Table 1 Hemodynamic parameters

Tracer		Normal control	Mild ischemia	Severe ischemia
Heart rate (min^{-1})	Rat $heart_{BMIPP}$	244 ± 76	304 ± 105	94 ± 140*
	Rat $heart_{MIBI}$	283 ± 90	290 ± 116	100 ± 123*
Circulation pressure (mmHg)	Rat $heart_{BMIPP}$	67 ± 13	101 ± 31	160 ± 84*
	Rat $heart_{MIBI}$	56 ± 20	93 ± 42	183 ± 70*

* $p < 0.05$ versus normal control and mild ischemia

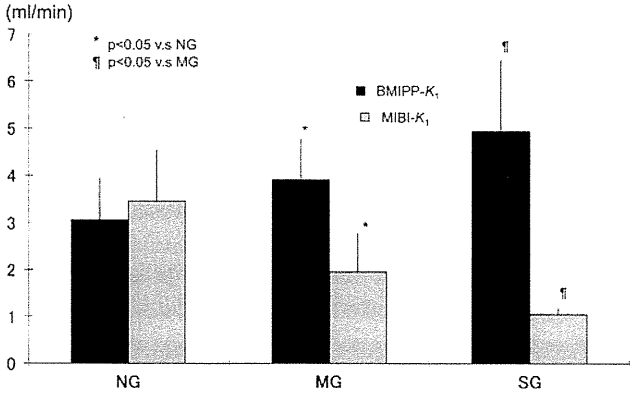

Fig. 2 Mean values ± SD for K_1 in each group. MIBI significantly decreased according to the duration of ischemia ($p < 0.05$ for NG versus MG and MG versus SG), whereas BMIPP significantly increased ($p < 0.05$ for NG versus MG and MG versus SG). NG, MG and SG: control, mild and severe ischemia groups

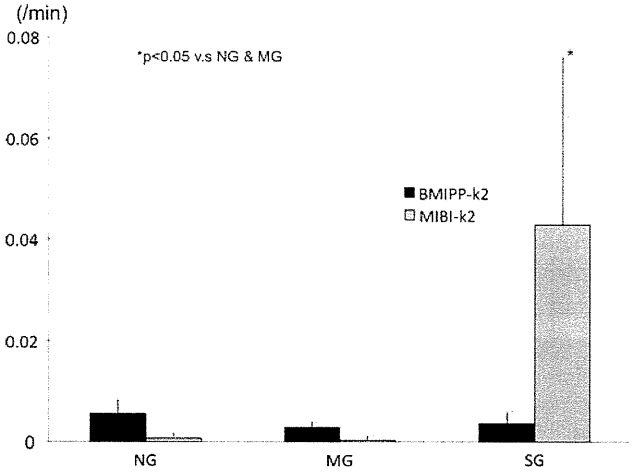

Fig. 3 Mean values ± SD for k_2 in each group. MIBI showed lower k_2 values in NG and MG, but significantly accelerated values in SG (3.45 ± 1.10, 1.95 ± 0.82, and 1.05 ± 0.13 ml/min for NG, MG and SG, respectively; $p < 0.01$ versus NG and MG). BMIPP showed comparable k_2 in all groups (3.06 ± 0.88, 3.91 ± 0.87 and 4.94 ± 1.51 ml/min for NG, MG, and SG)

Discussion

In the present study, we assessed the myocardial kinetics of BMIPP using the isolated rat heart model under acute reperfusion ischemia.

Myocardial perfusion uptake (MIBI-K_1) was significantly decreased in the mild ischemia group compared with the normal control, and further decreased in the groups with severe ischemia. In other words, deceased MIBI-K_1 reflected the severity of ischemia. These results are similar to those of a previous study using the same protocols in the same experimental setting [12]. Reperfused myocardium might become edematous during ischemia, with vascular beds becoming degraded so that myocardial flow decreased even after reperfusion.

In contrast to the kinetics of the perfusion tracer, BMIPP-K_1 was significantly increased with increasing duration of no-flow ischemia. This hemodynamic change followed by a reduction in MIBI extraction suggested that ischemic damage worsens in parallel with longer duration of ischemia, despite which BMIPP uptake increased. Myocardial fatty acid metabolism is promptly impaired under ischemic or hypoxic conditions. The changes in BMIPP uptake may be controversial, but some experimental evidence supports our findings. Higuchi and Noriyasu et al. found that BMIPP uptake increased during acute reperfusion ischemia in rats and persists for at least 48 h while myocardial perfusion decreased [10, 11]. Higuchi also investigated serial changes in BMIPP uptake over time and found that it decreased 3 days later. Miller found using a similar carbon labeled fatty acid analog that accelerated fatty acid metabolism might imply myocardial viability in the reperfused dog model in addition to small animals [13]. Renstrom et al. [14] reported that BMIPP uptake increases in hypoxic, compared with normal, pig models. While these studies have reported the phenomenon of increased BMIPP uptake after reperfusion for various animal models or serial time points, no studies have reported the change in the degrees of the duration of ischemia. Our study, to our knowledge, is the first to note increased BMIPP uptake in various durations of ischemia.

The metabolic fate of BMIPP is essentially similar to that of free fatty acids, which are thought to combine with fatty acid binding protein mediated by $CD36^+$ on the myocardial cell membrane, and then become transported into the triglyceride pool and mitochondria in the activated

form with acyl-CoA. Over half of the myocardial BMIPP is stored in the triglyceride pool and 15% is consumed in mitochondria [15, 16]. This process is distinct from endogenous free fatty acid metabolism. Morishita et al. [17] reported that BMIPP uptake is increased in the triglyceride pool and that its metabolite is decreased during low-flow ischemia and hypoxia in the isolated rat heart model. Saddik and Lopaschuk et al. reported that triglyceride synthesis significantly increases in the isolated rat heart model under reperfusion ischemia [18, 19]. Other investigators have speculated that $CD36^+$ on the myocardial membrane regulates and enhances the rate of fatty acid uptake and triacylglycerol esterification [20–22].

Several investigators contend that MIBI clearance is a useful marker of myocardial mitochondrial dysfunction [23–25]. We found here that the MIBI-k_2 increased in severe ischemia reperfusion whereas the BMIPP-k_2 did not. Hosokawa et al. [7] reported that the early phase of myocardial extraction and BMIPP clearance are frequently affected by a flood of non-metabolized BMIPP from the myocardium, which is referred to as back diffusion. They also found that back diffusion increases soon after reperfusion–ischemia and persists for 3–5 min in the canine model. Here, we maintained rat hearts under constant perfusion for over 20 min of wash-in and wash-out, and so we considered that back diffusion might not affect the calculated K_1 and k_2 values. The constant k_2 value in the ischemia groups implies the stable retention of BMIPP metabolites. Considering myocardial mitochondrial dysfunction indicated by the accelerated MIBI wash-out, the increased BMIPP uptake immediately after reperfusion is probably caused by an accelerated fatty acid transport system due to an expanded triglyceride pool. This phenomenon may be explained by physiologic properties of BMIPP, which was designed for stable retention in the triglyceride pool.

Several clinical reports have captured the increased BMIPP uptake in acute ischemia [26, 27], but it has been widely acknowledged that BMIPP uptake is reduced after myocardial ischemia either reperfused or not. And this might raise a question of the discrepancy between clinical experience and the results from experimental research including the present study. Several factors might be involved: (1) Species variability should be noticed. 2) Most fatty acid imaging studies are performed at a minimum of several hours after onset of acute coronary occlusion or/and reperfusion. This might be too late to visualize the alteration of BMIPP uptake on a minute-by-minute basis in the quite early phase of acute ischemia in man. (3) There are possibilities that fatty acid metabolism may be impaired as a result of occult and repeatable ischemia that is characterized by flow impairment in coronary artery disease [28], and it is unknown how fatty acid metabolism alters in the initial exposure to myocardial ischemia.

However, various alterations of BMIPP have been speculated, which may imply that the results from the present study might reflect a possible phenomenon. In conclusion, this is the first study to determine the phenomenon of increased uptake rate of BMIPP immediately after reperfusion ischemia from the viewpoint of tracer kinetics. BMIPP uptake increased and wash-out did not vary with decreased perfusion after no-flow ischemia. Further studies are therefore required to explore the discrepancy between BMIPP kinetics and true fatty acid metabolism under ischemic conditions.

Study limitations

Our perfusion system was not truly equivalent to coronary perfusion because it provided retrograde constant perfusion and did not provide physiological, systemic recirculation. Yamamichi [29] described that fatty acid metabolism would change according to the composition of the perfusion medium such as other fatty acids and albumin. However, we found no changes in BMIPP-K_1 between buffers with or without oleic acid and albumin (data not shown). As the rats were fed with a normal diet up until the time of sacrifice, the notion that stored fatty acid in myocardium had become depleted is difficult to accept. Even though myocardial fatty acid metabolism might depend on systemic energy consumption, the isolated heart system precludes the effects of radioactivity from proximal organs and enables measurements of tracer kinetics that would not be affected by recirculation.

Conclusion

BMIPP uptake increased immediately after reperfusion ischemia, and this phenomenon was mediated not by altering clearance but by accelerating extraction. Fatty acid uptake might become transiently accelerated during the hyperacute phase of reperfusion ischemia.

Acknowledgment We are grateful to Nihon-mediphysics and Fujifilm RI Pharma for continuous donations of BMIPP and MIBI.

Conflict of interest We declare no conflict of interest in connection with this paper.

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Clinical Implications of Midventricular Obstruction in Patients With Hypertrophic Cardiomyopathy

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Objectives We investigated the prevalence, clinical characteristics, and prognosis of hypertrophic cardiomyopathy (HCM) patients with midventricular obstruction (MVO).

Background Previous descriptions of patients with MVO have been confined to case reports or small patient series, and this subgroup of HCM patients has therefore remained underrecognized.

Methods The study population included 490 HCM patients. Left ventricular MVO was diagnosed when the peak midcavitary gradient was estimated to be ≥30 mm Hg.

Results MVO was identified in 46 patients (9.4%). Patients with MVO were more likely to be symptomatic than those without. MVO was found to be an independent determinant of HCM-related death in multivariate models (hazard ratio [HR]: 2.23, $p = 0.016$), and this trend was especially pronounced for the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 3.19, $p < 0.001$). Apical aneurysm formation was identified in 28.3% of patients with MVO and strongly predicted HCM-related death (HR: 3.47, $p = 0.008$) and the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 5.08, $p < 0.001$). In addition, MVO without apical aneurysm was also identified as an independent determinant of the combined endpoint of sudden death and potentially lethal arrhythmic events (HR: 2.43, $p = 0.045$).

Conclusions This analysis identified MVO as an independent predictor of adverse outcomes, especially the combined endpoint of sudden death and potentially lethal arrhythmic events. Our results suggest that longer periods of exposure to MVO might lead to unfavorable consequences. They also support the principle that the presence of MVO in patients with HCM has important pathophysiological implications. (J Am Coll Cardiol 2011;57:2346–55)

Hypertrophic cardiomyopathy (HCM) is a genetic cardiac disease characterized by marked variability in morphological expression and natural history (1). Left ventricular intracavitary obstruction is an important pathophysiological component of HCM and classically occurs at the subaortic level, mainly due to systolic anterior motion (SAM) of the anterior mitral valve leaflet (1). This subaortic obstruction, called left ventricular outflow tract obstruction (OTO), occurs at rest in approximately 25% of patients with HCM and is an independent predictor of adverse clinical consequences (2,3). In a minority of HCM patients, however, the impedance to flow occurs at the midcavitary level, unrelated to SAM, and is predominantly caused by marked septal hypertrophy coming in contact with a hypercontractile left ventricular free wall, often with the interposition of the hypertrophied papillary muscle (4). Previous descriptions of these patients with midventricular obstruction (MVO) have been confined to case reports or small patient series because of the relative rarity and unique pathophysiology of the condition (5–13). Consequently, this subgroup of patients with HCM has remained underappreciated, and the clinical profiles of patients with MVO are largely undefined. This study was therefore undertaken to investigate the prevalence, clinical characteristics, and long-term prognosis of HCM patients with MVO.

Methods

Patients. The study population included 490 patients with clinically diagnosed HCM who were enrolled and evaluated from 1980 to 2005 at Tokyo Women's Medical University Hospital, Tokyo, Japan. The initial evaluation was the first clinical assessment during which an echocardiogram diagnostic of HCM was obtained, and the most recent evaluation was

From the Department of Cardiology, Tokyo Women's Medical University, Tokyo, Japan. The authors have reported that they have no relationships to disclose.

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performed in the clinic or by telephone interview. The study was performed according to the principles of the Declaration of Helsinki, and the study protocol was approved by the institutional ethics committee.

HCM. The diagnosis of HCM was based on the identification by 2-dimensional echocardiography of a hypertrophied, nondilated left ventricle in the absence of any other cardiac or systemic disease capable of producing a similar degree of hypertrophy (1).

OTO and MVO. Left ventricular OTO, caused by SAM of the anterior mitral valve leaflet, was considered to be present when the estimated peak instantaneous gradient was ≥30 mm Hg (3,14). Left ventricular MVO was diagnosed when both of the following criteria were satisfied: 1) the peak instantaneous midventricular gradient was estimated to be ≥30 mm Hg; and 2) midventricular obliteration was caused by marked septal hypertrophy resulting in contact with a hypercontractile left ventricular free wall rather than by SAM of the anterior mitral valve leaflet (6). Patients with both OTO (SAM) and MVO were excluded from the MVO group and included in the OTO group (6). This accounted for 6 of the 110 OTO patients (5.5%) in the current study.

Apical hypertrophy and aneurysm. The diagnostic criteria for apical hypertrophy included asymmetrical left ventricular hypertrophy, confined predominantly to the left ventricular apex, with an apical wall thickness ≥15 mm (15). A left ventricular apical aneurysm was defined as a discrete, thin-walled dyskinetic or akinetic segment of the most distal portion of the chamber with a relatively wide communication to the left ventricular cavity (16).

Arrhythmias. Documentation of atrial fibrillation was based on electrocardiographic recordings obtained either after acute onset of symptoms or fortuitously during routine medical examinations in asymptomatic patients. Ambulatory electrocardiograms covering at least a 24-h period were reviewed in all patients for the occurrence of nonsustained ventricular tachycardia, defined as a minimum of 3 consecutive ventricular beats with a rate of ≥120 beats/min (1).

Mode of death. Three modes of HCM-related death were defined for the purposes of survival analysis (1): 1) a combined endpoint of sudden death and potentially lethal arrhythmic events, in which unexpected death occurred in the absence of or <1 h from symptom onset in patients who had previously experienced a relatively stable or uneventful course, including resuscitated cardiac arrest and appropriate implantable defibrillator interventions; 2) heart failure–related death in the context of progressive cardiac decompensation ≥1 year before death, particularly if complicated by pulmonary edema or evolution to end-stage phase; and 3) stroke-related death, which occurred in patients who died as a result of ischemic stroke.

Echocardiography. Echocardiographic studies were performed using commercially available ultrasound equipment. Complete M-mode, 2-dimensional, and Doppler studies were performed with the patient in the left lateral decubitus or supine position, using standard parasternal, apical, and subcostal approaches. Color Doppler imaging and pulse-wave Doppler echocardiography were used to localize the site of obstruction. Peak left ventricular intracavitary gradient was quantified using continuous-wave Doppler echocardiography under resting conditions. MVO was defined by systolic apposition of the mid-left ventricular walls, and often the papillary muscles, with abnormally high velocities persisting through late systole and often with early diastolic paradoxical jet flow (13). Contrast-enhanced echocardiography was performed by manual intravenous injection of 300 mg/ml galactose-palmitic acid (Levovist, Schering, Berlin, Germany) at a rate of 5 ml/5 s.

Abbreviations and Acronyms

CI = confidence interval
CMR = cardiovascular magnetic resonance
HCM = hypertrophic cardiomyopathy
HR = hazard ratio
MVO = midventricular obstruction
OTO = outflow tract obstruction
SAM = systolic anterior motion

Cardiovascular magnetic resonance (CMR) imaging. Studies were performed using a Magnetom Vision 1.5-T whole-body imaging system (Siemens Medical Systems, Erlangen, Germany [used from 2001 to July 2003]), or a Gyroscan Intera (Philips Medical Systems, Best, the Netherlands [used from July 2003 to 2005]). Breath-hold electrocardiography-gated cine steady-state free precession images were acquired in 7 to 10 short-axis slices and standard 2- and 4-chamber long-axis orientations. A delayed enhancement protocol was used 10 min after intravenous administration of 0.10 to 0.15 mmol/kg gadolinium-diethylenetriaminepentaacetic acid (Magnevist, Schering) with a breath-held segmented inversion-recovery sequence (inversion time, 230 to 300 ms, adjusted by a look-locker sequence) acquired in the same views as the cine images.

Statistical analysis. Analyses were performed using SAS system software, version 9.1 (SAS Institute, Cary, North Carolina). Data were presented as mean ± SD and frequencies. Student *t* tests were used to compare values between the 2 groups for continuous variables, and Mann-Whitney *U* tests were used for ordinal variables. Normality of distribution was assessed using the Kolmogorov-Smirnov test, and equality of variances was checked using the F statistic. A chi-square or Fisher exact test (when an expected value was <5) was used to compare nominally scaled variables. Event-free curves were estimated using the Kaplan-Meier method, and differences between curves were assessed by log-rank tests. Univariate and multivariate Cox proportional hazards models were applied to evaluate the influence of MVO and MVO with or without apical aneurysm on HCM-related death and the combined endpoint of sudden death and potentially lethal arrhythmic events. The proportional hazards assumption was confirmed by the log (−log survival function). The influences of profile, interaction, and collinearity in the models were examined using

regression diagnostic analysis. A 2-tailed p value <0.05 was considered to indicate a statistically significant difference.

Results

Prevalence and baseline characteristics. MVO was identified in 46 of 490 HCM patients (9.4%). The baseline demographic and clinical characteristics of the HCM patients with and without MVO are shown in Table 1. The mean age at diagnosis of the 46 patients with MVO was 53.2 ± 14.7 years (range 19 to 77 years). The New York Heart Association functional class at diagnosis in patients with MVO was significantly higher than that in those without MVO. However, there were no statistically significant differences with respect to sex, age, family history of sudden death, maximal left ventricular wall thickness, or arrhythmias between patients with and without MVO.

Comparison with OTO and treatments. OTO was identified in 110 of 490 HCM patients (22.4%). The demographic, clinical, and therapeutic characteristics of the 46 patients with MVO and the 110 patients with OTO are shown in Table 2. There was a higher proportion of male patients with MVO than with OTO, and patients with MVO had a lower left ventricular intracavitary gradient at diagnosis. Of the 46 patients with MVO, 43 (93.5%) were treated with negative inotropic agents, such as beta-blockers, calcium-channel blockers, and/or class I antiarrhythmic drugs (mainly disopyramide). Three patients (6.5%) underwent dual-chamber pacing therapy, and only 1 patient (2.2%) underwent surgery to reduce the gradient caused by MVO.

Outcomes. Six of the 46 patients with MVO (13.0%) experienced episodes of progressive heart failure with an increase to ≥3 New York Heart Association functional class, and 5 patients (10.9%) had nonfatal thromboembolic strokes over the mean follow-up period of 10.4 ± 8.2 years. Eleven patients (23.9%) experienced HCM-related death including 2 patients with sudden death, 7 patients with successfully resuscitated cardiac arrest (with documented ventricular fibrillation [n = 5] and with documented ventricular tachycardia with pulseless collapse [n = 2]), and 2 patients with appropriate implantable defibrillator interventions. In univariate analysis, patients with MVO had a significantly greater likelihood of HCM-related death than patients without MVO (log-rank p = 0.017) (Fig. 1A). The probability of the combined endpoint of sudden death and potentially lethal arrhythmic events among patients with MVO was also significantly higher than that among patients without MVO (log-rank p < 0.001) (Fig. 1B). The frequency of HCM-related death in patients with MVO was similar to that in patients with OTO (log-rank p = 0.451) (Fig. 2A). Conversely, the probability of the combined endpoint of sudden death and potentially lethal arrhythmic events among patients with MVO was significantly higher than that among patients with OTO (log-rank p = 0.038) (Fig. 2B). In multivariate modeling, entering MVO and established major primary prevention risk factors for sudden death (family history of sudden death, maximum left ventricular wall thickness ≥30 mm, nonsustained ventricular tachycardia, and unexplained syncope) (1,17), MVO was identified as an independent determinant of outcome, including the risk of HCM-related death (adjusted hazard ratio [HR]: 2.23, 95% confidence interval [CI]: 1.16 to 4.29; p = 0.016) and the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 3.19, 95% CI: 1.62 to 6.29; p < 0.001) (Table 3). Exercise tests were not performed in all HCM patients, and abnormal exercise blood pressure was therefore excluded from the analysis. The sensitivities of MVO for HCM-

Table 1 Baseline Characteristics of HCM Patients With and Without MVO

	Patients With MVO (n = 46)	Patients Without MVO (n = 444)	p Value
Male	28 (60.9)	288 (64.9)	0.590
Age at diagnosis, yrs	53.2 ± 14.7	50.4 ± 14.9	0.232
Family history of sudden death	6 (13.0)	55 (12.4)	0.898
Maximal left ventricular wall thickness, mm	19.1 ± 4.3	19.7 ± 4.2	0.345
Apical aneurysm formation	13 (28.3)	8 (1.8)	<0.001
Nonsustained ventricular tachycardia	14 (30.4)	182 (41.0)	0.164
Atrial fibrillation	11 (23.9)	140 (31.5)	0.287
Unexplained syncope	12 (26.1)	80 (18.0)	0.182
NYHA functional class at diagnosis			0.004
I	13 (28.3)	247 (55.6)	
II	31 (67.4)	159 (35.8)	
III	2 (4.3)	35 (7.9)	
IV	0 (0.0)	3 (0.7)	
Progressive heart failure	6 (13.0)	53 (11.9)	0.826
Stroke	5 (10.9)	56 (12.6)	0.733
Follow-up duration, yrs	10.4 ± 8.2	11.7 ± 7.3	0.266

Values are n (%) or mean ± SD.
HCM = hypertrophic cardiomyopathy; MVO = midventricular obstruction; NYHA = New York Heart Association.

Table 2 Demographic, Clinical, and Therapeutic Characteristics of HCM Patients With MVO and With OTO

	Patients With MVO (n = 46)	Patients With OTO (n = 110)	p Value
Male	28 (60.9)	48 (43.6)	0.050
Age at diagnosis, yrs	53.2 ± 14.7	55.1 ± 15.7	0.483
Family history of sudden death	6 (13.0)	11 (10.0)	0.578
Maximum left ventricular wall thickness, mm	19.1 ± 4.3	20.0 ± 4.9	0.239
Apical aneurysm formation	13 (28.3)	2 (1.8)	<0.001
Nonsustained ventricular tachycardia	14 (30.4)	36 (32.7)	0.780
Atrial fibrillation	11 (23.9)	36 (32.7)	0.274
Unexplained syncope	12 (26.1)	22 (20.0)	0.401
NYHA functional class at diagnosis			0.927
I	13 (28.3)	39 (35.5)	
II	31 (67.4)	57 (51.8)	
III	2 (4.3)	13 (11.8)	
IV	0 (0.0)	1 (0.9)	
Progressive heart failure	6 (13.0)	14 (12.7)	0.957
Stroke	5 (10.9)	13 (11.8)	0.866
Pressure gradient at diagnosis, mm Hg	45.9 ± 14.7	81.0 ± 30.1	<0.001
Treatments			
Beta-blockers	35 (76.1)	92 (83.6)	0.269
Calcium-channel blockers	14 (30.4)	26 (23.6)	0.375
Class I antiarrhythmic drugs	16 (34.8)	69 (62.7)	0.001
All interventions combined	4 (8.7)	36 (32.7)	0.002
Warfarin	13 (28.3)	35 (31.8)	0.661
Follow-up duration, yrs	10.4 ± 8.2	10.0 ± 6.7	0.761

Values are n (%) or mean ± SD.
OTO = outflow tract obstruction; other abbreviations as in Table 1.

related death/combined endpoint of sudden death and potentially lethal arrhythmic events were 17.2%/22.9%, respectively, and the corresponding specificities were 91.8%/92.1%, respectively.

Apical hypertrophy and apical aneurysm formation. Left ventricular apical hypertrophy was identified in 16 of the 46 patients with MVO (34.8%). All the 16 patients exhibited mid-left ventricular hypertrophy, and none had hypertrophy

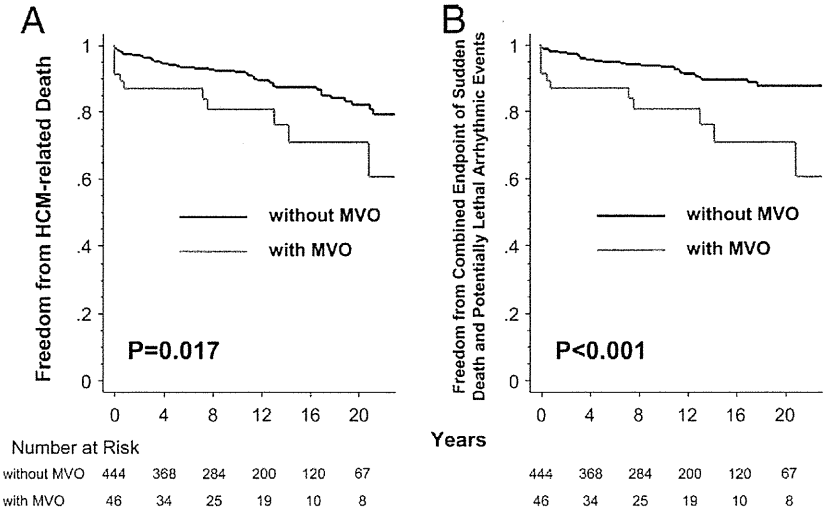

Figure 1 Kaplan-Meier Estimates of the Proportions of Patients With HCM-Related Adverse Events in 46 Patients With MVO and 444 Patients Without MVO

Patients with midventricular obstruction (MVO) had a significantly greater likelihood of hypertrophic cardiomyopathy (HCM)–related death **(A)** and the combined endpoint of sudden death and potentially lethal arrhythmic events **(B)** than patients without MVO.

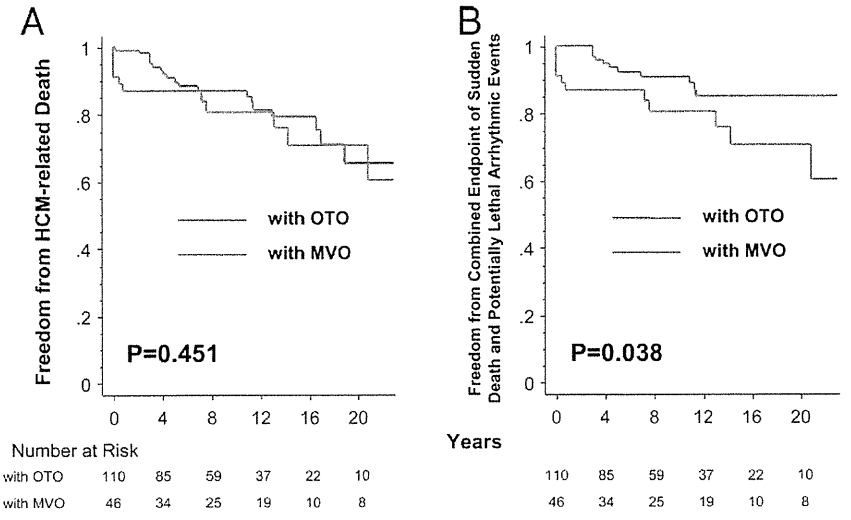

Figure 2 **Kaplan-Meier Estimates of the Proportions of Patients With HCM-Related Adverse Events in 46 Patients With MVO and 110 Patients With OTO**

There was no statistically significant difference in HCM-related death rate between patients with MVO and patients with outflow tract obstruction (OTO) **(A)**. However, patients with MVO had a significantly greater likelihood of the combined endpoint of sudden death and potentially lethal arrhythmic events than patients with OTO **(B)**. Abbreviations as in Figure 1.

confined only to the left ventricular apex below the papillary muscle level. Left ventricular apical aneurysm was identified in 13 of the 46 patients with MVO (28.3%). Coronary artery disease was excluded as a cause of apical aneurysm formation by the absence of significant coronary arterial narrowing (>50% stenosis) in the left anterior descending artery using conventional coronary angiography (n = 10) and no history of chest pain, coronary risk factors, or acute coronary syndrome (n = 3, all younger than 60 years of age). An apical aneurysm was confirmed by CMR in 8 of the 13 patients. All the 8 patients exhibited late gadolinium enhancement in the apical aneurysmal wall itself, with extension into the hypertrophic region of the left ventricle. An apical aneurysm was confirmed by contrast-enhanced echocardiography in the remaining 5 patients who did not undergo CMR. Development of an apical aneurysm from MVO was observed in 6 of 13 aneurysm patients during the follow-up period (Figs. 3 and 4). In the remaining 7 patients, an apical aneurysm was observed at the initial evaluation. In 2 of 6 patients in whom an apical aneurysm developed from MVO, CMR was performed both before and after aneurysm formation, and these 2 patients already exhibited late gadolinium enhancement in the apex before detection of the apical aneurysm formation (Fig. 3C). The baseline characteristics of the HCM patients with MVO, according to the presence or absence of an apical aneurysm, are shown in Table 4. The frequency of nonsustained ventricular tachycardia in patients with an aneurysm was significantly higher than in those without an aneurysm. In contrast to the situation in patients with MVO, only 2 of the 110 patients with OTO (1.8%), and only 8 of the 444 patients without MVO (1.8%) were complicated by an apical aneurysm (Tables 1 and 2).

Relationship of apical aneurysm formation to outcomes. When patients with MVO were divided into those with (n = 13) and those without (n = 33) an apical aneurysm, 5 of 13 MVO patients with an apical aneurysm (38.5%) experienced HCM-related death, including sudden death (n = 1), resuscitated cardiac arrest (n = 3), and appropriate implantable defibrillator interventions (n = 1). One of the 5 patients with adverse outcomes had no established major primary prevention risk factors for sudden death. Six of the 33 MVO patients without an apical aneurysm (18.2%) experienced HCM-related death. Two of the 6 patients with adverse outcomes had no established major primary prevention risk factors for sudden death. In multivariate models including MVO with or without an apical aneurysm and established major primary prevention risk factors for sudden death, apical aneurysm formation in patients with MVO strongly predicted HCM-related death (adjusted HR: 3.47, 95% CI: 1.38 to 8.73; p = 0.008) and the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 5.08, 95% CI: 1.97 to 13.05; p < 0.001). MVO without an apical aneurysm was also identified as an independent determinant of the combined endpoint of sudden death and potentially lethal arrhythmic events (adjusted HR: 2.43, 95% CI: 1.02 to 5.80; p = 0.045), but was not identified as an independent determinant of HCM-related death overall (adjusted HR: 1.72, 95% CI: 0.73 to 4.02; p = 0.213).

Discussion

In the current single-center patient cohort, MVO was confirmed in 9.4% of patients with HCM. Although no

Table 3 Predictors of HCM-Related Adverse Events in Univariate and Multivariate Analysis of MVO and Established Major Primary Prevention Risk Factors for Sudden Death

Variables	No. of Patients	HCM-Related Death				Combined Endpoint of Sudden Death and Potentially Lethal Arrhythmic Events			
		No. (%) of Events	Crude Hazard Ratio (95% CI)	p Value	Adjusted Hazard Ratio (95% CI)	p Value	No. (%) of Events	Crude Hazard Ratio (95% CI)	p Value	Adjusted Hazard Ratio (95% CI)	p Value
Family history of sudden death											
Absent	429	51 (11.9)	1.00		1.00		38 (8.9)	1.00		1.00	
Present	61	13 (21.3)	1.68 (0.91–3.09)	0.096	1.35 (0.73–2.51)	0.338	10 (16.4)	1.82 (0.90–3.65)	0.094	1.41 (0.69–2.85)	0.344
Left ventricular wall thickness ≥30 mm											
Absent	475	59 (12.4)	1.00		1.00		43 (9.1)	1.00		1.00	
Present	15	5 (33.3)	2.89 (1.15–7.25)	0.024	3.26 (1.29–8.25)	0.012	5 (33.3)	3.56 (1.41–9.02)	0.007	4.35 (1.69–11.19)	0.002
Nonsustained ventricular tachycardia											
Absent	294	30 (10.2)	1.00		1.00		21 (7.1)	1.00		1.00	
Present	196	34 (17.3)	1.54 (0.94–2.53)	0.084	1.37 (0.83–2.25)	0.218	27 (13.8)	1.80 (1.02–3.19)	0.043	1.54 (0.86–2.76)	0.146
Unexplained syncope											
Absent	398	37 (9.3)	1.00		1.00		24 (6.0)	1.00		1.00	
Present	92	27 (29.3)	3.40 (2.07–5.58)	<0.001	3.23 (1.94–5.38)	<0.001	24 (26.1)	4.66 (2.64–8.20)	<0.001	4.32 (2.41–7.78)	<0.001
MVO											
Absent	444	53 (11.9)	1.00		1.00		37 (8.3)	1.00		1.00	
Present	46	11 (23.9)	2.17 (1.13–4.15)	0.020	2.23 (1.16–4.29)	0.016	11 (23.9)	3.16 (1.61–6.20)	<0.001	3.19 (1.62–6.29)	<0.001

CI = confidence interval; other abbreviations as in Table 1.

extensive clinical studies have been designed to determine the true prevalence of MVO in patients with HCM, MVO with an akinetic apical chamber has been considered to be a rare form of HCM, occurring in 1% of cases in the non-Asian population (5). According to a report from the United States, however, MVO was found in 8 of 62 patients (12.9%) with a diagnosis of HCM (18). In addition, MVO was present in 10.9% of patients with HCM in a 5-year study performed at an echocardiography laboratory in Italy (19). Furthermore, diastolic paradoxical jet flow across the obliterated left ventricular apex toward the base, suggestive of MVO and a discrete apical chamber, was present in 20 of 198 patients (10.1%) with HCM in a previous study (20). These variations in prevalence could be the result of racial/ethnic differences, selection bias, underrecognition, misdiagnosis, or differences in the definitions of MVO. Despite being based on a highly selected population of patients with HCM from a single large tertiary referral center in Japan, the results of the current study have revealed novel epidemiological information about MVO in a relatively large HCM patient cohort.

A left ventricular apical aneurysm was identified in approximately one-fourth of HCM patients with MVO in the current study. Numerous previous case reports and studies have indicated that MVO is associated with an apical aneurysm in patients with HCM (5,7,8,16). Maron et al. (16) hypothesized that a left ventricular apical aneurysm and the associated regional myocardial scarring developed secondarily to increased left ventricular wall stress as a result of MVO and elevated intracavitary systolic pressures. Increased wall stress imposes an increased pressure load on the apical myocardium, increasing its oxygen demand, and impairs coronary flow through extravascular compression of the coronary artery, leading to chronic myocardial ischemia and aneurysm formation. The results of the current study, as well as those of previous studies, suggest the existence of a close overlap between MVO and an apical aneurysm in patients with HCM.

The presence of MVO was identified as an independent determinant of unfavorable outcomes in our analysis. In addition, apical aneurysm formation in patients with MVO more strongly predicted HCM-related adverse events. A recent study demonstrated a largely unfavorable clinical course in 28 HCM patients with an apical aneurysm. Twelve of the 28 patients (42.9%) either died of their disease or survived with severe adverse HCM-related events (16). Similarly, 5 of 13 patients (38.5%) with MVO and an apical aneurysm experienced HCM-related death in the present study. These results suggest that the higher mortality observed in patients with MVO might be due partly to aneurysm formation, which may develop secondarily to increased left ventricular wall stress as a result of MVO. Furthermore, the scarred rim of the aneurysm and the associated extensive areas of myocardial fibrosis have been regarded as arrhythmogenic substrates for the generation of malignant ventricular tachyarrhythmias (21,22). It is there-

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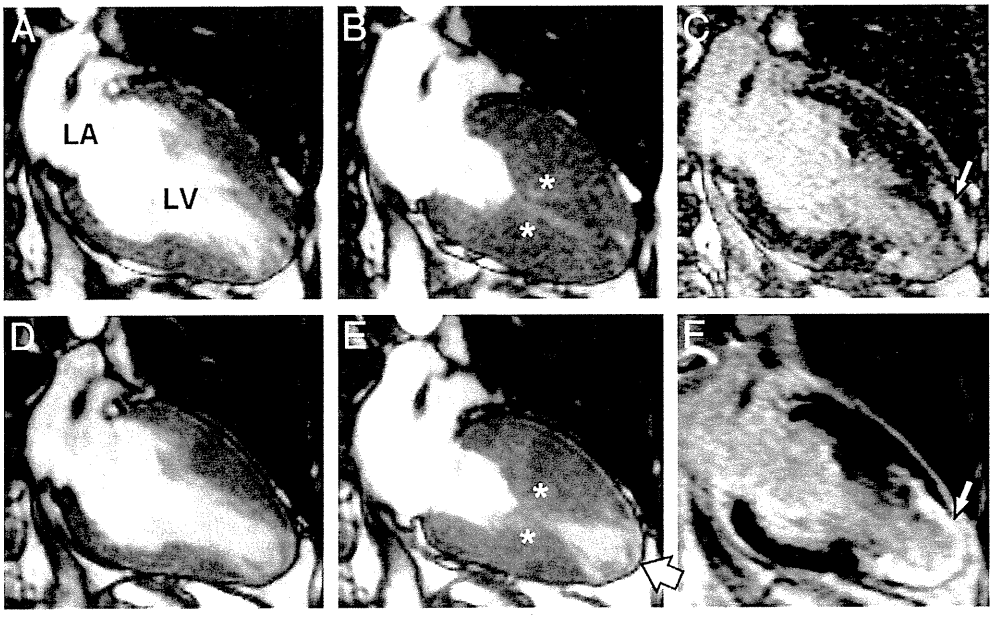

Figure 3 **CMR Images From an HCM Patient in Whom an Apical Aneurysm Developed From MVO**

Left ventricular long-axis 2-chamber cardiovascular magnetic resonance (CMR) cine images in end-diastole **(A)** and end-systole **(B)** from a 67-year-old HCM patient with MVO **(*)**. Identical imaging view in the same patient with gadolinium-diethylenetriaminepentaacetic acid already showing late gadolinium enhancement in the apex **(thin arrow, C)**. After 4 years, 2-chamber long-axis CMR images in end-diastole **(D)** and end-systole **(E)** demonstrating apical aneurysm formation **(thick arrow)**, which was associated with regional transmural late gadolinium enhancement of the aneurysmal wall **(thin arrow, F)**. LA = left atrium; LV = left ventricle; other abbreviations as in Figure 1.

fore not surprising that the majority of reported HCM-related events in patients with MVO and an apical aneurysm may be caused by ventricular arrhythmias (7,8). These observations suggest that the treatment of patients with MVO already complicated by an apical aneurysm should be modified to include primary prevention of sudden death with the use of an implanted defibrillator (16). In addition, MVO without an apical aneurysm was also associated with the risk of the combined endpoint of sudden death and potentially lethal arrhythmic events in this study. Furthermore, 2 MVO patients without an apical aneurysm and with no additional established major primary prevention risk factors for sudden death experienced adverse events. Additional clinical studies are needed to clarify whether the presence of MVO alone justifies the prophylactic use of an implantable defibrillator.

In this analysis, we also compared patients with MVO and those with OTO. Intriguingly, we found that the probability of HCM-related death in patients with MVO was similar to that in patients with OTO. Furthermore, the probability of the combined endpoint of sudden death and potentially lethal arrhythmic events in patients with MVO was higher than that in patients with OTO. This suggests that MVO could be as predictive of unfavorable outcomes as OTO because of increased wall stress, apical aneurysm formation, apical myocardial infarction, and myocardial scarring (16,21,22). Timely recognition of MVO might thus affect clinical practice decisions by prompting consideration of gradient and wall stress relief with negative inotropic agents and/or therapeutic interventions. Numerous previous studies have demonstrated a reduction in intracavitary pressure gradients in HCM patients with MVO after dual-chamber pacing and myectomy (9–13). Successful surgical septal myectomy in OTO patients can completely abolish the gradients, leading to marked improvement of symptoms and outcomes (23). Surgical relief of MVO by extensive mid-left ventricular resection may thus similarly reduce HCM-related adverse events. However, patients with MVO had a lower left ventricular intracavitary gradient than those with OTO in our study cohort. In addition, MVO patients with an apical aneurysm had slightly lower midcavitary gradient than those without. This may be due partly to apical systolic dysfunction (hypokinesia, akinesia, or dyskinesia) and the midsystolic decrease in flow that can occur in patients with MVO (13,24). Lower gradients might lead to underestimation of the prognostic significance of MVO, resulting in inadequate medication and/or therapeutic interventions for the gradients of MVO. In comparison with OTO, MVO patients in this study used class I antiarrhythmic drugs less and had fewer invasive procedures to reduce the gradient of MVO, despite poor outcomes in the MVO patient group. Further studies are required to evaluate the actual severity of MVO and to determine the most appropriate treatment strategies for gradient reduction in patients with MVO.

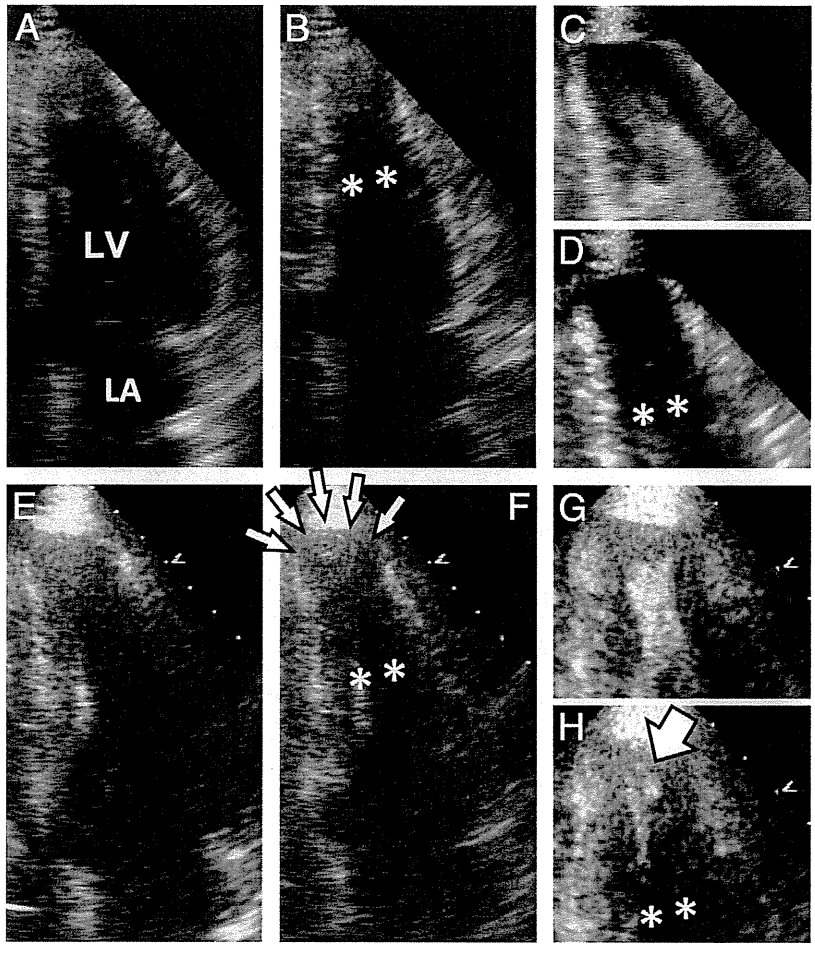

Figure 4 **Echocardiographic Images of an HCM Patient in Whom an Apical Aneurysm Developed From MVO**

Left ventricular apical 4-chamber views in end-diastole **(A)** and end-systole **(B)** in a 60-year-old HCM patient with MVO **(*)**. Contrast-enhanced 4-chamber views in end-diastole **(C)** and end-systole **(D)** showing no systolic pooling of contrast agent. Four-chamber views in end-diastole **(E)** and end-systole **(F)** in the same patient with MVO **(*)** after 4 years demonstrating apical aneurysm formation **(thin arrows)**. Contrast-enhanced 4-chamber views in end-diastole **(G)** and end-systole **(H)** showing apical systolic pooling of contrast agent **(thick arrow)**. Abbreviations as in Figures 1 and 3.

Study limitations. The present study was based on the retrospective enrollment of individual patients with HCM, which is an unavoidable limitation shared by virtually all large-scale clinical studies on HCM. This study was evaluated in a single tertiary referral center in Japan and was therefore subject to selection bias by including a highly selected population of patients with HCM. In addition, some HCM patients were taking medication before their referral to our center, and the initial echocardiographic studies in some patients were thus performed while they were taking medication. Our results were thus likely to underestimate the prevalence and severity of MVO and OTO in this HCM patient cohort. The detection of apical hypertrophy and aneurysms in this study was based partly on transthoracic echocardiography, which has proven to be less reliable for detecting apical hypertrophy and aneurysms compared with the higher spatial resolution and detection capability of CMR imaging. In addition to CMR, contrast-enhanced echocardiography allows better delineation of the apical endocardium when apical acoustic windows are difficult to obtain (25). However, CMR and contrast-enhanced echocardiography were not performed in all MVO cases in this study, and our data were therefore likely to underestimate the true prevalence of apical hypertrophy and aneurysms in this cohort of patients with MVO.

Conclusions

In this HCM patient cohort, MVO was identified as an independent determinant of HCM-related death, especially the combined endpoint of sudden death and potentially lethal arrhythmic events. In addition, apical aneurysm formation in patients with MVO was more

Table 4 Baseline Characteristics of HCM Patients With MVO According to the Presence or Absence of an Apical Aneurysm

	Patients With an Aneurysm (n = 13)	Patients Without an Aneurysm (n = 33)	p Value
Male	10 (76.9)	18 (54.5)	0.161
Age at diagnosis, yrs	50.5 ± 12.5	54.2 ± 15.5	0.447
Family history of sudden death	2 (15.4)	4 (12.1)	>0.999
Maximum left ventricular wall thickness, mm	19.1 ± 4.1	19.1 ± 4.5	0.991
Nonsustained ventricular tachycardia	7 (53.8)	7 (21.2)	0.041
Atrial fibrillation	3 (23.1)	8 (24.2)	>0.999
Unexplained syncope	5 (38.5)	7 (21.2)	0.276
NYHA functional class at diagnosis			0.513
I	3 (23.1)	10 (30.3)	
II	9 (69.2)	22 (66.7)	
III	1 (7.7)	1 (3.0)	
IV	0 (0.0)	0 (0.0)	
Progressive heart failure	2 (15.4)	4 (12.1)	>0.999
Stroke	1 (7.7)	4 (12.1)	>0.999
Pressure gradient at diagnosis, mm Hg	41.9 ± 12.1	47.5 ± 15.5	0.252
Treatments			
Beta-blockers	11 (84.6)	24 (72.7)	0.473
Calcium-channel blockers	2 (15.4)	12 (36.4)	0.286
Class I antiarrhythmic drugs	4 (30.8)	12 (36.4)	>0.999
All interventions combined	2 (15.4)	2 (6.1)	0.565
Warfarin	6 (46.2)	7 (21.2)	0.145
Follow-up duration, yrs	11.2 ± 10.3	10.1 ± 7.4	0.682

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

strongly associated with adverse outcomes. Our results suggest that longer periods of exposure to MVO and increased left ventricular wall stress might lead to apical aneurysm formation and clinically unfavorable consequences. The results also support the principle that the presence of MVO in patients with HCM has important pathophysiological implications. Timely recognition of MVO might thus prompt changes in clinical practice to allow for gradient relief and prophylactic defibrillator implantation and could also guide the challenge of improving the prognosis for HCM patients with MVO. Further studies are required to determine the most appropriate treatment strategies for patients with MVO.

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Key Words: epidemiology ■ hypertrophic cardiomyopathy ■ midventricular obstruction ■ prognosis.

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EXPEDITED PUBLICATION

A Prospective, Randomized Evaluation of a Novel Everolimus-Eluting Coronary Stent

The PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions) Trial

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New York, New York; La Jolla, California; Clayton, Victoria, Australia; Toulouse, France; Leuven and Genk, Belgium; Ocala, Florida; Tokyo, Japan; and Natick, Massachusetts

Objectives We sought to evaluate the clinical outcomes with a novel platinum chromium everolimus-eluting stent (PtCr-EES) compared with a predicate cobalt chromium everolimus-eluting stent (CoCr-EES) in patients undergoing percutaneous coronary intervention (PCI).

Background Randomized trials have demonstrated an excellent safety and efficacy profile for the CoCr-EES. The PtCr-EES uses the identical antiproliferative agent and polymer but with a novel platinum chromium scaffold designed for enhanced deliverability, vessel conformability, side-branch access, radiopacity, radial strength, and fracture resistance.

Methods A total of 1,530 patients undergoing PCI of 1 or 2 de novo native lesions were randomized at 132 worldwide sites to CoCr-EES (n = 762) or PtCr-EES (n = 768). The primary endpoint was the 12-month rate of target lesion failure (TLF), the composite of target vessel-related cardiac death, target vessel-related myocardial infarction (MI), or ischemia-driven target lesion revascularization (TLR) in the per-protocol population (patients who received ≥1 assigned study stent), powered for noninferiority.

Results The 12-month rate of TLF in the per-protocol population occurred in 2.9% versus 3.4% of patients assigned to CoCr-EES versus PtCr-EES, respectively (difference: 0.5%, 95% confidence interval: −1.3% to 2.3%, $p_{noninferiority}$ = 0.001, $p_{superiority}$ = 0.60). By intention-to-treat, there were no significant differences between CoCr-EES and PtCr-EES in the 12-month rates of TLF (3.2% vs. 3.5%, p = 0.72), cardiac death or MI (2.5% vs. 2.0%, p = 0.56), TLR (1.9% vs. 1.9%, p = 0.96), or Academic Research Consortium definite or probable stent thrombosis (0.4% vs. 0.4%, p = 1.00).

Conclusions In this large-scale, prospective, single-blind randomized trial, a novel PtCr-EES was noninferior to the predicate CoCr-EES for TLF, with nonsignificant differences in measures of safety and efficacy through 12-month follow-up after PCI. (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions: NCT00823212) (J Am Coll Cardiol 2011;57:1700–8) © 2011 by the American College of Cardiology Foundation

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Since the introduction of first-generation drug-eluting stents (DES), advances in stent technology have continued to improve the clinical outcomes for patients undergoing percutaneous coronary intervention (PCI). Specifically, the cobalt chromium everolimus-eluting stent (CoCr-EES) (manufactured as XIENCE V by Abbott Vascular, Santa Clara, California, also distributed as PROMUS by Boston Scientific, Natick, Massachusetts) has been shown in a series of randomized trials to reduce the rates of angiographic and clinical restenosis, myocardial infarction (MI), and stent thrombosis compared with a widely used paclitaxel-eluting stent (1–4). Recently, a novel stent based on a new metal alloy has been developed, the platinum chromium everolimus-eluting stent (PtCr-EES) (manufactured as PROMUS Element by Boston Scientific) (5,6), which uses the same durable, biocompatible, inert fluorocopolymer and antiproliferative agent (7) as the predicate CoCr-EES but with a modified scaffold designed to provide improved deliverability, vessel conformability, side-branch access, radiopacity, radial strength, and fracture resistance (Fig. 1, Table 1). The PtCr-EES and CoCr-EES provide comparable everolimus release kinetics, arterial tissue levels, and vascular responses in a noninjured porcine coronary artery model (8). The vascular responses to the PtCr-EES were assessed in 73 patients in whom follow-up angiography at 9 months was performed after PCI of a single coronary lesion with reference vessel diameter (RVD) ≥2.5 to ≤4.25 mm and lesion length ≤24 mm (9). The angiographic in-stent late loss was 0.17 ± 0.25 mm, similar to that previously reported with the CoCr-EES in the SPIRIT First trial (A Clinical Evaluation of an Investigational Device. The Abbott XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) (0.10 ± 0.21 mm at 6 months and 0.24 ± 0.27 mm at 1 year), the SPIRIT II trial (0.11 ± 0.27 mm at 6 months), and the SPIRIT III trial (0.16 ± 0.41 mm at 8 months) (3,4,10,11). By intravascular ultrasound, the percentage volume obstruction with PtCr-EES at 9-month follow-up was 7.2 ± 6.2%, also comparable to that reported with the CoCr-EES (8.0 ± 10.4% and 10 ± 7% at 6 and 12 months, respectively, from the SPIRIT First trial; 2.5 ± 4.7% at 6 months in the SPIRIT II trial, and 6.9 ± 6.4% at 8 months in the SPIRIT III trial) (1,2,10,11).

To further assess the clinical safety and efficacy of the PtCr-EES, we performed the PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two De Novo Coronary Artery Lesions), a large-scale, international, multicenter, prospective, single-blind randomized trial in which the PtCr-EES was compared with the CoCr-EES in patients undergoing PCI. The present report describes the principal analyses from the pivotal PLATINUM trial.

Methods

Enrollment criteria. Patients ≥18 years of age with stable or unstable angina pectoris or documented silent ischemia were considered for enrollment. Patients requiring PCI during the index procedure of 1 or 2 de novo native coronary artery target lesions with RVD 2.5 to 4.25 mm, lesion length ≤24 mm, and diameter stenosis ≥50% to <100% with Thrombolysis In Myocardial Infarction flow grade 2 or 3 (by visual estimate) were eligible for inclusion. If only 1 target lesion was to be randomized, an additional nontarget lesion in a different vessel could be treated before the target lesion, and the patient would still qualify as long as PCI of the nonstudy lesion was angiographically successful and uncomplicated. Principal clinical exclusion criteria were acute or recent MI; left ventricular ejection fraction (LVEF) <30%; prior or planned organ transplant; recent or scheduled chemotherapy; autoimmune disease or use of immunosuppressive therapy; platelet count <100,000 or >700,000 cells/mm^3; white blood cell count <3,000 cells/mm^3; liver disease, estimated creatinine clearance <50 ml/min (Cockcroft-Gault formula), or need for dialysis; active peptic ulcer or gastrointestinal bleeding, bleeding diathesis or coagulopathy, warfarin use, or will refuse blood transfusions; stroke or transient ischemic attack within 6 months or any permanent neurologic defect; target vessel treatment with atherectomy, laser, or cutting balloon before stent placement; any planned PCI or coronary artery bypass graft after the index procedure (lesions in nonstudy target vessels could have been treated >24 h before randomization); previous treatment with intracoronary brachytherapy; known allergy to any of the components of the study stent or study medications that could not be adequately pre-medicated; comorbidity that might reduce life expectancy to <24 months; participation in another investigational drug or device trial that has not reached its primary endpoint; and inability or unwillingness to comply with all protocol-required procedures. Additional angiographic exclusion criteria included lesion location in an ostial or left main location or in or through a bypass graft conduit; true bifurcation lesion (side branch ≥2.0 mm in diameter by visual estimate or with a significant ostial stenosis); excessive tortuosity, angulation, or calcification proximal to or within the lesion; or presence of thrombus in the target vessel. The study was approved by the institu-

Abbreviations and Acronyms

ARC = Academic Research Consortium
CI = confidence interval
CK-MB = creatine kinase-myocardial band
CoCr-EES = cobalt chromium everolimus-eluting stent
DES = drug-eluting stent(s)
ITT = intention-to-treat
MI = myocardial infarction
PCI = percutaneous coronary intervention
PtCr-EES = platinum chromium everolimus-eluting stent
RVD = reference vessel diameter
TLF = target lesion failure
TLR = target lesion revascularization
TVR = target vessel revascularization

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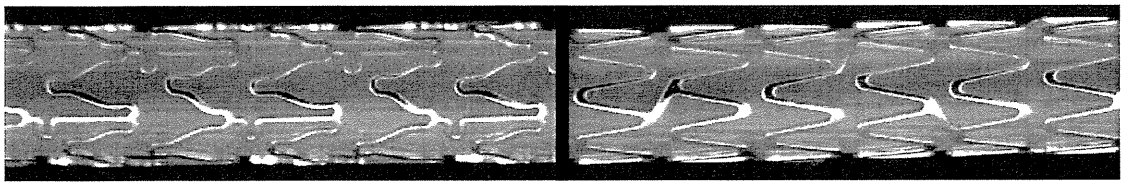

Figure 1 Photograph of CoCr-EES and PtCr-EES

Photograph of the PROMUS cobalt chromium everolimus-eluting stent (CoCr-EES) **(left)** and the PROMUS Element platinum chromium everolimus-eluting stent (PtCr-EES) **(right)** (Boston Scientific, Natick, Massachusetts). Both stents are 3.0 mm in diameter. See text for details.

tional review board or ethics committee at each participating center, and all eligible patients signed informed written consent.

Protocol. After successful target lesion pre-dilation, randomization was performed with an automated computerized system in randomly permuted blocks of 2 or 4 patients. Patients were randomized in 1:1 ratio to PtCr-EES or CoCr-EES, stratified by the presence or absence of medically treated diabetes mellitus, by the intent to treat 1 versus 2 target lesions, and by study site. Patients were considered enrolled upon randomization. Both stent types were available in diameters of 2.5 to 4.0 mm; available lengths were 12, 20, and 28 mm for PtCr-EES and 12, 18, and 28 mm for CoCr-EES. The operator performing the procedure was not blinded to the study stent, but patients and hospital caregivers remained blinded.

Table 1 Comparison of Cobalt Chromium and Platinum Chromium Everolimus-Eluting Stents

Parameter	CoCr-EES	PtCr-EES
Drug	Everolimus	Everolimus
Polymer	PBMA and PVDF-HFP*	PBMA and PVDF-HFP*
Polymer thickness (μm)	7	7
Metal composition (%)	Cobalt Chromium (L605)	Platinum Chromium
Iron	3.0 max	37†
Platinum	0	33
Cobalt	52†	0
Chromium	20	18
Nickel	10	9
Tungsten	15	0
Molybdenum	0	2.63
Manganese	1.50	≤0.05 max
Strut width (μm)	91	86
Strut thickness (μm)	81	81
Nominal balloon pressure (atm)	9	12
Balloon rated burst pressure (atm)	16	18
Surface/artery ratio (%)‡§	13.7	15.1
Scaffolding (mm) ¶	1.07	0.91
Radial strength (N/mm)§	0.14	0.23
Stent recoil (%)§	4.6	3.6
Conformability (N·mm)§#	0.30	0.09
Radiopacity/density (g/cm^3)	9.1	9.9
Trackability (g·cm catheter)**	158	133

Data are for 3.0-mm stents. *Primer layer is poly (n-butyl methacrylate) (PBMA); drug matrix layer is poly (vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP). †Balance value calculated from nominal values of other elements. Elements listed as maximums (max) are taken at midpoint for this calculation. ‡Percentage of artery wall area covered by the outer surface area of the stent. §n = 15 for platinum chromium everolimus-eluting stent (PtCr-EES); n = 10 for cobalt chromium everolimus-eluting stent (CoCr-EES). ||Average of the largest circle to fit in each cell. ¶n = 5 for PtCr-EES; n = 10 for CoCr-EES. #Conformability, a measure of the bending moment of the stent, describes ability of a stent to match the natural curvature of a vessel without causing vessel straightening; a lower value reflects better conformability. **16-mm PtCr-EES and 18-mm CoCr-EES, n = 10/group; assessed by measuring the amount of work required to pass the device through a tortuous artery model: a lower value (less work) indicates better trackability.

N/mm = Newtons/millimeter; N·mm = Newton millimeters.

The PCI was performed with unfractionated heparin, enoxaparin, or bivalirudin as per local practice, and glycoprotein IIb/IIIa inhibitors were permitted per investigator discretion. Loading doses of aspirin (≥300 mg p.o. recommended) and clopidogrel (≥300 mg p.o. required) were required in patients not taking these medications ≥72 h before the index procedure. Post-PCI daily aspirin was required indefinitely, with 162 to 325 mg p.o. daily recommended for at least the first 6 months and 75 to 162 mg p.o. daily thereafter. Clopidogrel 75 mg p.o. daily was required for at least 6 months after stent placement in all patients and for at least 12 months in those not at high risk of bleeding. Ticlopidine was allowed in patients intolerant of clopidogrel, and prasugrel was permitted in non-U.S. sites in accordance with approved country-specific labeling.

After hospital discharge, clinical follow-up was scheduled for 1 month and 6, 12, and 18 months and then annually from 2 to 5 years. Repeat angiographic follow-up was performed only for clinical indications. The primary endpoint was assessed at 1 year, the timing of the present report.

Data management. Study monitors verified all case report form data on-site. An independent Clinical Events Committee (CEC) blinded to study stent assignment adjudicated all death, MI, target vessel revascularization (TVR), and stent thrombosis events. An independent Data Safety and Monitoring Committee evaluated all reported and adjudicated adverse events at regular intervals, each time allowing the study to continue unchanged. Angiographic data were analyzed by an independent core angiographic laboratory. Study organization and oversight committee membership are provided in the Online Appendix.

Endpoints and definitions. The primary endpoint was the 12-month rate of target lesion failure (TLF), defined as the

composite of cardiac death (any death other than those confirmed to have a noncardiac cause) related to the target vessel, MI related to the target vessel, or ischemia-driven target lesion revascularization (TLR). Myocardial infarction was defined as: 1) the development of new Q waves in ≥2 leads lasting ≥0.04 s with creatine kinase-myocardial band (CK-MB) or troponin levels elevated above normal; or 2) in the absence of new Q waves, elevation of total CK levels >3× normal (peri-PCI) or >2× normal (spontaneous) with elevated CK-MB, or troponin >3× normal (peri-PCI) or >2× normal (spontaneous) plus at least 1 of the following: 1) electrocardiographic changes indicative of new ischemia (new ST-T changes or left bundle branch block); 2) imaging evidence of new loss of viable myocardium; or 3) new regional wall motion abnormality. Similar criteria were required for the diagnosis of MI after coronary artery bypass graft surgery, with a CK-MB or troponin threshold of >5× normal. Ischemia-driven TLR or TVR was defined as revascularization of the target lesion or vessel with the stenosis ≥50% by quantitative coronary angiography if associated with clinical or functional ischemia (ischemic symptoms, electrocardiographic changes, or positive functional study), or stenosis ≥70% by quantitative coronary angiography without documented ischemia. Additional clinical endpoints included target vessel failure (defined as the composite of cardiac death, MI, or ischemia-driven TVR); the components of TLF and target vessel failure; stent thrombosis defined according to the definite or probable Academic Research Consortium (ARC) criteria (12), subclassified as acute (<24 h), subacute (24 h to 30 days), and late (>30 days to 1 year); technical success (successful delivery and deployment of the study stent to the target vessel, without balloon rupture or stent embolization); and clinical procedural success (visually assessed lesion diameter stenosis <30% with Thrombolysis In Myocardial Infarction flow grade 3, without in-hospital MI, TVR, or cardiac death).

Sample size determination and statistical methods. The randomized trial was powered for noninferiority testing of PtCr-EES compared with CoCr-EES for the primary endpoint of 12-month TLF. A 2-group Farrington-Manning test was used to test the 1-sided hypothesis of noninferiority in differences with a noninferiority margin (delta) of 3.5%. A p value <0.05 would indicate noninferiority of PtCr-EES and would correspond to the upper limit of the 1-sided 95% confidence interval (CI) of the difference not exceeding 3.5%. The trial had 89% power to demonstrate noninferiority for TLF (accounting for an expected 1-year attrition rate of 5%), assuming a 1-year TLF rate of 5.5% for both stents (on the basis of the data available at the time of study design for CoCr-EES from the SPIRIT II and III trials [1,2]), with 766 patients enrolled/treatment group.

Treatment groups were compared with a 2-sided chi-square or Fisher exact test for categorical variables and Student *t* test for continuous variables. The Kaplan-Meier product-limit method was used to estimate event rates for time-to-event outcomes; data were compared with the log-rank test. The primary endpoint was pre-specified to be tested in the per-protocol population (patients receiving 1 or more assigned study stents). All endpoints were also analyzed in the intention-to-treat (ITT) population (including all patients who underwent randomization, regardless of treatment actually received). All statistical analyses were done with SAS software (version 8.2 or above, SAS Institute, Inc., Cary, North Carolina).

Results

Patient characteristics and procedural outcomes. Between January 27, 2009 and September 4, 2009, 1,530 patients were enrolled at 132 sites in the United States (n = 788), European Union (n = 562), Japan (n = 124), and other Asia Pacific countries (n = 56), and were randomized to CoCr-EES (n = 762) or PtCr-EES (n = 768). The baseline clinical and angiographic features of the randomized study groups were well-matched (Table 2). Mean patient age was 63.5 years, 28.6% were women, 23.5% had medically treated diabetes, and 24.4% presented with unstable angina. Multiple target lesions were treated in 10.7% of patients. The mean lesion RVD was 2.65 mm, and mean lesion length was 12.7 mm. Procedural and angiographic outcomes were also similar between the groups (Table 3), although slightly more CoCr-EES than PtCr-EES were used per lesion, and the maximum dilation pressure was higher for PtCr-EES. Nonetheless, angiographic acute gain and post-PCI target lesion luminal measures were not significantly different between the 2 stent types.

Among patients randomized to CoCr-EES and PtCr-EES, technical success was achieved in 98.8% and 99.4% of patients, respectively (p = 0.14), and clinical procedural success was achieved in 98.2% and 98.3%, respectively (p = 0.83). Unplanned (bail-out) stenting was required in 75 patients (9.8%) treated with CoCr-EES (for procedural complications [n = 36], inadequate lesion coverage [n = 26], or other reasons [n = 13]) compared with 45 patients (5.9%) treated with PtCr-EES (for procedural complications [n = 29], inadequate lesion coverage [n = 11], or other reasons [n = 5]) (p = 0.004). Other performance measures were comparable between the groups.

Clinical outcomes. Patient flow in the study is shown in Figure 2. Follow-up at 12 months was completed in 96.7% of patients. Among patients randomized to CoCr-EES versus PtCr-EES, aspirin was used by 99.6% and 98.7%, respectively, at hospital discharge (p = 0.053) and by 97.4% and 97.6%, respectively, at 1 year (p = 0.84). A thienopyridine (clopidogrel, ticlopidine, or prasugrel) was used by 99.1% and 98.8% of CoCr-EES and PtCr-EES–assigned patients, respectively, at the time of hospital discharge (p = 0.63) and in 89.4% and 90.9% of patients at 1 year,

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Table 2 Baseline Clinical and Angiographic Features of the Randomized Study Groups

	CoCr-EES (n = 762 Patients, n = 841 Lesions)	PtCr-EES (n = 768 Patients, n = 853 Lesions)	p Value
Demographic features			
Age (yrs)	63.1 ± 10.3 (762)	64.1 ± 10.3 (768)	0.09
Male	542/762 (71.1)	550/768 (71.6)	0.83
Hypertension*	558/762 (73.2)	544/767 (70.9)	0.32
Hypercholesterolemia*	579/760 (76.2)	598/765 (78.2)	0.36
Diabetes*	191/762 (25.1)	169/768 (22.0)	0.16
Insulin treated	48/762 (6.3)	59/768 (7.7)	0.29
Current smoker	131/741 (17.7)	158/751 (21.0)	0.10
Prior myocardial infarction	160/760 (21.1)	160/761 (21.0)	0.99
Unstable angina	188/762 (24.7)	185/767 (24.1)	0.80
Number of target lesions, mean	1.10 ± 0.31 (762)	1.11 ± 0.31 (768)	0.66
1	684/762 (89.8)	683/768 (88.9)	0.60
2	77/762 (10.1)	85/768 (11.1)	0.54
3	1/762 (0.1)	0/768 (0.0)	0.50
Target vessel			
Left anterior descending	343/813 (42.2)	347/824 (42.1)	0.97
Left circumflex	216/813 (26.6)	217/824 (26.3)	0.91
Right	254/813 (31.2)	260/824 (31.6)	0.89
Target lesion measures			
Reference vessel diameter, mm	2.63 ± 0.49	2.67 ± 0.49	0.09
Minimal lumen diameter, mm	0.74 ± 0.34	0.75 ± 0.35	0.40
Diameter stenosis, %	71.9 ± 11.5	71.8 ± 11.5	0.87
Lesion length, mm	12.5 ± 5.5	13.0 ± 5.7	0.10

Values are mean ± SD or n/N (%). *Requiring medication.
Abbreviations as in Table 1.

respectively (p = 0.34); prasugrel was taken by only 1 patient at discharge (in the PtCr-EES group) and by 6 patients in each group at 1 year.

The primary endpoint analysis appears in Figure 3. The rate of TLF at 12 months in the per-protocol population occurred in 2.9% of patients assigned to CoCr-EES and 3.4% of patients assigned to PtCr-EES (difference: 0.5%, 95% CI: −1.3% to 2.3%, $p_{superiority}$ = 0.60). The 1-sided 95% Farrington-Manning upper confidence bound was 2.13%, which is less than the pre-specified noninferiority margin of 3.5%. As such, the primary endpoint of noninferiority for PtCr-EES compared with CoCr-EES for TLF at 12 months was met ($p_{noninferiority}$ = 0.001). Similarly, in the ITT population, the 12-month rate of TLF was nonsignificantly different between CoCr-EES and PtCr-EES (3.2% vs. 3.5%, respectively; difference: 0.3%, 95% CI: −1.5% to 2.2%, $p_{noninferiority}$ = 0.0009, $p_{superiority}$ = 0.72) (Fig. 4).

Additional 12-month outcomes in the ITT population appear in Table 4. There were no significant differences detected in any safety or efficacy measure between the stent types. The 1-year rate of TLR was 1.9% for both groups (p = 0.96). ARC definite or probable stent thrombosis through 1 year of follow-up occurred in only 3 patients (0.4%) in each group (1 acute, 2 subacute, and 0 late events with CoCr-EES; and 1 acute, 0 subacute, and 2 late events with PtCr-EES).

Discussion

The principal findings from the present analysis, representing the pivotal 1-year outcomes from the multicenter, multinational, prospective, randomized PLATINUM trial, are that: 1) a novel PtCr-EES has been developed with noninferior 12-month rates of TLF compared with the predicate CoCr-EES; 2) clinical restenosis (ischemia-driven TLR) within 1 year occurred infrequently and to a similar degree with both stents in the patient population tested; and 3) both stents demonstrated an excellent safety profile, with nonsignificantly different 12-month rates of cardiac death, MI, and stent thrombosis.

Prior studies have demonstrated that, across a broad cross-section of patients undergoing PCI, the CoCr-EES results in low rates of TLF, a relatively stent-specific composite measure of safety and efficacy. In large-scale randomized trials, patients treated with the CoCr-EES have been shown to have reduced 1-year rates of TLF, TLR, MI, and stent thrombosis compared with the first-generation paclitaxel-eluting stent (5,6) and nonsignificantly different 1-year rates of TLF, TLR, and MI but less stent thrombosis compared with a second-generation zotarolimus-eluting stent (13). The favorable results with this device likely stem from the properties of its 3 main components: the polymer, the drug, and the metallic stent itself. The thin (7 μm), nonadhesive, durable and inert

Table 3 Procedural and Angiographic Outcomes of the Randomized Study Groups

	CoCr-EES (n = 762 Patients, n = 841 Lesions)	PtCr-EES (n = 768 Patients, n = 853 Lesions)	p Value
Procedural variables			
Stents/patient, n	1.20 ± 0.48	1.16 ± 0.44	0.16
Stents/target lesion, n	1.08 ± 0.35	1.05 ± 0.26	0.01
Maximum stent diameter/lesion (mm)	3.05 ± 0.44	3.09 ± 0.45	0.07
Maximum stent diameter/RVD ratio (mm)	1.18 ± 0.15	1.17 ± 0.15	0.63
Total stent length/lesion (mm)	19.7 ± 8.9	20.5 ± 7.0	0.06
Total stent length/lesion length ratio (mm)	1.7 ± 0.7	1.8 ± 0.7	0.25
Post-stent dilation performed	415/841 (49.3%)	425/853 (49.8%)	0.84
Maximum dilation pressure (atm)*	15.9 ± 3.2	16.3 ± 3.1	0.002
Glycoprotein IIb/IIIa inhibitors used	62/762 (8.1%)	56/768 (7.3%)	0.54
Non-target lesions treated	71/762 (9.3%)	69/768 (9.0%)	0.82
Fluoroscopy time (min)	11.3 ± 10.1	12.2 ± 11.8	0.10
Contrast used (cc)	184 ± 86	185 ± 87	0.85
Post-procedural results (per target lesion)			
Reference vessel diameter (mm)	2.67 ± 0.50	2.70 ± 0.49	0.27
Minimum lumen diameter (mm)			
In-stent	2.54 ± 0.44	2.57 ± 0.42	0.25
In-segment	2.16 ± 0.47	2.19 ± 0.47	0.15
Diameter stenosis, %			
In-stent	4.3 ± 8.7	4.3 ± 9.1	0.95
In-segment	19.2 ± 9.0	18.8 ± 8.6	0.43
Acute gain, %			
In-stent	1.80 ± 0.45	1.81 ± 0.43	0.73
In-segment	1.42 ± 0.47	1.44 ± 0.46	0.45

Values are mean ± SD or n/N (%). *Pre-dilation, stent implantation, or post-dilation balloon.

biocompatible fluorocopolymer has been shown to be resistant to platelet and thrombus deposition in blood-contact applications (14,15), possibly contributing to resistance to stent thrombosis. The polymer controls the release kinetics of the everolimus such that approximately 80% of the drug is released at 30 days, with none detectable after 120 days. The dose density of everolimus (100 $\mu g/cm^2$) is lower than with any comparable rapamycin-analogue DES. Finally, the thin (81 μm) CoCr stent struts facilitate rapid re-endothelialization (16) and are fracture-resistant. Preclinical studies have demonstrated more rapid coverage of the CoCr-EES struts with functional endothelialization than with other DES (17).

Through use of a more dense platinum chromium alloy and a modified scaffold architecture, the PtCr-EES was developed to further improve upon several of the mechanical

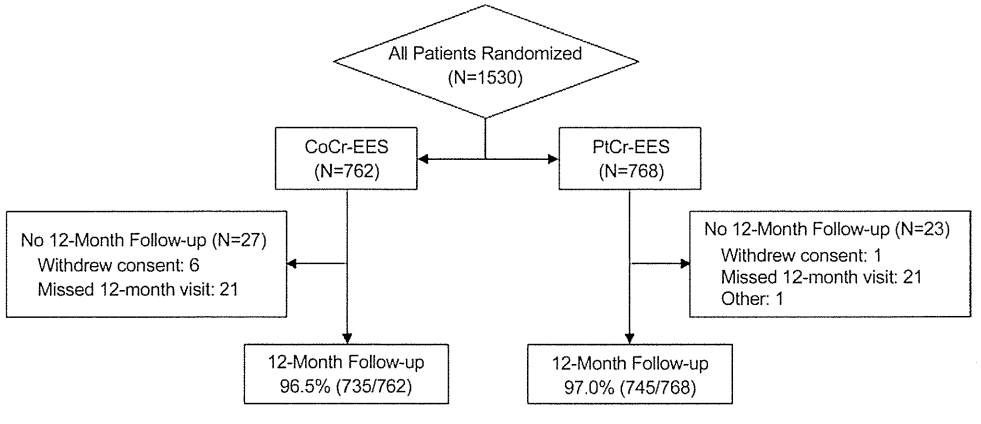

Figure 2 Patient Flow in the Randomized Trial

Abbreviations as in Figure 1.

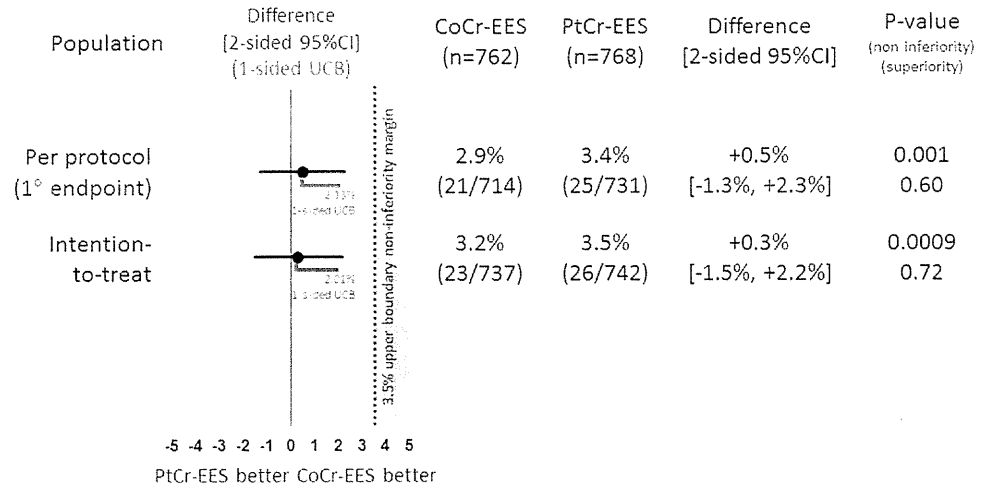

Figure 3 **Primary Endpoint of TLF at 1 Year**

Primary endpoint of target lesion failure (TLF) at 1 year for the per-protocol population (primary analysis) and the intention-to-treat (ITT) population (secondary analysis). Plot shows the difference in TLF at 1-year between the CoCr-EES and the test PtCr-EES, with the 2-sided confidence intervals (CIs) **(black line)** and the upper bound of the 1-sided 95% CI **(red line)**. The p values for noninferiority and superiority testing are 1- and 2-sided, respectively. Abbreviations as in Figure 1.

and physical properties of the CoCr-EES (specifically, to enhance trackability, vessel conformability, side-branch access, radiopacity, radial strength, and fracture resistance). A paclitaxel-eluting version of this stent (TAXUS Element, Boston Scientific) has previously been shown to have noninferior clinical outcomes compared with the predicate stainless steel TAXUS Express stent (18). A major design goal for the PtCr-EES was to preserve the clinical safety and efficacy profile of the CoCr-EES by maintaining the same polymer thickness, everolimus concentration, and pharmacokinetics present in the CoCr-EES while improving acute performance. In this regard, comparable everolimus release kinetics, arterial tissue levels, and vascular responses have been reported for the PtCr-EES and CoCr-EES in a noninjured porcine coronary artery model (8), and in a prior nonrandomized clinical study the PtCr-EES was found to have rates of angiographic in-stent and in-segment late loss comparable to those of the CoCr-EES (9). The current results from the large-scale PLATINUM randomized trial demonstrate noninferiority of the PtCr-EES to the CoCr-EES for the composite safety and efficacy measure of TLF at 1 year, with nonstatistically significant different rates present in death, MI, and TLR. Notably, the 0.4% 1-year rate of ARC definite or probable stent thrombosis in both groups in the present trial confirms the low thrombosis rates reported with the EES in prior studies (1–4,10,11,14). Thus, along with stainless steel and cobalt chromium, platinum chromium may now be considered an acceptable metal alloy for use in DES.

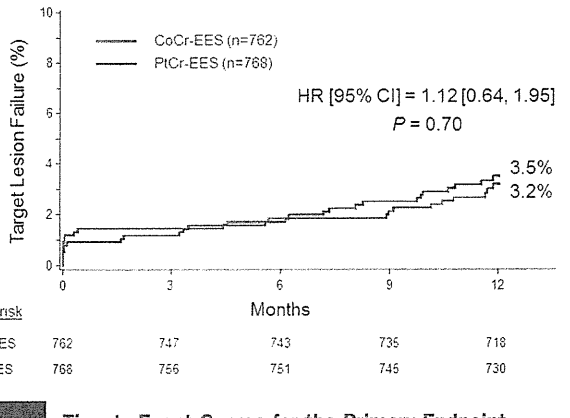

Figure 4 **Time-to-Event Curves for the Primary Endpoint of TLF in the ITT Population**

The event rates presented here were calculated by Kaplan-Meier methodology and compared with the log-rank test. Thus, the p value differs slightly from that in the text and Table 4, which were calculated using categorical variables and compared with the chi-square test. HR = hazard ratio; other abbreviations as in Figures 1 and 3.

Although the rates of technical and clinical procedural success achieved with the 2 stents were similar in the present study, a higher rate of unplanned (bail-out) stenting was observed with CoCr-EES compared with PtCr-EES. The clinical relevance of this finding is uncertain. The present study was not designed to evaluate whether the PtCr-EES is indeed more deliverable, conformable, and/or more radiopaque; affords better side-branch access; is more resistant to recoil; and/or is more fracture resistant than the CoCr-EES. These properties might be difficult to measure in patients, because differences between devices that are detectable on the bench might not be clinically relevant or otherwise perceptible in vivo (19). Typically, extensive multicenter clinical experience in patients with complex