Table 1. Baseline Characteristics of Patients With or Without ULMCA Stenting

	ULMCA (n=582)	Non-ULMCA (n=12 242)	P
Age, y	70.7±10.6	68.3±10.2	<0.0001
Age ≥75 y	39.5	29.9	<0.0001
Male	72.7	75.4	0.14
Emergent procedure	20.5	14.8	0.0003
Presence of shock	3.4	1.3	<0.0001
Acute myocardial infarction	12.5	12.2	0.75
Unstable angina	18.4	12.4	<0.0001
Hypertension	74.6	73.5	0.56
Diabetes mellitus	42.6	41.4	0.58
Diabetes (insulin use)	12.0	9.3	0.029
Current smoking	15.1	20.6	0.0013
Estimated GFR, mL · min^{-1} · 1.73 mm^{-2}	55±24	59±23	<0.0001
Renal insufficiency	15.3	10.0	<0.0001
Dialysis	7.4	5.2	0.029
Ejection fraction	56±15	58±13	0.0061
Heart failure	24.1	13.5	<0.0001
EuroSCORE	5.8±3.6	4.6±3.1	<0.0001
EuroSCORE ≥6	46.6	33.2	<0.0001
Bifurcation lesion	81.4	24.0	<0.0001
Bifurcation: 2-stent treatment	29.6	4.6	<0.0001
No. of treated vessels	1.9±0.8	1.3±0.5	<0.0001
Prior PCI	43.3	46.6	0.13
Prior CABG	7.9	7.1	0.45
Prior myocardial infarction	25.1	27.3	0.25
History of stroke	13.2	9.3	0.0029
Extracardiac arteriopathy	13.4	11.8	0.24
Extent of coronary artery disease			
Left main only	6.9	0.0	
1 Vessel	23.9	47.8	
2 Vessel	40.0	30.2	<0.0001
3 Vessel	21.3	14.9	
Post-CABG	7.9	7.1	
Total stent length, mm	56.3±37.2	41.8±27.6	<0.0001
No. of implanted stents	2.6±1.6	1.9±1.6	<0.0001
Intravascular ultrasound use	63.4	46.7	<0.0001

GFR indicates glomerular filtration rate; CABG, coronary artery bypass grafting.

Values are percentages or mean±SD.

Probability was significant at a level of <0.05. All statistical tests were 2-tailed. Statistical analyses were conducted by a physician (M. Toyofuku) and by an independent statistician (T.M.) with the use of JMP5.1.1 (SAS Institute Inc, Cary, NC) and SAS 9.1 (SAS Institute Inc) software. The study sponsor was not involved in the study design; the collection, analysis, and interpretation of data; the writing of the report; or the decision to submit the article for publication.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Table 2. Unadjusted Event Rates in Patients With or Without ULMCA Stenting Through 3 Years

	Events, Incidence (%)		
	ULMCA (n=582)	Non-ULMCA (n=12 242)	P
Total deaths	76 (14.6)	911 (9.2)	<0.0001
Cardiac deaths	39 (7.3)	450 (4.5)	<0.0001
Sudden deaths	9 (1.6)	155 (1.6)	0.50
Myocardial infarction	17 (3.7)	338 (3.4)	0.76
Stroke	23 (5.1)	404 (4.1)	0.31
Definite/probable ST	13 (2.5)	128 (1.3)	0.0059
Definite ST	10 (2.0)	111 (1.2)	0.040
TLR	73 (14.8)	1439 (13.8)	0.33
CABG	9 (1.7)	181 (1.9)	0.81
Any revascularization	180 (35.9)	3407 (32.2)	0.022

CABG indicates coronary artery bypass grafting.

Results

Baseline and Procedural Characteristics

Patients in the ULMCA group were significantly older and sicker than those in the non-ULMCA group, as reflected by the higher incidences of stroke, heart failure, renal insufficiency, unstable angina, shock, and bifurcation disease (Table 1). However, 53% of the patients in the ULMCA group had a EuroSCORE <6, and the procedures were performed electively in 79% of the patients.

Aspirin and thienopyridines were prescribed in 98.7% and 99.2% of patients with ULMCA stenting and 97.8% and 98.6% of patients with non-ULMCA stenting, respectively (online-only Data Supplement Table I). The proportion of patients with dual-antiplatelet therapy longer than 1 year was significantly greater in the ULMCA group than in the non-ULMCA group (73% versus 62%, $P<0.0001$).

Outcomes of Patients With or Without ULMCA Stenting

The median follow-up intervals were 942 days in the ULMCA group and 924 days in the non-ULMCA group, with complete 1-year follow-up in 97.0% and 96.5% ($P=0.62$) of patients, respectively. The crude rates of all-cause death and cardiac death up to 3 years were significantly higher in patients with ULMCA disease (Table 2; Figure 2; online-only Data Supplement Table II). Significant risk factors for all-cause death by multivariable Cox proportional hazard model included age >75 years, male gender, shock, heart failure, renal insufficiency, extracoronary arteriopathy, triple-vessel disease, diabetes mellitus, no statin use, absence of intravascular ultrasound guidance, and EuroSCORE ≥6 (online-only Data Supplement Table III). After adjustment for these confounders, there were no significant differences between the ULMCA group and the non-ULMCA group for all-cause death risk (hazard ratio 1.23, 95% confidence interval 0.95 to 1.60, $P=0.12$) or cardiac death risk (hazard ratio 1.10, 95% confidence interval 0.71 to 1.63, $P=0.64$). The adjusted 3-year survival rates were not different between the 2 groups (92.6% versus 93.9%, $P=0.12$; Figure 2).

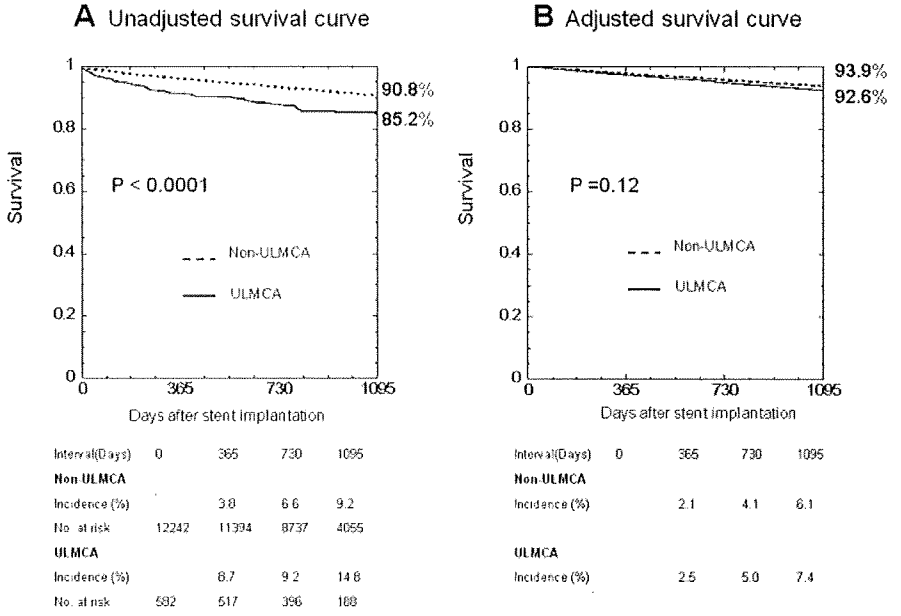


Figure 2. Unadjusted (A) and adjusted (B) survival rate in patients with or without ULMCA stenting.

Distributions of the causes of death were comparable between patients with and without ULMCA treatment (Table 3). There was no excess of patients with documented ventricular fibrillation and/or sudden death in the ULMCA group.

Rates of ST (both definite and definite/probable) were significantly higher in the ULMCA group than in the non-ULMCA group; however, the incidence of definite ST of the ULMCA lesion was relatively low (0.9% at 3 years). Furthermore, the cumulative incidence of myocardial infarction was not different between the ULMCA group and the non-ULMCA group. Angiograms and details of 4 patients with definite ST of ULMCA lesions treated exclusively by SES are shown in Figure 3 and online-only Data Supplement Table IV. No ST occurred in the main body of the ULMCA.

The rate of stroke was not different between the 2 groups with and without ULMCA treatment. The rate of TLR also was not different between the 2 groups, although the rate of any repeated revascularization was slightly but significantly higher in the ULMCA group than in the non-ULMCA group.

Table 3. Causes of Death in Patients With or Without ULMCA Stenting

	ULMCA Group (n=582)	Non-ULMCA Group (n=12 242)	*P*
No. of deaths	76	911	
Documented VF/sudden death	11 (14.5)	152 (16.7)	0.35
Heart failure	14 (18.4)	144 (15.8)	
Acute myocardial infarction	8 (10.5)	50 (5.5)	
Bleeding	0 (0.0)	9 (1.0)	
Stroke	4 (5.3)	85 (9.3)	
Noncardiovascular causes	39 (51.3)	471 (51.7)	

VF indicates ventricular fibrillation.
Values are n (%).

Clinical Outcomes According to Left Main Lesion Location

Among 476 patients whose ULMCA lesions were treated exclusively with SES, 96 (20%) had ostial/shaft left main lesions, whereas 380 patients (80%) had distal left main bifurcation lesions. With regard to lesion and procedural characteristics, patients with ostial/shaft lesions had less calcification, shorter stent length, and higher maximal balloon inflation pressure (Table 4).

Clinical outcomes were markedly favorable in the ostial/shaft group (Table 5; online-only Data Supplement Table V). There was no definite ST of the ULMCA lesion among 97 patients in the ostial/shaft group. The incidence of TLR at 3 years in that group was remarkably lower than in the bifurcation group. (3.6% versus 17.1%, $P=0.0047$; Figure 4). After adjustment for dialysis, small diameter (<3 mm), and diabetes mellitus, the hazard ratio for TLR with ostial/shaft lesions was 0.22 (0.07 to 0.70, $P=0.011$).

There was no difference in the rates of cardiac death between the 2 groups (Figure 4). After adjustment for confounders of heart failure, renal insufficiency, shock, elderly age, and intravascular ultrasound guidance, the hazard ratio for ostial/shaft lesions was 1.10 (95% confidence interval 0.60 to 2.00, $P=0.76$) for all-cause death and 1.40 (0.65 to 3.04, $P=0.39$) for cardiac death.

Clinical Outcomes According to Left Main Bifurcation Stenting Strategies and Extent of Coronary Artery Disease

Among 380 patients treated for ULMCA bifurcation lesions, 261 (69%) underwent bifurcation 1-stent procedures, whereas 119 patients (31%) were treated with 2-stent procedures (Table 6). Among 119 patients with 2-stent procedures, elective and provisional 2-stent strategies were adopted in 99 and 20 patients, respectively. Compared with patients undergoing bifurcation 1-stent procedure, patients with 2-stent

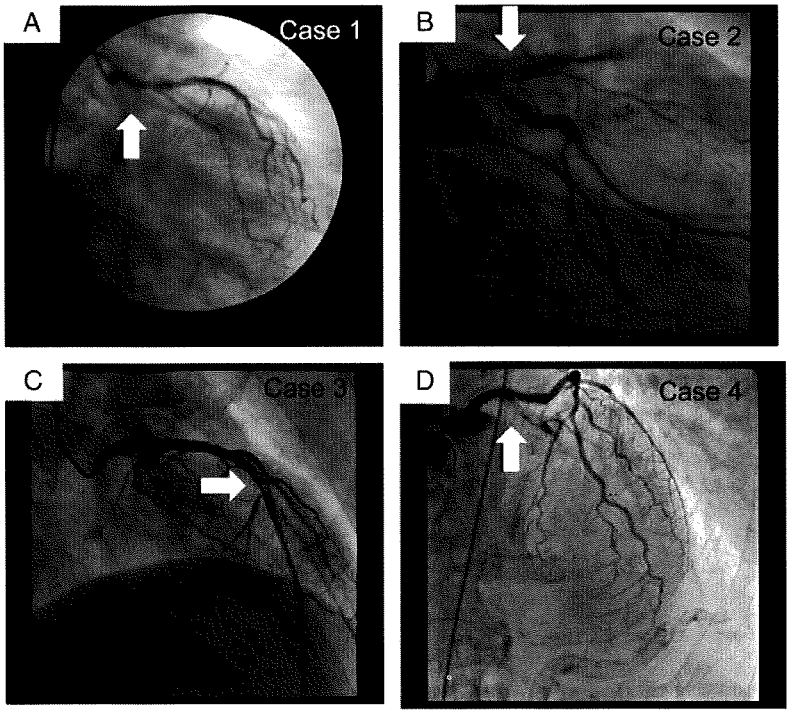


Figure 3. Angiograms of 4 cases of ST after left main coronary artery stenting.

procedures had more severe stenosis of the origin of the circumflex and larger vessel diameter of the circumflex.

Patients in the 2-stent group showed a trend toward a higher incidence of all-cause death and a significantly higher rate of cardiac death than patients in the 1-stent group (Table 7; Figure 5; online-only Data Supplement Table VI). After adjustment for confounders, the hazard ratio of bifurcation 2-stent treatment was 1.64 (95% confidence interval 0.93 to 2.90, $P=0.088$) for all-cause death and 2.78 (1.27 to 6.05, $P=0.010$) for cardiac death. The prevalence of documented ventricular fibrillation or sudden cardiac death among patients who died throughout the 3-year follow-up period was 4 (19%) of 21 patients in the bifurcation 2-stent group and 2 (6.7%) of 30 patients in the bifurcation 1-stent group. The rate of definite ST in the ULMCA lesion also tended to be higher in patients with bifurcation 2-stent treatment than in patients with bifurcation 1-stent treatment (2.8% versus 0.4%; $P=0.050$).

Furthermore, the rate of TLR in the 2-stent group was markedly higher than that in the 1-stent group (30.9% versus 11.1%, $P<0.0001$; Figure 5). After adjustment for confounders, the hazard ratio for TLR with bifurcation 2-stent treatment was 3.17 (95% confidence interval 1.82 to 5.52, $P<0.0001$). When analyzed according to the number of diseased vessels other than the left main coronary artery, the rates of cardiac death, definite/probable ST and any revascularization were significantly higher in patients with ULMCA plus 3-vessel disease (Table 8).

Table 4. Baseline and Procedure Characteristics in Patients With ULMCA Stenting According to Lesion Location

	Ostial/Shaft (n=96)	Bifurcation (n=380)	*P*
Age ≥75 y	46.9	38.7	0.16
Shock	5.2	3.7	0.56
Heart failure	25.0	26.1	0.90
Renal insufficiency	14.6	15.3	0.87
De novo lesion	83.3	78.7	0.39
In-stent restenosis	11.5	9.2	0.56
Calcification (severe)	4.2	14.7	0.0033
Intravascular ultrasound guidance	60.6	65.0	0.47
Total stent length per lesion, mm	16.6±6.8	29.7±13.9	<0.0001
Nominal stent diameter, mm	3.29±0.27	3.30±0.28	0.84
Maximum balloon pressure, atm	20.0±3.0	18.8±3.2	0.0013

Values are percentages or mean±SD.

Table 5. Outcomes After ULMCA Stenting According to Lesion Location Through 3 Years

	Events, Incidence (%)		
	Ostial/Shaft (n=96)	Bifurcation (n=380)	*P*
Total deaths	14 (14.9)	51 (15.1)	0.66
Cardiac deaths	9 (9.8)	27 (7.6)	0.41
Sudden deaths	3 (3.5)	5 (1.4)	0.20
Myocardial infarction	1 (1.2)	13 (4.5)	0.24
Stroke	7 (10.7)	13 (4.2)	0.070
Definite/probable ST	1 (1.0)	10 (3.0)	0.38
Definite ST	0	8 (2.5)	0.17
Definite ST (ULMCA)	0	4 (1.1)	0.33
TLR	3 (3.6)	55 (17.1)	0.0047
CABG	1 (1.2)	5 (1.5)	0.88
Any revascularization	21 (25.9)	124 (37.9)	0.11

CABG indicates coronary artery bypass grafting.
Values are n (%).

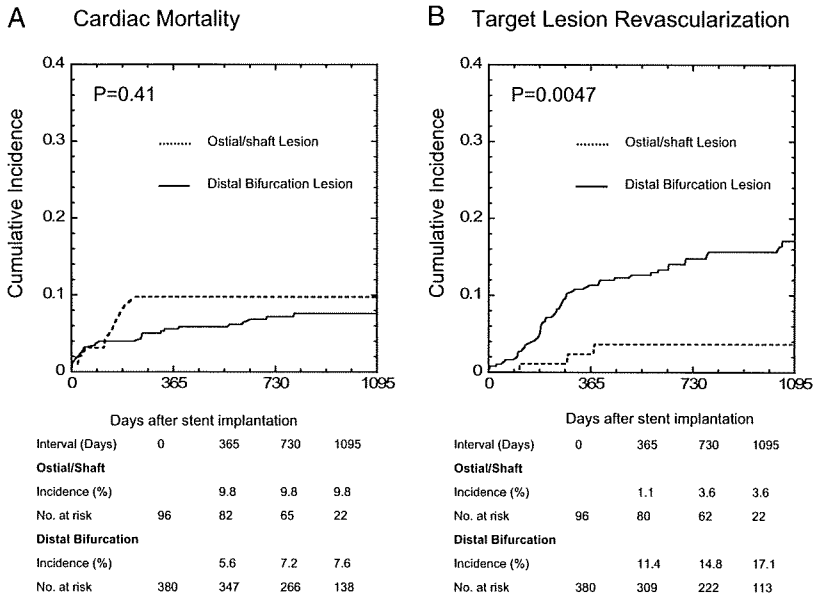


Figure 4. Kaplan–Meier curves for cumulative incidences of cardiac death (A) and TLR (B) among patients treated for ULMCA according to lesion location.

Discussion

The main findings of this study are as follows: (1) PCI for ULMCA lesions was relatively safe, with adjusted mortality rates similar to those with non-ULMCA lesions, which indicates that fatal events due to stent failure manifesting as thrombosis or restenosis were rare; (2) SES implantation in ostial/shaft left main lesions was associated with an excellent 3-year TLR rate; and (3) bifurcation 2-stent treatment was associated with significantly higher rates of cardiac death and TLR.

Table 6. Baseline and Procedure Characteristics in Patients With ULMCA Stenting According to Bifurcation Stenting Strategy

	One-Stent Bifurcation (n=261)	Two-Stent Bifurcation (n=119)	*P*
Age ≥75 y	38.1	39.5	0.82
Shock	4.2	2.5	0.56
Heart failure	26.4	25.2	0.90
Renal insufficiency	13.8	18.5	0.28
De novo lesion	79.7	76.5	0.48
In-stent restenosis	7.3	13.5	0.058
Calcification (severe)	12.3	20.2	0.060
Intravascular ultrasound guidance	67.1	60.5	0.25
Final kissing balloon technique	74.7	93.3	<0.0001
Total stent length per lesion, mm	24.1±10.7	42.0±12.3	<0.0001
Nominal stent diameter(main branch), mm	3.30±0.29	3.29±0.27	0.70
Nominal stent diameter (side branch), mm	. . .	2.91±0.38	. . .
Max balloon pressure, atm	18.9±3.3	18.6±3.0	0.51
50% Stenosis of ostial CX	34	85	<0.0001
Vessel diameter of CX, mm	2.66±0.52	2.81±0.61	0.02

CX indicates circumflex coronary artery.
Values are percentages or mean±SD.

Mortality Rate After ULMCA Stenting

In patients with ULMCA disease, surgical revascularization has significantly improved the survival rate compared with medical management.[9] Therefore, PCI in patients with ULMCA disease should demonstrate at least comparable mortality rates to those with surgical revascularization, if PCI is a clinically acceptable alternative.

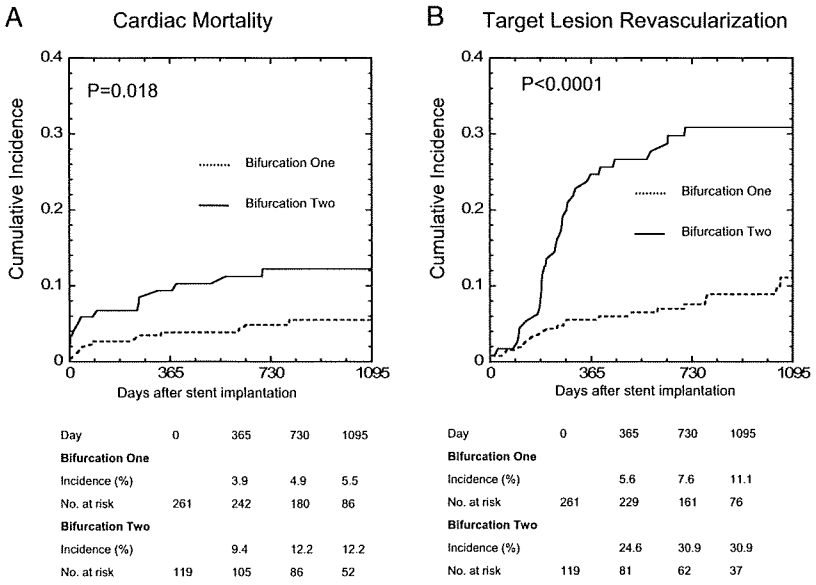
Recent reports comparing percutaneous and surgical revascularization for ULMCA disease have shown similar survival rates between the 2 therapies.[10,11] Likewise, 1-year results of the SYNTAX (Synergy Between PCI With TAXUS and Cardiac Surgery) trial showed comparable mortality rates after PCI with DES or coronary artery bypass graft.[12]

In the present study, the crude mortality rate was 1.7% and 14.6% at 30 days and 3 years, respectively. The 30-day mortality rate was comparable to that in a recent systematic review of ULMCA stenting with DES[13] and current benchmarks with coronary artery bypass graft for ULMCA[14,15];

Table 7. Outcomes After ULMCA Stenting According to Bifurcation Stenting Strategies Through 3 Years

	Events, Incidence (%)		
	One-Stent Bifurcation (n=261)	Two-Stent Bifurcation (n=119)	*P*
Total death	30 (13.4)	21 (18.8)	0.12
Cardiac deaths	13 (5.5)	14 (12.2)	0.018
Sudden deaths	2 (0.8)	3 (2.7)	0.15
Myocardial infarction	8 (4.5)	5 (4.7)	0.58
Stroke	10 (4.7)	3 (3.0)	0.53
Definite/probable ST	3 (1.5)	7 (6.3)	0.0076
Definite ST	3 (1.5)	5 (4.7)	0.054
Definite ST (ULMCA)	1 (0.4)	3 (2.8)	0.050
TLR	22 (11.1)	33 (30.9)	<0.0001
CABG	2 (0.9)	3 (0.3)	0.15
Any revascularization	77 (35.5)	47 (44.0)	0.017

CABG indicates coronary artery bypass grafting.



Day	0	365	730	1095
Bifurcation One				
Incidence (%)		3.9	4.9	5.5
No. at risk	261	242	180	86
Bifurcation Two				
Incidence (%)		9.4	12.2	12.2
No. at risk	119	105	86	52

Day	0	365	730	1095
Bifurcation One				
Incidence (%)		5.6	7.6	11.1
No. at risk	261	229	161	76
Bifurcation Two				
Incidence (%)		24.6	30.9	30.9
No. at risk	119	81	62	37

Figure 5. Kaplan–Meier curves for cumulative incidences of cardiac death (A) and TLR (B) among patients treated for ULMCA according to distal bifurcation stenting strategy.

however, the late mortality rates appeared to be higher in the present series. The prevalence of comorbidities in the present study population may explain the relatively high late mortality rates. Indeed, the 1-year mortality rate of 4.2% in low-risk patients (EuroSCORE <6) in the present study was similar to the 4.8% seen in the low-risk patients in the systematic review mentioned above.[13] Moreover, after adjustment for confounders, there was no significant difference in the risk of all-cause death at 3 years between the 2 groups of patients with or without ULMCA stenting. These results suggest that fatal events were secondary to clinical presentation and comorbidities rather than to the performance of the implanted device. This finding is consistent with recent reports[11,16,17] that the occurrence of fatal events owing to stent failure such as thrombosis or restenosis after ULMCA stenting is rare.

Stent Thrombosis

The present study population included high-risk conditions for ST, such as renal failure, heart failure, diabetes mellitus, and bifurcation lesions; however, the incidence of definite ST of the ULMCA lesion was relatively low (0.9% at 3 years). Moreover, no ST occurred in the main body of the ULMCA. This result is consistent with some reports that have suggested that the incidence of definite ST after ULMCA stenting is relatively lower than in other lesion subsets.[16,17] However, the ST rate tended to be higher with the bifurcation 2-stent strategy than with the bifurcation 1-stent strategy.

Lesion Location and Bifurcation Stenting Strategy

Experiences with DES implantation for ULMCA showed marked reduction of restenosis rates compared with bare-metal stents.[1,2] Chieffo et al[18] recently showed that SES or paclitaxel-eluting stent implantation in ostial or mid-shaft lesions is associated with an excellent long-term restenosis rate of 0.9%, a finding that is consistent with the 3-year TLR rate of 3.6% seen in the present study. Patients with ostial and mid-shaft left main coronary artery lesions that did not

Table 8. Estimated Event Rates at 3 Years After ULMCA Treatment According to Extent of Coronary Artery Disease

	ULMCA Only (n=40)	ULMCA+SVD (n=113)	ULMCA+DVD (n=188)	ULMCA+TVD (n=93)	ULMCA+CABG (n=42)	*P*
Total death	21.4	11.2	14.0	21.7	9.5	0.15
Cardiac death	2.5	7.3	7.8	15.1	0.0	0.033
Sudden death	0.0	1.9	1.7	3.5	0.0	0.56
Myocardial infarction	4.4	2.1	4.9	5.6	0.0	0.57
Stroke	0.0	8.6	4.4	4.9	8.8	0.40
Definite/probable ST	0.0	0.0	1.9	8.4	2.6	0.0029
Definite ST	0.0	0.0	1.9	5.4	2.6	0.13
Definite ST (ULMCA)	0.0	0.0	0.6	3.6	0.0	0.07
TLR	2.6	7.1	18.7	18.9	15.6	0.027
Any revascularization	25.2	31.3	37.1	48.3	24.5	0.0016

SVD indicates single-vessel disease; DVD, double-vessel disease; TVD, triple-vessel disease; and CABG, coronary artery bypass grafting.

Values are percentages.

require bifurcation treatment appeared to be good candidates for percutaneous treatment with DES.

However, distal left main disease has been reported to be associated with relatively high TLR rates of 13% to 38%, particularly when a bifurcation 2-stent procedure was undertaken.[19,20] In the present study, SES deployment with a bifurcation 2-stent strategy was the strongest predictor of TLR after ULMCA stenting (3-year TLR rate of 30.9%), a finding that is in line with previous reports. The present results also point to an increased incidence of thrombotic events and a significantly higher incidence of cardiac death in patients treated with bifurcation 2-stent strategies, although the statistical power is obviously insufficient to detect differences in the incidences of these hard events. Also, survival analysis of cardiac death could be seen as a competing risk situation, because there are multiple types of death. Use of the Kaplan–Meier method in this situation may result in an overestimation of the true cumulative incidence of cardiac death.[21]

Because the patients with bifurcation 1-stent treatment had relatively favorable outcomes in terms of survival and need for TLR, one should make every effort to finish with main-branch stenting alone when treating left main bifurcation lesions. Also, foreseeing the likelihood of the need for a 2-stent approach appears to be important in selecting patients for ULMCA stenting. The use of DES in patients with distal bifurcation lesions that are likely to require a 2-stent strategy is probably premature. Future innovative solutions are crucial for the percutaneous treatment of left main true bifurcation lesions.

The higher rates of cardiac death and any revascularization in patients with ULMCA plus 3-vessel disease observed in the present study are consistent with the findings from the SYNTAX trial.[12] Therefore, serious consideration must be given to the indication for PCI in this subgroup of patients with the most complex coronary anatomy.

Relative to the selection of revascularization strategies in patients with extensive coronary artery disease, the SYNTAX trial highlighted the lower incidence of stroke after PCI than after coronary artery bypass graft. Although the rate of stroke in the ULMCA group in the present study (2.8% at 1 year) appeared to be higher than in the PCI arm of the SYNTAX trial (0.6% at 1 year), the rates of stroke were similar between the 2 groups with or without ULMCA stenting. The relatively high incidence of stroke in the present study cohort might be related to the high prevalence of stroke at baseline.

Study Limitations

There are several limitations to the present study. First, this was an observational study, and comparison of the clinical outcomes between patients treated for ULMCA and those treated for non-ULMCA disease might be biased even after adjustment for known confounders. Furthermore, the treatment strategy for bifurcation lesions was not based on randomized assignment. Second, TLR events in the present study included both clinically driven and angiographically driven events. The clinical significance of angiographically driven TLR of ULMCA remains unclear. Third, the length of clinical follow-up is still limited. Fourth, although the number of study patients was larger than reported previously, the present study population included heterogeneous patients with a high prevalence of elderly age, renal failure, and heart failure. Cautious interpretation is required to generalize our results. Fifth, we could not incorporate the SYNTAX score, which would have helped us to stratify the risk among patients undergoing ULMCA stenting. Finally, the relatively lower rate of ST (1.3% at 1 year) in the present study than reported in the SYNTAX trial (3.3% at 1 year) might result from the much more complex anatomic characteristics of patients in the SYNTAX trial. Alternatively, the different rates of ST could be derived from differences related to ethnicity. Therefore, it might be difficult to extrapolate the present study results outside Japan.

Conclusions

The higher unadjusted mortality rate in patients undergoing ULMCA stenting did not appear to be related to treatment of ULMCA itself but rather to the high-risk profile of the ULMCA patients treated by PCI in real-world clinical practice. Although long-term outcomes of patients with ostial/shaft ULMCA lesions were favorable, outcomes of patients who underwent bifurcation 2-stent treatments appeared unacceptable.

Appendix

A complete list of investigators and committees of the j-Cypher registry has been published previously.[11]

Acknowledgments

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Disclosures

Drs Kimura and Isshiki have served as advisory board members and have received honoraria from Cordis Cardiology, Japan, Johnson & Johnson. Dr Mitsudo has received honoraria from Cordis Cardiology, Japan, Johnson & Johnson. The remaining authors report no conflicts.

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CLINICAL PERSPECTIVE

Despite the growing popularity of stenting unprotected left main coronary arteries with drug-eluting stents, long-term outcomes have not been assessed adequately. This large multicenter registry in Japan (the j-Cypher registry) compared the 3-year clinical outcomes of 582 patients undergoing percutaneous coronary intervention for unprotected left main coronary artery (ULMCA) lesions with those of 12 242 patients undergoing percutaneous coronary intervention for non-ULMCA lesions only. The influence of lesion location and bifurcation stenting strategy on clinical outcomes was also assessed in 476 patients whose ULMCA lesions were treated exclusively with sirolimus-eluting stents. The main findings of this study are as follows: (1) Percutaneous coronary intervention for ULMCA lesions was associated with a higher late mortality rate than for lesions located elsewhere, but this finding was mainly related to factors other than the left main being the treatment site; (2) sirolimus-eluting stent implantation in ostial/shaft left main lesions was associated with a better 3-year target-lesion revascularization rate than in distal bifurcation lesions; and (3) patients with ULMCA plus 3-vessel disease had poor long-term outcome in terms of coronary revascularization, stent thrombosis, and cardiac death. Therefore, although ULMCA stenting with a sirolimus-eluting stent is an attractive option, clinical outcomes are less satisfactory in patients who need bifurcation 2-stent treatment or who have extensive coronary artery disease outside the ULMCA. Consideration of the individual patient's risk stratification is important when selecting coronary revascularization strategies in patients with ULMCA disease.

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ORIGINAL ARTICLE

Incidence and outcome of surgical procedures after sirolimus-eluting stent implantation: a report from the j-Cypher registry

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Abstract The incidence of surgical procedures after sirolimus-eluting stent (SES) implantation and, more importantly, the rate of perioperative stent thrombosis (ST) and/or other adverse events have not yet been adequately addressed. The incidence and outcome of the surgical procedures after SES implantation were prospectively evaluated in a large-scale multicenter registry of patients undergoing SES implantation. Among 12,824 patients enrolled in the registry, cumulative incidences of surgical procedures were 0.7% at 60 days, 5.1% at 1 year and 14.7% at 3 years. Surgical procedures were performed in 1,430 patients including non-coronary artery bypass graft (CABG) surgery in 1,275 patients and CABG in 189 patients. The incidences of death/myocardial infarction/ST (definite or probable) and ST (definite or probable) at 30 days after surgical procedures were 2.7 and 0.35%, respectively. Surgery performed within 60 days after SES implantation as compared with that performed beyond 60 days was associated with significantly higher incidences of death/myocardial infarction/ST (definite or probable) and ST (definite or probable) at 30 days after surgical procedures (6.4 vs. 2.5%: $P = 0.02$ and 2.2 vs. 0.23%: $P = 0.002$, respectively). Surgery within 60 days as well as hemodialysis and small body mass index were independent risk factors of death/myocardial infarction/ST (definite or probable) identified by multivariable analysis. Surgical procedures were required fairly often after SES implantation. The incidences of adverse cardiac events including ST after surgical procedures were acceptably low. Surgery within 60 days after SES implantation carried significantly higher risks as compared with those beyond 60 days.

On behalf of the j-Cypher Registry investigators.

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Keywords Stent · Thrombosis · Revascularization · Surgery · Aspirin

Introduction

Non-cardiac surgical procedures after bare-metal stent (BMS) implantation have been reported to be associated with a high rate of perioperative stent thrombosis (ST) and/or serious adverse events in the first 6 weeks after stent implantation [1–4]. When surgical procedures were performed beyond 6–8 weeks after BMS implantation, the risk of perioperative ST was reported to attenuate markedly [1, 2, 4]. In the era of the drug-eluting stent (DES), a report of three cases with postoperative ST late (343–442 days) after DES implantation highlighted the exaggerated ST risk after surgical procedures [5]. Pressed by this and other reports suggesting safety concerns related to DES [6–8], a consensus statement from the American College of Cardiology and the American Heart Association recommended postponing elective surgery for at least 1 year in patients in whom a DES had been implanted [9]. However, the incidence of surgical procedures after DES implantation and more importantly the rates of perioperative ST and/or serious adverse events have not yet been systematically evaluated [10]. Furthermore, although perioperative management of antiplatelet therapy (APT) is an issue discussed frequently in clinical practice, optimal perioperative management of patients with prior DES implantation has not yet been adequately defined. To address these issues, the incidence and outcome of the surgical procedures after percutaneous coronary intervention (PCI) using DES were prospectively evaluated in a large-scale multicenter registry of patients undergoing sirolimus-eluting stent (SES) implantation.

Methods

Study population

The j-CYPHER registry is a physician-initiated prospective multicenter observational study in Japan enrolling consecutive patients undergoing SES implantation. The study design and the 2-year outcome were reported previously [11]. Between August 2004 and November 2006, 12,824 patients with 19,675 lesions were enrolled in the registry.

Surgical procedures during follow-up including CABG were captured as follow-up events. Percutaneous endovascular procedures were not regarded as surgical procedures. Gastrointestinal endoscopic therapeutic procedures were included in the surgical procedures. Although the data on the type of the surgical procedures were reported, we did not collect detailed information on the surgical procedures such as the type of anesthesia, urgency of the surgical procedures and periprocedural bleeding complications. The timing of the surgical procedures after SES implantation was categorized into the two groups (within 60 days and beyond 60 days after SES implantation) based on the previous reports suggesting increased risk of severe adverse events in patients undergoing surgical procedures within 6–8 weeks after BMS implantation [1–4].

Status on APT for both aspirin and thienopyridine was also prospectively recorded. The recommended APT regimen was aspirin (≥81 mg daily) indefinitely and thienopyridine (200 mg ticlopidine or 75 mg clopidogrel daily) for at least 3 months after SES implantation. The duration of dual APT and management of perioperative APT was left to the discretion of each attending physician. Status of APT at the time of the surgical procedures was categorized into four groups (dual, aspirin alone, thienopyridine alone and none). Information regarding periprocedural bridging use of heparin and/or other short-acting antiplatelet agents was not systematically collected.

Follow-up data were obtained from hospital charts or by contacting patients and/or referring physicians at 30 days, 6 months, 1, 2 and 3 years. Complete 1-year follow-up was achieved in 97% of patients; median duration of follow-up was 883 days (interquartile range 632–1,095 days) for survival status and 820 days (interquartile range 502–1,095 days) for surgical procedures. The relevant review boards in all 37 participating centers approved the study protocol (Supplementary Appendix). Written informed consent for participation in the study was obtained from all patients.

Outcomes and definitions

The primary outcome measure for the current analysis was the time, until 30 days after the surgical procedures, to the first occurrence of composite of death, myocardial infarction (MI) and/or ST (definite or probable). Individual components of the primary outcome measure as well as definite ST within 30 days after the surgical procedures were also evaluated.

Death was regarded as cardiac in origin unless obvious non-cardiac causes could be identified. Sudden death was defined as unexplained death in previously stable patients. MI was adjudicated according to the definition in the Arterial Revascularization Therapy Study [12]. Measurement of cardiac biomarkers such as troponin or creatinine phosphokinase was not performed routinely after the surgical procedures, but was generally performed only when periprocedural MI was clinically suspected. ST was defined according to the Academic Research Consortium (ARC) definition [13]. Both ARC definite and definite/probable ST were evaluated.

Statistical analysis

Baseline characteristics were compared between the patients with surgical procedures and those patients who completed 3-year follow-up without surgical procedures. Baseline characteristics of patients were not evaluated at the time of the surgical procedures, but at the time of the index SES implantation. Categorical variables were compared with the chi-square test. Continuous variables were compared using the Student's *t* test or Wilcoxon rank sum test based on the distribution.

Cumulative incidences of the surgical procedures and the adverse events after the surgical procedures were estimated by the Kaplan–Meier method. Differences in the adverse event rates after the surgical procedures according to the timing of the surgical procedures and the status of perioperative APT were assessed with the log-rank test.

A Cox proportional hazards model was used to identify independent risk factors of the primary outcome measure. We used the variables listed in Table 1 and the timing of the surgical procedures after SES implantation as potential independent variables. The continuous variables were dichotomized by clinically meaningful reference values or median values. To determine the independent risk factors, we selected variables with *P* values less than 0.05 in the univariable Cox models and included them simultaneously

Table 1 Baseline characteristics of patients with or without surgical procedures during 3-year follow-up

Variables	All patients ($N = 12,824$)	With surgery ($N = 1,430$)	Without surgery ($N = 3,685$)	*P* value
Age (years)	68.4 ± 10.3	69.5 ± 9.4	67.3 ± 10.0	<0.0001
Age >70 years	5,925 (46%)	734 (51%)	1,541 (42%)	<0.0001
Male gender	9,653 (75%)	1,087 (76%)	2,794 (76%)	0.88
BMI	23.9 ± 3.4	23.7 ± 3.5	24.1 ± 3.3	<0.0001
BMI ≤25.0	8,384 (65%)	990 (69%)	2,329 (63%)	<0.0001
Emergency procedure for				
ACS	1,925 (15%)	197 (14%)	459 (12%)	0.21
STEMI	1,253 (9.8%)	117 (8.2%)	299 (8.1%)	0.95
Prior heart failure	1,793 (14%)	283 (20%)	373 (10%)	<0.0001
Prior MI	3,488 (27%)	407 (28%)	1,094 (30%)	0.39
Prior stroke	1,218 (9.5%)	175 (12%)	270 (7.3%)	<0.0001
Prior coronary revascularization	6,305 (49%)	724 (51%)	2,016 (55%)	0.009
Peripheral vascular disease	1,524 (12%)	276 (19%)	340 (9.2%)	<0.0001
eGFR	58.6 ± 23.1	53.1 ± 27.2	60.9 ± 21.0	<0.0001
eGFR <30 ml/min/1.73 m^2/				
Non-HD	630 (4.9%)	116 (8.1%)	129 (3.5%)	<0.0001
HD	682 (5.3%)	160 (11%)	113 (3.1%)	<0.0001
Hypertension	9,559 (75%)	1,096 (77%)	2,676 (73%)	0.003
Diabetes	5,320 (41%)	677 (47%)	1,560 (42%)	0.001
Diabetes on insulin therapy	1,205 (9.4%)	182 (13%)	334 (9.1%)	0.0001
Current smoker	2,606 (20%)	282 (20%)	714 (19%)	0.78
Single vessel disease	5,770 (45%)	578 (40%)	1,689 (46%)	0.0005
Target of unprotected LMCA	582 (4.5%)	72 (5.0%)	163 (4.4%)	0.35
Target of LAD	6,984 (54%)	734 (51%)	1,966 (53%)	0.19
LVEF	57.8 ± 13.4	56.2 ± 13.9	58.3 ± 12.7	<0.0001
LVEF ≤ 40%	1,259 (11%)	183 (15%)	311 (9.7%)	<0.0001
Multivessel dilatation	3,568 (28%)	420 (29%)	952 (26%)	0.02
Number of stents per patient	1.93 ± 1.19	2.0 ± 1.23	1.91 ± 1.17	0.02
Number of stents per patient ≥2	6,844 (53%)	775 (54%)	1,950 (53%)	0.39
Total stent length (mm)	42.5 ± 28.3	44.3 ± 30.2	41.2 ± 27.1	<0.0001
Total stent length >36 mm	5,813 (45%)	657 (46%)	1,636 (44%)	0.3

Patients without surgery included only those patients who completed 3-year follow-up without surgical procedures

ACS acute coronary syndrome, *BMI* body mass index, *eGFR* estimated glomerular filtration rate, *HD* hemodialysis, *LAD* left anterior descending coronary artery, *LMCA* left main coronary artery, *LVEF* left ventricular ejection fraction, *STEMI* ST segment elevation myocardial infarction

in the multivariable models. All analyses were conducted by a physician (Takeshi Kimura) with the use of JMP 8 (SAS Institute Inc, Cary, NC), and all reported *P* values were two-sided.

The study sponsor was not involved in the study design, in the collection, analysis and interpretation of data, the writing of the report or the decision to submit the paper for publication.

Results

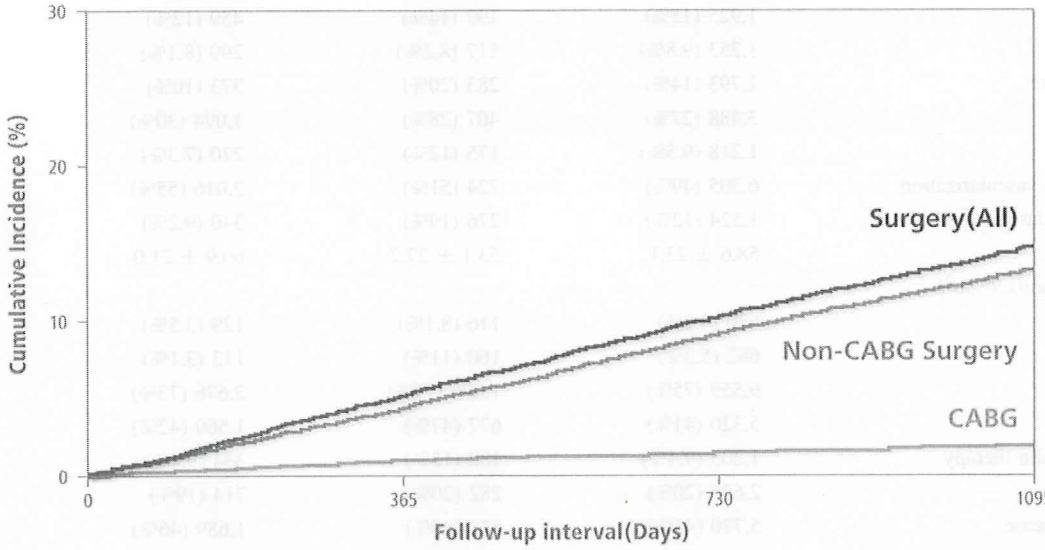
Incidence of surgical procedures after SES implantation

Patients with high-risk features such as old age, diabetes and renal failure were commonly enrolled in the j-Cypher registry (Table 1). During the 3-year follow-up after PCI using SES, surgical procedures were performed commonly and constantly (annual rate of 5%). Cumulative incidences of surgical procedures were 0.7% at 60 days, 5.1% at 1 year, 10.2% at 2 years and 14.7% at 3 years (Fig. 1). Surgical procedures were performed in 1,430 patients including non-CABG surgery in 1,275 patients and CABG in 189 patients. Common surgical fields for non-CABG surgery included abdominal surgery, vascular surgery, orthopedic surgery, ophthalmic surgery, pacemaker implantation, gastrointestinal endoscopic procedures and urologic surgery (Table 2).

As compared with patients who did not have surgery, patients who had surgery were older and had smaller body mass indexes. Patients who had surgery more often had comorbidities such as heart failure, stroke, peripheral vascular disease, end-stage renal disease, hypertension and diabetes. In terms of extensiveness of coronary artery disease and procedural complexities, patients who had surgery more often had multi-vessel coronary artery disease and low left ventricular ejection fraction, and more often underwent multi-vessel dilatation with longer total stent length. The proportion of patients undergoing emergency procedures for acute coronary syndrome was similar in both groups (Table 1).

Clinical outcome after SES implantation and after surgical procedures

Adverse event rates through 3 years for the entire j-Cypher registry cohort are summarized in Table 3. The slopes of



		60 Days	1 year	2 years	3 years
Surgery(All)					
Incidence		0.7%	5.1%	10.2%	14.7%
Number of events		94	626	1146	1430
Number of patients at risk	12824	12492	11358	8264	3687
Non-CABG Surgery					
Incidence		0.6%	4.3%	9.0%	13.3%
Number of events		75	526	1011	1275
Number of patients at risk	12824	12509	11448	8367	3751
CABG					
Incidence		0.2%	0.9%	1.4%	1.9%
Number of events		20	111	161	189
Number of patients at risk	12824	12559	11814	8984	4149

Fig. 1 Cumulative incidences of surgical procedures after sirolimus-eluting stent implantation. *CABG* coronary artery bypass grafting surgery

the cumulative incidence curves between 30 days and 3 years were 0.3% per month for death/MI/ST (definite or probable), 0.25% per month for death, 0.07% per month for MI, and 0.02% per month for both definite and definite/probable ST. Clinical outcomes after surgical procedures are summarized in Fig. 2 and Table 4. The incidences of death/MI/ST (definite or probable) and ST (definite or probable) at 30 days after surgical procedures were 2.7 and 0.35%, respectively. The cumulative incidence curve for death/MI/ST (definite or probable) revealed increased early risk at 30 days and relatively constant risk beyond 30 days after surgical procedures (Fig. 2a). The slope of the cumulative incidence curve beyond 30 days after surgical procedures was relatively steep (0.67% per month). Stent thrombosis occurred mostly within 30 days after surgical procedures (Fig. 2b). One patient who had ST while stopping APT before the scheduled but aborted surgical procedure was not included in the group with surgical procedures.

Causes of death within 30 days after surgical procedures included cardiac death in 15 patients and non-cardiac death in 18 cases. Stent thrombosis was suspected as the cause of death in only two patients (a probable ST and a sudden cardiac death post CABG) (Table 5).

Table 2 Fields of surgical procedures other than CABG

Surgical fields	Number of patients (%)
All	1,275 (100)
Abdominal surgery	241 (19)
Vascular surgery	224 (18)
Orthopedic surgery	173 (14)
Ophthalmic surgery	161 (13)
Pacemaker implantation	97 (7.6)
Gastrointestinal endoscopic procedures	96 (7.5)
Urologic surgery	76 (6.0)
Cardiac surgery	46 (3.6)
Neurosurgery	32 (2.5)
Respiratory surgery	31 (2.4)
Otorhinolaryngological surgery	29 (2.3)
Dermatologic surgery	21 (1.7)
Oral and maxillofacial surgery	18 (1.4)
Gynecological surgery	9 (0.7)
Mammary surgery	9 (0.7)
Others	10 (0.8)
Unknown	2 (0.2)

CABG coronary artery bypass grafting surgery

Timing of surgical procedures and clinical outcome

Surgery performed within 60 days after SES implantation as compared with that performed beyond 60 days was associated with significantly higher incidences of death/MI/ST (definite or probable) and ST (definite or probable) within 30 days after surgical procedures (6.4 vs. 2.5%: $P = 0.02$ and 2.2 vs. 0.23%: $P = 0.002$, respectively) (Fig. 3, Table 6). Increased risk for surgical procedures performed within 60 days after SES implantation was consistently seen after excluding CABG (Table 6).

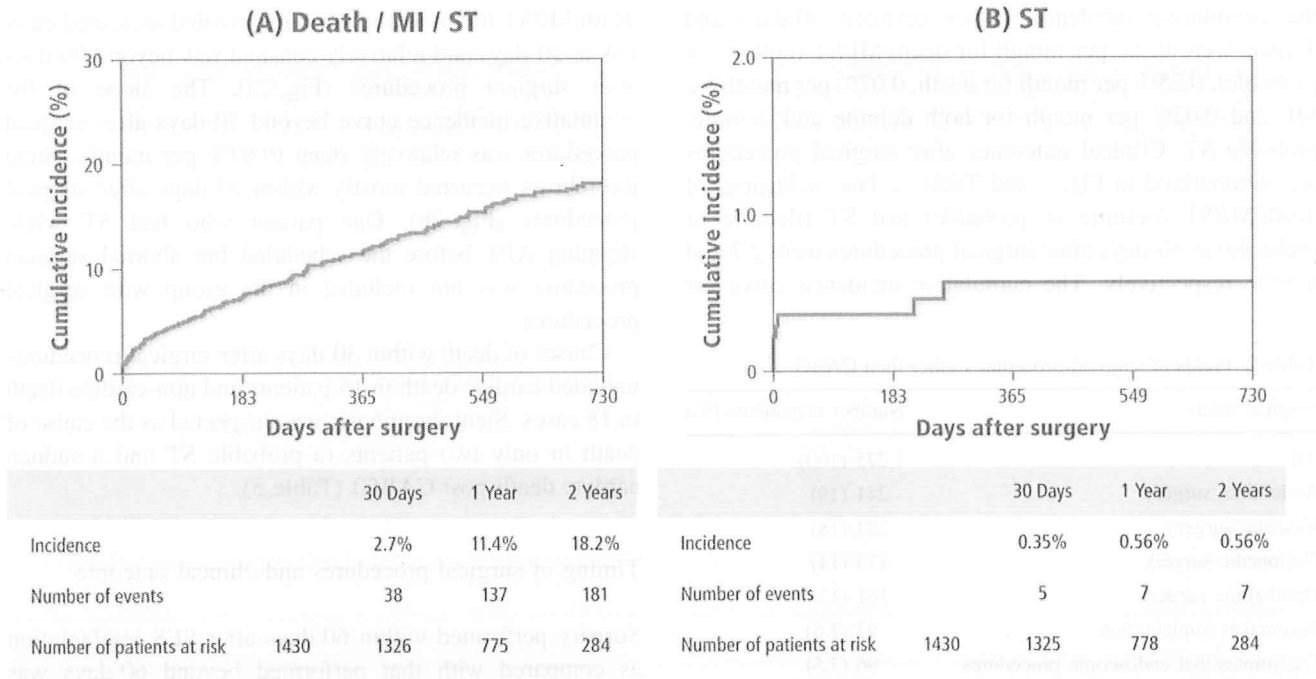
Perioperative status of antiplatelet therapy

Antiplatelet therapy before surgery was dual in 400 patients (28%), aspirin alone in 434 patients (30%),

Table 3 Adverse event rates for 3 years after SES implantation in the entire j-Cypher registry cohort

	Cumulative event rate			
	30 days (%)	1 year (%)	2 years (%)	3 years (%)
Death/MI/ST (definite or probable)	1.2	4.9	8.2	11.6
Death	0.74	4.0	6.8	9.5
Cardiac death	0.72	2.4	3.5	4.6
Sudden death	0.08	0.68	1.2	1.6
MI	0.38	1.1	1.7	2.8
Related to stent thrombosis	0.29	0.54	0.74	1.1
Stroke	0.39	1.9	3.2	4.1
Stent thrombosis				
Definite	0.36	0.61	0.84	1.2
Definite/probable	0.48	0.77	1.0	1.3
Definite/probable/possible	0.49	1.5	2.3	3.3
Target lesion revascularization	0.71	9.0	12.0	14.1
Coronary artery bypass grafting	0.11	0.91	1.4	1.9
Any coronary revascularization	2.7	21.6	27.8	32.4

MI myocardial infarction, *SES* sirolimus-eluting stent, *ST* stent thrombosis



		30 Days	1 Year	2 Years
Incidence		2.7%	11.4%	18.2%
Number of events		38	137	181
Number of patients at risk	1430	1326	775	284

		30 Days	1 Year	2 Years
Incidence		0.35%	0.56%	0.56%
Number of events		5	7	7
Number of patients at risk	1430	1325	778	284

Fig. 2 Cumulative incidences of death/MI/ST (**a**) and ST (**b**) after surgical procedures. *MI* myocardial infarction and *ST* stent thrombosis (definite or probable)

Table 4 Adverse event rates after surgical procedures

Endpoints	*N* of events (incidence)		
	30 days (%)	1 year (%)	2 years (%)
Death/MI/ST (definite or probable)	38 (2.7)	137 (11.4)	181 (18.2)
Death	33 (2.4)	128 (10.7)	171 (17.3)
MI	9 (0.65)	16 (1.3)	18 (1.6)
ST (definite or probable)	5 (0.35)	7 (0.56)	7 (0.56)
ST (definite)	4 (0.28)	6 (0.49)	6 (0.49)

MI myocardial infarction, *ST* stent thrombosis

thienopyridine alone in 19 patients (1.3%) and none in 577 patients (40%). Incidences of death/MI/ST (definite or probable) and ST (definite or probable) at 30 days after surgical procedures were not different according to the perioperative status of APT (Table 7).

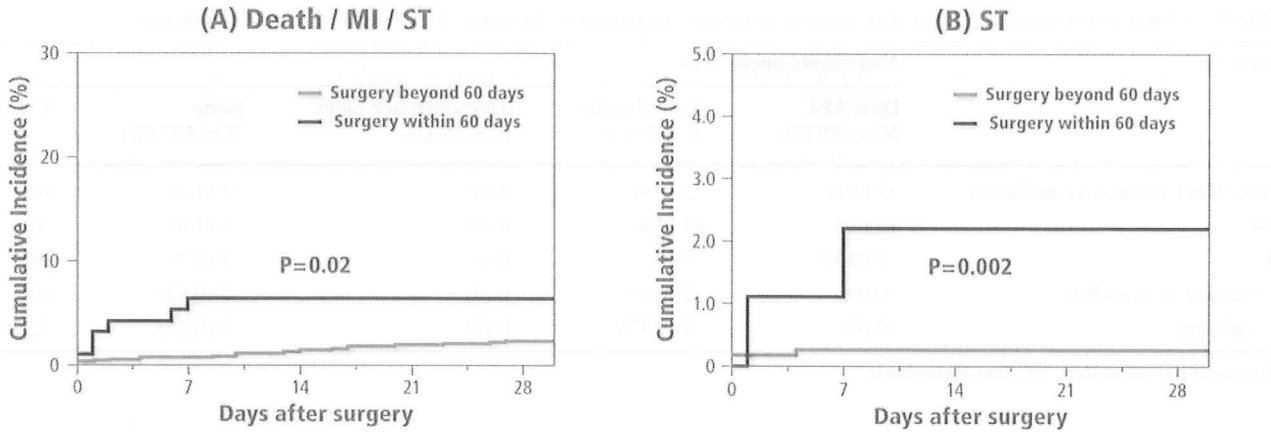
Risk factors of perioperative death/MI/ST (definite or probable)

Risk factors of perioperative death/MI/ST (definite or probable) identified by univariate analysis included hemodialysis, small body mass index, prior heart failure and surgery within 60 days after SES implantation. Surgery within 60 days after SES implantation as well as hemodialysis and small body mass index were independent risk factors of perioperative death/MI/ST (definite or probable) identified by multivariable analysis (Table 8).

Table 5 Causes of death within 30 days after surgical procedures

Causes of death	Number of cases
Cardiac death	15
MI, probable ST	1
Sudden cardiac death (post CABG)	1
Postoperative MI, no evidence of ST	3
Heart failure, no evidence of MI	5
Complications of preoperative MI	4
Unknown	1
Non-cardiac death	18
Infection	7
Renal failure	3
Stroke	3
Bleeding	1
Others	4

CABG coronary artery bypass grafting surgery, *MI* myocardial infarction, *ST* stent thrombsis



Surgery within 60 days		7 Days	30 Days
Incidence		6.4%	6.4%
Number of events		6	6
Number of patients at risk	94	89	87
Surgery beyond 60 days			
Incidence		0.8%	2.5%
Number of events		10	32
Number of patients at risk	1336	1306	1239

Surgery within 60 days		7 Days	30 Days
Incidence		2.2%	2.2%
Number of events		2	2
Number of patients at risk	94	89	87
Surgery beyond 60 days			
Incidence		0.23%	0.23%
Number of events		3	3
Number of patients at risk	1336	1306	1238

Fig. 3 Cumulative incidences of death/MI/ST (**a**) and ST (**b**) after surgical procedures compared between surgery within and beyond 60 days after sirolimus-eluting stent implantation. *MI* myocardial infarction and *ST* stent thrombosis (definite or probable)

Table 6 Adverse event rates at 30 days after surgical procedures according to the timing after SES implantation

Endpoints	*N* of events (incidence) at 30 days after surgery		
	Surgery within 60 days	Surgery beyond 60 days	*P* value
Surgery (all)	*N* = 94	*N* = 1336	
Death/MI/ST (definite or probable)	6 (6.4%)	32 (2.5%)	0.02
Death	4 (4.3%)	29 (2.2%)	0.17
MI	2 (2.2%)	7 (0.54%)	0.06
ST (definite or probable)	2 (2.2%)	3 (0.23%)	0.002
ST (definite)	2 (2.2%)	2 (0.15%)	0.0004
Non-CABG surgery	*N* = 75	*N* = 1200	
Death/MI/ST (definite or probable)	5 (6.5%)	27 (2.3%)	0.02
Death	3 (3.9%)	24 (2.1%)	0.25
MI	2 (2.7%)	7 (0.6%)	0.03
ST (definite or probable)	2 (2.7%)	3 (0.25%)	0.001
ST (definite)	2 (2.7%)	2 (0.17%)	0.0002

MI myocardial infarction, *SES* sirolimus-eluting stent, *ST* stent thrombosis

Discussion

The main findings of the present study were that surgical procedures were often required after PCI using SES (5% per year) and that the incidences of adverse cardiac events including ST after surgical procedures were acceptably low, although surgery within 60 days after SES implantation carried significantly higher risks as compared with surgery beyond 60 days after SES implantation.

A consensus statement from the American College of Cardiology and the American Heart Association recommended BMS implantation or balloon angioplasty with

Table 7 Adverse event rates at 30 days after surgical procedures according to the status of preoperative antiplatelet therapy

Endpoints	*N* of events (incidence)				
	Dual APT $N = 400$ (%)	Aspirin alone $N = 434$ (%)	Thienopyridine alone $N = 19$ (%)	None $N = 577$ (%)	*P* value
Death/MI/ST (definite or probable)	15 (3.8)	12 (2.9)	0 (0)	11 (1.9)	0.3
Death	15 (3.8)	10 (2.4)	0 (0)	8 (1.4)	0.09
MI	2 (0.53)	3 (0.7)	0 (0)	4 (0.7)	0.96
ST (definite or probable)	0 (0)	2 (0.47)	0 (0)	3 (0.52)	0.55
ST (definite)	0 (0)	2 (0.47)	0 (0)	2 (0.35)	0.62

MI myocardial infarction, *ST* stent thrombosis

Table 8 Univariate and multivariable analysis for risk factors of perioperative death/MI/ST (definite or probable)

Variables	Univariate analysis			Multivariable analysis		
	N of events (incidence)			Odds ratio	95% CI	*P* value
	Yes (%)	No (%)	*P* value			
Age >70 years	19 (2.6)	18 (2.6)	0.98			
Male gender	27 (2.5)	10 (2.9)	0.66			
BMI ≤25.0	32 (3.3)	5 (1.2)	0.02	1.59	1.03–2.73	0.03
Emergency procedure for						
ACS	8 (4.1)	29 (2.4)	0.16			
STEMI	4 (3.6)	33 (2.6)	0.51			
Prior heart failure	13 (4.7)	24 (2.1)	0.02	1.32	0.92–1.86	0.13
Prior MI	12 (3.0)	25 (2.5)	0.57			
Prior stroke	8 (4.6)	29 (2.4)	0.08			
Prior coronary revascularization	16 (2.3)	21 (3.0)	0.36			
Peripheral vascular disease	10 (3.7)	27 (2.4)	0.23			
eGFR <30 ml/min/1.73 m^2/						
Non-HD	5 (4.4)	32 (2.5)	0.22			
HD	11 (6.9)	26 (2.1)	0.003	1.64	1.12–2.34	0.01
Hypertension	28 (2.6)	9 (2.8)	0.86			
Diabetes	12 (1.8)	25 (3.4)	0.06			
Diabetes on insulin therapy	5 (1.2)	32 (2.6)	0.92			
Current smoker	8 (2.9)	29 (2.6)	0.77			
Single vessel disease	12 (2.1)	25 (3.0)	0.33			
Target of unprotected LMCA	0 (0)	37 (2.8)	0.16			
Target of LAD	15 (2.1)	22 (3.2)	0.19			
LVEF ≤40%	6 (3.3)	23 (2.2)	0.36			
Multivessel dilatation	13 (3.1)	24 (2.4)	0.45			
Number of stents per patient ≥ 2	22 (2.9)	15 (2.4)	0.53			
Total stent length > 36 mm	16 (2.5)	21 (2.8)	0.72			
Surgery within 60 days after SES implantation	6 (6.4)	31 (2.4)	0.02	1.68	1.03–2.52	0.04

ACS acute coronary syndrome, *HD* hemodialysis, *LAD* left anterior descending coronary artery, *LMCA* left main coronary artery, *LVEF* left ventricular ejection fraction, *SES* sirolimus-eluting stent, *STEMI* ST-segment elevation myocardial infarction

provisional BMS implantation instead of DES implantation in patients undergoing PCI who would be likely to require invasive or surgical procedures within 12 months [9]. However, several previous studies clearly demonstrated that preoperative coronary revascularization is not beneficial in many patients undergoing major vascular surgery [14, 15]. Those patients who truly need PCI before surgical procedures are considered to be a minority of patients undergoing surgical procedures. The present study clearly demonstrated that the need for surgical procedures

often develops after a DES has been implanted. It is our contention that the recommendation to avoid the use of DESs could hardly address the issues concerning surgical procedures after DES implantation. Furthermore, non-cardiac surgical procedures after BMS implantation have been reported to be associated with a high rate of perioperative ST and/or serious adverse events in the first 6 weeks after stent implantation [1–4]. Also, a meta-analysis comparing SES with BMS clearly demonstrated that the incidence and the timing of ST up to 1 year were not different between SES and BMS [16]. Therefore, if a given surgical procedure is truly required shortly after PCI, the choice of BMS seems not to provide much advantage over the choice of DES. Avoiding unnecessary PCI before surgical procedures is therefore much more important than the selection of the types of stent.

A report of three cases with perioperative ST late (343–442 days) after DES implantation highlighted the exaggerated ST risk after surgical procedures [5]. The reported incidences of ST of DES after surgical procedures ranged from 0 to 2% in several small series of patients [17–20]. A recent report of 481 patients undergoing surgical procedures after DES implantation showed ST (definite or modified probable) and composite of death, MI or ST at 30 days after surgery in 2.0 and 9.0% of patients, respectively [21]. The present study, which was evaluating the largest ever reported number of patients undergoing surgical procedures after DES implantation, suggested that surgical procedures are one of the risk factors for ST after SES implantation. The rate of ST at 30 days after surgical procedures (0.35%), seemed to be higher than the slope of the cumulative incidence curves of ST beyond 30 days (0.02% per month) in the entire j-Cypher registry cohort. The potential mechanisms for increased risk for ST appear to be related to discontinuation of antiplatelet therapy, activation of the sympathetic nervous system and the existence of a hypercoagulable state associated with surgery. However, the incidences of death/MI/ST (definite or probable) and ST (definite or probable) at 30 days after surgical procedures in this study were very low (2.7 and 0.35%, respectively) and reassuring. The lower incidence of adverse cardiac events as compared with the previous report [21] might be related to inclusion of minor surgeries in our study and generally low incidence of ST and other coronary events in the Japanese patient population [11].

Although the case report suggesting an increased risk of ST with DES highlighted the occurrence of ST late after DES implantation [5], several reports demonstrated that surgical procedures weeks after DES implantation were associated with an increased risk of adverse cardiac events [19, 21]. Our current result was consistent with those previous reports. Surgical procedures performed within 60 days after SES implantation as compared with those beyond 60 days carried a higher risk for adverse cardiac events including ST. A consensus statement from the American College of Cardiology and the American Heart Association recommended postponing elective surgery for at least 1 year in patients in whom a DES has been implanted [9]. Although the optimal duration of the delay is not yet known, duration shorter than 1 year would be appropriate considering the very low incidence of ST in patients with surgery beyond 60 days in the current study and the constant rate of occurrence of ST between 30 days and 3 years after DES implantation [8].

In the present study, we could not address the issue of optimal management of APT before and after surgical procedures. The incidences of adverse cardiac events including ST did not differ significantly according to the perioperative status of APT. This result was consistent with a previous study [21]. The risk of adverse cardiac events after surgical procedures are influenced by several factors other than the perioperative status of APT, including morbidities of patients, invasiveness of surgical procedures, timing of surgery after DES implantation and different lengths of time of discontinuation of APT. In real clinical practice, perioperative management of APT would have had been modified according to the risk factors that a given patient has. This would be the reason why we could not see clear differences in the rates of adverse cardiac events according to the perioperative status of APT.

However, optimal perioperative management of APT should certainly be better defined since this is the issue so frequently discussed in clinical practice. Since surgical procedures early after PCI were consistently reported to be associated with an increased risk for adverse cardiac events including ST, strict adherence to dual APT would be desirable up to 6 weeks to 2 months after PCI. Discontinuation of both aspirin and thienopyridine was reported to be associated with ST even beyond 1 year after DES implantation [11]. In a meta-analysis evaluating 50,279 patients at risk of or with coronary artery disease, aspirin non-adherence/withdrawal was reported to be associated with threefold higher risk of major adverse cardiac events [22]. In another meta-analysis involving 49,590 patients undergoing surgical procedures, aspirin increased the rate of bleeding complications by a factor of 1.5 (median, interquartile range: 1.0–2.5), but it did not lead to a higher level of the severity of bleeding complications [23]. Considering the risk and benefit profile of APT, it should be recommended to continue aspirin in most patients undergoing surgical procedures after DES implantation except for surgical procedures such as intracranial surgery and spinal surgery where serious clinical consequences are expected after bleeding. When discontinuation was unavoidable, it seems practically important to make the duration of discontinuation as short as possible, since the

majority of ST events were reported to have occurred beyond 1 week after discontinuation of APT [11]. Since bleeding time was reported to recover to the baseline level after 3–5 days of aspirin cessation, discontinuation of aspirin 3–5 days before surgical procedures would be long enough to minimize bleeding risk when discontinuation of aspirin is unavoidable [24, 25].

There are several important limitations of this study. First, surgical procedures constituting the study population were follow-up events in the j-CYPHER registry. Although we had extensive data on clinical, lesion and procedural characteristics at the time of the index PCI procedures, we did not collect detailed information on the surgical procedures such as the type of anesthesia, urgency of the surgical procedures and periprocedural bleeding complications. Therefore, analysis of the risk factors for the primary outcome measure was conducted based on baseline characteristics at the time of index PCI procedures. Secondly, we did not make systematic evaluation of electrocardiogram and cardiac biomarkers such as troponin to detect perioperative MI. This would be likely to underestimate the rate of perioperative MI. Thirdly, although data on surgical procedures during follow-up were prospectively collected in the j-Cypher registry, it is possible that the attending physicians in the cardiology division did not recognize and record details of all the surgical procedures conducted. This would be likely to underestimate the incidence of surgical procedures during follow-up. Finally, although data on discontinuation of APT were prospectively collected, it is possible that the surgeons might have discontinued APT without notice to the attending physicians in the cardiology division. Also, when follow-up information was obtained by contact with patients, information regarding discontinuation of APT was based on retrospective recall by the patients or relatives, suggesting a potential for recall bias. These factors would be likely to underestimate the prevalence of patients who discontinued APT before surgical procedures.

Conclusions

Despite these study limitations, we would conclude that surgical procedures were often required after PCI using SES (5% per year) and that the incidences of adverse cardiac events including ST after surgical procedures were acceptably low. Surgery within 60 days after SES implantation carried significantly higher risk as compared with those beyond 60 days.

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Conflict of interest statement The authors have following relationship with the sponsor of the study: Takeshi Kimura and Takaaki Isshiki are advisory board members and in receipt of honoraria.

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QUARTERLY FOCUS ISSUE: HEART RHYTHM DISORDERS

D85N, a KCNE1 Polymorphism, Is a Disease-Causing Gene Variant in Long QT Syndrome

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Objectives This study aims to address whether D85N, a KCNE1 polymorphism, is a gene variant that causes long QT syndrome (LQTS) phenotype.

Background KCNE1 encodes the beta-subunit of cardiac voltage-gated K^+ channels and causes LQTS, which is characterized by the prolongation of the QT interval and torsades de pointes, a lethal arrhythmia. D85N, a KCNE1 polymorphism, is known to be a functional variant associated with drug-induced LQTS.

Methods In order to elucidate the prevalence and clinical significance of this polymorphism, we performed genetic screening in 317 LQTS probands. For comparison, we examined its presence in 496 healthy control subjects. We also conducted biophysical assays for the D85N variant in mammalian cells.

Results The allele frequency for D85N carriers was 0.81% in healthy people. In contrast, among LQTS probands, there were 1 homozygous and 23 heterozygous carriers (allele frequency 3.9%). Seven of 23 heterozygous carriers had additional mutations in LQTS-related genes, and 3 female subjects had documented factors predisposing to the symptom. After excluding these probands, the D85N prevalence was significantly higher compared with control subjects (allele frequency 2.1%, $p < 0.05$). In a heterologous expression study with Chinese hamster ovarian cells, KCNE1-D85N was found to exert significant loss-of-function effects on both KCNQ1- and KCNH2-encoded channel currents.

Conclusions The KCNE1-D85N polymorphism was significantly more frequent in our LQTS probands. The functional variant is a disease-causing gene variant of LQTS phenotype that functions by interacting with KCNH2 and KCNQ1. Since its allele frequency was ~1% among control individuals, KCNE1-D85N may be a clinically important genetic variant. (J Am Coll Cardiol 2009;54:812–9) © 2009 by the American College of Cardiology Foundation

Long QT syndrome (LQTS) is a disorder that is characterized by repolarization abnormalities in the heart, leading to torsades de pointes (TdP), syncope, and sudden death. Among the LQTS-related genes identified to date, KCNQ1 and KCNE1 are known to encode the alpha and beta subunits of voltage-gated K^+ channels, which carry I_{Ks}, a slowly activating component of delayed rectifier K^+ current (1,2). KCNE1 is also known to regulate KCNH2 (3), which encodes the Kv11.1 protein, the alpha subunit of rapidly activating delayed rectifier K^+ current (I_{Kr}) (4–6).

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A KCNE1 C-terminal polymorphism, D85N, has been found in the normal population and is known to cause a G-to-A transition at codon 253 (c.253G>A), which leads to the amino acid substitution of aspartic acid for asparagines (7). This has been shown to cause an approximately 50% reduction in KCNQ1-encoded currents in a heterologous expression system using *Xenopus* oocytes (8), although biophysical study data are not available for mammalian cells.

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The allele frequency of the polymorphism is reported to be 0.7% in apparently healthy Asians (7). Paulussen et al. (9) demonstrated in a European population that the allele frequency of D85N was 5% in acquired LQTS patients who experienced TdP as a result of drug administration, but was 0% in the control group. Iwasa et al. (10) reported that the allele frequency was 2% in 100 Japanese cases, but their cohort contained both LQTS patients and normal individuals.

In the present study, we examined the incidence rate of KCNE1-D85N polymorphisms in 317 LQTS probands from unrelated families and 496 control healthy individuals. We identified 23 heterozygous and 1 homozygous probands (allele frequency 3.9%), described the demographics of these index patients, and examined the possibility that the D85N polymorphism is an LQTS-causing genetic variant. We also conducted detailed functional assays of the variant while it was coexpressed with the 2 alpha subunits of cardiac delayed rectifier K^+ channels, KCNQ1 and KCNH2, by using a heterologous expression system involving Chinese hamster ovarian (CHO) cells.

Abbreviations and Acronyms

CHO = Chinese hamster ovarian
LQTS = long QT syndrome
QTc = corrected QT interval
TdP = torsades de pointes

Methods

Study subjects. Three hundred and seventeen consecutive LQTS probands who showed a prolongation of the QT interval were referred to our laboratory for genetic evaluation and were enrolled in our analysis. The electrocardiogram diagnostic criteria of Keating and Sanguinetti (11) included a corrected QT interval (QTc) of ≥470 ms in asymptomatic individuals and a QTc of >440 ms for male subjects and of >460 ms for female subjects that had 1 or more of the following: 1) stress-related syncope; 2) documented TdP; or 3) a family history of early sudden cardiac death.

The protocol for genetic analysis was approved by our institutional ethics committee and was performed under its guidelines. Informed consent was obtained from all individuals or their guardians before the analysis. The QT intervals were measured from electrocardiographic lead II or an available rhythm strip and were corrected for heart rate according to Bazett's formula. As for the control cohort, we screened the frequency of the D85N polymorphism in 496 randomly selected cases, consisting of healthy volunteers and mutation-negative family members such as probands' spouses. Their QTc were <440 ms for male subjects and <460 ms for female subjects.

Genotyping. Genomic deoxyribonucleic acid (DNA) was isolated from venous blood by use of the QIAamp DNA midikit (Qiagen, Hilden, Germany). Genetic screening for KCNE1-D85N was performed by direct polymerase chain reaction. Other LQTS-related genes, including KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2, and KCNJ2, were assayed by denaturing high-performance liquid chromatography using a WAVE System Model 3500 (Transgenomic, Omaha, Nebraska). Abnormal conformers were amplified by polymerase chain reaction. Sequencing was performed with an ABI PRISM3100 DNA sequencer (Applied Biosystems, Wellesley, Massachusetts).

Site-directed mutagenesis. Complementary deoxyribonucleic acid (cDNA) for human KCNQ1 (GenBank AF000571) and KCNE1 (GenBank M26685) were kindly provided by Dr. J. Barhanin (Institut de Pharmacologie Moléculaire et Cellulaire, CNRS, Valbonne, France). The cDNAs were subcloned into pIRES2-EGFP (for KCNQ1) and pIRES-CD8 (for both wild-type and mutated KCNE1) vectors. cDNA for human KCNH2 (GenBank AF363636) was kindly donated by Dr. M. Sanguinetti (University of Utah, Salt Lake City, Utah). The cDNA was subcloned into a pRc-CMV vector. A KCNE1-D85N variant was constructed using a Quick Change II XL Site-Directed Mutagenesis Kit, according to the manufacturer's instructions (Stratagene, La Jolla, California). Nucleotide sequence analysis was performed on each variant construct before the expression study to confirm their sequences.

Cell transfection. CHO cells were maintained at 37°C in Dulbecco's modified Eagle medium and Ham's F12 nutritional mixture (Gibco-BRL, Rockville, Maryland) containing 10% fetal bovine serum supplemented with 1% penicillin and 1% streptomycin. Wild-type KCNQ1, KCNH2, and wild-type and/or variant KCNE1 clones were expressed transiently in CHO cells using the LipofectAMINE method according to the manufacturer's instructions (Invitrogen, Carlsbad, California).

To identify the cells that were positive for KCNH2 expression, CHO cells were cotransfected with 1 μg of pRc-CMV/KCNH2 vector and 0.5 μg of pEGFP-N1/CMV vector. Forty-eight to 72 h after transfection, green fluorescent protein-positive cells and anti-CD8 antibody-coated bead (Dynabeads CD8, Dynal Biotech, Oslo, Norway) decorated cells were used for the patch-clamp study.

Electrophysiological assays. Whole-cell configuration of patch-clamp techniques was employed to record membrane currents at 37°C with an EPC-8 patch-clamp amplifier (HEKA, Lambrecht, Germany). Pipette resistance ranged from 2.5 to 4 MΩ when filled with the pipette solutions described in the following text. The series resistance was electronically compensated for at 70% to 85%. The extracellular solution contained (mmol/l): 140 NaCl, 0.33 NaH_2PO_4, 5.4 KCl, 1.8 $CaCl_2$, 0.5 $MgCl_2$, 5.5 glucose, and 5 HEPES, and the pH was adjusted to 7.4 with NaOH. The internal (pipette) solution contained (mmol/l): 70 potassium aspartate, 70 KOH, 40 KCl, 10 KH_2PO_4, 1 Mg_2SO_4, 3 Na_2-ATP, 0.1 Li_2-GTP, 5 EGTA, and 5 HEPES, and the pH was adjusted to 7.2 with KOH.

KCNQ1/KCNE1-encoded currents were measured by depolarizing pulses from a holding potential of −90 mV to test potentials between −70 and +50 mV (with a 10-mV step increment), before being repolarized to −50 mV in