Left-sided complete revascularization with bilateral internal thoracic arteries in diabetic patients

Running Head: BITA grafting in diabetes

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Abstract

Background

There are few reports on the long-term patency of bilateral internal thoracic artery (BITA) grafts in diabetic patients. We evaluated the relationship between the long-term patency of BITAs and the clinical outcomes in diabetes.

Methods

We retrospectively identified 569 patients (321 diabetic, 248 nondiabetic) who underwent isolated BITA grafting for left-sided complete revascularization at our institution from 2000 to 2015. The primary endpoint was the incidence of major adverse cardiovascular events (MACEs) comprising death, re-revascularization and myocardial infarction. The secondary endpoint was the patency of the BITAs.

Results

There were no differences in the MACE rate (10-year: diabetic, 33.7%, nondiabetic, 22.3%; $p = 0.15$) or overall mortality rate (24.0% vs. 12.2%; $p = 0.066$) between the diabetic patients and the nondiabetic patients. The incidence of cardiac death (3.3% vs. 1.8%; $p = 0.80$) or re-revascularization and myocardial infarction (11.4% vs. 11.8%; $p = 0.67$) was similar between the groups. The patency of free internal thoracic artery (ITA) grafts to the left circumflex artery was associated with greater patency in diabetic patients than in nondiabetic patients (4-year: 99.3% vs. 95.5%; $p = 0.049$); the patency of other ITA grafts did not differ between the groups.

Conclusions

All-cause death, re-revascularization and myocardial infarction showed no differences between diabetic and non-diabetic patients who underwent left-sided revascularization with the BITAs. Although diabetes did not affect the patency of the ITA, free ITA grafts to the left circumflex artery showed very good long-term patency in diabetic patients.

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Introduction

Many cohort observational studies have revealed that revascularization using the bilateral internal thoracic arteries (BITAs) improved the life expectancy in comparison to revascularization using a single internal thoracic artery (ITA), and that the patient's diabetes status was not associated with this outcome [1-7]. However, BITAs were used in <5% of isolated coronary artery bypass grafting (CABG) in the USA and approximately 20% in Europe based on the risk of sternal wound infection [8]. In contrast, BITAs were used in 40.7% of isolated CABG in Japan [9]. We did not regard the diabetic status as a contraindication of BITA use. Few reports have compared the long-term patency and re-revascularization for target lesion of BITAs between diabetic and nondiabetic patients. This study aimed to reveal the influence of diabetes on the long-term patency of BITAs used for left-sided revascularization and the relationship between revascularization with BITAs and the long-term outcomes.

Material and Methods

Our institutional review board approved this study. Written informed consent to use anonymized data that was collected from mailed communications was obtained from each patient.

Patient population

A total of 758 patients underwent isolated CABG with the BITAs in Japanese Red Cross Nagoya First Hospital between January 2000 and December 2015. From these patients, we identified 569 who underwent left-sided complete revascularization with the BITAs. One hundred eighty-nine cases in which ITA was used as an I-composite (n=121) or interposed (n=48) graft, grafted to the right coronary artery (n=13) or grafted to the left anterior descending artery (LAD) as a free graft (n=7) were excluded from the study (Fig 1). Of the 569 patients, 321 patients were diabetic, and 248 patients were nondiabetic. Three hundred twenty-one of the diabetic patients who had been previously diagnosed with diabetes were treated with diet, oral antidiabetic medication, or insulin.

Operative strategy

Our surgical procedures for CABG and using the BITAs have been reported previously [10-12]. The BITAs were used for left-sided complete revascularization and an *in situ* ITA was used to revascularize the LAD. The left circumflex artery (LCX) was revascularized with the other ITA as an *in situ* graft, a Y-graft from an *in situ* contralateral ITA or a free graft in an aorto-coronary fashion with modified proximal anastomosis. Contraindications for the use of the BITAs were ≥80 years of age, severe hemodynamic instability at the time of surgery and the administration of corticosteroids; the diabetic status was not regarded as a contraindication. The right coronary artery was revascularized either with a saphenous vein graft (SVG), radial artery graft (RAG), or right gastroepiploic artery graft (GEA).

The ITAs were harvested in a skeletonized fashion and, from the time of harvesting, a warm milrinone solution (1000 U heparin and 10 mg milrinone in 100 ml of 0.9% [w/v] saline) was used to prevent spasm of the ITAs. We grafted on diseased coronary vessels with >50% stenosis and did not use the distal part of the ITA beyond the final bifurcation. GEA and RA were grafted to the right coronary artery with ≥90% stenosis. The off-pump technique was used whenever possible; however, the final decision to adopt off-pump procedure depended on the quality of the ascending aorta, the anatomy of the coronary arteries, the hemodynamic status, and the surgeon's preference. Since 2002, we have routinely measured the flow of the ITA using a transit time flowmeter (MediStim, Oslo, Norway) before closing the chest in all patients.

Blood glucose levels were checked from the time of surgery and insulin was injected to maintain a blood glucose level of <150 mg/dL. From the first postoperative day, all patients received lifelong aspirin treatment with a daily maintenance dose of 100 mg.

Endpoints and data collection

The primary endpoint was the incidence of major adverse cardiovascular events (MACEs), which included all-cause death, non-fatal myocardial infarction and re-revascularization (either CABG or percutaneous coronary intervention). In addition, we estimated the myocardial infarction and re-revascularization for the

target lesion of the ITA. The secondary endpoint was the patency of the ITA used for left-sided revascularization. Graft patency was evaluated via catheter angiography or coronary computed tomography. Graft failure was defined as anastomosis with the presence of a string sign, severe stenosis (>90%), or complete occlusion. In sequential grafts, each site of distal anastomosis was defined as a separated data point.

We collected the basic and follow-up data from physicians' reports, medical records, or letters to the patients. We retrospectively reviewed and collected all data prospectively until 31 October 2017. The clinical follow-up rate was 83% during a mean follow-up period of 5.9 years (range 0-17.1 years); there was no difference between the groups (diabetic, 82%; nondiabetic, 85%; $p = 0.32$). Those who were lost to follow-up had higher incidences of insulin use and renal failure than those who were followed (Supplemental Table 1).

The baseline characteristics of the groups are presented in Table 1. The ratio of men in diabetic patients was smaller than that in nondiabetic patients. Diabetic patients had higher incidences of hypertension, chronic renal failure, peripheral vascular disease and carotid artery stenosis. With regard to coronary vessel disease, the ratio of two vessel disease in nondiabetic patients was larger than that in diabetic patients.

The graft-target combinations are shown in the Table 2. There were no differences in the graft-target combinations or in the number of sequential procedures for each graft between the groups. The rate of ≤75% proximal stenosis in the LCX in diabetic patients was higher than that in nondiabetic patients.

Angiography follow-up

Postoperative angiography was routinely conducted in the early postoperative period (within 2 months postoperatively) and at 5 years or later, irrespective of the symptoms of the patients who gave their written informed consent before the commencement of the study. In addition, symptom-driven studies were performed when indicated. In asymptomatic patients, coronary computed tomography was initially performed. When graft failure was observed on coronary computed tomography, catheter angiography was

performed. We did not perform catheter angiography or coronary computed tomography when asymptomatic patients had a creatinine level >1.5 mg/dL or other contraindications to contrast dye.

The angiographic follow-up rate was 88% (503/569) during a mean follow-up period of 2.5 years (0-14.6 years); there was no difference between the groups (diabetic, 87% [279/321]; nondiabetic, 90% [224/248]; $p = 0.21$). The non-angiogram cohort had higher incidences of insulin use, chronic renal failure and peripheral arterial disease than the angiogram cohort (Supplemental Table 2). Late angiography sessions were performed in 26% (53/203) of the cases in diabetic patients and 34% (57/169) of the cases in nondiabetic patients ($p = 0.12$). The two groups had a similar rate of symptom-driven angiography (diabetic, 4.4%; nondiabetic, 6.5%; $p = 0.27$).

Statistical analyses

The data were expressed as the mean ± standard deviation or frequency. Continuous variables were analyzed using Student's *t*-test or the Mann-Whitney *U* test, depending on the normality data. Categorical variables were analyzed using the $\chi 2$-test or Fisher's exact test, as appropriate. MACEs and all-cause death were compared using Kaplan-Meier analyses, together with a log-rank test. For non-mortality events (non-fatal myocardial infarction and re-revascularization), we used the cumulative incidence function to account for death as a competing variable (Gray's test).

A Cox proportional hazards regression model or Fine-Gray competing risks regression model was used to estimate the hazard ratio or subdistribution hazard ratio of diabetes, with adjustment for clinically relevant covariates (Table 1; plus graft type, sequential grafting, severity of proximal stenosis, off-pump procedure and Intra-aortic balloon pump use). A Cox regression model was used for all-cause death and MACEs. A Fine-Gray model was used for non-mortality events.

Because the number of covariates entered into the multivariable regression models was limited by the number of events, an inverse probability-weighted (IPW) method was applied to obtain the weighted hazard ratio or subdistribution hazard ratio of diabetes using the propensity score. The propensity score with diabetes was calculated using a multivariate logistic regression model included the covariates (Table

1; plus off-pump procedure and Intra-aortic balloon pump use). In the IPW cohorts, individual weights were stabilized to prevent the excess influence of extreme weights. The standardized differences after IPW were <10% across the baseline covariates (Supplemental Fig 1).

Graft patency was compared using the time-dependent Cox proportional hazard regression analysis. We used the Cox regression model with consideration of clustering for the timing of multiple times of angiogram within a single patient. The factors influencing the failure of the ITA were estimated by a multivariable Cox regression analysis with data clustering. *P*-values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the SPSS 24.0 (IBM Corp., Armonk, NY), STATA 15.0 (StataCorp LLC, College Station, TX) and R 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria) software programs.

Results

Early clinical outcomes

Although diabetic patients had more overall anastomoses than nondiabetic patients ($p = 0.019$), there were no differences in the number of anastomoses of the ITA between the groups (Table 3). The diabetic patients had a high graft flow and low pulsatility index in the LAD but a similar flow and high pulsatility index in the LCX (Supplemental Table 3). Furthermore, although the rate of major adverse events in the perioperative period did not differ between the groups, deep sternal wound infection (DSWI) only occurred in diabetic patients (Table 4). Diabetic patients had a longer length of hospital stay than nondiabetic patients ($p = 0.001$).

Long-term clinical outcomes

During follow-up, there were 37 non-cardiac deaths and 4 cardiac deaths in diabetic patients; 21 non-cardiac deaths and 3 cardiac deaths in nondiabetic patients. There were no differences in the overall mortality rate between the groups ($p = 0.066$; Fig 2A), nor did the rate of cardiac death differ between the groups (10-year rate: diabetic, 3.3%; nondiabetic, 1.8%; $p = 0.80$).

There were no differences in the rate of re-revascularization and myocardial infarction between the groups (Fig 2B); these rates for the target lesion of BITA did not differ (Fig 2C). The MACE rate of the diabetic group was higher than that of the nondiabetic group due to the increased mortality rate of the diabetic group (Fig 2D), which did not differ between the groups. A multivariable regression analysis and IPW method confirmed these results (Table 5).

Angiographic outcomes

The patency of ITA grafts is shown in Fig 3. In addition, the graft grade is presented based on the FitzGibbon classification (Supplemental Table 4). When the ITA was grafted to the LCX, free right internal thoracic artery (RITA) was associated with greater patency in diabetic patients than in nondiabetic patients (4-year rate: diabetic, 99.3%; nondiabetic, 95.5%, $p = 0.049$); there were no differences between the groups with regard to other graft-target combinations. The 4-year Y-graft patency rate was 89.5% in diabetic patients and 92.9% in nondiabetic patients ($p = 0.64$).

With regard to additional grafts, there were no differences between the groups in the patency rate of the SVG and GEA (4-year SVG patency rate: diabetic, 87.3%; nondiabetic, 88.5%; $p = 0.80$; 4-year GEA patency rate: diabetic, 89.4%; nondiabetic, 97.4%; $p = 0.62$). The 4-year RAG patency rate in nondiabetic patients was higher than that in diabetic patients (diabetic, 93.3%; nondiabetic, 100%; $p < 0.001$).

Diabetes was not identified as an independent predictor of ITA graft failure (Table 6). In the ITA grafted to the LCX, using a free ITA graft were associated with a decreased risk of failure, whereas non-elective surgery and ≤75% proximal stenosis increased the risk of failure.

Subgroup analyses

We compared the outcomes of diabetes treated with medication or insulin with the outcomes of the non-diabetic group. The MACE rate in the insulin-treated diabetic group was higher than that of the non-diabetic group, which did not differ between the groups ($p = 0.054$, Supplemental Fig 2).

Comment

The present study revealed that the long-term patency of BITAs used for left-sided revascularization was not decreased by diabetes. In addition, there were no marked differences in the rates of cardiac death, re-revascularization and myocardial infarction between the groups.

Diabetes contributes to the faster progression of coronary atherosclerosis and negative artery remodeling [13-15]. However, diabetic patients who received BITA or total arterial grafting had similar rates of cardiac death, re-revascularization and myocardial infarction to nondiabetic patients [16-18]. Although these results appear to reflect the good patency of the ITA, few reports have compared the ITA graft patency between diabetic and nondiabetic patients. The Bypass Angioplasty Revascularization Investigation (BARI) trial [19] and a retrospective study [16] showed that diabetes did not affect the ITA patency. A recent retrospective study reported that the patency of BITAs applied as Y-grafts was not affected by diabetes [17]. Our findings in relation to the patency of BITAs were basically consistent with these studies.

The present study newly revealed that the patency of ITA grafts to the LCX in diabetic patients could be better than that in nondiabetic patients; however, diabetic patients had a high percentage of cases with ≤75% proximal stenosis and a high pulsatility index. To date, no studies have reported a higher patency rate of free ITA grafts in diabetic patients. In addition, the configuration of the RITA grafted to the LCX in diabetes had good patency, although in situ RITA grafted to the LCX had insufficient power to reach statistical significance. The higher proximal flow restriction in the diabetic coronary arteries, as evaluated by angiography, may account for this result. The diffusely narrowed, or poor quality of the coronary arteries in diabetic patients may have prevented the flow competition of the ITA grafts, and overwhelmed the unfavorable effect of poor distal run-off. In addition, the hemodynamic superiority of the aorto-coronary bypass may have had an effect.

Although the superior outcome of BITA grafting was revealed, the risk of DSWI makes surgeons reluctant to use BITAs. In the present study, DSWIs only occurred in diabetic patients, although no difference was noted. Harvesting the BITAs in a skeletonized fashion may reduce the incidence of DSWIs

and affect this outcome, as many reports have demonstrated [18]. All patients with DSWI were successfully treated by surgery and DSWIs did not influence the mortality rate.

The present clinical study is associated with several limitations. First, it was not a randomized-controlled, retrospective observational study. Potential differences in the follow-up of insulin-treated diabetes with angiopathy might have affected the outcomes in the diabetes patients. Second, the study population was relatively small because of the single-center setting. In particular, all configurations aside from left internal thoracic artery to LAD and free RITA to LCX, and the subgroup analysis had insufficient power to reach statistical significance. Third, although the time-dependent Cox regression method was used, the graft patency might have been overestimated, as the exact date of graft failure was rarely known. Finally, we did not compare these results in diabetic patients undergoing single ITA.

In conclusion, the rates of all-cause death, re-revascularization and myocardial infarction did not differ between the diabetic and non-diabetic patients who underwent left-sided revascularization with the BITAs. The patency rates of ITA grafts in any graft-target combination in the left coronary territory were not affected by diabetes. Free ITA grafts to the LCX showed very good long-term patency in diabetic patients, which was comparable to that of ITA grafts to the LAD.

Disclosures: The authors declare no conflicts of interest.

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Table 1. Preoperative characteristics of the patients

Variable [a]	Diabetic (n = 321)	Nondiabetic (n = 248)	*p* Value
Males	254 (79)	216 (87)	0.013
Age, years	66.5 ± 8.6	66.3 ± 9.2	0.97
Body surface area, m^2	1.66 ± 0.17	1.67 ± 0.16	0.43
Diabetes mellitus			
HbA1c	7.6 ± 1.4	5.8 ± 0.4	<0.001
Medication	190 (59)		
Insulin use	98 (31)		
Hypertension	246 (77)	169 (68)	0.024
Hyperlipidemia	225 (70)	162 (65)	0.23
Chronic renal failure (Creatinine >2.0 mg/dL)	29 (9.0)	11 (4.4)	0.033
Creatinine	1.2 ± 1.3	1.0 ± 0.7	0.025
Hemodialysis	9 (2.8)	3 (1.2)	0.19
Cerebral vascular accident	52 (16)	33 (13)	0.34
Peripheral vascular disease	36 (11)	15 (6.0)	0.032
Carotid artery stenosis	29 (9.0)	9 (3.6)	0.010
Chronic obstructive pulmonary disease	10 (3.1)	15 (6.0)	0.091
Smoking history	193 (60)	156 (63)	0.50
Previous myocardial infarction	135 (42)	107 (43)	0.79
Previous percutaneous coronary intervention	70 (22)	58 (23)	0.65
Left ventricular dysfunction (Ejection fraction <30%)	15 (4.7)	11 (4.4)	0.95
Ejection fraction, %	59.8 ± 13.4	61.5 ± 13.8	0.15
Non-elective surgery	59 (18)	51 (21)	0.51

Coronary vessel disease			
Triple	259 (81)	184 (74)	0.064
Double	49 (15)	55 (22)	0.034
Left main	116 (36)	109 (44)	0.059
SYNTAX score	32.7 ± 10.2	32.2 ± 9.9	0.75

[a] Values are *n* (%) or mean ± SD.

Table 2. Conduits and anastomosed sites

Variable [a]	Diabetic	Nondiabetic	*p* Value
Conduit to LAD region			
In situ LITA	234 (73)	180 (73)	0.93
Sequential	27 (8.4)	12 (4.8)	0.093
In situ RITA	87 (27)	68 (27)	0.93
Sequential	1 (0.3)	2 (0.8)	0.41
Conduit to LCX region			
In situ LITA	86 (27)	68 (27)	0.87
Sequential	10 (3.1)	13 (5.2)	0.20
In situ RITA	41 (13)	45 (18)	0.076
Sequential	1 (0.3)	0	0.48
Free RITA	167 (52)	116 (47)	0.21
Sequential	77 (24)	52 (21)	0.83
ITA as a Y-graft	27 (8.4)	19 (7.7)	0.75
Sequential	14 (4.4)	5 (2.0)	0.083
Additional graft			
Gastroepiploic artery	32 (10)	21 (8.5)	0.54
Sequential	3 (0.9)	1 (0.4)	0.48
Radial artery	12 (3.7)	15 (6.0)	0.20
Sequential	5 (1.6)	2 (0.8)	0.11
Saphenous vein	217 (68)	152 (61)	0.12
Sequential	66 (21)	34 (14)	0.087

Severity of proximal stenosis			
LAD region			
≤75%	76 (22)	65 (25)	0.39
75%<	273 (78)	198 (75)	
LCX region			
≤75%	136 (32)	81 (25)	0.042
75%<	288 (68)	240 (75)	

[a] Values are *n* (%) or mean ± SD.

ITA, internal thoracic artery; LAD, left anterior descending artery; LCX, left circumflex artery; LITA, left internal thoracic artery; RITA, right internal thoracic artery.

Table 3. Intraoperative characteristics of the patients

Variable [a]	Diabetic (n = 321)	Nondiabetic (n = 248)	*p* Value
Anastomoses per patient	3.5 ± 1.0	3.3 ± 0.9	0.019
Anastomoses per ITA to left anterior descending artery	1.1 ± 0.3	1.1 ± 0.3	0.17
Anastomoses per ITA to left circumflex artery	1.3 ± 0.5	1.3 ± 0.5	0.40
Operation time (min)	267.2 ± 56.2	260.0 ± 55.8	0.12
Cardiopulmonary bypass time (min)	106.7 ± 39.5	98.0 ± 41.9	0.13
Cardiac ischemic time (min)	79.9 ± 22.7	78.2 ± 22.5	0.61
Off-pump procedure	246 (77)	186 (75)	0.65
Intra-aortic balloon pump use	22 (6.9)	20 (8.1)	0.58

[a] Values are *n* (%) or mean ± SD.

ITA, internal thoracic artery.

Table 4. Perioperative characteristics of the patients

Variable [a]	Diabetic (n = 321)	Nondiabetic (n = 248)	*p* Value
Intensive care unit stay (days)	1.7 ± 2.1	1.7 ± 1.3	0.99
Postoperative hospital stay (days)	15.3 ± 12.5	12.3 ± 5.8	0.001
Major adverse events			
Stroke	3 (0.9)	7 (2.8)	0.085
Re-thoracotomy for bleeding	4 (1.2)	3 (1.2)	0.64
Respiratory failure	6 (1.9)	8 (3.2)	0.30
Renal failure	9 (2.8)	2 (0.8)	0.076
Perioperative myocardial infarction	3 (0.9)	5 (2.0)	0.23
Deep sternal wound infection	4 (1.2)	0	0.10
Hospital death	1 (0.3)	0	0.56

[a] Values are *n* (%) or mean ± SD.

Table 5. The effect of diabetes on major adverse cardiovascular events

Variable	Unadjusted		Multivariable regression		IPW	
	HR or SHR (95% CI)	*p* Value	HR or SHR (95% CI)	*p* Value	HR or SHR (95% CI)	*p* Value
Major adverse cardiovascular events	1.328 (0.898-1.964)	0.16	1.266 (0.852-1.882)	0.24	1.267 (0.857-1.874)	0.24
All-cause death	1.598 (0.966-2.645)	0.068	1.558 (0.937-2.590)	0.087	1.531 (0.926-2.533)	0.097
Non-fatal myocardial infarction and re-revascularization	0.905 (0.497-1.647)	0.74	0.893 (0.498-1.598)	0.70	0.897 (0.494-1.629)	0.72
For target lesion of internal thoracic artery	0.391 (0.118-1.298)	0.13	0.399 (0.121-1.315)	0.13	0.343 (0.102-1.157)	0.085

CI, confidence interval; HR, hazard ratio; SHR, subdistribution HR; IPW, inverse probability-weighted.

Table 6. Predictors of ITA graft failure

Variable	Hazard Ratio	95% confidence interval	*p* Value
ITA graft to the left anterior descending artery			
Diabetes	0.516	0.204-1.304	0.16
≤75% proximal stenosis	5.677	2.303-13.992	<0.001
ITA graft to the left circumflex artery			
Diabetes	0.487	0.234-1.013	0.054
Use of free ITA	0.268	0.126-0.571	0.001
≤75% proximal stenosis	3.047	1.501-6.183	0.002
Non-elective surgery	3.309	1.591-6.881	0.001

ITA, internal thoracic artery.

Abbreviations and Acronyms

BITAs	=	bilateral internal thoracic arteries
CABG	=	coronary artery bypass grafting
DSWI	=	deep sternal wound infection
GEA	=	right gastroepiploic artery graft
IPW	=	inverse probability-weighted
ITA	=	internal thoracic artery
LAD	=	left anterior descending artery
LCX	=	left circumflex artery
MACEs	=	major adverse cardiovascular events
RAG	=	radial artery graft
RITA	=	right internal thoracic artery
SVG	=	saphenous vein graft

Figure legends

Figure 1. Recruitment flow chart.

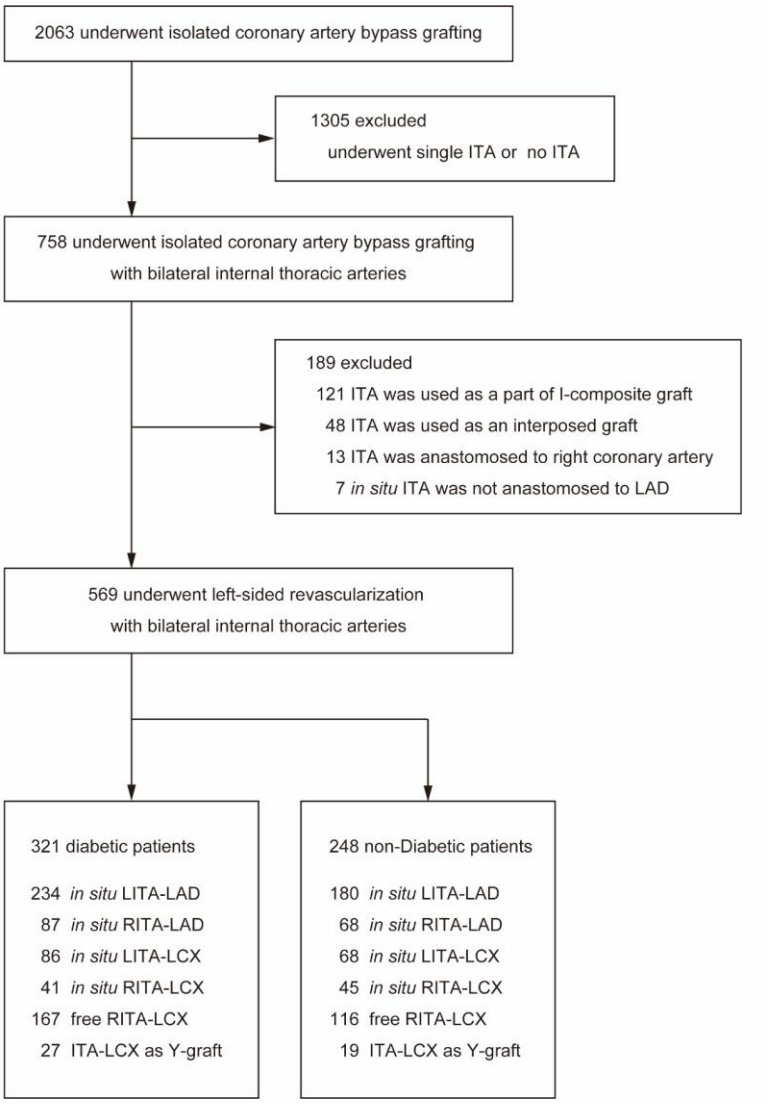
ITA, internal thoracic artery; LAD, left anterior descending artery; LCX, left circumflex artery; LITA, left internal thoracic artery; RITA, right internal thoracic artery.

Figure 2. A comparison of the events between the diabetic and nondiabetic groups. (A) All-cause death. (B) Re-revascularization and myocardial infarction (MI) event rate. (C) Re-revascularization and MI event rate related to the bilateral internal thoracic arteries (BITA). (D) Major adverse cardiovascular event rate.

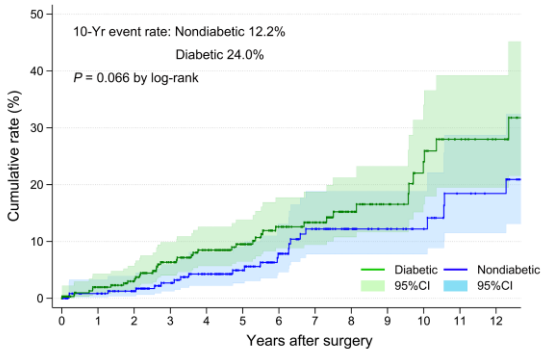
CI, confidence interval.

Figure 3. A comparison of the patency of the internal thoracic artery in the diabetic and nondiabetic groups. (A) LITA to LAD. (B) RITA to LAD. (C) Free RITA to LCX. (D) *In situ* LITA to LCX. (E) *In situ* RITA to LCX.

CI, confidence interval; HR, hazard ratio; LAD, left anterior descending artery; LCX, left circumflex artery; LITA, left internal thoracic artery; RITA, right internal thoracic artery.


2063 underwent isolated coronary artery bypass grafting
1305 excluded
underwent single ITA or no ITA
758 underwent isolated coronary artery bypass grafting
with bilateral internal thoracic arteries
189 excluded
121 ITA was used as a part of I-composite graft
48 ITA was used as an interposed graft
13 ITA was anastomosed to right coronary artery
7 in situ ITA was not anastomosed to LAD
569 underwent left-sided revascularization
with bilateral internal thoracic arteries
321 diabetic patients
234 in situ LITA-LAD
87 in situ RITA-LAD
86 in situ LITA-LCX
41 in situ RITA-LCX
167 free RITA-LCX
27 ITA-LCX as Y-graft
248 non-Diabetic patients
180 in situ LITA-LAD
68 in situ RITA-LAD
68 in situ LITA-LCX
45 in situ RITA-LCX
116 free RITA-LCX
19 ITA-LCX as Y-graft

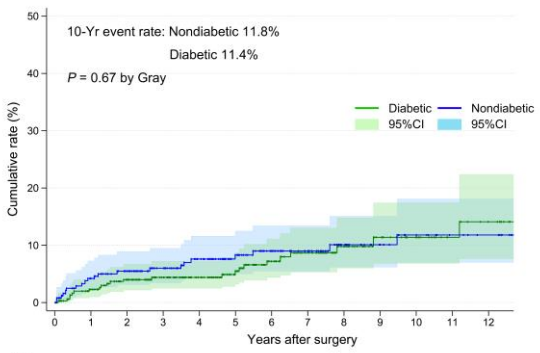
A All-cause death



Number at risk

Nondiabetic	248	233	220	193	168	142	119	96	70	56	46	36	33
Diabetic	321	294	271	234	201	168	128	106	71	52	39	29	22

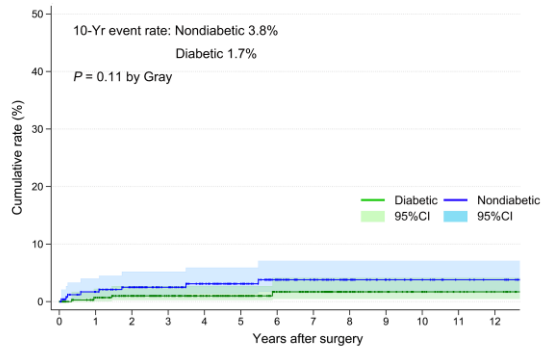
B Re-revascularization and MI



Number at risk

Nondiabetic	248	223	207	181	156	130	107	87	63	49	39	31	28
Diabetic	321	287	260	223	190	158	119	96	63	44	33	23	18

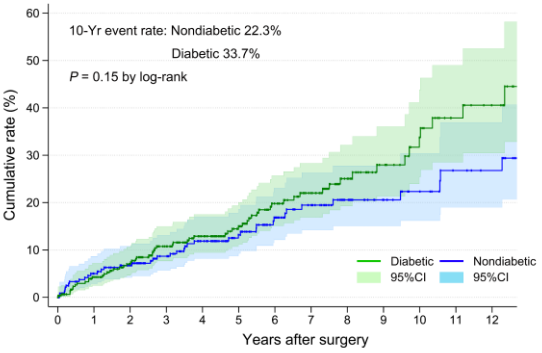
C Re-revascularization and MI related to BITA



Number at risk

Nondiabetic	248	229	214	187	162	136	112	90	67	53	44	35	32
Diabetic	321	292	268	231	198	165	127	105	70	52	39	29	22

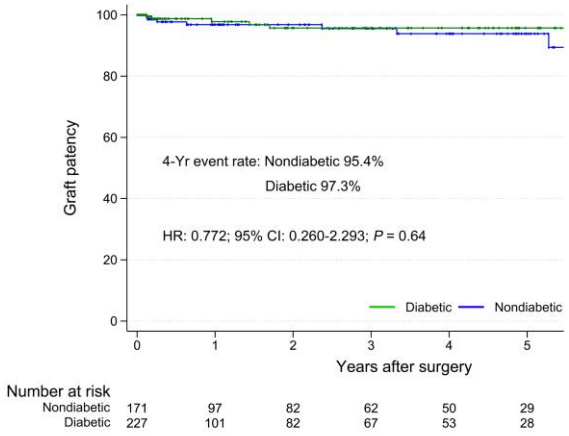
D Major adverse cardiovascular events



Number at risk

Nondiabetic	248	223	207	181	156	130	107	87	63	49	39	31	28
Diabetic	321	287	260	223	190	158	119	96	63	44	33	23	18

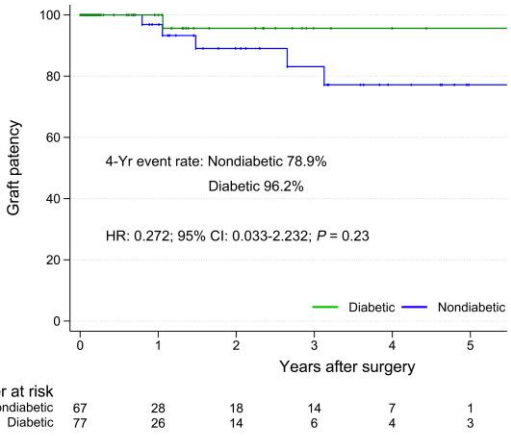
A LITA-LAD patency



Number at risk

Nondiabetic	171	97	82	62	50	29
Diabetic	227	101	82	67	53	28

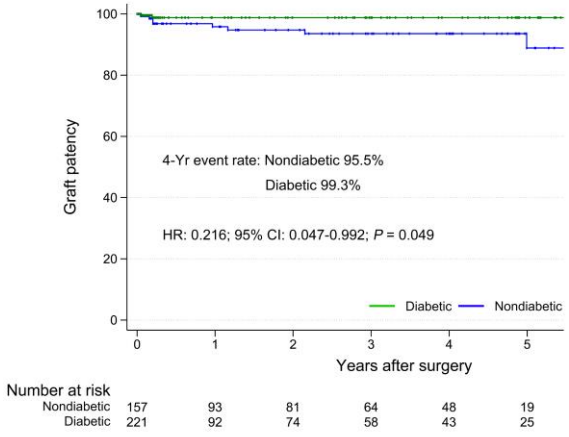
B RITA-LAD patency



Number at risk

Nondiabetic	67	28	18	14	7	1
Diabetic	77	26	14	6	4	3

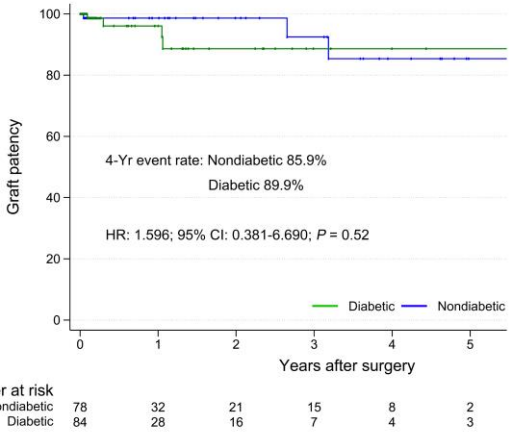
C free RITA-LCX patency



Number at risk

Nondiabetic	157	93	81	64	48	19
Diabetic	221	92	74	58	43	25

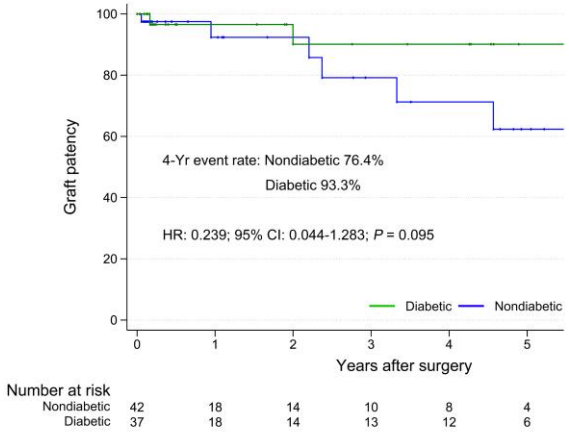
D *in situ* LITA-LCX patency



Number at risk

Nondiabetic	78	32	21	15	8	2
Diabetic	84	28	16	7	4	3

E *in situ* RITA-LCX patency



Number at risk

Nondiabetic	42	18	14	10	8	4
Diabetic	37	18	14	13	12	6

Supplemental Table 1. The differences in the characteristics between patients with and without follow-up

Variable [a]	Follow-up (n = 474)	Loss to follow-up (n = 95)	*p* Value
Males	395 (83)	75 (79)	0.30
Age, years	66.5 ± 8.8	65.8 ± 9.4	0.60
Body surface area, m^2	1.66 ± 0.16	1.66 ± 0.18	0.82
Diabetes mellitus	263 (55)	58 (61)	0.32
HbA1c	6.9 ± 1.3	7.3 ± 1.9	0.29
Medication	182 (38)	32 (34)	0.39
Insulin use	74 (16)	24 (25)	0.023
Hypertension	348 (73)	67 (71)	0.56
Hyperlipidemia	332 (70)	55 (58)	0.021
Chronic renal failure (Creatinine >2.0 mg/dL)	27 (5.7)	13 (14)	0.005
Creatinine	1.1 ± 1.0	1.3 ± 1.2	0.16
Hemodialysis	9 (1.9)	3 (3.2)	0.32
Cerebral vascular accident	70 (15)	15 (16)	0.80
Peripheral vascular disease	42 (8.9)	9 (9.5)	0.85
Carotid artery stenosis	31 (6.5)	7 (7.4)	0.77
Chronic obstructive pulmonary disease	13 (2.7)	12 (13)	<0.001
Smoking history	282 (59)	67 (71)	0.044
Previous myocardial infarction	197 (42)	45 (47)	0.30
Previous percutaneous coronary intervention	110 (23)	18 (19)	0.36
Left ventricular dysfunction (Ejection fraction <30%)	23 (4.9)	3 (3.2)	0.47
Ejection fraction, %	60.7 ± 13.5	59.4 ± 14.1	0.37
Non-elective surgery	88 (19)	22 (23)	0.30

Coronary vessel disease			
Triple	367 (77)	76 (80)	0.58
Double	85 (18)	19 (20)	0.63
Left main	192 (41)	33 (35)	0.29
SYNTAX score	32.3 ± 9.9	33.3 ± 10.9	0.58

[a] Values are *n* (%) or mean ± SD.

Supplemental Table 2. The differences in the characteristics between patients with and without an angiography analysist

Variable [a]	Angiogram (n = 503)	Non-angiogram (n = 66)	*p* Value
Males	414 (82)	56 (85)	0.61
Age, years	66.1 ± 9.0	69.0 ± 7.3	0.010
Body surface area, m^2	1.66 ± 0.16	1.63 ± 0.17	0.092
Diabetes mellitus	279 (55)	42 (64)	0.21
HbA1c	6.9 ± 1.3	7.4 ± 1.8	0.091
Medication	191 (38)	23 (35)	0.62
Insulin use	80 (16)	18 (27)	0.021
Hypertension	363 (72)	52 (79)	0.26
Hyperlipidemia	347 (69)	40 (61)	0.17
Chronic renal failure (Creatinine >2.0 mg/dL)	21 (4.2)	19 (29)	<0.001
Creatinine	1.1 ± 0.9	1.8 ± 1.8	<0.001
Hemodialysis	8 (1.6)	4 (6.1)	0.040
Cerebral vascular accident	70 (14)	15 (23)	0.059
Peripheral vascular disease	36 (7.2)	15 (23)	<0.001
Carotid artery stenosis	26 (5.2)	12 (18)	0.001
Chronic obstructive pulmonary disease	20 (4.0)	5 (7.6)	0.15
Smoking history	305 (61)	44 (67)	0.34
Previous myocardial infarction	212 (42)	30 (45)	0.61
Previous percutaneous coronary intervention	117 (23)	11 (17)	0.23
Left ventricular dysfunction (Ejection fraction <30%)	25 (5.0)	1 (1.5)	0.18
Ejection fraction, %	60.4 ± 13.5	61.2 ± 14.3	0.93

Non-elective surgery	95 (19)	15 (23)	0.46
Coronary vessel disease			
Triple	394 (78)	49 (74)	0.45
Double	89 (18)	15 (23)	0.32
Left main	203 (40)	22 (33)	0.27
SYNTAX score	32.2 ± 10.0	35.6 ± 9.9	0.064

[a] Values are *n* (%) or mean ± SD.

Supplementary Table 3: Intraoperative graft flow and pulsatility index

Variable	Diabetic	Nondiabetic	*p* Value
ITA to the left anterior descending artery			
Mean graft flow (mL/min)	41.3 ± 26.1	37.2 ± 22.4	0.037
PI	2.5 ± 0.9	2.7 ± 1.1	0.035
ITA to the left circumflex artery			
Mean graft flow (mL/min)	35.6 ± 19.0	34.8 ± 20.0	0.48
PI	2.9 ± 1.6	2.6 ± 1.3	0.069

ITA, internal thoracic artery; Pulsatility index, PI.

Y-graft was excluded because the number of grafts measured the flow was small.

Supplemental Table 4. Number of grafts according to the FitzGibbon classification

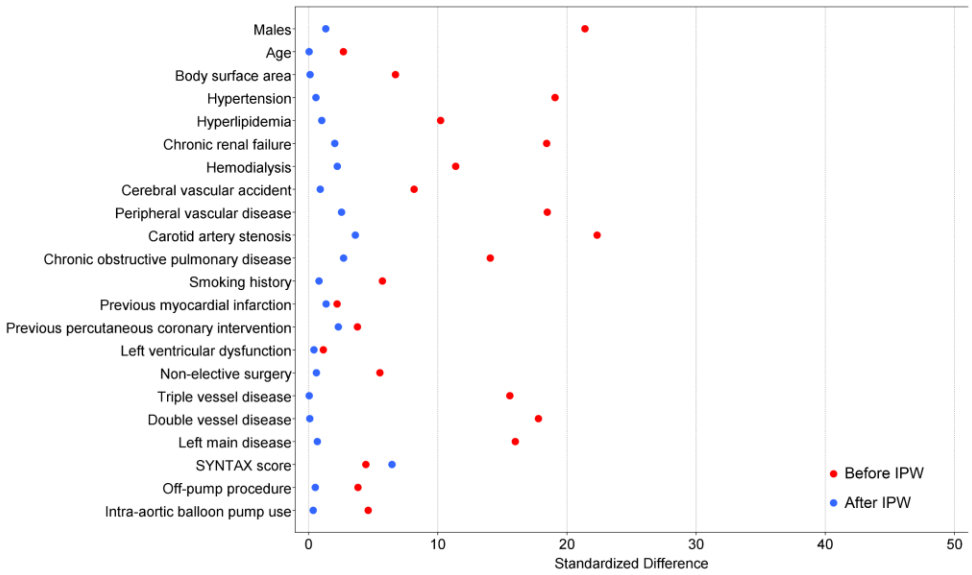
Conduits	Diabetic			Nondiabetic		
	Grade A	Grade B	Grade O	Grade A	Grade B	Grade O
LITA-LAD	254	5	2	185	5	3
RITA-LAD	87	1	1	65	4	0
Free RITA-LCX	242	2	1	160	2	7
In situ LITA-LCX	92	3	1	79	3	0
In situ RITA-LCX	39	2	1	38	3	4
Y-graft	36	3	0	24	0	1

LAD, left anterior descending artery; LCX, left circumflex artery; LITA, left internal thoracic artery; RITA, right internal thoracic artery.

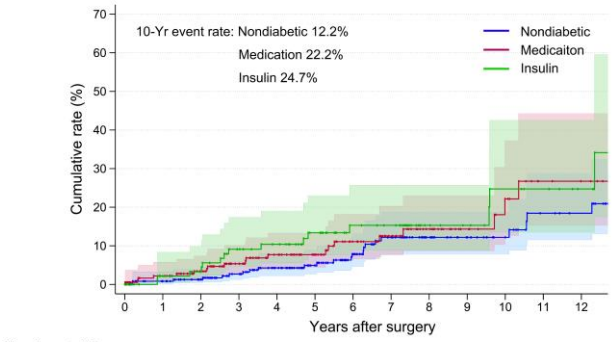
Supplemental figure legends

Supplemental Figure 1. Standardized differences before and after inverse probability-weighted (IPW) adjustment for diabetes mellitus.

Supplemental Figure 2. Comparison of the diabetes cases treated with oral antidiabetic medication (red line) or insulin (green line) with the non-diabetes group. (A) All-cause death: Medication vs non-diabetes, $p = 0.19$; insulin vs non-diabetes, $p = 0.12$. (B) Re-revascularization and myocardial infarction (MI) event rate: Medication vs non-diabetes, $p = 0.42$; insulin vs non-diabetes, $p = 0.43$. (C) Re-revascularization and MI event rate related to the bilateral internal thoracic arteries (BITA): Medication vs non-diabetes, $p = 0.32$; insulin vs non-diabetes, $p = 0.25$. (D) Major adverse cardiovascular event rate: Medication vs non-diabetes, $p = 0.50$; insulin vs non-diabetes, $p = 0.054$. The shaded regions indicate the 95% confidence interval.


Males
Age
Body surface area
Hypertension
Hyperlipidemia
Chronic renal failure
Hemodialysis
Cerebral vascular accident
Peripheral vascular disease
Carotid artery stenosis
Chronic obstructive pulmonary disease
Smoking history
Previous myocardial infarction
Previous percutaneous coronary intervention
Left ventricular dysfunction
Non-elective surgery
Triple vessel disease
Double vessel disease
Left main disease
SYNTAX score
Off-pump procedure
Intra-aortic balloon pump use
Before IPW
After IPW
0
10
20
30
40
50
Standardized Difference

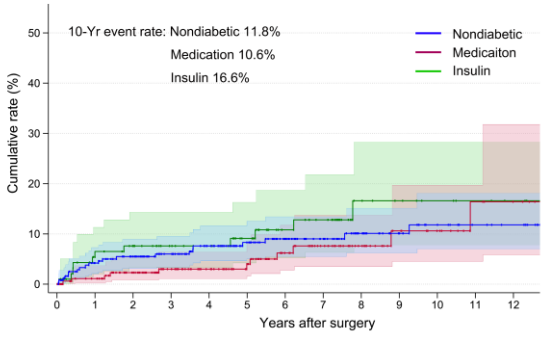
A All-cause death



Number at risk

Nondiabetic	248	233	220	193	168	142	119	96	70	56	46	36	33
Medication	190	173	154	131	108	90	68	54	39	26	19	12	10
Insulin	98	88	84	74	69	57	43	40	23	20	16	14	10

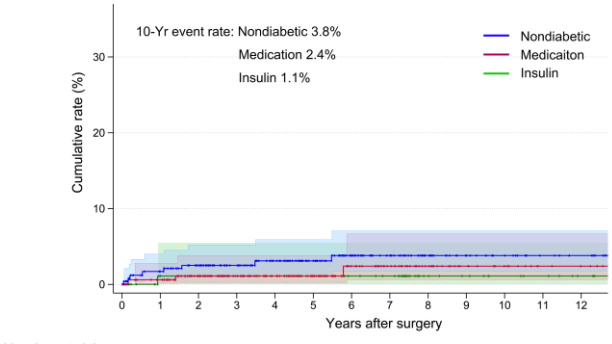
B Re-revascularization and MI



Number at risk

Nondiabetic	248	223	207	181	156	130	107	87	63	49	39	31	28
Medication	190	171	151	127	104	87	66	52	37	24	18	11	8
Insulin	98	83	77	68	63	51	37	33	18	15	12	10	8

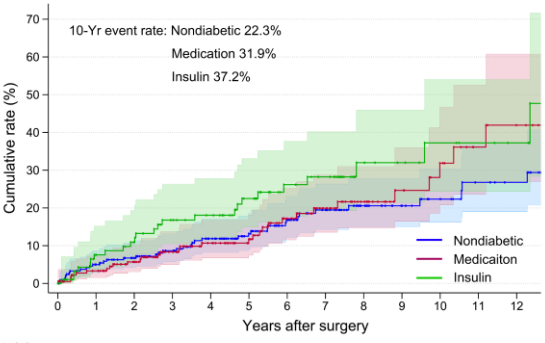
C Re-revascularization and MI related to BITA



Number at risk

Nondiabetic	248	229	214	187	162	136	112	90	67	53	44	35	32
Medication	190	172	152	129	106	88	67	53	38	26	19	12	10
Insulin	98	87	83	73	68	56	43	40	23	20	16	14	10

D Major adverse cardiovascular events



Number at risk

Nondiabetic	248	223	207	181	156	130	107	87	63	49	39	31	28
Medication	190	171	151	127	104	87	66	52	37	24	18	11	8
Insulin	98	83	77	68	63	51	37	33	18	15	12	10	8