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Abstract: Abstract
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Comparison of Three-Year Clinical Outcomes after Sirolimus-eluting Stent Implantation among Insulin-treated Diabetic, Non-insulin-treated Diabetic and Non-diabetic Patients From the j-Cypher Registry

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Running head: Sirolimus-eluting stent in diabetic patients.

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Abstract

The purpose of this study was to evaluate 3-year clinical outcomes following percutaneous coronary intervention with sirolimus-eluting stents (SES) in insulin-treated diabetic (DM-insulin) patients and non-insulin-treated diabetic (DM-non-insulin) patients compared with non-diabetic (non-DM) patients. Among 10778 consecutive patients treated exclusively with SES in the j-Cypher registry, we identified 996 DM-insulin patients, 3404 DM-non-insulin patients, and 6378 non-DM patients. As compared with the non-DM group, the adjusted risk for serious cardiovascular event (composite of all-cause death, myocardial infarction, and stroke) was significantly higher in the DM-insulin group (hazard ratio (HR): 1.12, 95% confidence interval (CI): 1.03 to 1.23; p=0.01), but not in the DM-non-insulin group (HR: 1.02, 95% CI: 00.96 to 1.09; p=0.47). The adjusted risk for target lesion revascularization (TLR) was significantly higher both in the DM-insulin group (odds ratio (OR): 1.52, 95% CI: 1.19 to 1.92; p=0.0006), and in the DM-non-insulin group (OR: 1.24, 95% CI: 1.05 to 1.45; p=0.009). In conclusion, there was diabetes-associated excess risk of TLR regardless of insulin use in this large, real world study in Japanese patients with SES implantation. However, regarding serious cardiovascular events, an excess risk was seen only in the DM-insulin group. The risk for serious cardiovascular events was similar between DM-non-insulin and non-DM patients.

Keywords: Diabetes mellitus, Insulin, Percutaneous coronary intervention

TEXT

The present study evaluates the impact of insulin-treated and non-insulin-treated diabetes mellitus (DM) on the incidences of serious cardiovascular events and repeated coronary revascularization following sirolimus-eluting stent (SES) implantation. We evaluated 3-year clinical outcomes of both insulin-treated and non-insulin-treated diabetic patients relative to non-diabetic patients in a large cohort of patients who underwent percutaneous coronary intervention (PCI) using SES in the real world clinical practice in Japan.

Methods

The design and patient enrollment of the j-Cypher registry has been published previously(1). In brief, the j-Cypher registry is a physician-initiated prospective, multicenter prospective cohort study in Japan enrolling consecutive patients who underwent SES implantation at 37 centers in Japan (Supplemental Appendix A). Institutional review boards at all 37 participating centers approved this study. Written informed consent was obtained from all patients.

After SES implantation, dual antiplatelet treatment with aspirin plus thienopyridine derivative (ticlopidine 200 mg/day or clopidogrel 75mg/day) was to be maintained for at least 3 months. Thereafter, the decision regarding the duration of dual antiplatelet therapy was left to the discretion of each attending physician. Life-long use of aspirin was recommended after the procedure.

Although data entry was basically left to the individual sites, the clinical research coordinators (Supplemental Appendix B) in the data management center (Kyoto University Hospital, Department of

Cardiology) supported data entry when necessary. Logical inconsistencies were resolved by inquiries to the site investigators and/or by audits against the original data sources. Follow-up data were obtained from hospital charts or by contacting patients or referring physicians at 30 days, 6 months, and 1 year after the procedure, and yearly thereafter. When death, myocardial infarction, and stent thrombosis were reported, the events were adjudicated using the original source documents by a clinical events committee (Supplemental Appendix C). Adjudication of target lesion revascularization (TLR) events was left to the judgment of the local investigators.

Between August 2004 and November 2006, 12824 patients (19675 lesions) were enrolled in the j-Cypher registry, and 10778 patients (14811 lesions) who were treated exclusively with sirolimus-eluting stent (SES) constituted the study population for the present analysis. There were 4400 diabetic patients and 6378 non-diabetic patients (non-DM). The diabetic patients were stratified to 3404 patients without insulin therapy (DM-non-insulin) and 996 patients treated with insulin (DM-insulin) (Figure 1). Among 3404 DM-non-insulin patients, 2330 patients were treated with oral glucose-lowering drugs and remaining 1074 patients were managed without pharmacologic treatment. In this post-hoc subanalysis of the j-Cypher registry, baseline characteristics, and clinical outcomes in the DM-insulin group and in the DM-non-insulin group were compared with those in the non-DM group. The primary outcome measure for the current analysis was serious cardiac events (a composite of all-cause death, myocardial infarction and stroke) assessed at 3 years after SES implantation. The

secondary outcome measure included the individual components of the primary outcome events, definite stent thrombosis, target lesion revascularization (TLR), non-TLR, and any coronary revascularization.

Diabetes mellitus was defined as fasting plasma glucose level ≥ 126 mg/dl, glucose level >200mg/dl 2 hour after 75g oral glucose tolerance test, casual plasma glucose level >200mg/dl or use of anti-diabetic medications. Diagnosis of diabetes and use of insulin at the time of the index sirolimus-eluting stent (SES) implantation were reported by the site investigators.

Death was regarded as *cardiac in origin* unless obvious non-cardiac causes could be identified. Any death during the index hospitalization was regarded as cardiac death. *Sudden death* was defined as unexplained death in previously stable patients. *Myocardial infarction* was adjudicated according to the definition in the Arterial Revascularization Therapy Study(2). Within 1 week of index procedure, only Q-wave myocardial infarction was adjudicated as myocardial infarction. *TLR* was defined as either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) due to restenosis or thrombosis of the target lesion, including the proximal and distal edge segments as well as the ostium of the side-branches. *Non-TLR* was defined as coronary revascularization procedures, either PCI or CABG, other than TLR. Stent thrombosis was defined according to Academic Research Consortium definition(3). Unless otherwise noted, definite stent thrombosis assessed on a patient-level basis was used as the endpoint for stent thrombosis.

Continuous variables are presented with mean ± standard deviation, and categorical variables are expressed as number and percentages. Categorical variables were compared with the Chi-square test. Continuous variables were compared with the *t* test or Wilcoxon rank-sum test based on the distribution. Incidences of the primary and secondary outcome measures were estimated by the Kaplan-Meier method and differences were assessed with the log-rank test.

Adjusted risks of DM-insulin versus non-DM and DM-non-insulin compared to non-DM for the primary outcome measure were estimated by multivariable Cox proportional hazard model by incorporating variable DM-insulin or DM-non-insulin into multivariable models with 23 risk-adjustment variables listed in supplemental table 1 and 2. Continuous risk-adjustment variables were dichotomized according to the clinically meaningful reference values. The results were expressed as adjusted hazard ratios and their 95% confidence intervals. For the evaluation of adjusted risk for target lesion revascularization (TLR), a multivariable logistic regression model instead of Cox proportional hazard model was used, because restenosis has been well known to be a time-related phenomenon and also the timing of TLR could be highly influenced by physicians' and patients' decision. By using logistic regression model, we could minimize the influence of the timing of TLR on the adjusted analysis for TLR(4). Patients included in the multivariable logistic regression model were 1882 patients with TLR within 3 years and 2415 patients who completed 3-year follow-up without TLR. Same independent variables used in the Cox proportional hazard model were incorporated in the multivariable logistic

regression model. The results were expressed as adjusted odds ratio and their 95% confidence intervals. All analyses were conducted using JMP Version 7.1 (SAS Institute Inc., Cary, North Carolina). All reported p-values were 2-sided and p-values less than 0.05 were considered significant.

Results

As compared with non-DM patients, both DM-insulin and DM-non-insulin patients were younger, had higher body mass index, and more often had hypertension, end-stage renal disease including hemodialysis, heart failure, prior stroke, multi-vessel disease, and prior coronary revascularization procedures. Furthermore, DM-insulin patients were more often women, more often had peripheral vascular disease, and less often had smoking habit and acute coronary syndrome as compared with non-DM patients (Table 1).

Both DM-insulin and DM-non-insulin patients, as compared with non-DM patients, had more complex lesion and procedural characteristics such as long lesions, small vessel size, severe calcification, longer total stent length and higher final inflation pressure.

Cumulative incidences of clinical events through 3 years are listed in Table 2. Crude incidence of serious cardiovascular events (all-cause death, myocardial infarction and stroke) was significantly higher in the DM-insulin group than that in the non-DM group. However, although the cumulative incidence of serious cardiovascular events in the DM-non-insulin group tended to be higher than that in the non-DM group, the difference did not reach statistical significance (Figure 2). After adjusting the confounders with multivariable

Cox proportional hazard model, the risk of DM-insulin versus non-DM for serious cardiovascular events remained significant (hazard ratio: 1.12, 95% confidence intervals: 1.03 to 1.23; p = 0.01). However, after adjusting confounders, there was no more a trend for the excess risk of DM-non-insulin versus non-DM for serious cardiovascular events (hazard ratio 1.02, 95% confidence intervals: 0.96 to 1.09; p = 0.47) (Supplemental table 1).

Crude incidence of all-cause death was markedly higher in the DM-insulin-group and significantly higher in the DM-non-insulin group than that in the non-DM group. The incidence of stroke was significantly higher in the DM-insulin group than that in the non-DM group, while the incidence of stroke was not different between the DM-non-insulin group and the non-DM group. The incidences of myocardial infarction and stent thrombosis were not different among the 3 groups (Table 2 and Figure 3).

Crude incidences of target lesion revascularization (TLR) in the DM-insulin-group and in the DM-non-insulin group were significantly higher than that in the non-DM group (Figure 4(A)). After adjusting confounders by multivariable logistic regression analysis, the risks of both DM-insulin versus non-DM and DM-non-insulin versus non-DM for TLR remained significant (odds ratio: 1.52, 95% confidence intervals: 1.19 to 1.92; p = 0.0006, and odds ratio: 1.24, 95% confidence intervals: 1.05 to 1.45; p= 0.009, respectively) (Supplemental table 2).

Crude incidences of non-target lesion revascularization (TLR) and any coronary revascularization in the DM-insulin-group and in the DM-non-insulin group were also significantly higher than that in the non-DM group (Table 2 and Figure 4(B)).

Discussion

The major findings of the current analysis are as follows: (1) Insulin-treated diabetic patients as compared with non-diabetic patients had significantly higher adjusted risk for the serious cardiovascular events such as death, myocardial infarction, and stroke during 3 years after sirolimus-eluting stent (SES) implantation; (2) The risk of non-insulin-treated diabetic patients for the serious cardiovascular events was not different from the risk of non-diabetic patients; and (3) Both insulin-treated and non-insulin-treated diabetic patients had significantly higher risk for TLR than non-diabetic patients.

Although insulin-treated diabetic patients has been known to be associated with worse outcome as compared with non-insulin-treated diabetic patients, the risk of non-insulin-treated diabetic patients relative to non-diabetic patients for adverse cardiovascular events after percutaneous coronary intervention (PCI) has not been adequately evaluated and there is only a few studies including small number of diabetic patients(5-7). In the current analysis encompassing large number of diabetic patients, both insulin-treated and non-insulin-treated diabetic patients had more co-morbidities such as renal failure, stroke, and heart failure than non-diabetic

patients. Also, triple vessel disease was more prevalent in both insulin-treated and non-insulin-treated diabetic patients than in non-diabetic patients. Insulin-treated diabetic patients had significantly higher risk for serious cardiovascular events, even after adjusting these confounding factors. However, the risk for serious cardiovascular events was similar between non-insulin-treated diabetic patients and non-diabetic patients. It was noteworthy that there were absolutely no differences in the incidences of myocardial infarction and stroke between non-insulin-treated diabetic patients and non-diabetic patients (Figure 3(B)(C)). This finding seemed to be in contradiction to the observations suggesting that non-insulin-treated diabetic patients without known cardiovascular disease had higher risk for future cardiovascular events than non-diabetic patients(8). Patients with cardiovascular disease without a previous diagnosis of diabetes were reported to have very high (60-66%) prevalence of diabetes or impaired glucose tolerance when oral glucose tolerance test was conducted(8, 9). The potential differences in the incidences of serious cardiovascular events between non-insulin-treated diabetic patients and non-diabetic patients might have been diluted by the presence of patients with undiagnosed diabetes or impaired glucose tolerance in patients included in the non-diabetic group. Additionally, the good prognosis of non-insulin-treated diabetic patients in the current study might reflect the generally low cardiovascular event rates among Japanese diabetic patients. Lesser degree of hyperinsulinemia and insulin resistance of Japanese diabetic patients as compared with diabetic patients in United States and Europe might be related to low cardiovascular event rates among Japanese diabetic patients(10-12).

The observation that the risk for serious cardiovascular events was similar between non-insulin-treated diabetic patients and non-diabetic patients might have some clinical implication in selecting coronary revascularization strategy in diabetic patients. Although a meta-analysis of randomized controlled trials comparing coronary artery bypass grafting (CABG) with percutaneous coronary intervention (PCI) before drug-eluting stent era suggested higher mortality in the PCI group in diabetic patients, non-insulin-treated and insulin-treated diabetic patients were not discriminated in any of these trials(13). Considering the equivalent clinical outcome in terms of serious cardiovascular events between non-insulin-treated diabetic patients and non-diabetic patients, it might be important to discriminate non-insulin-treated and insulin-treated diabetic patients in the comparison between PCI and CABG.

Although insulin-treated diabetic patients had worse outcome even after adjusting co-morbidities in the current study, relationship between insulin use and vascular events is debatable. Previous epidemiological studies demonstrated the increased cardiovascular risk with higher serum insulin levels(14-16). This might suggest that insulin use was causally related to the higher rate of cardiovascular events. On the other hand, the Diabetes Control and Complications Trial and the subsequent Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) illustrated that intensive insulin therapy in type 1 diabetic patients reduced the risk of any cardiovascular disease by 42% and the risk of non-fatal myocardial infarction, stroke, or cardiovascular death by 57%(17). Patients with insulin producing neoplasm do not have an increase in clinically overt

atherosclerotic disease(18). Because insulin has both proatherogenic and antiatherogenic properties, insulin therapy may differentially modify risk of cardiovascular events depending on the presence of insulin resistance and hyperinsulinemia(19, 20).

Regarding target lesion revascularization (TLR) after sirolimus-eluting stent (SES) implantation, both insulin-treated diabetic and non-insulin-treated patients had significantly higher risk than non-diabetic patients. Diabetic patients are known to have smaller vessel size, longer lesion length, greater atherosclerotic burden and heavier calcification as compared with non-diabetic patients. Although these anatomic characteristics of diabetic patients predispose to restenosis, the higher risk of insulin-treated and non-insulin-treated diabetic patients relative to non-diabetic patients for TLR remained highly significant even after adjusting anatomical confounders such as multi-vessel disease, reference diameter, and total stent length. This finding might suggest that insulin resistance and resultant hyperinsulinemia played an important role in augmenting neo-intimal proliferation after SES implantation. Indeed, insulin stimulates vascular smooth muscle cell proliferation both directly and by enhancing the effects of other mitogens(21). Although drug-eluting stents reduced restenosis rate and TLR rate in diabetic patients in the same magnitude as in non-diabetic patients, absolute rates of restenosis and TLR in diabetic patients, particularly in insulin-treated diabetic patients, still remained far from satisfactory, highlighting the need for development of drug-eluting stent with more potent anti-restenosis efficacy.

Both insulin-treated and non-insulin-treated diabetic patients also had significantly higher risk for non-target lesion revascularization (TLR) than non-diabetic patients, suggesting more aggressive atherosclerotic progression in the coronary artery territories other than the target stented-area in diabetic patients. It is intriguing why this more aggressive atherosclerotic progression did not lead to higher incidence of serious cardiovascular events in non-insulin-treated diabetic patients relative to non-diabetic patients.

Although diabetes has been shown to be an independent predictor of stent thrombosis in patients treated with drug-eluting stent in the previous studies(3, 22, 23), the rates of stent thrombosis were very low in all 3 groups in our study and we did not observe increased risk of stent thrombosis in insulin-treated and non-insulin-treated diabetic patients. However, owing to the small number of stent thrombosis events, this finding should be interpreted with caution.

There were several important limitations to interpret the results of this study. First, we did not have detailed information on the status of diabetes. The proportion of patients with type 1 and type 2 diabetes was not recorded, nor were the glycosylated hemoglobin values. Second, although we made extensive statistical adjustment, there might still be unmeasured confounding factors. Third, we could not discriminate between clinically-driven and angiography-driven TLR. Japanese practice of routine follow-up angiography after percutaneous coronary intervention (PCI) might have exaggerated the differences in TLR among insulin-treated diabetic patients, non-insulin-treated diabetic patients, and non-diabetic patients.

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Figure legends

Figure 1.

Title: Study Flow Chart

Caption: BMS = bare metal stent, DES = drug-eluting stent, DM = diabetes mellitus, SES = sirolimus-eluting stent

Figure 2.

Title: Cumulative Incidence of Death/MI/Stroke: DM-insulin vs. non-DM and DM-non-insulin vs. non-DM

Caption: DM = diabetes mellitus, MI = myocardial infarction, SES = sirolimus-eluting stent

Figure 3.

Title: Cumulative Incidence of Death (A), Stroke (B), MI (C) and ST (D): DM-insulin vs. non-DM and DM-non-insulin vs. non-DM

Caption: DM = diabetes mellitus, MI = myocardial infarction, SES = sirolimus-eluting stent, ST = stent thrombosis

Figure 4.

Title: Cumulative Incidence of TLR (A) and non-TLR (B): DM-insulin vs. non-DM and DM-non-insulin vs. non-DM

Caption: DM = diabetes mellitus, SES = sirolimus-eluting stent, TLR = target lesion revascularization

Table(s)

Table 1. Baseline Characteristics

	non-DM	DM-non-insulin	p value*	DM-insulin	p value*
Characteristics					
No. of patients	6378	3404		996	
Age (years)	68.8 ± 10.6	67.9 ± 9.4	<0.0001	66.7 ± 9.4	<0.0001
Age > 80 years	952, (15%)	347, (10%)	<0.0001	63, (6%)	<0.0001
Men	4867, (76%)	2585, (76%)	0.68	671, (67%)	<0.0001
Body mass Index (%)	23.7 ± 4.0	24.3 ± 3.7	<0.0001	24.1 ± 3.4	0.0007
Hypertension	4670, (73%)	2638, (78%)	<0.0001	761, (76%)	0.03
Current smoking	1265, (20%)	696, (21%)	0.47	158, (16%)	0.003
eGFR < 30ml /min/1.73m^2					
without hemodialysis	229, (3.7%)	192, (6.0%)	<0.0001	101, (12%)	<0.0001
with hemodialysis	238, (3.7%)	191, (5.6%)	<0.0001	165, (17%)	<0.0001
Peripheral vascular disease	697, (11%)	409, (12%)	0.11	170, (17%)	<0.0001
Prior myocardial infarction	1713, (27%)	1026, (30%)	0.0006	285, (29%)	0.25
Prior stroke	523, (8.2%)	354, (10%)	0.0003	130, (13%)	<0.0001
Prior PCI	2962, (46%)	1704, (50%)	0.0006	513, (52%)	0.003
Prior coronary artery bypass grafting	401, (6.3%)	274, (8.1%)	0.001	112, (11%)	<0.0001
Heart failure	718, (11%)	511, (15%)	<0.0001	231, (23%)	<0.0001
Acute coronary syndrome	1403, (25%)	734, (22%)	0.62	171, (17%)	0.0004
STEMI	455, (7.1%)	225, (6.6%)	0.33	53, (5.3%)	0.03
Multivessel disease	2911, (46%)	1884, (55%)	<0.0001	597, (60%)	<0.0001
Triple-vessel disease	594, (9.3%)	498, (15%)	<0.0001	164, (17%)	<0.0001
Unprotected Left main	356, (5.6%)	206, (6.1%)	0.34	73, (7.3%)	0.03
No. of lesions treated	1.34 ± 0.63	1.40 ± 0.68	<0.0001	1.47 ± 0.76	<0.0001
Total No. of stents	1.69 ± 0.98	1.81 ± 1.06	<0.0001	1.95 ± 1.21	<0.0001
Total length of stents, (mm)	37.3 ± 24.3	40.5 ± 26.4	<0.0001	43.9 ± 29.6	<0.0001
Treatment of DM					
Oral hypoglycemic agent	-	2330, (69 %)		92, (9%)	
Insulin dependent DM	-	-		996, (100%)	
Baseline medications					

Cilostazol	207, (3.3%)	100, (3.0%)	0.43	44, (4.5%)	0.07
Statins	3057, (48%)	1687, (50%)	0.08	474, (48%)	0.87
ACE inhibitors	965, (15%)	597, (18%)	0.002	169, (17%)	0.14
ARBs	2283, (36%)	1336, (40%)	0.0004	407, (41%)	0.002
Beta blockers	1692, (27%)	1012, (30%)	0.0004	304, (31%)	0.009
Lesion Characteristics					
No. of lesions	8574	4774		1463	
Target Lesion location			<0.0001		<0.0001
Left anterior descending	3673, (43%)	1944, (41%)		521, (36%)	
Left circumflex	1801, (21%)	1010, (21%)		319, (22%)	
Right	2758, (32%)	1610, (34%)		545, (37%)	
Left main	278, (3.2%)	160, (3.4%)		61, (4.2%)	
Saphenous vein graft	51, (0.6%)	43, (0.9%)		15, (1.0%)	
Lesion length >= 30mm	1135, (13%)	741, (16%)	0.0004	270, (19%)	0.0001
Reference diameter < 2.5mm	2268, (27%)	1438, (30%)	<0.0001	490, (34%)	<0.0001
In-stent restenosis	1074, (13%)	625, (13%)	0.36	196, (13%)	0.36
Chronic total occlusion	734, (8.6%)	478, (10%)	0.006	136, (9.3%)	0.36
Severe calcium	656, (7.7%)	454, (9.5%)	0.0002	201, (14%)	0.0001
Bifurcation lesion	1743, (20%)	848, (18%)	0.0003	266, (18%)	0.054
Total stent length per lesion (mm)	28.1 ± 14.8	29.2 ± 15.8	<0.0001	30.3 ± 16.5	0.0001
Minimal stent size (mm)	2.91 ± 0.37	2.87 ± 0.37	<0.0001	2.83 ± 0.36	0.0001
Post dilatation	3755, (44%)	2048, (43%)	0.29	688, (48%)	0.01
Maximum inflation pressure (atm)	17.9 ± 4.4	18.3 ± 4.2	0.006	18.6 ± 4.4	0.0004

All data are number unless otherwise indicated. Continuous variables were expressed as mean value ± standard deviation. * p value : vs. non-DM.

ACE inhibitors = angiotensin-converting enzyme inhibitors, ARBs = angiotensin receptor blockers, CABG = coronary artery bypass grafting, DM = diabetes mellitus, eGFR = estimated glomerular filtration rate, PCI = percutaneous coronary intervention and STEMI= ST-segment

elevation myocardial infarction.

Table(s)

Table 2. Clinical Event Rates Through 3 years

	non-DM	DM-non-insulin		DM-insulin	
	n = 6378	n = 3404	p value*	n = 996	p value*
Death/MI/Stroke	649, (12.7%)	392, (13.8%)	0.057	185, (22.3%)	<0.0001
All-cause Death	412, (8.2%)	267, (9.3 %)	0.01	132, (16.2%)	<0.0001
Cardiac Death	203, (3.8%)	135, (4.6%)	0.046	62, (8.1%)	<0.0001
associated with Heart Failure	58, (1.1%)	44, (1.5%)	0.08	19, (2.7%)	0.003
associated with Myocardial Infarction	17, (0.3%)	19, (0.7%)	0.02	6, (0.6%)	0.07
Sudden Death	76, (1.5%)	39, (1.4%)	0.85	25, (3.5%)	0.0007
Myocardial infarction	124, (2.7%)	61, (2.5%)	0.57	26, (2.9%)	0.14
Stroke	193, (3.7%)	110, (4.0%)	0.57	51, (6.6%)	<0.0001
Stent Thrombosis: definite	57, (1.2%)	32, (1.2 %)	0.84	12, (1.3%)	0.33
definite/probable	65, (1.4%)	38, (1.4%)	0.67	13, (1.4%)	0.39
definite/probable/possible	153, (3.1%)	84, (3.1%)	0.84	41, (5.1%)	0.001
Target lesion revascularization	535, (10.2%)	394, (13.8%)	<0.0001	168, (19.3%)	<0.0001
Coronary artery bypass graft	85, (1.8%)	57, (2.0%)	0.17	19, (2.4%)	0.13
Non-target lesion revascularization	1199, (22.1%)	815, (28.1%)	<0.0001	274, (32.8%)	<0.0001
Any Revascularization	1481, (27.2%)	999, (34.0%)	<0.0001	346, (40.1%)	<0.0001

All data are number unless otherwise indicated. * p value : vs. non-DM

DM = diabetes mellitus, MI = myocardial infarction,

Figure(s)
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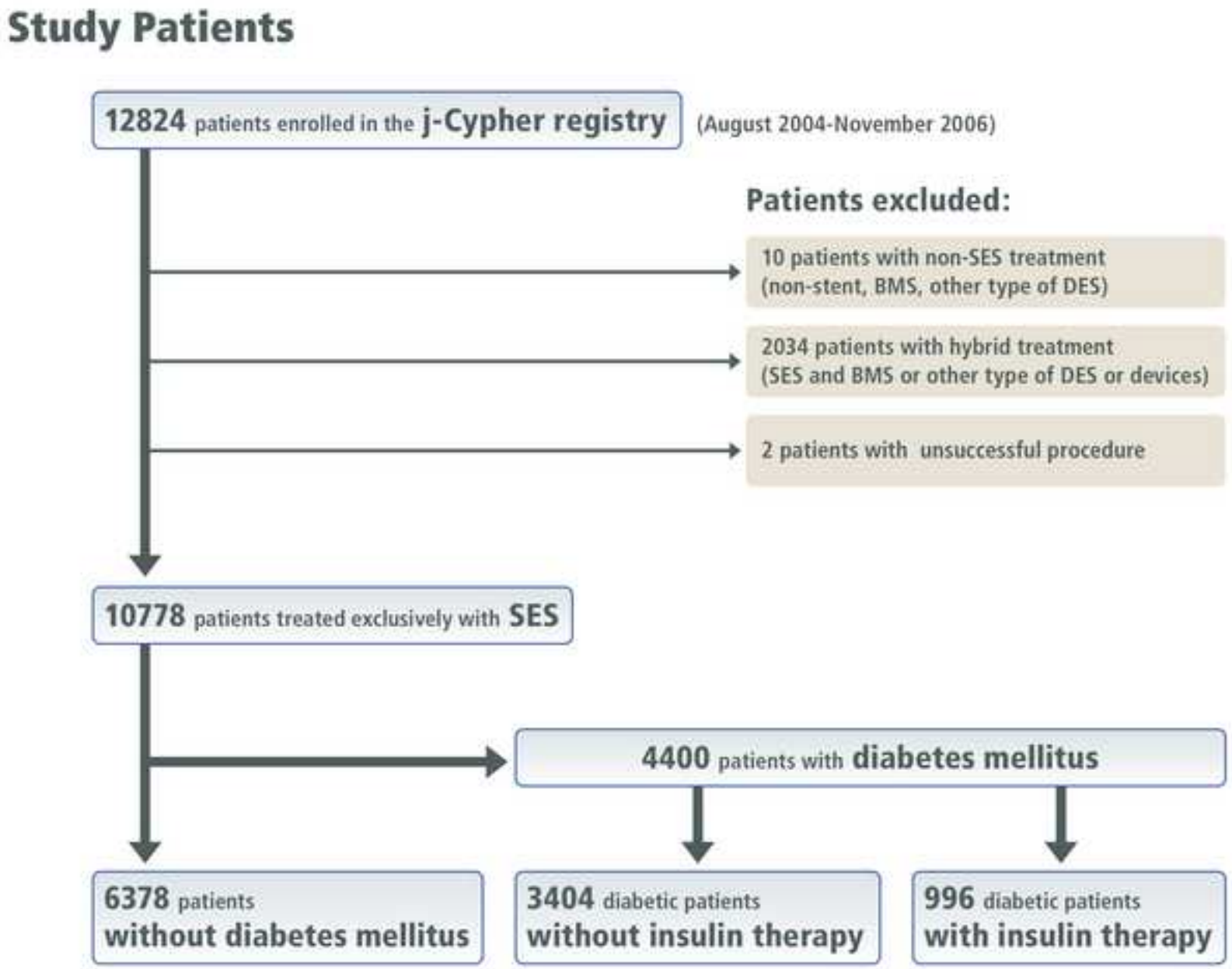

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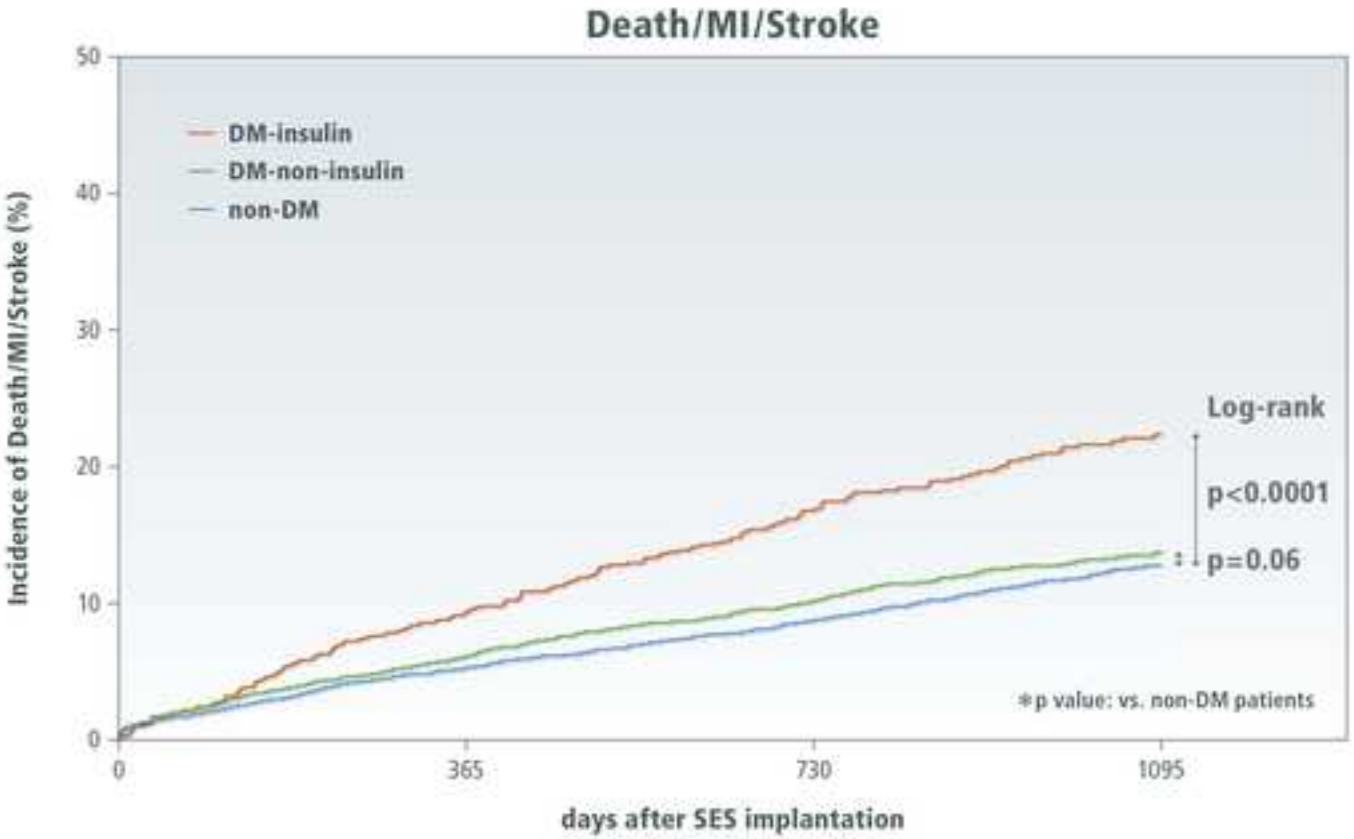

Days		0	30	365	730	1095
DM-insulin	at risk	996	984	873	636	312
cumulative incidence	n, %	0%	11, 1.1%	92, 9.4%	154, 16.8%	185, 22.3%
DM-non-insulin	at risk	3404	3348	3088	2361	1135
cumulative incidence	n, %	0%	45, 1.3%	206, 6.1%	322, 10.1%	382, 13.8%
non-DM	at risk	6378	6271	5863	4442	1977
cumulative incidence	n, %	0%	84, 1.3%	331, 5.3%	516, 8.7%	649, 12.7%

Figure(s)

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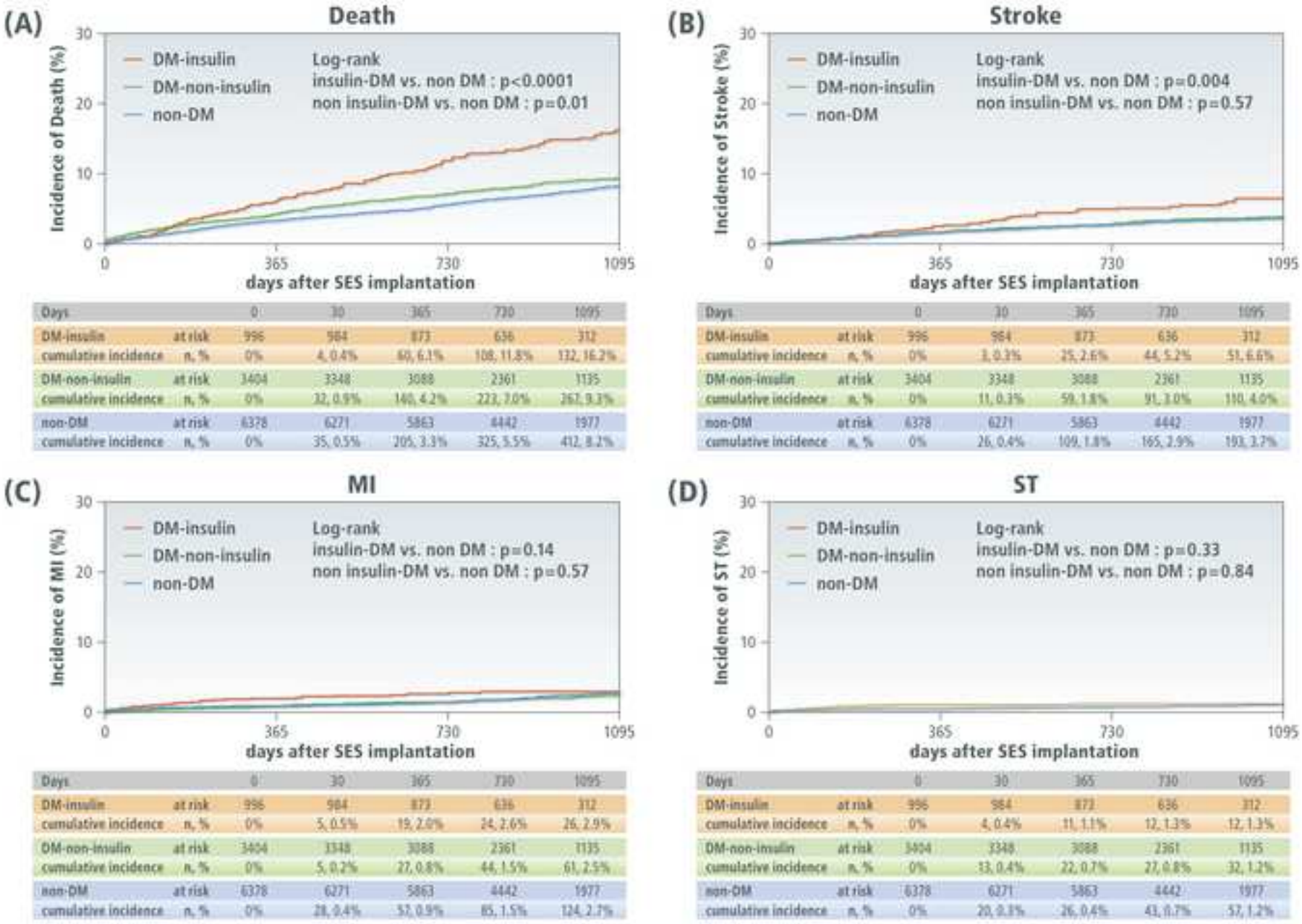

Days		0	30	365	730	1095
DM-insulin	at risk	996	984	873	636	312
cumulative incidence	n, %	0%	4, 0.4%	60, 6.1%	108, 11.8%	132, 16.2%
DM-non-insulin	at risk	3404	3348	3088	2361	1135
cumulative incidence	n, %	0%	32, 0.9%	140, 4.2%	223, 7.0%	267, 9.3%
non-DM	at risk	6378	6271	5863	4442	1977
cumulative incidence	n, %	0%	35, 0.5%	205, 3.3%	325, 5.5%	412, 8.2%

Days		0	30	365	730	1095
DM-insulin	at risk	996	984	873	636	312
cumulative incidence	n, %	0%	3, 0.3%	25, 2.6%	44, 5.2%	51, 6.6%
DM-non-insulin	at risk	3404	3348	3088	2361	1135
cumulative incidence	n, %	0%	11, 0.3%	59, 1.8%	91, 3.0%	110, 4.0%
non-DM	at risk	6378	6271	5863	4442	1977
cumulative incidence	n, %	0%	26, 0.4%	109, 1.8%	165, 2.9%	193, 3.2%

Days		0	30	365	730	1095
DM-insulin	at risk	996	984	873	636	312
cumulative incidence	n, %	0%	5, 0.5%	19, 2.0%	24, 2.6%	26, 2.9%
DM-non-insulin	at risk	3404	3348	3088	2361	1135
cumulative incidence	n, %	0%	5, 0.2%	27, 0.8%	44, 1.5%	61, 2.5%
non-DM	at risk	6378	6271	5863	4442	1977
cumulative incidence	n, %	0%	28, 0.4%	57, 0.9%	85, 1.5%	124, 2.2%

Days		0	30	365	730	1095
DM-insulin	at risk	996	984	873	636	312
cumulative incidence	n, %	0%	4, 0.4%	11, 1.1%	12, 1.3%	12, 1.3%
DM-non-insulin	at risk	3404	3348	3088	2361	1135
cumulative incidence	n, %	0%	13, 0.4%	22, 0.7%	27, 0.8%	32, 1.2%
non-DM	at risk	6378	6271	5863	4442	1977
cumulative incidence	n, %	0%	20, 0.3%	26, 0.4%	43, 0.7%	57, 1.2%

Figure(s)

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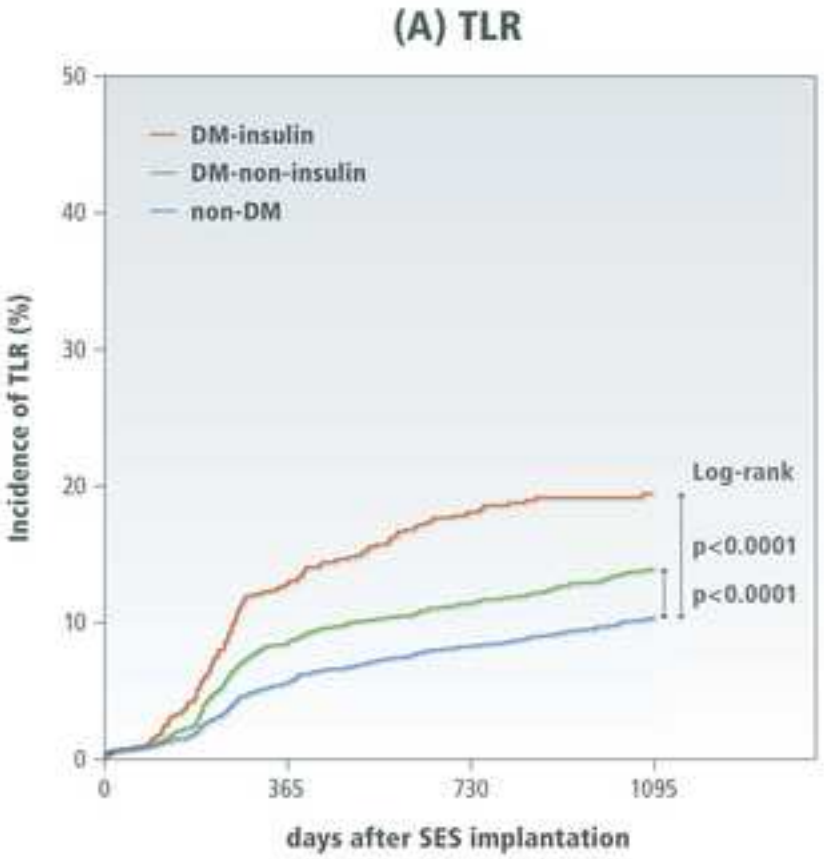

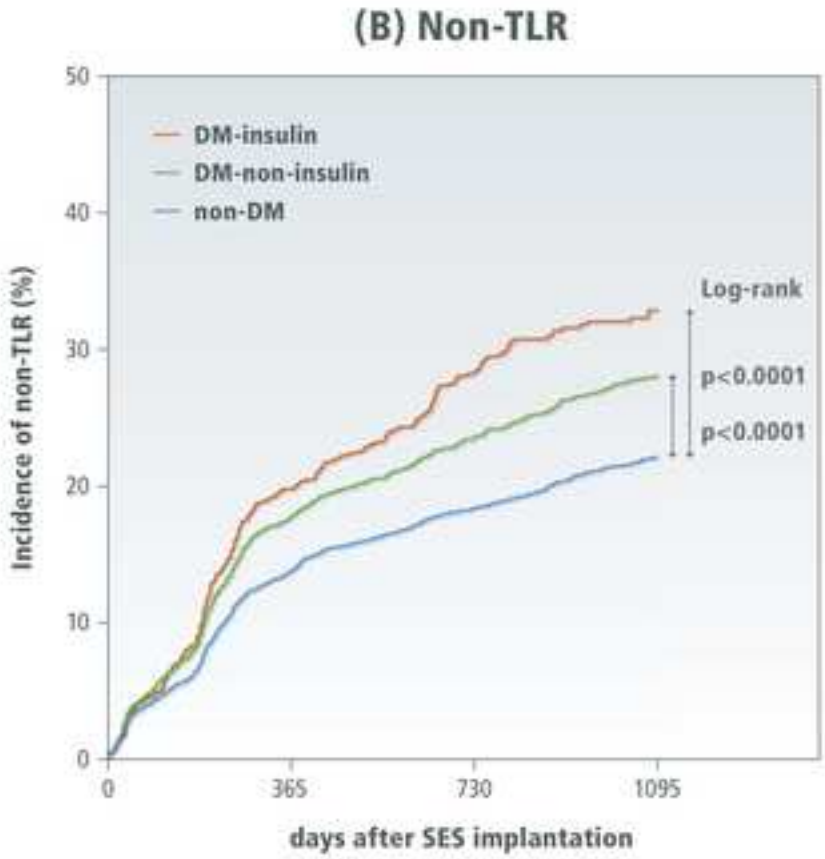

Days		0	30	365	730	1095
DM-insulin	at risk	996	984	873	636	312
cumulative incidence	n, %	0%	6, 0.6%	121, 12.8%	161, 18.0%	168, 19.2%
DM-non-insulin	at risk	3404	3348	3088	2361	1135
cumulative incidence	n, %	0%	16, 0.5%	273, 8.4%	352, 11.3%	394, 13.8%
non-DM	at risk	6378	6271	5863	4442	1977
cumulative incidence	n, %	0%	30, 0.5%	330, 5.4%	471, 8.1%	535, 10.2%

Days		0	30	365	730	1095
DM-insulin	at risk	996	984	873	636	312
cumulative incidence	n, %	0%	16, 1.6%	187, 19.7%	251, 28.2%	274, 32.8%
DM-non-insulin	at risk	3404	3348	3088	2361	1135
cumulative incidence	n, %	0%	72, 2.1%	577, 17.7%	736, 23.5%	815, 28.1%
non-DM	at risk	6378	6271	5863	4442	1977
cumulative incidence	n, %	0%	135, 2.1%	843, 13.6%	1080, 18.2%	1199, 22.1%