Impact of Simultaneous Pancreas and Kidney Transplantation on Progression of Coronary Atherosclerosis in Patients With End-Stage Renal Failure due to Type 1 Diabetes

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OBJECTIVE — Mortality in type 1 diabetic patients with end-stage renal failure is high and dominated by coronary atherosclerotic events. With regard to prognosis, simultaneous transplantation of pancreas and kidney (SPK) may be superior to kidney transplantation alone (KTA) in type 1 diabetic patients, because normalization of blood glucose levels may reduce progression of coronary atherosclerosis and because it is well known that progression of coronary atherosclerosis is one of the major factors that determines clinical prognosis. However, no data are available on progression of coronary atherosclerosis after SPK.

RESEARCH DESIGN AND METHODS — We performed an observational angiographic study comparing progression of coronary atherosclerosis, analyzed with quantitative coronary angiography, in patients with (n = 26) and those without (n = 6) a functioning pancreas graft after SPK, to test the hypothesis that normalization of blood glucose levels by SPK may indeed reduce progression of coronary atherosclerosis in type 1 diabetic patients and thereby improve prognosis.

RESULTS — Mean follow-up was 3.9 years. Average glucose control was significantly worse for the patients without a pancreas graft than for patients with a functioning pancreas graft: 11.3 (SD 3.5) vs. 5.9 mmol/l (SD 1.1) (P = 0.03). Mean segment diameter loss (progression of diffuse coronary atherosclerosis) was 0.024 mm/year (SD 0.067) in patients with a functioning pancreas graft, compared with 0.044 mm/year (SD 0.038) in patients in whom the pancreas graft was lost. Minimum obstruction diameter loss (progression of focal coronary atherosclerosis) was 0.037 mm/year (SD 0.086) in patients with a functioning pancreas graft compared with 0.061 mm/year (SD 0.038) in patients in whom the pancreas graft was lost. Regression of atherosclerosis occurred in 38% of patients with a functioning pancreas graft compared with 0% of patients of whom the pancreas graft was lost (P = 0.035).

CONCLUSIONS — Our study provides, for the first time, evidence that in patients who have undergone SPK, progression of coronary atherosclerosis in patients with a functioning pancreas graft is reduced compared with patients with pancreas graft failure. Our observation is an important part of the explanation for the observed improved mortality rates reported in type 1 diabetic patients with end-stage renal failure after SPK compared with KTA. In light of these findings described above, SPK must to be carefully considered for all diabetic transplant candidates.

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Diabetes is an increasing worldwide health problem that often leads to severe medical and psychosocial problems, including blindness, kidney failure, amputation, and death (1). Mortality in type 1 diabetic patients with end-stage renal failure is high and dominated by coronary artery disease events (2). Although the possibilities of training and treating particularly young motivated patients with type 1 diabetes are numerous and nowadays rather sophisticated, none are able to normalize the metabolism of people who have been diabetic for years or even decades (3,4).

Simultaneous transplantation of pancreas and kidney (SPK) may be superior to kidney transplantation alone (KTA) in type 1 diabetic patients (5,6), because normalization of blood glucose levels might reduce progression of coronary atherosclerosis and because it is well known that progression of coronary atherosclerosis is one of the major factors that determines clinical prognosis (7–9). However, no data are available on progression of coronary atherosclerosis after SPK.

Because a randomized study comparing SPK with KTA to assess progression of coronary atherosclerosis is not ethically and practically feasible, we performed a well-controlled prospective observational angiographic study, comparing progression of coronary atherosclerosis in patients with and without a functioning

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Abbreviations: CAG, coronary arteriography; KTA, kidney transplantation alone; MOD, minimum obstruction diameter; MSD, mean segment diameter; PTCA, percutaneous transluminal coronary angioplasty; QCA, quantitative coronary arteriography; SPK, simultaneous transplantation of pancreas and kidney.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

pancreas graft (defined as need to reinstitute insulin therapy) after SPK, to evaluate the hypothesis that normalization of blood glucose levels by SPK may indeed reduce progression of coronary atherosclerosis in type 1 diabetic patients and thereby improve prognosis.

RESEARCH DESIGN AND METHODS

Referrals for SPK

As part of a prospective study, 50 consecutive type 1 diabetic patients with end-stage renal failure were evaluated according to protocol and underwent SPK at the Leiden University Medical Center, Leiden, the Netherlands. All patients had additional secondary diabetic complications, including retinopathy and neuropathy. Preoperative workup, (surgical) procedure, transplant characteristics, as well as antibiotic and immunosuppression are described in detail elsewhere (10). The protocol was approved by the Institutional Review Board of the university. Preoperative workup also routinely included coronary arteriography (CAG) according to quantitative coronary arteriography (QCA) standards; therefore, no referral bias on the base of coronary angiography for a clinical reason is present. Patients underwent standardized follow-up CAG at least 2 years after transplantation to evaluate progression of coronary atherosclerosis. Also, clinical events (cardiac), death, myocardial infarction, revascularization procedures (percutaneous transluminal coronary angioplasty [PTCA] and coronary artery bypass grafting), and cerebrovascular events (cerebrovascular accident and transient ischemic attack) were monitored during follow-up. This report focuses on progression of coronary atherosclerosis as assessed by QCA.

QCA

For CAG and QCA analyses, the protocol of the Regression Growth Evaluation Statin Study (REGRESS) was followed (11). In brief, quality assurance of catheterization laboratory and cine films was strictly maintained (12). Only catheters approved for QCA were used (13). The distal tip of the catheter was cut off and sent to the QCA Core Laboratory (Heart Core, Leiden, the Netherlands) for measurement and was used as scaling device in the QCA analysis. Panning of the image had to be avoided as much as possible. The protocol required administration of coronary vasodilators (5–10 min before CAG, 5–10 mg isosorbide dinitrate was administered sublingually). The exact filming sequence of the initial coronary cineangiography and the precise rotational and angulational views, as well as table height, were noted. Analysis of the coronary arteriograms was performed by QCA using the QCA-CMS system (MEDIS Medical Imaging Systems, Leiden, the Netherlands). For calibration, the boundaries of a nontapering part of the catheter were determined automatically over a length of ~2 cm. To determine the contours of the vessel, the user only had to indicate the beginning and end of the coronary segment to be analyzed, after which a pathline was computed connecting these two points. The contours of the vessel were then computed in multiple iterations by the minimal cost contour detection technique.

For QCA, the coronary tree was divided into 13 segments, according to the American Heart Association classification, excluding the posterolateral branches. Obstructions within the 13 segments were coded and analyzed separately if the diameter narrowing was ≥20% at either baseline or follow-up. As a result, obstruction data were always available in paired format (baseline and follow-up), with at least one of the two severities ≥20% diameter stenosis. Baseline and follow-up coronary arteriograms of each patient were viewed simultaneously on a dual Tagarno projector (Tagarno A/S) by an experienced cardiologist blinded to pancreas graft function. The complete procedure is described in detail elsewhere (11) and has been extensively validated (12–16).

Angiographic end points

The angiographic end point was a comparison between the patients with a functioning pancreas graft and the patients without a functioning pancreas graft after initial successful SPK. Because the interval between the repeat angiographies was not fixed (range 2–5.5 years; requirement: at least 2 years) and progression is time dependent, we calculated annual rates of progression per patient. This annual-rate approach has been used and validated for other trials as well (17). The angiographic end points were defined as follows: *1*) change in average mean segment diameter (MSD) on a by patient basis per year as parameter for diffuse changes/progression of coronary atherosclerosis; and *2*) change in average minimum obstruction diameter (MOD) on a by patient basis per year as parameter for focal changes/progression of coronary atherosclerosis (Fig. 1). These definitions have been described earlier in detail and have been evaluated and validated extensively (11,14,17).

Statistical methods

Patients with or without a follow-up coronary angiogram were compared using Student's *t* tests, Mann-Whitney *U* tests, and χ^2 tests on baseline characteristics to assess whether a systematic group of patients was selected who had undergone follow-up angiography. In the group of patients with a follow-up angiogram, patients with or without pancreas loss were compared to assess baseline differences that might explain a difference in angiographic progression between these two patient groups. The difference in angiographic progression between patients with or without pancreas loss was tested using covariance analysis with baseline MSD/MOD as the covariate. Finally, this difference in angiographic progression was adjusted for confounding factors using multiple regression.

RESULTS

Follow-up CAG and clinical events

A total of 50 consecutive patients were included and prospectively followed (33 men and 17 women, mean age 38 years, mean duration of type 1 diabetes 24 years). Mean follow-up was 3.9 years. All patients had a baseline CAG; two patients were lost to follow-up. Therefore, in 48 patients (32 men and 16 women), an evaluable baseline CAG was available.

According to the protocol, i.e., before SPK and at least 2 years after SPK, 31 patients underwent follow-up CAG, on average of 3.9 years post-transplantation. No follow-up CAG was available in 17 patients: 7 due to death (4 cardiac) and 10 due to patient refusal. One additional patient lost pancreas function between the follow-up angiogram and a third angiogram, and angiographic values of this second time frame were also analyzed.

Of the 10 patients who refused to undergo follow-up CAG, seven had a func-

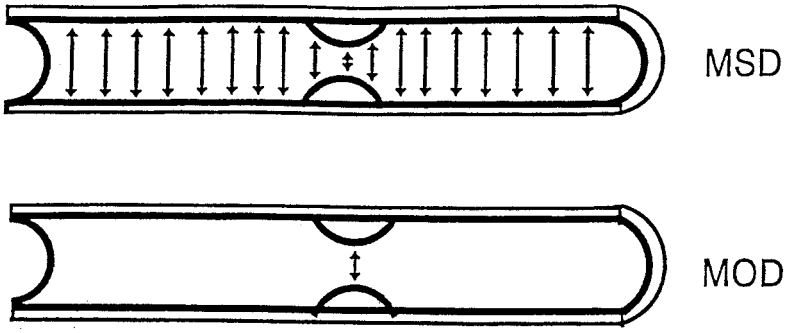

Figure 1—*Stylized diagram of vessel indicating MSD and MOD. MSD* = $\Sigma_1^N \updownarrow / N$.

tioning pancreas graft and three patients had no functioning pancreas graft.

Of the seven patients who died before follow-up CAG could be performed, five patients already had lost their pancreas graft; three of these patients died due to myocardial infarction, and the other two patients died due to infection. The two patients who died before follow-up CAG was performed and who had a functioning pancreas graft died due to myocardial infarction and infection, respectively.

During follow-up, only two nonfatal cardiovascular events occurred: one PTCA and one myocardial infarction, both in patients with a functioning pancreas graft.

Baseline characteristics of patients with and without follow-up CAG, including sex, age, BMI, duration of diabetes, months of dialysis, (immunosuppressant) medication, HbA_{1c}, albumin level, lipid level, blood pressure, smoking, number of rejection episodes, history of myocardial infarction, and amount of left ventricular dysfunction, did not differ, with the exception of sex; there were relatively more women without follow-up CAG.

The characteristics of patients in whom the pancreas graft was lost before follow-up CAG and patients who had a functioning pancreas at the time of follow-up CAG are summarized in Table 1. We found no significant differences. Therefore, patients without follow-up CAG or with loss of pancreas graft do not seem to be a selected group of the entire cohort, because such a selection is not reflected by the recorded baseline characteristics.

Glucose control related to pancreas graft survival

Average (SD) fasting glucose levels for the patients at baseline before SPK was not different for the patients who were going to lose their pancreas graft versus those patients with maintained function of the pancreas graft: 12.0 (SD 7.2) vs. 11.9 (SD 6.3) mmol/l, respectively (P = NS). However, during follow-up after SPK, average glucose control was significantly worse in patients without pancreas graft than in those with a functioning pancreas graft: 11.3 (SD 3.5) vs. 5.9 (SD 1.1) mmol/l (P = 0.03), despite optimal conservative management of the group with failure of the pancreas graft.

HbA_{1c} measurements yielded similar results (not available for all patients during follow-up).

Progression of coronary atherosclerosis related to pancreas graft survival

Within the group of 31 patients who underwent follow-up CAG, the pancreas graft was lost in five patients before follow-up CAG. As stated, in one additional patient, the pancreas was lost between the second and third angiogram. Consequently, we were able to compare 26 cases without pancreas graft loss with 6 cases with loss of the pancreas graft. In the analysis, we ignored the possible association. Five of the six cases were an early loss of graft function due to graft-thrombosis/early rejection (<3 months after treatment: days 1, 4, 5, 36, and 81, respectively), and in the sixth patient, the pancreas was lost 2 months after the first follow-up CAG (at 2 years) but 3 years before the second follow-up CAG 2 years later (see above). For most of their follow-up, these six patients had a nonfunctioning pancreas graft; therefore, it is unlikely that the timing of pancreas loss has influenced the results. If anything, this possible influence leads to underestimation of the difference in progression between those with and those without a functioning pancreas graft and not to overestimation.

At baseline, a total of 127 lesions were identified in the 48 patients: 116 with 20–50% diameter stenosis, and 11 with ≥50% diameter stenosis. Eight patients had no lesion >20%. In the other patients, the number of lesions per patient varied from one to nine (mean 3.4). MSD varied between 2.11 and 3.89 mm (mean 3.03) and MOD varied between 0.91 and 3.59 mm (mean 2.06). The total number of lesions in the analyzed angiographic follow-up cohort was 86 (average 2.66 per patient). Baseline MSD and MOD values are provided in Table 1.

MSD loss (progression of diffuse coronary atherosclerosis) was 0.024 mm/year (SE 0.067) in patients with a functioning pancreas graft, compared with 0.044 mm/year (SE 0.038) in patients in whom the pancreas graft was lost (Fig. 2).

MOD loss (progression of focal coronary atherosclerosis) was 0.037 (SE 0.086) in patients with a functioning pancreas graft compared with 0.061 mm/year (SE 0.038) in patients in whom the pancreas graft was lost.

Although the observed progression, on average, was almost doubled in patients in whom the pancreas graft was lost compared with patients with a functioning pancreas graft, this difference did not reach statistical significance, as expected given the observational character of the study and the relatively small number of patients. Figure 3 displays the individual changes in MSD (MOD changes yielded similar results). It is interesting to note that in the patients with a functioning pancreas graft, 10 of 26 patients (38%) have a negative change in MSD, i.e., regression of coronary atherosclerosis, whereas none of the patients in whom pancreas function was lost showed a tendency to regression. This difference in the amount of cases tending to regression is statistically significant (P = 0.035).

The MSD and MOD change was correlated to (possible) risk factors of coronary atherosclerosis (blood pressure, smoking, cholesterol, BMI, creatinine clearance, number of rejection episodes, and kidney loss) in a multiple regression model, in addition to pancreas graft loss. The multiple correlations were 0.68 for change in MSD and 0.48 for change in MOD. Adjusted for the effect of the above-mentioned confounders, the effect

Table 1—*Patients with a follow-up CAG: baseline characteristics with regard to pancreas loss*

	Pancreas loss before follow-up CAG		
	No (n = 26)	Yes (n = 6)	P*
Men	20 (77%)	5 (83%)	0.73
Age (years)	37.5 (7.1)	35.0 (4.3)	0.42
Weight (kg)	68.7 (8.9)	71.0 (6.1)	0.55
Length (m)	1.75 (0.08)	1.77 (0.08)	0.69
BMI (kg/m^2)	22.5 (3.0)	22.8 (1.3)	0.80
Duration of diabetes (years)	24.3 (6.2)	21.3 (5.2)	0.29
Months on dialysis: median (IQR)	12 (14)	11 (12.)	0.71
Statin medication	1 (4%)	0 (0%)	0.65
ACE-inhibiting medication	13 (52%)	4 (80%)	0.25
β-blocking medication	4 (16%)	1 (20%)	0.83
Diuretic medication	10 (40%)	3 (60%)	0.41
HbA_{1c} (mmol/l)	8.58 (1.52)	9.62 (2.83)	0.21
Albumin (g/l)	42.0 (4.0)	42.2 (5.0)	0.93
Systolic blood pressure (mmHg)	160 (24)	154 (15)	0.62
Diastolic blood pressure (mmHg)	87 (9)	90 (8)	0.56
Total cholesterol (mmol/l)	6.28 (1.25)	7.10 (0.90)	0.21
Triglycerides (mmol/l)	2.28 (0.95)	3.08 (1.47)	0.13
Smoking: never/ever/current (n)	9/11/4	3/1/1	0.21
Rejection episodes	3 (0–4)	2 (0–2)	0.64
Baseline MSD (mm)	3.05 (0.41)	3.21 (0.41)	0.43
Baseline MOD (mm)	2.26 (0.60)	2.09 (0.82)	0.61

*Data are n (%), means (SD), and median (range) unless otherwise indicated. P value of Student's t test, Mann-Whitney U-test, or χ^2 test, where appropriate. IQR, interquartile range.

of pancreas graft loss was even slightly higher and was estimated as 0.034 mm/year on the MSD (P = 0.09) and 0.066 mm/year on the MOD (P = 0.13).

Based on our results, a clinical trial comparing SPK and KTA, which probably will never take place because of the ethical and practical problems involved, would require ~80 patients per group to reach, with 80% power, statistically significant results, showing that SPK is superior to KTA with regard to progression of coronary atherosclerosis.

CONCLUSIONS — Vascular disease remains the major cause of both morbidity and mortality after transplantation in diabetic recipients (18–20). Therefore, for patients undergoing SPK, the potential benefits of normoglycemia are of great importance. Because SPK has been performed on a larger scale for only ~10 years, data with respect to the long-term benefits concerning diabetic complications are very limited. Unfortunately, an extended period of exposure to hyperglycemia with its adverse sequelae, such as retinopathy, neuropathy, and life-shortening atherosclerosis, is likely to be in more advanced stages before the patient presents for a transplant (4,21,22). Although initial (functional) abnormalities are reversible with correction of hyperglycemia, later, more structural changes such as capillary sclerosis or retinal neovascularization are not. The best one could hope for would be that further changes in vascular structural abnormalities would be prevented by normoglycemia.

Pancreas transplantation seems to have little demonstrated benefit for established diabetic retinopathy, largely because most patients receiving a combined transplant have advanced eye disease (23–25). Presumably, pancreas transplantation was performed too late to be of benefit for retinopathy.

The influence of improved glycemic control on the progression of neuropathy

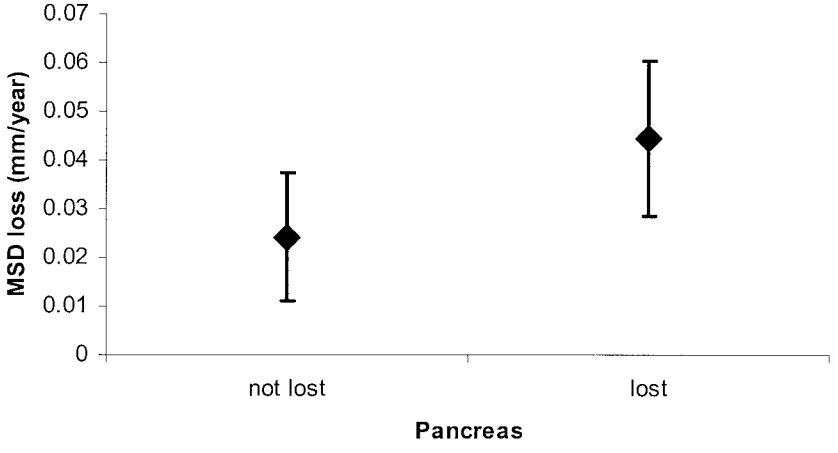

Figure 2—*Change in average MSD in mm/year ± SEM related to functional status of the pancreas graft. Vessel diameter loss (progression) is almost doubled in patients without functioning pancreas grafts as compared with patients with functioning pancreas graft.*

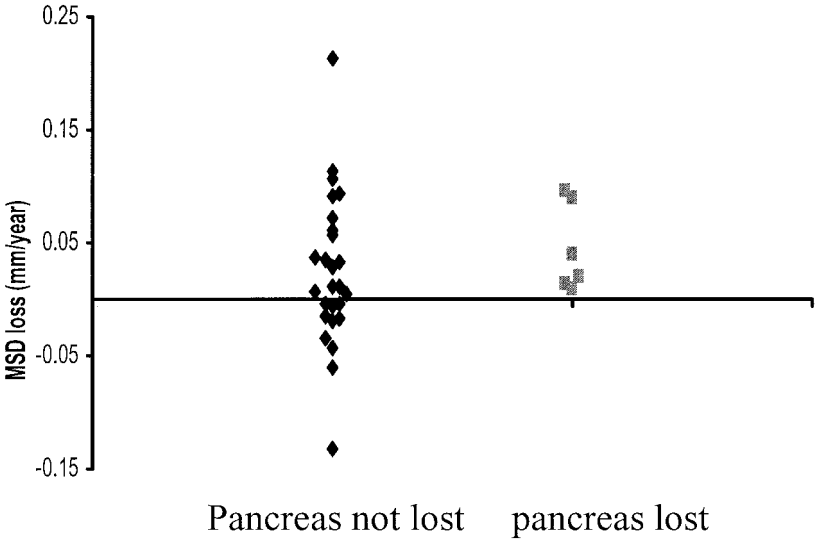

Figure 3—*Change in MSD depicted per individual patient related to pancreas graft function. Note that in the patients with a functioning pancreas graft, 10 of 26 patients (38%) have a "negative loss" in MSD, i.e., regression of coronary atherosclerosis, whereas none of the 6 cases in whom pancreas function was lost showed a tendency to regression* ($P = 0.035$).

is somewhat more encouraging (26–32). Stabilization of neuropathy seems feasible.

As stated, vascular disease remains the major cause of both morbidity and mortality after transplantation in diabetic recipients (18–20). In an individual patient, the risk of sustaining vascular complications is related to the degree of vascular disease before transplantation (20,33). When coronary angiography is performed before transplantation, patients found to have one or more coronary artery stenoses >50% have a 55% risk of sustaining a vascular event within 3 years of transplantation, independent of the type of transplant (20). For these reasons, it is of great importance to know whether pancreas transplantation might decrease progression of (coronary) atherosclerosis with its subsequent clinical events.

However, virtually no data on this topic are available. Our study provides unique material and supports the concept that in patients who have undergone SPK, progression of coronary atherosclerosis in patients with a functioning pancreas graft is reduced, compared with patients in whom the pancreas graft has failed. Furthermore, La Rocca et al. (34) described that carotid atherosclerotic lesions documented with carotid ultrasound continue to progress in both patients who have undergone SPK and those who have undergone KTA, but that progression was faster in patients with poor glycemic control. This is comparable with what we found in the coronary arteries with angiography. Possibly due to these beneficial effects of SPK, it has been described that left ventricular function seems to improve to a greater degree after a successful SPK than with KTA (35).

It is interesting to note that the beneficial effects of a functioning pancreas graft on progression of coronary atherosclerosis are at least as large as the effects of statin therapy in lipid-lowering trials such as the Regression Growth Evaluation Statin Study (REGRESS), which did not include type 1 diabetic patients, and that even perhaps SPK, like the statins, is capable of inducing regression of coronary atherosclerosis in a non-neglectable proportion of cases (11).

The pathogenesis of atherosclerosis is complex. Hyperglycemia is believed to contribute to atherosclerotic plaque formation in a number of ways, including glycation of collagen, alteration of endothelial cell function, glycoxidation of LDL cholesterol, and increased platelet reactivity (36,37). Therefore, SPK might, apart from slowing down progression of coronary atherosclerosis, also stabilize atherosclerotic plaques, restore endothelial reactivity, and reverse functional changes, thereby reducing clinical atherosclerotic events as well, as has been postulated for lipid-lowering studies with HMG-CoA reductase inhibitors, which were not prescribed yet at large scale to our study population during the study period.

Recognizing the limitations caused by the obligatory observational character of our study and the relatively small number of patients, it can be concluded that now, for the first time, evidence exists that after SPK, progression of coronary atherosclerosis in patients with a functioning pancreas graft is reduced, compared with patients in whom the pancreas graft has failed.

Our observation is an important part of the explanation for improved mortality rates reported in type 1 diabetic patients with end-stage renal failure after SPK compared with KTA (38–40).

Therefore, although a functioning pancreas transplant is associated with increased perioperative morbidity, normalization of blood glucose levels by SPK may indeed reduce progression of coronary atherosclerosis in type 1 diabetic patients and, in this way, improve clinical outcome as well as result in improved quality of life and stabilization of neuropathy. In light of the findings described above, SPK must be carefully considered for all diabetic transplant candidates.

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