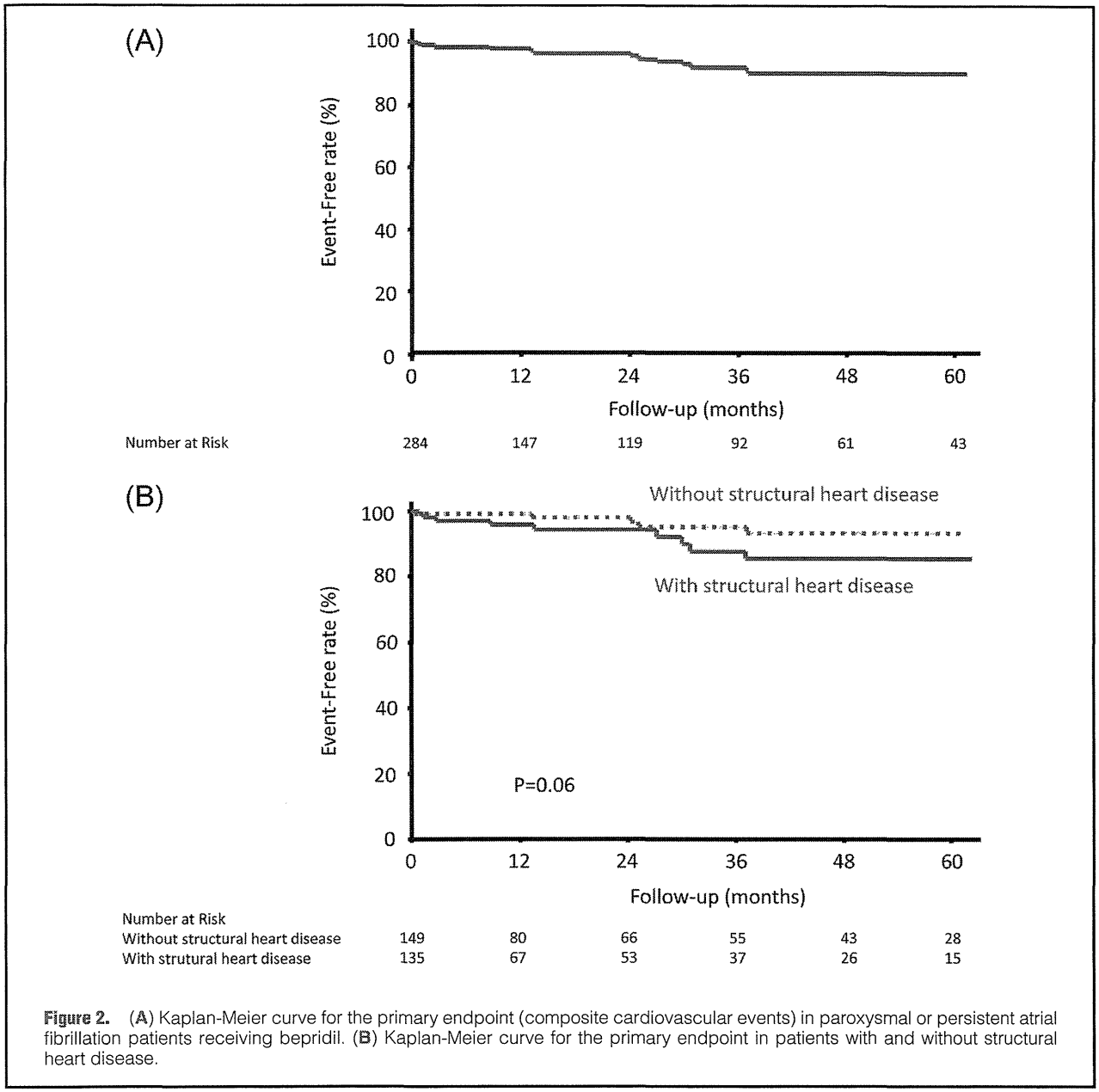

Figure 2. (A) Kaplan-Meier curve for the primary endpoint (composite cardiovascular events) in paroxysmal or persistent atrial fibrillation patients receiving bepridil. (B) Kaplan-Meier curve for the primary endpoint in patients with and without structural heart disease.

Side Effects

We observed bepridil-related cardiac adverse events, including sudden arrhythmic death, ventricular tachyarrhythmia (including Tdp), excessive QTc prolongation (>0.50 s), excessive bradycardia requiring the discontinuation of bepridil and/or additional therapy. Extracardiac adverse events, such as gastrointestinal symptoms and liver dysfunction (alanine aminotransferase ≥3×normal and/or alkaline phosphatase >normal), were also observed.

Statistical Analysis

Summary data are presented either as mean±SD or number of patients. Categorical variables were subjected to chi-square analysis. Time to first occurrence of events was analyzed using the Kaplan-Meier method with the log-rank test. $P<0.05$ was considered significant. Data analyses were performed with SPSS statistical software (version 11.01, SPSS Inc, Chicago, IL, USA).

Results

Patients' Characteristics

The patients' baseline characteristics are shown in **Table 1**. The mean age when bepridil was started was 59±13 years, and 25% of the patients treated were women. A total of 21 patients (7%) had persistent AF; 135 patients (48%) had structural heart diseases; 63 (22%) had a history of congestive heart failure; 80 (28%) had hypertension; 39 (14%) had diabetes. Regarding concomitant medications at baseline, 126 patients (44%) had taken angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, 143 patients (50%) had taken β-blockers, and 38 patients (13%) had taken

Table 2. Death and Cardiovascular Events in the Patients With AF	
Cardiovascular death	
Sudden death	1
Heart failure	5
Cerebral infraction	1
Dissection of aorta	1
Non-cardiovascular death	6
Non-fatal myocardial infarction	1
Hospitalization for unstable angina	2
Hospitalization for heart failure	1
Non-fatal cerebral infarction	5
Non-fatal cerebral hemorrhage	2
Torsade de pointes	2

Values are n. AF, atrial fibrillation.

a statin. The proportion of patients with a $CHADS_2$ score of 0, 1 or ≥2 was 44%, 31% and 25%, respectively. 152 patients (54%) used warfarin, and 108 (38%) used aspirin. We lost 8 patients to follow-up; the remaining 276 patients (97%) were followed completely. Bepridil was discontinued because of ineffective prevention of AF (86 patients), progression to permanent AF (30 patients), side effects (17 patients) or the patient's own decision (1 patient). The median follow-up period was 17 months (range 4–157 months).

Endpoints

The Kaplan-Meier curve for the primary endpoint is shown in Figure 2. Each primary endpoint is shown in Table 2. A primary endpoint was obtained for 21 (7%) of the 284 patients. The cumulative rate for the time to first cardiovascular event at 1, 3, and 5 years was 2.4%, 8.1%, and 10.1%, respectively. A trend toward increased cardiovascular events was observed

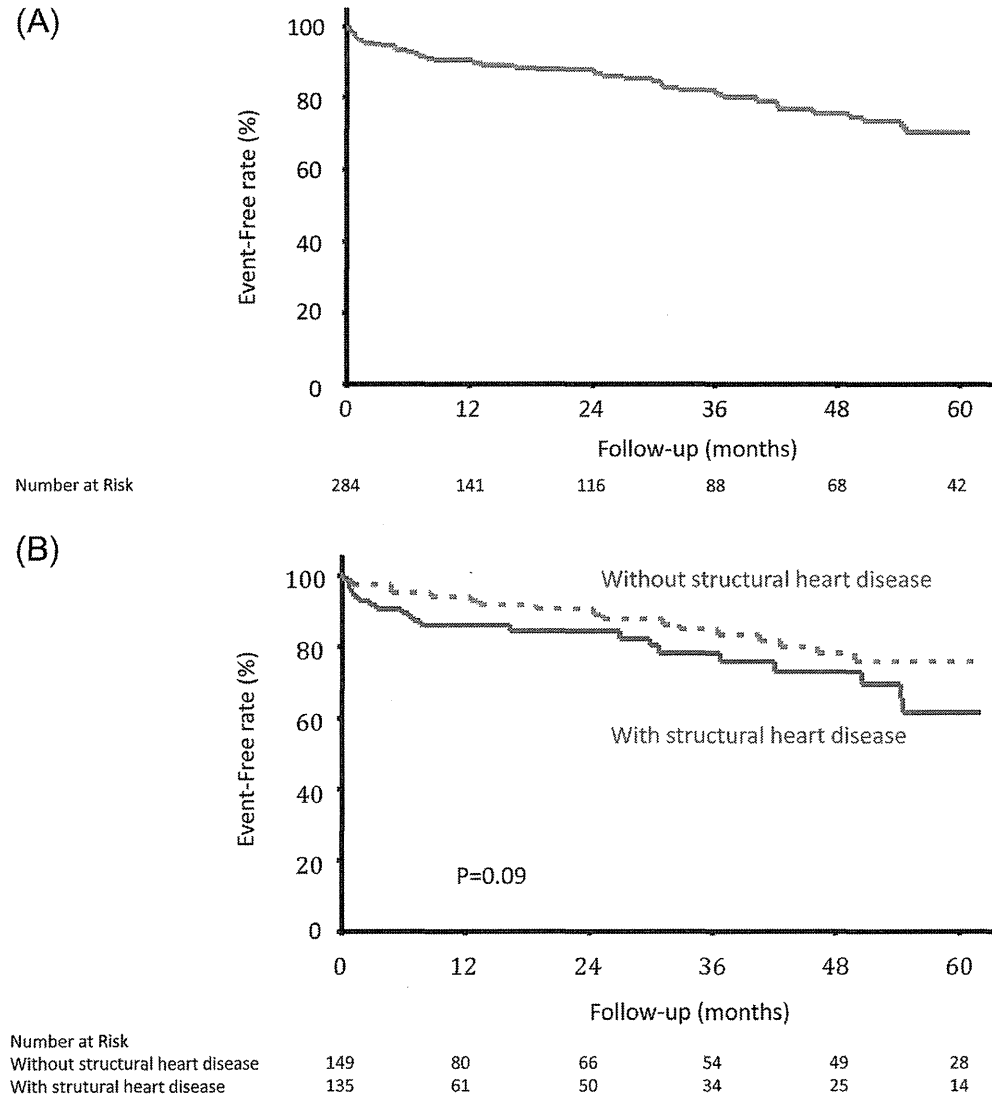

Figure 3. (A) Kaplan-Meier curve for the main secondary outcome (composite of mortality, symptomatic cerebral infarction, systemic embolism, major bleeding and hospitalization for heart failure) in paroxysmal or persistent atrial fibrillation patients receiving bepridil. (B) Kaplan-Meier curve for the main secondary endpoint in patients with and without structural heart disease.

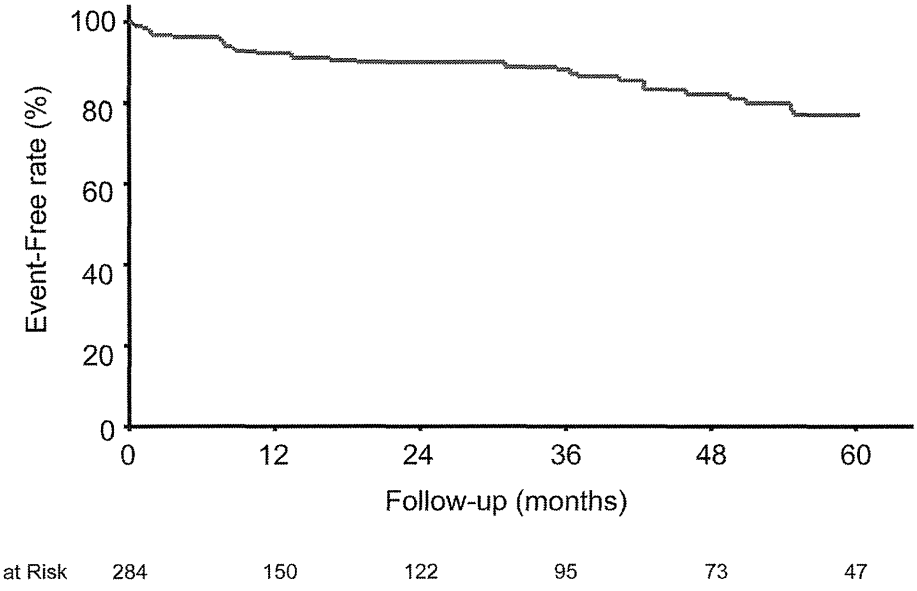

Figure 4. Kaplan-Meier curve for the progression to permanent atrial fibrillation in paroxysmal or persistent atrial fibrillation patients receiving bepridil.

in patients with structural heart disease compared with those without. The Kaplan-Meier curve for the main secondary outcome is shown in Figure 3. The cumulative rate for the main secondary endpoint at 1, 3, and 5 years was 9.7%, 18.2%, and 29.6%, respectively. A trend toward higher rates for the main secondary endpoint was observed in patients with structural heart disease compared with those without. The causes of death were sudden death (1 patient), heart failure (5 patients), dissection of aorta (1 patient) and non-cardiac causes (7 patients). Permanent AF was the diagnosis in 39 patients during bepridil therapy. The cumulative rate for the time to permanent AF diagnosis at 1, 3, and 5 years during bepridil therapy was 8.3%, 12.1%, and 23.5%, respectively (Figure 4).

Adverse Events

The numbers of patients who experienced adverse events according to their maintenance dose of bepridil are shown in Table 3. Regarding serious adverse events, sudden death occurred in 1 patient who had a prior MI (200 mg daily), and Tdp occurred in 2 patients without structural heart disease (both 200 mg daily). The rate of QTc prolongation (>0.50 s) was highest (11%) in patients taking 200 mg bepridil. A total of 17 patients (6%) discontinued bepridil therapy due to its side effects, which included the following: Tdp (2 patients), QT prolongation (3 patients), sinus bradycardia (1 patient), and non-cardiac causes such as gastrointestinal symptoms (4 patients), liver dysfunction (4 patients) and neurological symptoms (3 patients).

Blood Concentration

The distribution of plasma bepridil concentrations according to the maintenance dose (77 patients, 439 points) is shown in Figure 5. With dosages of ≤100 mg daily, a dose-dependent effect was observed. However, a high variation in plasma concentration was found, and a dose-dependent effect was not always observed with dosages ≥100 mg daily. Excessive QTc prolongation (>0.50 s) was found in plasma concentrations >800 ng/ml.

Table 3. Daily Dose of Bepridil and Adverse Events in the Patients With AF

	<100 mg	100 mg	150 mg	200 mg
n	22	112	106	44
Torsade de pointes	0	0	0	2
QTc prolongation (>0.50 s)	0	7	9	5
Bradycardia	1	0	0	0
Gastrointestinal symptoms	0	1	2	1
Liver dysfunction	0	0	3	1
Neurological symptoms	0	2	0	1

Values are n. AF, atrial fibrillation.

Discussion

Our study revealed the following: (1) a probability of cardiovascular events of 10.1% at 5 years in AF patients receiving bepridil; (2) a total of 75.7% of patients receiving bepridil had paroxysmal or persistent AF that was refractory to class I antiarrhythmic drugs; (3) a probability of progression to permanent AF of 23.5% at 5 years in paroxysmal or persistent AF patients receiving bepridil; (4) adverse events, especially Tdp, seemed to occur in a dose-dependent manner; (5) high variation in plasma concentrations even among patients taking the same dose of bepridil, and excessive QTc prolongation occurred mostly at concentrations >800 ng/ml.

In our study, we evaluated clinical outcome (AF-related, complicated heart disease-related and bepridil-related) as the primary endpoint and general outcome in AF patients (for comparison with the previous AF outcome study in Japan) as the main secondary endpoint. On average, our subjects were 10 years younger than the subjects in previous AF mortality

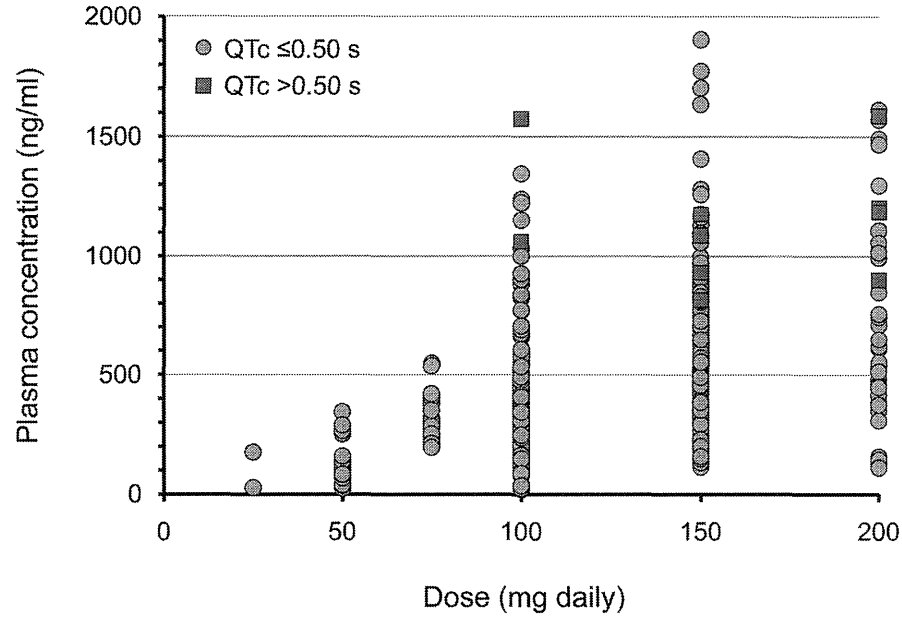

Figure 5. Dose and plasma concentration in 77 paroxysmal or persistent atrial fibrillation patients receiving bepridil (439 points).

studies, so the mortality and cardiovascular event rates were low.[10,11] However, the overall rate of the main secondary outcome, which was the hard endpoint in the J-RHYTHM study, was higher than in the J-RHYTHM study, in which the subjects were older (mean age: 65 years).[13] In particular, both the incidence of death due to worsening heart failure and of non-cardiac death was high in our study. Compared to subjects in the J-RHYTHM study, our subjects had a similar distribution of $CHADS_2$ scores, but a higher proportion of patients in our study had structural heart disease or a history of congestive heart failure. A trend toward a higher rate of cardiovascular events in patients with structural heart disease compared to patients without structural heart disease was observed. Nevertheless, because the proportion of warfarin use among our patients was similar to that in the J-RHYTHM study, the incidence of stroke was identical (our study: 2.1%; J-RHYTHM study: 2.1%[13]). Although the clinical backgrounds of the patients contributed to the outcomes, bepridil may not be helpful in improving the outcomes of AF patients with structural heart disease.

The Canadian Registry of Atrial Fibrillation study consisted of 757 patients with paroxysmal AF (mean age: 61 years; ≈40% with structural heart disease). This study showed that the probability of progression to permanent AF was 8.6% and 24.7% at 1 and 5 years, respectively.[31] Moreover, another study with a small sample number reported that among patients with drug-intolerant or drug-refractory paroxysmal AF on long-term antiarrhythmic drug therapy, the probability of progression to permanent AF was more than 30% at 5 years.[32] Factors such as age and structural or substrate abnormalities contribute to the progression to a permanent form of AF.[31,33] The rate of progression to permanent AF was not as high among our subjects (mean age: 59 years; 48% with structural heart disease) as in previous studies, even though our subjects were mostly AF patients who did not respond to class I antiarrhythmic drugs. Bepridil is an antiarrhythmic drug with multiple therapeutic actions,[15,16] and it has been found to be effective in converting AF to sinus rhythm and maintaining sinus rhythm in persistent AF or AF that is refractory to class I antiarrhythmic drugs.[17–24]

However, the safety of bepridil is a major problem, especially with respect to Tdp associated with QT prolongation.[15–25,34] In our study, sudden death and Tdp occurred in patients who took 200 mg daily. Moreover, 17 patients (6%) discontinued bepridil therapy due to its side effects, including QT prolongation, which seem to occur in a dose-dependent manner. Hypokalemia, bradycardia, heart failure, LV hypertrophy and high drug concentrations are recognized as risk factors for Tdp in the presence of a culprit drug.[35] In practice, as long as bepridil is used to manage AF, physicians must carefully monitor these factors, and bepridil should be avoided in AF patients with heart failure or LV hypertrophy.

We also monitored the blood concentration of bepridil, starting in May 2007. Bepridil has complex pharmacokinetic properties: low systemic bioavailability (approximately 60%), a large volume of distribution (8 L/kg), and a long elimination half-life (1–2 days) with a single oral dose and even longer at steady state.[26,27] Therefore, large interindividual differences in blood concentrations were observed, even among patients taking the same dose. Sugi et al reported that the bepridil blood concentration was 270±140 ng/ml in patients receiving 100 mg daily, 530±520 ng/ml in patients receiving 150 mg daily and 680±360 ng/ml in patients receiving 200 mg daily. Additionally, the proportion of patients whose AF was prevented by taking bepridil (vs. those who continued to experience AF while taking bepridil) was highest among patients receiving 200 mg daily with blood concentrations >600 ng/ml.[36] In contrast, Kurita et al reported that most of the patients who developed Tdp during bepridil therapy had taken 200 mg daily and had blood concentrations >500 ng/ml.[37] This demonstrates that there is considerable overlap between the effective dose/concentration and toxicity with bepridil therapy. In our results,

excessive QTc prolongation occurred in patients with plasma bepridil concentrations >800 ng/ml, and blood concentrations of at least 1,000 ng/ml might be a risk factor for developing Tdp. After we began monitoring blood concentrations, the mean maintenance dose of bepridil was decreased from 141±46 mg daily (February 1988 to April 2007) to 126±44 mg daily (May 2007 to August 2010). No Tdp occurred from June 2007 onward.

Study Limitations

First, this study was a retrospective observational study conducted in a single center, so treatment bias existed. We could not evaluate the relationship between AF recurrence and outcome. It is difficult to obtain the exact time to first recurrence or the frequency of AF recurrence from a patient's symptoms and routine ECGs in clinical practice. Second, the clinical characteristics of the subjects varied, and the number of subjects was small. Therefore, subgroup analysis was not feasible.

Conclusions

Bepridil is mostly used as a second-line therapy for AF patients who are refractory to class I or class III antiarrhythmic drugs. However, bepridil might not improve the clinical outcomes in these AF patients, especially those with structural heart disease. Moreover, its severe adverse events, including QT prolongation and Tdp, occur in a dose- and concentration-dependent manner. Monitoring the blood bepridil concentration and low-dose treatment regimens may help decrease adverse events.

Acknowledgments

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Disclosure

Competing interests: None declared.

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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

Gregg W. Stone, MD,* Paul S. Teirstein, MD,† Ian T. Meredith, MBBS, PHD,‡ Bruno Farah, MD,§ Christophe L. Dubois, MD, PHD,‖ Robert L. Feldman, MD,¶ Joseph Dens, MD, PHD,# Nobuhisa Hagiwara, MD,** Dominic J. Allocco, MD,†† Keith D. Dawkins, MD,†† for the PLATINUM Trial Investigators

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

From the *Columbia University Medical Center/New York-Presbyterian Hospital and the Cardiovascular Research Foundation, New York, New York; †Scripps Clinic, Division of Cardiovascular Diseases, La Jolla, California; ‡MonashHEART, Southern Health, Monash Medical Centre, Clayton, Victoria, Australia; §Clinique Pasteur, Toulouse, France; ‖UZ Gasthuisberg, Leuven, Belgium; ¶Munroe Regional Medical Center, Ocala, Florida; #Ziekenhuis Oost Limburg, Genk, Belgium; **Tokyo Women's Medical University Hospital, Shinjuku, Tokyo, Japan; and ††Boston Scientific Corporation, Natick, Massachusetts. A complete list of the study organization and participating sites and investigators from the PLATINUM trial may be found in the Online Appendix. Dr. Stone reports serving on the scientific advisory boards for and receiving honoraria from Boston Scientific and Abbott Vascular and is a consultant to Medtronic. Dr. Teirstein reports having received research grants, honoraria, and consulting fees from Boston Scientific, Abbott Laboratories, Cordis, and Medtronic. Dr. Meredith reports serving on the scientific advisory boards for and receiving honoraria from Boston Scientific. Dr. Farah reports receiving honoraria from Boston Scientific and Abbott Vascular. Dr. Dubois reports serving on the scientific advisory board for Boston Scientific. Dr. Feldman reports serving on the scientific advisory board for and receiving honoraria from Boston Scientific. Drs. Allocco and Dawkins report being full-time employees and stockholders of Boston Scientific. All other authors have reported that they have no relationships to disclose.

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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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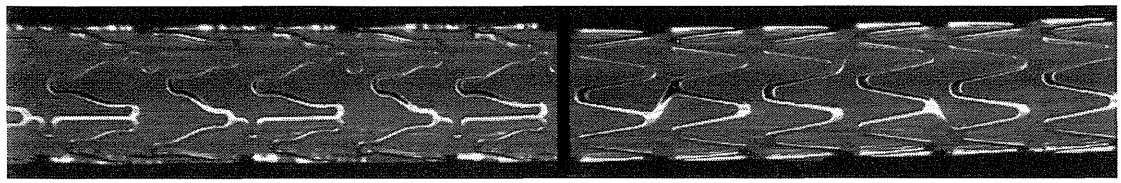

Figure 1 Photograph of CoCr-EES and PtCr-EES

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

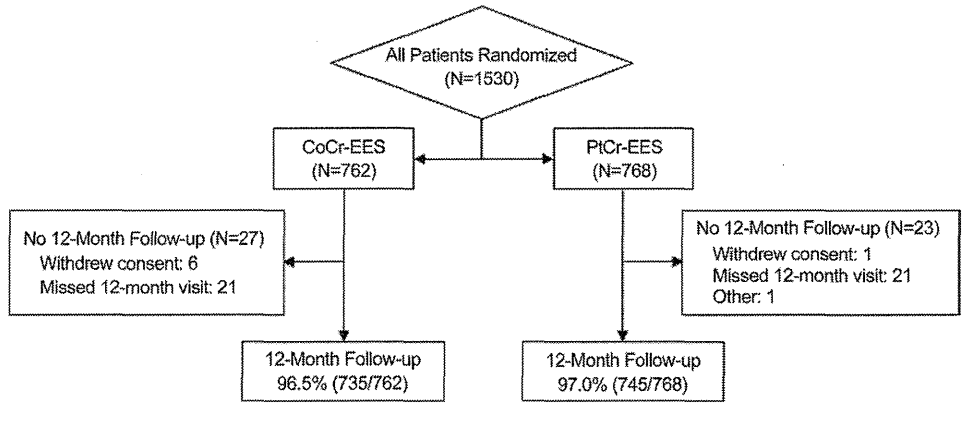

Figure 2 Patient Flow in the Randomized Trial

Abbreviations as in Figure 1.

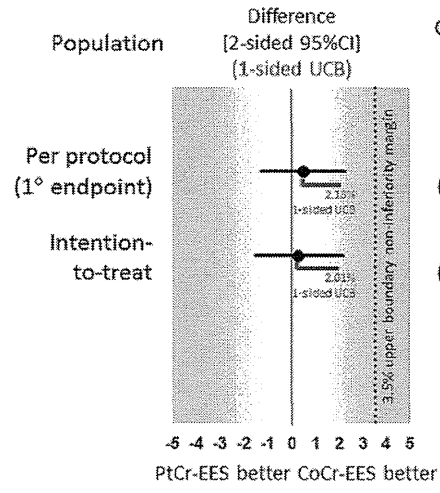

Figure 3 Primary Endpoint of TLF at 1 Year

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.

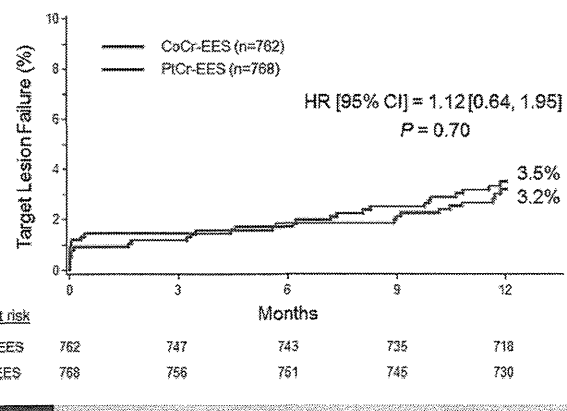

Figure 4 Time-to-Event Curves for the Primary Endpoint of TLF in the ITT Population

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

Table 4 1-Year Clinical Outcomes in the ITT Population

	CoCr-EES (n = 762)	PtCr-EES (n = 768)	p Value
All-cause death, MI, TVR	36/732 (4.9)	37/745 (5.0)	0.97
All-cause death or MI	22/732 (3.0)	18/745 (2.4)	0.49
All death	9/732 (1.2)	10/745 (1.3)	0.85
Cardiac death	5/732 (0.7)	7/745 (0.9)	0.58
Related to the TV	3/732 (0.4)	6/745 (0.8)	0.51
Not related to the TV	2/732 (0.3)	1/745 (0.1)	0.62
Noncardiac death	4/732 (0.5)	3/745 (0.4)	0.72
MI	13/732 (1.8)	8/745 (1.1)	0.25
Related to the TV	12/732 (1.6)	6/745 (0.8)	0.14
Not related to the TV	1/732 (0.1)	2/745 (0.3)	1.00
Q-wave MI	5/732 (0.7)	1/745 (0.1)	0.12
Non–Q-wave MI	9/732 (1.2)	7/745 (0.9)	0.59
TVR, overall	21/732 (2.9)	20/745 (2.7)	0.83
TLR, overall	14/732 (1.9)	14/745 (1.9)	0.96
TLR, PCI	12/732 (1.6)	10/745 (1.3)	0.64
TLR, CABG	2/732 (0.3)	4/745 (0.5)	0.67
Non-TLR TVR, overall	8/732 (1.1)	7/745 (0.9)	0.77
Cardiac death or MI	18/732 (2.5)	15/745 (2.0)	0.56
Target lesion failure	23/727 (3.2)	26/742 (3.5)	0.72
Target vessel failure	29/727 (4.0)	31/742 (4.2)	0.85
Stent thrombosis (ARC definite or probable)	3/725 (0.4)	3/735 (0.4)	1.00
Definite	3/725 (0.4)	3/735 (0.4)	1.00
Probable	0/725 (0.0)	0/735 (0.0)	—

Values are n/N (%).

ARC = Academic Research Consortium; CABG = coronary artery bypass graft; ITT = intention-to-treat; MI = myocardial infarction; PCI = percutaneous coronary intervention; TLR = target lesion revascularization; TV = target vessel; TVR = target vessel revascularization; other abbreviations as in Table 1.

coronary anatomy is required to reach a consensus regarding stent deliverability and other ease-of-use characteristics.

Study limitations. The 1-year TLF rate with the control CoCr-EES (2.9% in the per-protocol population, and 3.2% in the ITT population) was less than the 5.5% rate assumed during sample size estimation, which was based on prior data from the SPIRIT II and III trials. In the larger SPIRIT IV trial, in which slightly more complex lesions were enrolled than in either of the earlier SPIRIT trials (or the present study), the 1-year TLF rate was only 4.2%, lower than had previously been reported. As such, small absolute differences in event rates between the PtCr-EES and CoCr-EES cannot be excluded by the present study. Nonetheless, the observed 2-sided 95% CI of the difference in the rate of 12-month TLF (−1.3% to 2.3%) ensures that a large absolute difference in TLF between the 2 stent types is unlikely in the lesions tested. Longer-term follow-up and in more complex lesions is required for a comprehensive evaluation between these 2 devices. In this regard, to meet regulatory requirements, the SPIRIT and PLATINUM trials excluded many high-risk patients, such as those with acute or recent MI or visible thrombus, chronic total occlusions, true bifurcations, and lesions in the left main coronary artery or a saphenous vein graft. In contrast, in a large-scale randomized trial in which these patients were actively enrolled, the 1-year rate of TLF with the CoCr-EES was greater (8.2%) than observed in the present study (13). In the future, adoption of the so-called "all-comers" design for regulatory approval stent trials would permit low-frequency but clinically relevant differences between devices to become statistically apparent (or more reliably be excluded), while maintaining reasonable sample size.

Conclusions

In summary, a novel PtCr-EES has been developed and shown to have noninferior 1-year clinical outcomes compared with the predicate CoCr-EES in patients undergoing PCI of up to 2 noncomplex de novo native coronary artery lesions.

Reprint requests and correspondence: Dr. Gregg W. Stone, Columbia University Medical Center, New York-Presbyterian Hospital, The Cardiovascular Research Foundation, 111 East 59th Street, 11th Floor, New York, New York 10022. E-mail: gs2184@columbia.edu.

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Key Words: angioplasty ■ coronary artery disease ■ restenosis.

APPENDIX

For complete list of the study organization and participating sites and investigators, please see the online version of this article.

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ORIGINAL ARTICLE
Preventive Medicine

Depression and Outcomes in Hospitalized Japanese Patients With Cardiovascular Disease

– Prospective Single-Center Observational Study –

Tsuyoshi Suzuki, MD; Tsuyoshi Shiga, MD; Kazue Kuwahara, MD; Sayaka Kobayashi; Shinichi Suzuki, PhD; Katsuji Nishimura, MD; Atsushi Suzuki, MD; Hisako Omori, MD; Fumiaki Mori, MD; Jun Ishigooka, MD; Hiroshi Kasanuki, MD; Nobuhisa Hagiwara, MD

Background: Several studies have suggested that depression poses a risk in cardiovascular patients. The aim of the present study was to evaluate the prevalence of depression and its effect on cardiovascular events and mortality in Japanese inpatients with cardiovascular disease.

Methods and Results: A total of 505 patients hospitalized with cardiovascular disease (28% female; mean age, 61±14 years; 31% ischemic heart disease; 47% New York Heart Association [NYHA] class II–IV; 25% implantation of pacing devices) were enrolled in the present prospective observational study. The Zung Self-Rating Depression Scale (SDS) was used to screen for depression. The primary outcome was the time to death or cardiovascular event, and the secondary outcome was death. In total, 109 patients (22%) were diagnosed with depression (Zung SDS index score ≥60). NYHA class III/IV, defibrillator implantation, and being unmarried were independently associated with depression. During an average follow-up period of 38±15 months, 92 patients (18%) reached the primary outcome. There was a higher incidence of the primary outcome in patients with depression than in those who were not depressed (P<0.01). Depressed patients had a significantly higher rate of mortality than non-depressed patients (P<0.01). Depression was an independent predictor of the primary outcome (hazard ratio, 2.25; 95% confidence interval: 1.30–3.92, P<0.01).

Conclusions: Depression was not uncommon in Japanese inpatients with cardiovascular disease and was associated with cardiovascular outcomes. (*Circ J* 2011; **75:** 2465–2473)

Key Words: Cardiovascular disease; Depression; Inpatient; Mortality; Outcome

Several studies have suggested that depression is a possible risk factor for adverse outcomes in patients with coronary artery disease or heart failure.[1–7] While cardiac events may cause and prolong depression in patients with cardiac disease,[8–10] the prevalence of depression is reported to be approximately 20% in outpatients with coronary artery disease and 30–40% in outpatients with heart failure.[6,11–14] In patients hospitalized for acute myocardial infarction, 16–45% are depressed,[6,8,11] and the presence of depressive symptoms is a significant risk factor for subsequent cardiac events in elderly myocardial infarction patients.[15] In hospitalized heart failure patients, depression is also common and is independently associated with poor outcomes.[2,3,16,17] Understanding these issues could help cardiologists identify inpatients with depression and deliver the most appropriate care.

Cultural and ethnic differences influence depressive symptoms and the interpretation of depression as an illness.[18–20] In Japan, there have been few reports about the prevalence of depression and its effect on patients with cardiovascular disease.[14,15,21] To date, there have been no reports concerning the prevalence of depression in hospitalized patients with cardiovascular disease in Japan.

The aim of the present study was to evaluate the prevalence of depression and the effect of depression on subsequent cardiovascular events and mortality in Japanese patients hospitalized with cardiovascular disease.

Methods

We conducted a prospective observational study in patients who

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Department of Cardiology (T. Suzuki, T. Shiga, K.K., A.S., H.O., F.M., N.H.), Department of Psychiatry (K.K., S.K., K.N., J.I.), Tokyo Women's Medical University, Tokyo; Faculty of Science and Engineering, Waseda University, Tokyo (H.K.); and Faculty of Human Sciences, Waseda University, Tokorozawa (S.S.), Japan

Mailing address: Tsuyoshi Shiga, MD, Department of Cardiology, Tokyo Women's Medical University, 8-1 Kawada-cho, Shinjuku-ku, Tokyo 162-8666, Japan. E-mail: mshiga@hij.twmu.ac.jp

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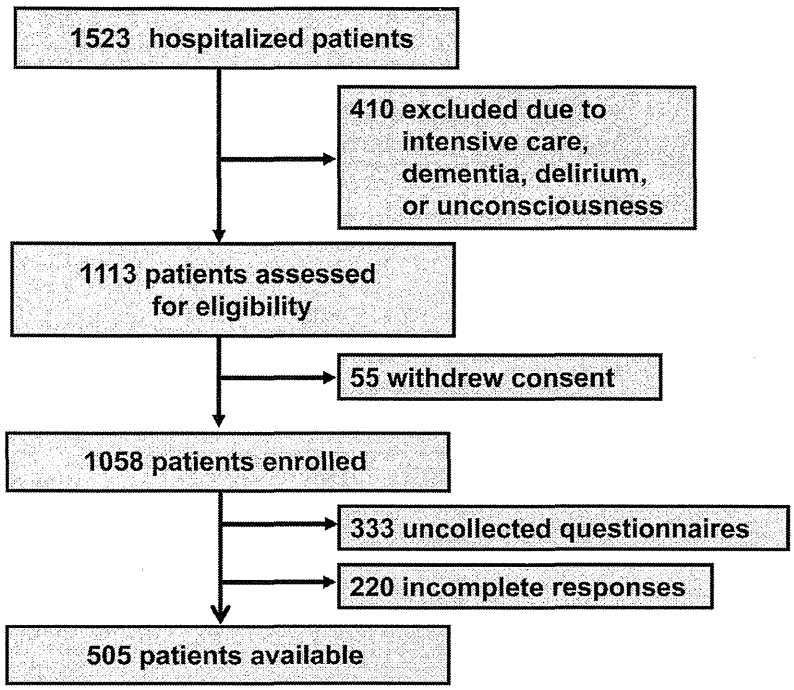

Figure 1. Flow diagram of the study subjects.

were admitted to the cardiology department of Tokyo Women's Medical University Hospital between June 2006 and April 2008. Patients with dementia, delirium, or other conditions that make it difficult to complete a self-reported written questionnaire (eg, unconsciousness, in intensive care, end-stage of another life-threatening disease) were excluded. The protocol was approved by the institutional review board of Tokyo Women's Medical University. All patients gave written informed consent.

Cardiovascular Disease

In the present study, structural heat disease consisted of the following disorders: left ventricular (LV) systolic dysfunction and/or marked LV dilatation (unless secondary to severe valve regurgitation), LV diastolic dysfunction associated with congestive heart failure, coronary heart disease, right heart disease with at least moderate right ventricular dilation, moderate or severe tricuspid regurgitation, pulmonary hypertension, LV hypertrophy, left-sided valvular disease, and congenital heart disease. Coronary artery disease was defined as positive stress test findings, coronary angiography demonstrating at least 75% of stenosis or coronary spastic angina as documented on an acetylcholine provocation test, a history of prior myocardial infarction, or a history of revascularization procedures. Valvular and congenital heart diseases were diagnosed on angiographic, hemodynamic or echocardiographic findings or a history of valvular or congenital cardiac surgery. Aortic and mitral regurgitation were defined as valvular disease with at least moderate regurgitation on color-flow Doppler echocardiography. Non-ischemic cardiomyopathies were defined as ventricular myocardial abnormalities in the absence of coronary artery disease, or valvular, pericardial or congenital heart disease. Pulmonary artery hypertension was defined as an increase in mean pulmonary arterial pressure of ≥25 mmHg with a pulmonary wedge pressure of ≤15 mmHg at rest, as estimated on right heart catheterization. Aortic disease, peripheral artery disease and other vascular diseases were diagnosed on angiographic or echocardiographic findings, or a history of vascular surgery or intervention. Arrhythmias and conduction disorders without structural heart disease included atrial, supraventricular and ventricular arrhythmias, sick sinus syndrome and atrioventricular block in the absence of structural heart disease. Hypertension was defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or a history of treatment for hypertension. LV ejection fraction (LVEF) was calculated using left ventriculography, echocardiography or radionuclide angiography.

Assessment of Depression

Most patients received psychological questionnaires within a few days after hospital admission. For patients who initially required intensive treatment, these questionnaires were given after their transfer to the general cardiology wards. The Zung Self-Rating Depression Scale (SDS) has been used to screen for depression and to measure the severity of depression in numerous settings.[22–26] The Zung SDS is a self-reporting, 20-question instrument that assesses the psychological and somatic symptoms of depression. It has good internal consistency and validity, encompassing most DSM-IV criteria for major depression.[26–32] The Zung SDS has been found to be the primary discriminating variable for distinguishing depressed from non-depressed people.[33] It has shown a positive likelihood ratio for major depression of 3.3 (95% confidence interval [CI]: 1.3–8.1), and negative likelihood ratio of 0.35 (95%CI: 0.2–0.8).[24] The Zung SDS has also been used in clinical studies to assess depression in cardiovascular disease.[15,34–37] Ten questions are positively worded, and 10 are negatively worded. Each question is scored on the following 4-point scale: 1, a little of the time; 2, some of the time; 3, good part of the time; and 4, most of the time. To obtain a total score, the positive items are reversed, and then the items are summed. This raw score is converted to a 100-point scale (SDS index). Zung SDS index scores range from 25 to 100 and are interpreted as follows: within the nor-

Table 1. Patient Characteristics

	Total (n=505)	Depression (n=109)	No depression (n=396)	P value
Age (years)	61±14	61±13	59±15	0.45
Female	143 (28)	36 (33)	107 (27)	0.26
Cardiovascular disease				0.24
Coronary artery disease	159 (31)	24 (22)	135 (34)	
Non-ischemic cardiomyopathy	114 (23)	30 (28)	84 (21)	
Valvular heart disease	65 (13)	15 (14)	50 (13)	
Arrhythmia without structural heart disease	143 (28)	32 (29)	111 (28)	
Pulmonary artery hypertension	3 (1)	1 (1)	2 (1)	
Congenital heart disease	6 (1)	2 (1)	4 (1)	
Others	15 (3)	5 (5)	10 (3)	
Plasma BNP on admission (pg/ml)	251 (4–4,335)	378 (5–4,335)	215 (4–3,400)	<0.01
NYHA functional class on admission (I/II/III/IV)	269/191/30/15	41/45/16/7	228/146/14/8	<0.01
NYHA functional class at discharge (I/II/III/IV)	275/206/23/1	41/46/21/1	234/160/2/0	<0.01
LVEF (%)	48±15	49±15	46±16	0.11
eGFR ($ml \cdot min^{-1} \cdot 1.73 m^{-2}$)	61±14	61±14	61±14	0.73
Current smoker	70 (14)	14 (12)	56 (14)	0.72
History of atrial fibrillation	85 (17)	16 (15)	69 (17)	0.49
Medical comorbidities				
Hypertension	166 (32)	29 (27)	137 (35)	0.11
Diabetes	86 (17)	16 (15)	70 (18)	0.46
Dyslipidemia	141 (28)	23 (21)	118 (30)	0.06
Hemodialysis	32 (6)	10 (9)	22 (6)	0.18
Cerebrovascular disease	8 (1.5)	2 (2)	6 (2)	0.81
Major depression	8 (1.5)	5 (5)	3 (1)	0.01
Implanted pacing devices before admission				
Pacemaker/CRT-P	54 (11)	13 (12)	41 (10)	0.64
ICD/CRT-D	73 (14)	26 (24)	47 (12)	0.02
Implanted pacing devices at discharge				
Pacemaker/CRT-P	64 (13)	13 (12)	51 (13)	0.79
ICD/CRT-D	95 (19)	29 (27)	66 (17)	0.01
Medications at the time of questionnaire				
β-blockers	248 (49)	52 (48)	196 (49)	0.74
ACE inhibitors/ARBs	278 (55)	60 (55)	218 (55)	0.99
Spironolactone/eplerenone	120 (24)	37 (34)	83 (21)	0.68
Calcium channel blockers	284 (56)	54 (50)	230 (58)	0.11
Aspirin	172 (34)	29 (27)	143 (36)	0.06
Warfarin/heparin	142 (28)	34 (32)	108 (27)	0.64
Amiodarone/nifekalant	60 (12)	22 (20)	40 (10)	<0.01
Intravenous inotropics	3 (1)	2 (2)	1 (0.3)	<0.01
Intravenous vasodilator	5 (1)	4 (4)	1 (0.3)	<0.01
Antidepressants	8 (2)	5 (5)	3 (1)	0.01
Medications at discharge				
β-blockers	259 (51)	57 (52)	202 (51)	0.81
ACE inhibitors/ARBs	308 (61)	72 (66)	236 (59)	0.21
Spironolactone/eplerenone	136 (27)	40 (37)	96 (24)	0.01
Calcium channel blockers	289 (57)	55 (50)	234 (59)	0.10
Aspirin	186 (37)	33 (30)	153 (39)	0.10
Warfarin	160 (32)	44 (40)	116 (29)	0.03
Amiodarone	68 (13)	25 (23)	43 (11)	0.05
Antidepressants	8 (2)	5 (5)	3 (1)	0.01
Education				0.33
High school	314 (62)	74 (68)	240 (61)	
College	124 (25)	24 (22)	100 (25)	
Others	67 (13)	11 (10)	56 (14)	
Marital status				<0.01
Unmarried	35 (7)	13 (12)	22 (6)	
Married	448 (89)	83 (76)	365 (92)	
Widowed	22 (4)	13 (12)	9 (2)	
Work status				0.02
Employed	205 (41)	32 (29)	173 (44)	
Housewife	89 (18)	26 (24)	63 (16)	
Unemployed/retired	211 (42)	51 (47)	160 (40)	

Data given as n (%) or mean±SD or median (range).
BNP, B-type natriuretic peptide; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; CRT, cardiac resynchronization therapy; CRT-P, CRT with a pacemaker; ICD, implantable cardioverter defibrillator; CRT-D, CRT with a defibrillator; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker.

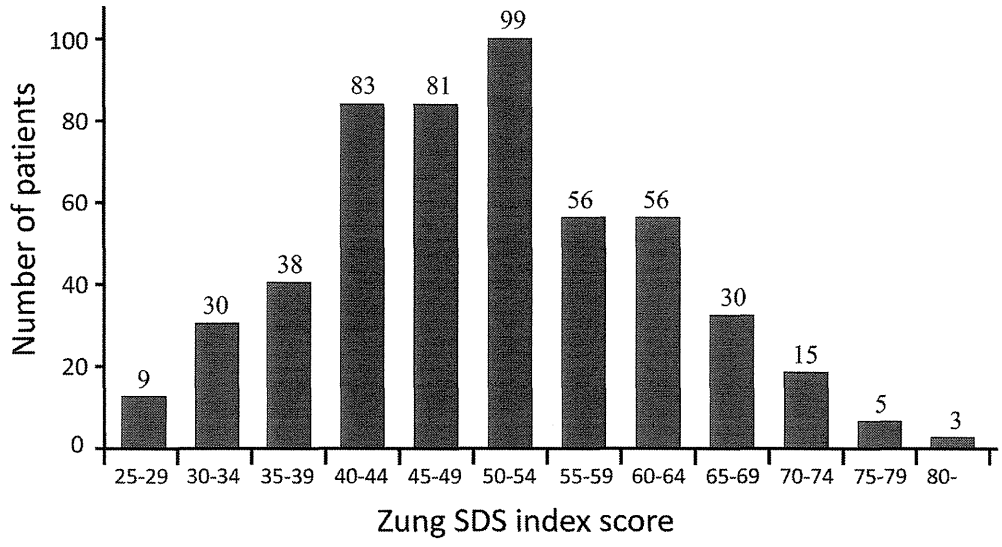

Figure 2. Zung Self-Rating Depression Scale (SDS) index score in 505 hospitalized patients with cardiovascular disease. Red, depression defined by a Zung SDS index score ≥60.

mal range, <50; mildly depressed, 50–59; moderately depressed, 60–69; and severely depressed, ≥70. Because the psychological and physical symptoms of depression may overlap with those of cardiovascular disease, there is a possibility that cardiovascular symptoms may be attributed to depression. Previous studies with cardiovascular disease have often used a cut-off index score of 50 (raw score 40) as a definition of depression.[15,34–37] Higher depression scores (eg, SDS score index ≥60) are associated with increased morbidity and mortality in patients with coronary artery disease.[37,38] A cut-off index score of 60 has been shown to detect clinical depression while avoiding an abundance of false-positive results in patients with cardiovascular or other disease.[10,39–41] In the present study, depression was defined as a Zung SDS index score ≥60.

Follow-up

After discharge, patients were seen as outpatients or at their general practitioner's clinic at 1–3-month intervals up to October 2010. Patients receiving pacing device therapy, including pacemakers, cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD), were also followed every 3–6 months at the pacemaker/ICD clinic. The occurrence of ventricular tachyarrhythmias requiring ICD therapy, including shock and anti-tachycardia pacing, was obtained by reviewing event details and electrograms stored on the ICD disks. Only episodes of ventricular tachycardia or fibrillation requiring ICD therapy for termination were included in the analysis. Information about deceased subjects was obtained from medical records, family members, their general practitioners and the admitting hospital.

Clinical Outcomes

The primary outcome was a composite of death from any cause or cardiovascular events from the time of enrollment to the first event. Cardiovascular death was defined as death due to myocardial or cerebral infarction, other vascular causes, heart failure or documented sudden cardiac death. Cardiovascular events included non-fatal myocardial infarction, hospitalization for heart failure, unstable angina, revascularization, stroke, refractory arrhythmia, and ventricular tachyarrhythmia requiring ICD therapy. Unstable angina was defined according to the Braunwald criteria.[42] Revascularization included angioplasty, stenting and coronary artery bypass grafting. Heart failure was defined on the basis of symptoms and signs such as dyspnea, rales and ankle edema and the need for treatment with diuretics, vasodilators, positive inotropic drugs or an intra-aortic balloon pump. Stroke was defined as a new focal neurological deficit of vascular origin lasting >24 h. Stroke was further classified by etiology, including intracranial hemorrhage, ischemia (diagnosed on computed tomography or magnetic resonance imaging if available) or uncertain cause. Refractory arrhythmia was defined as supraventricular or ventricular tachyarrhythmia requiring external defibrillation or pacing, i.v. anti-arrhythmics such as amiodarone and nifekalant, catheter ablation, or implantation of an ICD, and bradyarrhythmia requiring implantation of a pacemaker. Other cardiovascular events included peripheral artery disease, dissecting aortic aneurysm, and rupture of an aortic aneurysm. The second outcome was death from any cause.

Statistical Analysis

The data are given as either mean ± SD or numbers of patients. Baseline clinical data were compared between groups with and without depression using Student's t-test and the Mann–Whitney U-test. Categorical variables were subjected to chi-squares analysis. Multivariate analysis using the Cox proportional hazards model was performed to assess the relationship of the following baseline characteristics to depression: age ≥65 years, female gender, New York Heart Association (NYHA) functional class III/IV, LVEF≤35%, estimated glomerular filtration rate (eGFR) by the Modification of Diet in Renal Disease formula $<60\,ml \cdot min^{-1} \cdot 1.73\,m^{-2}$,[43] diabetes mellitus, hemodialysis, implantation of an ICD/CRT with a defibrillator (CRT-D), β-blocker use on admission, marital status and work status. Cumulative event-free rate was calculated using the Kaplan–Meier method. Differences in event-free rates were

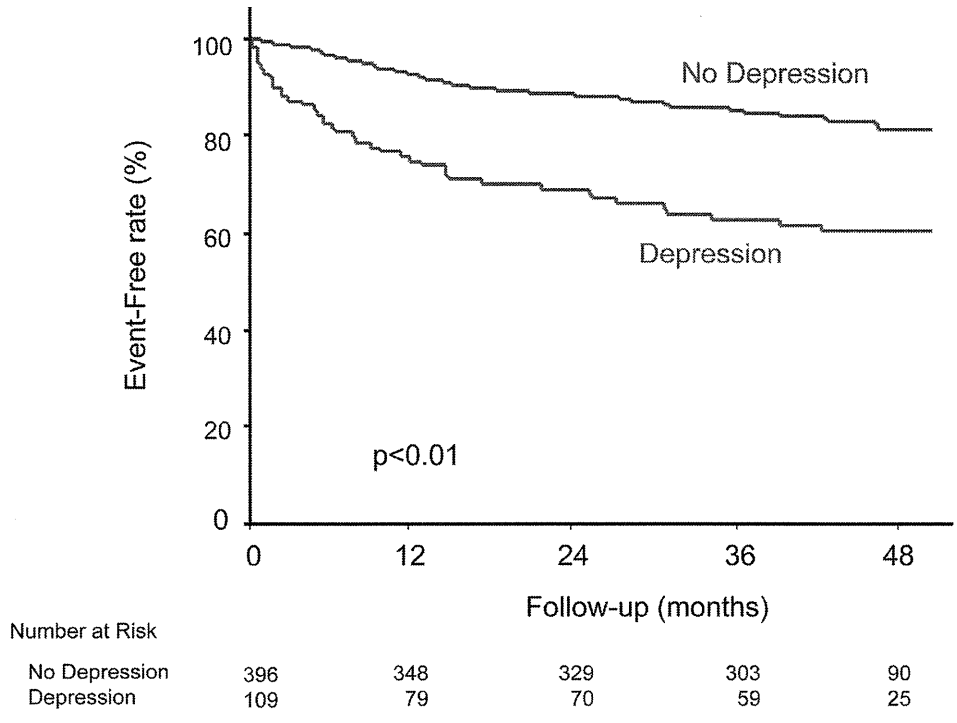

Figure 3. Kaplan–Meier curve for the primary outcome (death from any cause or cardiovascular events) in cardiovascular inpatients with or without depression.

compared using the log-rank test. Multivariate analysis using the Cox proportional hazards model was performed to assess the relationships between depression and the primary outcome, independent of the following confounders at discharge: age ≥65 years, female gender, NYHA functional class III/IV, LVEF≤35%, eGFR<60 ml·min^{-1}·1.73 m^{-2}, diabetes mellitus, hypertension and implantation of an ICD/CRT-D. P<0.05 was considered significant. SPSS version 11.01 (SPSS, Chicago, IL, USA) was used for analysis.

Results

Patients

Of the 1,523 consecutively hospitalized patients, 1,058 patients were enrolled in the present study. Seven hundred and twenty-five questionnaires were collected (collection rate of 68%). Of these, 505 questionnaires had valid responses (response rate of 48%), and these patients were available to participate in the study (**Figure 1**). The patient characteristics are shown in **Table 1**. The mean age on admission was 61±14 years, and 28% of the patients were female. A total of 159 patients (31%) had coronary artery disease, 236 (47%) were rated as being in NYHA functional class II–IV on admission, and 127 (25%) had implanted pacing devices on admission. Eight patients (2%) had been treated for major depressive disorder prior to admission. All 505 patients were discharged from hospital, and 230 (46%) were in NYHA functional class II–IV at discharge. At discharge, 159 (31%) had implanted pacing devices. Regarding concomitant medications at discharge, 259 patients (51%) were taking β-blockers, and 68 patients (13%) were taking amiodarone. Eight patients (2%) who were diagnosed with major depression by a psychiatrist were taking antidepressants. No patients were receiving non-pharmacological therapy such as cognitive behavior therapy.

Depression Prevalence

The Zung SDS index scores of all studied patients at baseline are shown in **Figure 2**. In total, 109 patients (22%) had depression. A comparison of patients' clinical characteristics according to the presence or absence of depression is shown in **Table 1**. There was no significant difference in age, gender, underlying cardiovascular disease, coexisting conditions or implanted devices between groups. The plasma B-type natriuretic peptide (BNP) level on admission and NYHA functional class on admission and at discharge were higher in patients with depression than in those who were not depressed. There was a higher rate of ICD/CRT-D implantation on admission in patients with depression. There were higher rates of amiodarone/nifekalant use, i.v. inotropic use, i.v. vasodilator use and antidepressant use at the time of the questionnaire in patients with depression. There was no significant difference, however, in the rate of β-blocker use between patients with (48%) and without depression (49%). There were higher rates of spironolactone/eplerenone use, warfarin use and antidepressant use at discharge in patients with depression. Compared with patients without depression, fewer depressed patients were married or employed. Multivariate analysis showed that ICD implantation (hazard ratio [HR], 1.92; 95%CI: 1.00–3.80, P=0.04), NYHA functional class III/IV (HR, 3.03; 95%CI: 1.38–6.67, P<0.01), and unmarried status (HR, 4.32; 95%CI: 2.31–8.09, P<0.01) were significantly associated with depression.

Depression and Clinical Outcomes

During an average follow-up period of 38±15 months, 92