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Impact of Intravascular Ultrasound Imaging on Early and Late Clinical Outcomes Following Percutaneous Coronary Intervention With Drug-Eluting Stents

Bimmer E. Claessen, MD,*§ Roxana Mehran, MD,*† Gary S. Mintz, MD,* Giora Weisz, MD,*‡ Martin B. Leon, MD,*‡ Ozgen Dogan, MD,‡ José de Ribamar Costa, Jr, MD,‡ Gregg W. Stone, MD,*‡ Irene Apostolidou, MD,‡ Andy Morales, MD,‡ Vasiliki Chantziara, MD,‡ George Syros, MD,‡ Elias Sanidas, MD,‡ Ke Xu, PhD,* Jan G. P. Tijssen, PhD,§ José P. S. Henriques, MD,§ Jan J. Piek, MD,§ Jeffrey W. Moses, MD,*‡ Akiko Maehara, MD,* George D. Dangas, MD, PhD*†

New York, New York; and Amsterdam, the Netherlands

Objectives This study sought to assess the impact of intravascular ultrasound (IVUS)-guided versus angiography-guided drug-eluting stent (DES) implantation.

Background There are limited data on IVUS guidance in the DES era. Therefore, we investigated the impact of IVUS guidance on clinical outcomes in the MATRIX (Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions) registry.

Methods The MATRIX registry prospectively enrolled consecutive, unselected patients treated with sirolimus-eluting stents (SES) (n = 1,504); 631 patients (42%) underwent IVUS-guided stenting, and 873 (58%) had only angiographic guidance. We assessed 30-day, 1-year, and 2-year rates of death/myocardial infarction (MI), major adverse cardiac events (cardiac death, MI, or target vessel revascularization), and definite/probable stent thrombosis in 548 propensity-score matched patient pairs.

Results After matching, baseline and angiographic characteristics were similar in IVUS and no-IVUS groups. Patients in the IVUS group had significantly less death/MI at 30 days (1.5% vs. 4.6%, $p < 0.01$), 1 year (3.3% vs. 6.5%, $p < 0.01$), and 2 years (5.0% vs. 8.8%, $p < 0.01$). Patients in the IVUS group had significantly less major adverse cardiac events at 30 days (2.2% vs. 4.8%, $p = 0.04$) and numerically less major adverse cardiac events at 1 year (9.1% vs. 13.5%, $p = 0.07$) and 2 years (12.9% vs. 16.7%, $p = 0.18$). Rates of MI were significantly lower in the IVUS group at 30 days (1.5% vs. 4.0%, $p < 0.01$), 1 year (1.8% vs. 4.8%, $p < 0.01$), and 2 years (2.1% vs. 5.7%, $p < 0.01$).

Conclusions IVUS-guided stent implantation appears to be associated with a reduction in both early and long-term clinical events. Further investigation in randomized controlled trials is warranted. (J Am Coll Cardiol Intv 2011;4:974–81) © 2011 by the American College of Cardiology Foundation

From the *Cardiovascular Research Foundation, Clinical Trial Center, New York, New York; †Department of Cardiology, Mount Sinai Medical Center, New York, New York; ‡Department of Cardiology, Columbia University Medical Center, New York, New York; and the §Department of Cardiology, Academic Medical Center, Amsterdam, the Netherlands. The MATRIX registry was funded by a research grant from Cordis/Johnson & Johnson to the Cardiovascular Research Foundation, New York, New York. Dr. Claessen has received grant support from Boston Scientific and Volcano. Dr. Mehran has received speaker honoraria (modest)/consulting fees from Cordis/Johnson&Johnson Intervention Systems, Abbott Vascular, AstraZeneca, Cerdiva, Regado Biosciences, and The Medicines Company; and research support from BMS/Sanofi-Aventis. Dr. Mintz has received grant support from and is a consultant for Boston Scientific and Volcano. Dr. Leon was a member of Cordis/Johnson & Johnson Science Advisory Board. Dr. Stone has served on the scientific advisory boards of and received honoraria from Medtronic, Volcano, Boston Scientific, and Abbott Vascular. Dr. Moses has served as a speaker/consultant for Cordis/Johnson & Johnson and Boston Scientific. Dr. Maehara has received research grant support from Boston Scientific; and speaker fees from Volcano. Dr. Dangas has received research grant support from Cordis (to Cardiovascular Research Foundation for the MATRIX study), The Medicines Co., Sanofi-Aventis, and Bristol-Myers Squibb; is a clinical study

Intravascular ultrasound (IVUS) is useful during stent implantation to assess lesion severity, length, and morphology before stent implantation; to optimize stent expansion, extension, and apposition; and to identify and treat possible complications after stent implantation (1). Most of the evidence from the era of bare-metal stents indicates that IVUS guidance offers incremental information leading to lower rates of angiographic restenosis and repeat revascularization (2). In the current era of drug-eluting stents (DES) with ensuing low restenosis rates, the relationship between IVUS-guided DES implantation and clinical outcomes is less well established. Therefore, we investigated the impact of IVUS guidance on clinical outcomes after sirolimus-eluting stent (SES) implantation in an unselected population of patients with obstructive coronary artery disease from the large MATRIX (Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions) registry (3).

Methods

The study design has been previously described (3). Briefly, the MATRIX registry was conducted under an investigative device exemption approved by the U.S. Food and Drug Administration. MATRIX was a prospective, open-label, nonrandomized registry of 1,504 consecutive patients undergoing percutaneous coronary intervention (PCI) with placement of at least 1 SES for single- or multivessel coronary artery disease. Inclusion criteria included de novo or restenotic (including in-stent restenosis and coronary brachytherapy failure) lesions needing stenting with cumulative length ≤108 mm and arterial reference diameter 2.5 to 3.5 mm. Exclusion criteria included known allergies to aspirin, clopidogrel or ticlopidine, heparin, bivalirudin, or any component of a SES. After appropriate institutional review board approval, between March 2004 and August 2006, consecutive consented patients who underwent PCI at the clinical sites using SES were enrolled in this study; all patients granted written informed consent.

PCI and stent implantation were performed in the standard manner. Heparin was administered to maintain an activated clotting time >250 s, although bivalirudin was used as the procedural anticoagulant in most cases (85%) per standard clinical practice at the 2 clinical sites (Columbia University Medical Center, New York, New York, and Lenox Hill Medical Center, New York, New York). Following the intracoronary injection of nitroglycerin, pre- and post-procedural angiography of the involved vessel(s) was performed in at least 2 orthogonal views showing the target lesion with the least amount of foreshortening or vessel overlap to allow for accurate quantitative coronary angiography measurements. Pre- and post-dilation was performed at the operator's discretion. In the event of an additional stent requirement, additional SES use was mandated by the protocol. Use of glycoprotein IIb/IIIa inhibitors were left to the discretion of the operator. Successful stent implantation was defined as a final diameter stenosis of <50% by quantitative coronary angiography with normal flow. Per protocol, physicians prescribed aspirin 325 mg daily for 1 month and 81 mg daily thereafter plus clopidogrel 75 mg daily for at least 1 year after the procedure.

IVUS imaging. IVUS was performed routinely at both participating centers and was performed pre-intervention, post-intervention, or both pre- and post-intervention at the discretion of the operator with use of dedicated imaging personnel for setup and acquisition of high-quality images. Automated pullback was used routinely. The reasons for IVUS use included restenotic lesion, interrogation of intermediate lesion, imaging of dubious angiographic findings, stent expansion assessment, and final result verification. Commercially available IVUS catheters used in this study included Atlantis S (40 MHz, Boston Scientific, Natick, Massachusetts) or Eagle Eye (20 MHz, Volcano, Rancho Cordova, California) interfaced with their respective machine consoles. All IVUS studies were performed after intracoronary administration of 100 to 200 μg nitroglycerin. The IVUS catheter was advanced >5 mm distal to the lesion, and imaging was performed using an automated pullback device to the proximal reference at a pullback speed of 0.5 mm/s. Routine measurements were recorded pre- and post-stent implantation. The treatment response to IVUS findings was at the discretion of the interventional cardiologist.

Abbreviations and Acronyms

DES = drug-eluting stent(s)
IVUS = intravascular ultrasound
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
SES = sirolimus-eluting stent(s)

Follow-up and study endpoints. Follow-up was available in 99.1%, 95.5%, and 85.3% of patients at 30 days, 1 year, and 2 years, respectively; an independent clinical events committee (3) adjudicated all clinical endpoints. The primary endpoint for the current analysis was the occurrence of the composite endpoint of death/MI at 2-year follow-up. Secondary clinical endpoints included major adverse cardiac events (MACE) (a composite of cardiac death, MI or clinically driven target vessel revascularization), death (cardiac death and noncardiac death), MI (Q-wave MI and non–Q-wave MI), clinically driven target vessel revascularization, and stent thrombosis. Stent thrombosis was categorized according to the definitions proposed by the Academic Research Consortium as definite or probable stent thrombosis (4).

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Statistical analysis. Continuous variables were summarized using mean ± SD values and compared using the Student *t* test or Wilcoxon rank-sum test. Categorical variables were summarized using percentages and compared using the chi-square test. The propensity score was estimated from a nonparsimonious logistic regression model for treatment with IVUS versus no IVUS. To calculate the propensity score, the following variables were entered into the model: age, prior coronary artery bypass graft surgery, prior PCI, diabetes mellitus, number of diseased vessels, number of treated vessels, number of treated lesions, location of treated lesions (bypass graft, left main, left anterior descending, circumflex, right coronary artery), and indication for index procedure (elective or acute coronary syndrome). Odds ratios for covariates in this model are shown in Online Table 1. Patients receiving IVUS were then 1-to-1 matched to the patients receiving no IVUS on propensity score using the nearest available pair matching method. Continuous variables were summarized using mean ± SD and were compared using the paired *t* test or Wilcoxon signed-ranks test adjusting for the matched pair. Categorical variables were summarized using frequencies and percentages and compared with Cochran-Mantel-Haenszel test adjusting for the matched pair. Clinical event rates at 30-day and 2-year follow-up were estimated using the Kaplan-Meier method, and differences between groups were compared using the log-rank test. A Value of $p < 0.05$ indicates statistical significance.

A number of sensitivity analyses were performed to investigate the robustness of the results yielded by the propensity-score matched-pair method. First, stepwise multivariate Cox proportional hazards models were constructed for 30-day and 2-year clinical outcomes in the overall study cohort and the propensity-matched cohort with use of IVUS during the procedure forced into every model to evaluate the consistency of the data across all ischemic events. Entry and exit criteria were set at $p < 0.10$ for other candidate variables. The following variables were considered in the models: age (years), male sex, prior MI, prior coronary artery bypass grafting, prior PCI, prior brachytherapy, prior cerebrovascular accident or transient ischemic attack, congestive heart failure, history of peripheral vascular disease, hypertension, hyperlipidemia, diabetes mellitus, smoking, family history of coronary artery disease, chronic renal insufficiency, acute MI (<48 h), cardiogenic shock, and multivessel stenting. Moreover, additional Cox models were constructed in the overall study cohort with use of IVUS during the procedure and the propensity score as the only variables (analysis of covariates), forced into every model as proposed by Rosenbaum and Rubin (5) in their original article on the propensity score.

Table 1. Baseline Characteristics

	Overall MATRIX Cohort			Propensity-Matched Cohort		
	IVUS (n = 631)	No IVUS (n = 873)	p Value	IVUS (n = 548)	No IVUS (n = 548)	p Value
Age, yrs	64.3 ± 11.1	65.2 ± 11.1	0.11	64.8 ± 10.9	64.4 ± 11.4	0.53
Body mass index, kg/m^2	29.0 ± 5.7	29.0 ± 5.5	0.91	29.0 ± 5.7	29.0 ± 5.6	0.89
Male	74.3%	74.7%	0.90	73.7%	73.9%	1.00
Diabetes mellitus	30.1%	36.2%	0.01	31.6%	31.0%	0.90
Hypertension	81.2%	83.4%	0.27	81.5%	80.7%	0.76
Hyperlipidemia	84.5%	84.8%	0.88	83.9%	82.1%	0.47
Family history of coronary artery disease	42.2%	40.3%	0.48	40.6%	40.8%	0.95
Current smoker	11.1%	10.8%	0.87	10.8%	11.5%	0.70
Chronic renal insufficiency	8.5%	11.1%	0.10	8.8%	10.1%	0.54
Congestive heart failure	7.9%	10.7%	0.07	8.5%	9.0%	0.83
History of CVA/TIA	6.8%	8.8%	0.17	7.1%	7.6%	0.73
History of myocardial infarction	29.9%	36.6%	0.02	29.7%	34.0%	0.13
Percutaneous coronary intervention	47.8%	41.3%	0.02	43.6%	42.2%	0.67
Coronary artery bypass grafting	14.2%	25.6%	<0.01	15.7%	16.1%	0.93
Coronary brachytherapy	2.3%	1.9%	0.71	2.2%	1.7%	0.66
Peripheral vascular disease	6.3%	7.9%	0.26	6.5%	7.9%	0.41
Indication for index procedure						
Stable angina with abnormal stress test	65.9%	61.8%	0.68	66.6%	64.0%	0.79
Unstable angina	30.9%	34.7%	0.12	30.5%	32.7%	0.47
Acute myocardial infarction	3.1%	3.5%	0.77	2.9%	3.3%	0.86
Moderate/severe left ventricular dysfunction	7.4%	8.8%	0.26	6.0%	7.8%	0.56

Values are mean ± SD or %.
CVA = cerebrovascular accident; IVUS = intravascular ultrasound; MATRIX = Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions; TIA = transient ischemic attack.

Results

A total of 1,504 patients were enrolled in MATRIX; IVUS was performed during the index procedure in 42.0% of patients (n = 631). There was considerable imbalance in baseline clinical and angiographic characteristics between patients in the IVUS group versus the no-IVUS group, including the rates of diabetes and previous revascularization by PCI or surgery (Tables 1 and 2). After propensity matching, 548 of 631 patients (87%) in the IVUS group were successfully matched to an equal number of controls. The propensity-score model discriminated well (C-statistic: 0.67). The 2 matched groups had similar clinical and angiographic characteristics (Tables 1 and 2). In the IVUS group, lesion pre-dilation was less often used (54.0% vs. 70.2%, $p < 0.01$), post-dilation was performed more often (42.5% vs. 34.1%, $p < 0.01$), the maximum stent inflation pressure was somewhat higher (15.5 ±2.6 atm vs. 15.3 ±2.6 atm, $p = 0.04$), and the final stent diameter was slightly larger than in the no-IVUS group (3.1 ±0.4 mm vs. 3.0 ±0.4 mm, $p < 0.01$).

Clinical outcome. Clinical event rates are presented in Table 3. In the entire MATRIX population, the 30-day rate of death/MI was significantly lower in the IVUS group with numerically lower mortality ($p = 0.056$). At 1 year, patients in the IVUS group had significantly less death/MI, MACE, and MI. At 2 years, patients in the IVUS group had significantly lower rates of death/MI and MI and numerically lower MACE ($p = 0.053$).

In the propensity-matched cohort, at 30 days, patients in the IVUS group had significantly lower rates of death/MI, MACE, mortality, and MI than did the patients in the no-IVUS group. At 1-year follow-up, the significant reduction in mortality with IVUS was no longer present; however, rates of death/MI, MACE, and MI were still significantly lower in the IVUS group. At 2-year follow-up, there was a significant reduction in death/MI and MI and numerically lower MACE in the IVUS group ($p = 0.06$). Although rates of clinically driven TVR and definite/probable stent thrombosis were numerically lower in the IVUS group throughout the 2-year follow-up period, there was no significant difference. Figure 1 shows Kaplan-Meier curves for all clinical endpoints up to 2-year follow-up in the propensity-matched cohort.

Table 2. Angiographic and Procedural Characteristics

	Overall MATRIX Cohort			Propensity-Matched Cohort		
	IVUS (n = 631)	No IVUS (n = 873)	p Value	IVUS (n = 548)	No IVUS (n = 548)	p Value
Number of lesions treated	1,260	1,619		1,091	1,070	
Number of lesions treated per patient	1.9 ± 1.0	1.8 ± 1.0	0.12	1.9 ± 1.0	1.9 ± 1.0	0.71
Number of vessels treated per patient	1.4 ± 0.6	1.3 ± 0.5	<0.01	1.3 ± 0.6	1.3 ± 0.6	0.91
Treated vessel			<0.01			0.96
Left main coronary artery	4.8%	2.3%		3.3%	3.3%	
Left anterior descending coronary artery	55.3%	36.8%		51.1%	50.9%	
Left circumflex coronary artery	35.8%	35.2%		37.8%	38.3%	
Ramus intermedius	5.7%	3.4%		5.5%	4.0%	
Right coronary artery	26.1%	36.2%		28.5%	28.3%	
Saphenous vein graft	1.7%	7.0%		1.6%	1.6%	
Arterial bypass graft	0.2%	0.9%		0.2%	0.4%	
Lesion location			<0.01			0.43
Ostial	8.7%	6.7%		8.3%	7.3%	
Proximal	31.0%	30.3%		31.9%	31.6%	
Mid	36.4%	32.3%		35.8%	32.7%	
Distal	12.9%	17.3%		13.4%	15.0%	
Lesion length, mm	17.3 ± 9.6	18.5 ± 10.0	<0.01	17.5 ± 9.6	17.9 ± 9.3	0.33
AHA/ACC lesion type B2/C	68.2%	65.5%	0.17	67.0%	62.8%	0.25
Rotational atherectomy	1.0%	0.8%	0.42	1.2%	0.9%	0.52
Stent length, mm	23.5 ± 12.24	24.5 ± 13.0	0.05	23.3 ± 12.0	23.8 ± 12.2	0.38
Stent diameter, mm	3.09 ± 0.41	3.00 ± 0.41	<0.01	3.1 ± 0.4	3.0 ± 0.4	<0.01
Maximum inflation pressure, atm	15.4 ± 4.7	14.6 ± 4.6	<0.01	15.5 ± 2.6	15.3 ± 2.6	0.04
Pre-dilation performed	54.5%	71.2%	<0.01	54.0%	70.2%	<0.01
Post-dilation performed	43.8%	33.6%	<0.01	42.5%	34.1%	<0.01
Glycoprotein IIb/IIIa inhibitor used	8.9%	7.7%	0.45	8.2%	8.4%	0.91

Values are mean ± SD or %.

ACC = American College of Cardiology; AHA = American Heart Association; other abbreviations as in Table 1.

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Table 3. Clinical Outcome in the Entire MATRIX Population and the Propensity-Matched Cohort

	Overall MATRIX Cohort			Propensity-Matched Cohort		
	IVUS (n = 631)	No IVUS (n = 873)	p Value	IVUS (n = 548)	No IVUS (n = 548)	p Value
30-day outcome						
Death/MI	1.6%	3.6%	0.02	1.5%	4.6%	<0.01
MACE	2.5%	3.8%	0.18	2.2%	4.8%	0.04
Mortality	0.0%	0.6%	0.056	0.0%	0.7%	0.99
Cardiac death	0.0%	0.3%	0.14	0.0%	0.6%	0.99
Noncardiac death	0.0%	0.3%	0.14	0.0%	0.2%	0.99
MI	1.6%	3.1%	0.06	1.5%	4.0%	<0.01
Q-wave	0.2%	0.2%	0.76	0.2%	0.2%	1.0
Non–Q-wave	1.4%	2.9%	0.06	1.3%	3.9%	0.01
Clinically driven TVR	1.0%	1.2%	0.71	0.7%	1.1%	0.53
Definite/probable ST	0.2%	0.5%	0.32	0.2%	0.4%	0.57
1-yr outcome						
Death/MI	3.6%	5.8%	0.04	3.3%	6.5%	<0.01
MACE	9.6%	13.0%	0.04	9.1%	13.5%	0.07
Mortality	1.8%	2.1%	0.64	1.7%	2.1%	0.49
Cardiac death	1.0%	0.8%	0.77	0.7%	0.9%	0.74
Noncardiac death	0.8%	1.3%	0.23	1.0%	1.1%	0.85
MI	1.9%	4.1%	0.02	1.8%	4.8%	<0.01
Q-wave	0.2%	0.6%	0.21	0.2%	0.6%	0.34
Non–Q-wave	1.8%	3.5%	<0.05	1.7%	4.2%	0.01
Clinically driven TVR	7.3%	9.9%	0.09	7.3%	9.3%	0.43
Definite/probable ST	0.3%	0.9%	0.15	0.4%	0.7%	0.42
2-yr outcome						
Death/MI	5.0%	9.1%	<0.01	5.0%	8.8%	<0.01
MACE	13.4%	17.0%	0.053	12.9%	16.7%	0.18
Mortality	3.0%	4.5%	0.18	3.1%	3.8%	0.39
Cardiac death	1.2%	1.9%	0.63	1.0%	1.8%	0.28
Noncardiac death	1.9%	1.6%	0.32	2.2%	2.0%	0.62
MI	2.1%	5.1%	<0.01	2.1%	5.7%	<0.01
Q-wave	0.2%	0.6%	0.21	0.2%	0.6%	0.34
Non–Q-wave	2.0%	4.6%	<0.01	1.9%	5.1%	<0.01
Clinically driven TVR	11.1%	12.8%	0.25	11.0%	12.1%	0.70
Definite/probable ST	0.5%	0.9%	0.16	0.6%	1.0%	0.48

MACE = major adverse cardiac events; MI = myocardial infarction; ST = stent thrombosis; TVR = target vessel revascularization; other abbreviations as in Table 1.

Figure 2 shows consistent adjusted hazard ratios for the use of IVUS imaging in association with all 30-day and 2-year clinical outcomes for multivariate Cox regression models in the entire MATRIX cohort and the propensity-matched cohort. IVUS imaging was a statistically significant predictor of early (30-day) events including death/MI in the entire MATRIX cohort and also of death/MI and MACE in the propensity-matched cohort. Additionally, IVUS-guidance was identified as a statistically significant predictor of death/MI and MI at 2 years in both the entire MATRIX cohort and the propensity-matched cohorts. Additional Cox models in the entire MATRIX cohort into which we forced only use of IVUS imaging and the propensity score as covariates (analysis of covariates) yielded qualitatively similar hazard ratios (results shown in Online Table 2).

Discussion

Notwithstanding the low overall event rates after SES implantation in this "real world" patient population, the main finding from the current study with blinded evaluation of endpoints was that IVUS guidance was associated with a reduction in early (30-day), medium-term (1-year), and long-term (2-year) clinical outcomes, mostly driven by a reduction in the incidence of MI and the composite endpoint of death or MI.

Due to its ability to provide additional information on lesion characteristics (pre-intervention) and stent deployment (post-intervention), IVUS imaging plays an important role in optimizing DES placement (6). However, only a modest number of studies have been published investigating the impact of

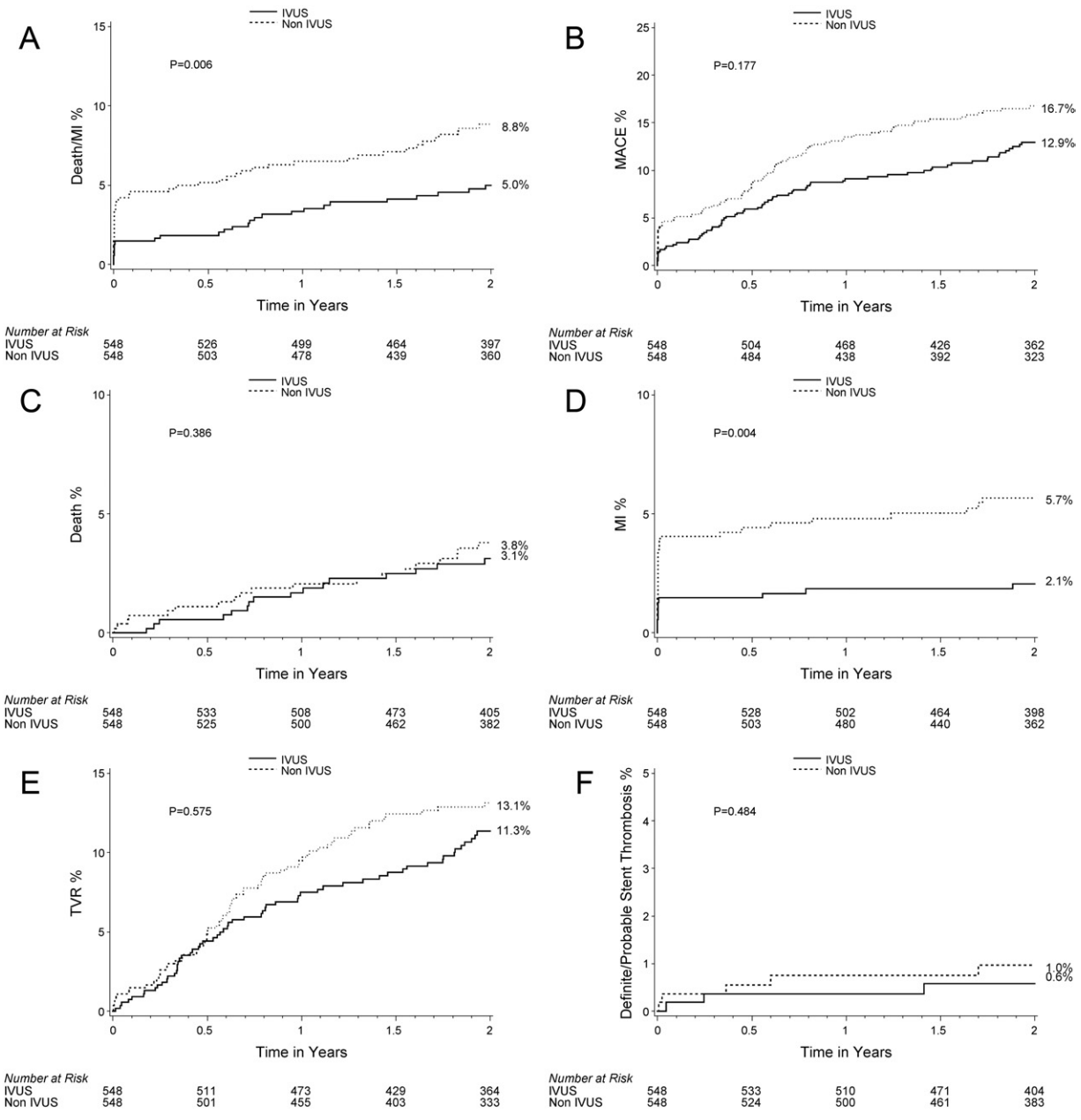

Figure 1. Kaplan-Meier Curves of Clinical Outcomes to 2-Year Follow-Up in the Propensity-Matched Cohort

IVUS = intravascular ultrasound; MACE = major adverse cardiovascular events; MI = myocardial infarction; TVR = target vessel revascularization.

IVUS-guided compared with angiography-guided DES implantation. A study by Roy et al. (7) compared 1-year clinical outcomes in 884 patients who underwent IVUS-guided PCI with a propensity-matched cohort of angiographically guided patients. IVUS guidance was found to be associated with lower rates of definite stent thrombosis at 30 days (0.5% vs. 1.4%, $p < 0.05$) and 1 year (0.7% vs. 2.0%, $p = 0.01$) with a trend toward lower target lesion revascularization at 12 months (5.1% vs. 7.2%, $p = 0.07$). These investigators did not find a significant difference in MI between patients treated with IVUS guidance and those without. This difference can possibly be explained by the fact that only Q-wave MI was collected by Roy et al. (7), whereas both Q-wave and non–Q-wave MIs were collected in the present study. Park et al. (8) reported a significant reduction in 3-year mortality with IVUS guidance in a propensity-matched cohort of 145 matched patient pairs who underwent DES implantation for unprotected left main coronary artery lesions. A recent study by Kim et al. (9)

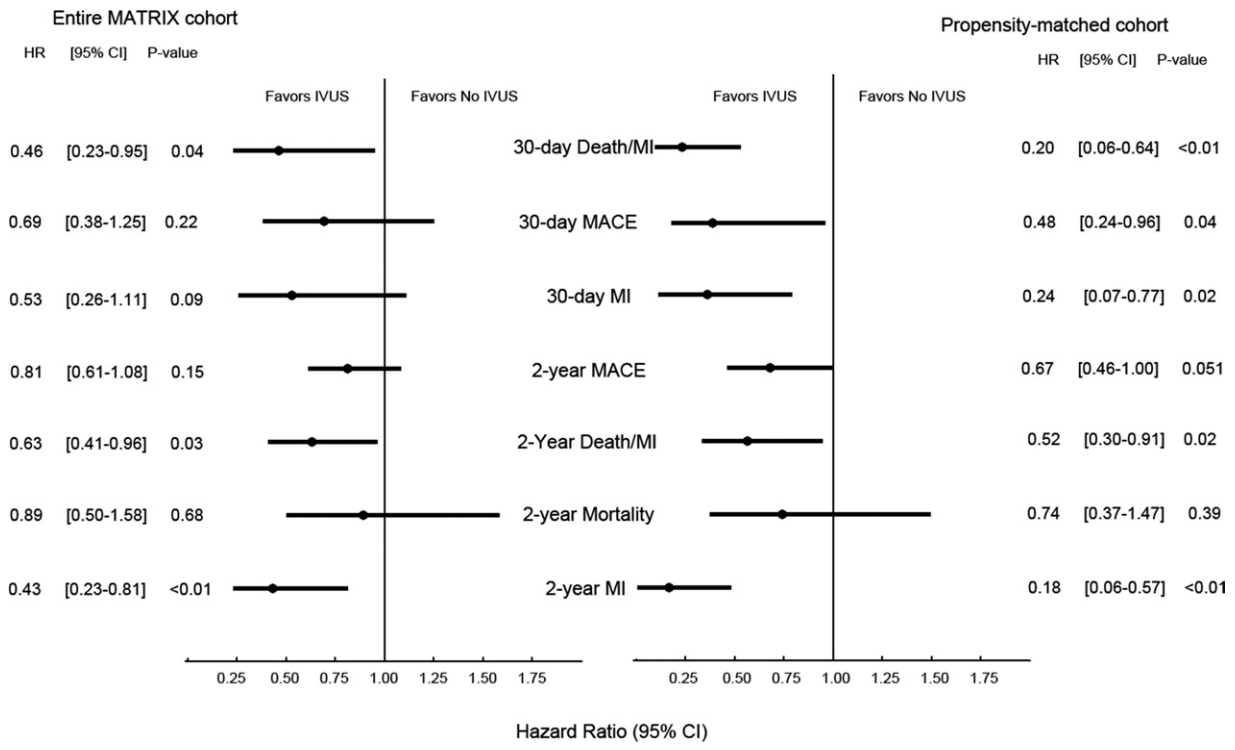

Figure 2. Adjusted Hazard Ratios for IVUS Use for 30-Day and 2-Year Clinical Outcome in the MATRIX and Propensity-Matched Cohorts

Adjusted hazard ratios (HR) (multivariate analysis by Cox methods) for IVUS use for 30-day and 2-year clinical outcome in the entire MATRIX (Comprehensive Assessment of Sirolimus-Eluting Stents in Complex Lesions) cohort and the propensity-matched cohort. HRs are consistent (qualitatively unidirectional) across both statistical approaches, and indicate a favorable effect of IVUS use. CI = confidence interval; other abbreviations as in Figure 1.

reported that IVUS guidance significantly reduced 4-year mortality and very late stent thrombosis after propensity-score adjustment in 420 patients receiving DES for bifurcation lesions. The studies by Roy et al. (7), Park et al. (8), and the current investigators were performed at institutions that routinely, systematically, and similarly use IVUS during stent implantation. Additional information provided by IVUS that, unlike angiography, allows a tomographic image of coronary artery lesions (pre-procedure) and implanted stents (post-procedure), likely influenced the treatment approach as illustrated by the increased usage of post-dilation and direct stenting in the IVUS cohort, especially in the current study.

In the present study, multiple statistical approaches were used to evaluate the impact of IVUS guidance on clinical outcomes (propensity-matching, multivariate Cox methods, and covariate adjustment with the propensity score), yielding similar results (Table 3, Online Table 2, Fig. 2). The analyses suggested IVUS-guided SES implantation was associated with a reduction in both early (30-days) and long-term (up to 2 years) events, most notably a reduction in MI.

Clinical event rates in the IVUS and no-IVUS groups started to diverge soon after the procedure; at 30 days, there were significant differences in death/MI, MACE, mortality, and MI in favor of the IVUS group. Optimization of stent placement in terms of adequate lesion coverage and minimal presence of residual reference segment disease, adequate stent expansion and apposition, and detection of dissections and other complications could explain these favorable short-term results. Visual evaluation of the Kaplan-Meier event curves suggests that clinical events occurred with similar frequency after the early (30-day) separation of events similar to the stent thrombosis free curves reported by Roy et al. (7). Early events were, presumably, mostly related to mechanical issues and were reduced by use of IVUS, whereas later events were more likely related to natural progression of atherosclerotic disease or biologic effects of the DES, but not to mechanical issues and, therefore, were not affected by IVUS guidance.

Due to the low incidence of the important and frequently catastrophic adverse event of stent thrombosis, our study was underpowered to detect any differences in stent thrombosis rates with IVUS guidance. Definite/probable stent thrombosis was numerically lower in the IVUS group throughout the 2-year follow-up period, but there were no statistically significant differences as in the study by Roy et al. (7). Procedural mechanical factors such as inadequate stent expansion and residual edge problems or geographic miss are important correlates of stent thrombosis that can be identified and corrected with IVUS (10,11). Moreover, a recent study suggested optimal stent sizing

with IVUS might contribute to complete neointimal coverage (that is thought to contribute to very late stent thrombosis) after SES implantation (12). Finally, IVUS guidance can be useful in understanding the mechanisms of restenosis (13).

The current study adds to the evidence supporting IVUS guidance in DES placement, although no randomized trials have been completed to date to confirm these findings. Therefore, a large, adequately powered randomized trial investigating the impact of IVUS versus angiography-guided PCI with DES seems warranted.

Study limitations. This was a nonrandomized, observational study performed in 2 centers where IVUS guidance is used in a significant proportion of everyday practice. We used propensity matching to reduce potential bias in patient selection. Although clinical and angiographic characteristics were well balanced in matched patients, the possibility remains of unknown confounders that were not accounted for in the propensity-matching process. For example, we were unable to adjust for the operator performing the procedure, as this variable was not collected in the study database. Some of the analyses were based on a small number of endpoint events; however, results were directionally similar in the propensity-matched comparison as well as in multivariate models with few variables (only IVUS performed a propensity score) and models using more covariates. Although the U.S. Food and Drug Administration–approved SES was the only stent used in this registry, there is no strong rationale for why the impact of IVUS on clinical outcomes ought to differ for other DES. In our clinical practice, the decision to use IVUS imaging was independent of the type of stent. This is especially true because the separation in curves is all in the first 30 days, implying mechanical rather than drug-related effects. Finally, quantitative IVUS assessment was not performed; therefore, we could not assess the relationship between quantitative imaging parameters and clinical outcomes.

Conclusions

IVUS-guided stent implantation appears to be associated with a reduction in both early and long-term clinical events. These findings may be considered hypothesis-generating and further investigation in randomized controlled trials is warranted.

Reprint requests and correspondence: Dr. George D. Dangas, Cardiovascular Institute, Mount Sinai Medical Center, One Gustave L. Levy Place (Box 1030), New York, New York 10029. E-mail: george.dangas@mssm.edu or gdangas@crf.org.

REFERENCES

1. Mintz GS, Nissen SE, Anderson WD, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS). A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2001; 37:1478–92.
2. Parise H, Maehara A, Stone GW, Leon MB, Mintz GS. Meta-analysis of randomized studies comparing intravascular ultrasound versus angiographic guidance of percutaneous coronary intervention in the pre-drug-eluting stent era. Am J Cardiol 2011;107:374–82.
3. Claessen BE, Mehran R, Leon MB, et al. Two-year safety and effectiveness of sirolimus-eluting stents (from a prospective registry). Am J Cardiol 2011;107:528–34.
4. Cutlip DE, Windecker S, Mehran R, et al., for the Academic Research Consortium. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
5. Rosenbaum P, Rubin D. The central role of the propensity score in observational studies for causal effects. Biometrika 1983;70: 41–55.
6. Mintz GS. Features and parameters of drug-eluting stent deployment discoverable by intravascular ultrasound. Am J Cardiol 2007;100:26M–35M.
7. Roy P, Steinberg DH, Sushinsky SJ, et al. The potential clinical utility of intravascular ultrasound guidance in patients undergoing percutaneous coronary intervention with drug-eluting stents. Eur Heart J 2008;29:1851–7.
8. Park SJ, Kim YH, Park DW, et al., for the MAIN-COMPARE Investigators. Impact of intravascular ultrasound guidance on long-term mortality in stenting for unprotected left main coronary artery stenosis. Circ Cardiovasc Interv 2009;2:167–77.
9. Kim SH, Kim YH, Kang SJ, et al. Long-term outcomes of intravascular ultrasound-guided stenting in coronary bifurcation lesions. Am J Cardiol 2010;106:612–8.
10. Holmes DR Jr., Kereiakes DJ, Garg S, et al. Stent thrombosis. J Am Coll Cardiol 2010;56:1357–65.
11. Costa MA, Angiolillo DJ, Tannenbaum M, et al., for the STLLR Investigators. Impact of stent deployment procedural factors on long-term effectiveness and safety of sirolimus-eluting stents (final results of the multicenter prospective STLLR trial). Am J Cardiol 2008;101: 1704–11.
12. Sera F, Awata M, Uematsu M, Kotani J, Nanto S, Nagata S. Optimal stent-sizing with intravascular ultrasound contributes to complete neointimal coverage after sirolimus-eluting stent implantation assessed by angioscopy. J Am Coll Cardiol Intv 2009;2:989–94.
13. Dangas GD, Claessen BE, Caixeta A, Sanidas EA, Mintz GS, Mehran R. In-stent restenosis in the drug-eluting stent era. J Am Coll Cardiol 2010;56:1897–907.

Key Words: drug-eluting stents ■ intravascular ultrasound ■ long-term outcomes ■ percutaneous coronary intervention.

APPENDIX

For the odds ratios for covariates in the propensity score logistic regression model and for independent predictors of clinical outcome according to 3 different methods, please see the online version of this paper.