to CABG in patients with ULMCA stenosis. The previous meta-analysis by Naik and associates,¹ combining unadjusted ORs from 10 studies, had shown no difference between PCS and CABG at 1 year (OR, 1.00; 95% CI, 0.70–1.41), 2 years (OR, 1.27; 95% CI, 0.83–1.94), and 3 years (OR, 1.11; 95% CI, 0.66–1.86). We abstracted HRs, however, the most appropriate intervention effect for summarizing time-to-event data, adjusted for potential confounding from each individual observational study, and combined them in our meta-analysis. Furthermore, metaregression analyses indicated that off-pump CABG may serve as a potential covariate associated with impaired CABG treatment effects.

Results of 2 randomized trials excluded from our analysis (Table 2) were controversial. In the small (105 patients) trial by Buszman and colleagues,³ there was a trend toward better late (28 ± 9.9 months) survival after PCS (3 vs 7 deaths in PCS vs CABG group, risk ratio, 0.44; 95% CI, 0.12–1.60). A post hoc analysis of the large (1800 patients) SYNTAX (Synergy between Percutaneous Coronary Intervention

with Taxus and Cardiac Surgery) trial by Serruys and coworkers⁴ showed 1-year rates of major adverse cardiac or cerebrovascular events among patients with ULMCA stenosis to be similar in the PCS and CABG groups (15.8% and 13.7%, respectively, $P = .44$). Regrettably, the SYNTAX trial did not provide mortality data exclusively for patients with ULMCA stenosis. Late results of large, randomized trials are needed to confirm our findings.

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