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RISK FACTORS FOR RECURRENT CAROTID ARTERY STENOSIS FOLLOWING SURGICAL INTERVENTIONS.

Surgery

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ABSTRACT

Aims: We aim to assess restenosis rates following carotid interventions and to identify factors influencing restenosis. Primary endpoint was the incidence of restenosis and time to restenosis following carotid revascularization. Secondary endpoints included risk factors contributing to restenosis, reintervention rates, stroke and stroke free survival and overall survival.

Methods: All patients who underwent carotid repair interventions from July 2003 to May 2016 were reviewed. Patients were followed with duplex ultrasound. The Society for Vascular Surgery Carotid Reporting Standards were used as a guideline to assessment of patient demographics, risk factors and clinical presentation.

Results: Over 13 years, 9585 patients with carotid disease were referred. 690 carotid interventions were performed (633 carotid endarterectomy (CEA), 54 carotid angioplasty and stenting (CAST), 3 bypass). Restenosis occurred in 13.6% of patients (n=94). 12% occurred in the first postoperative year, 1% in the second year and 0.57% subsequently. Female gender (OR 3.051)(P<.001), contralateral stenosis (90-99%)(P=.016) and ASA grades 2 (P<.001) and 3 (P=.003) were found to be independent predictors of restenosis. There was a significant association between restenosis and hyperfibrinogenaemia (OR 2.03, 95%-CI:1.26-3.27). Four restenosis patients (4.26%) required reintervention surgery, compared to 0.84% of patients without restenosis. One of the four patients who underwent redo surgery for restenosis sustained an ipsilateral stroke (1.1% of patients with restenosis) compared to 0% of the 90 restenosis patients who did not undergo surgery (P<.001).

Conclusion: Female gender, contralateral stenosis, ASA grades 2 and 3, are independent predictors of carotid restenosis. Hyperfibrinogenemia and open procedures are significantly associated with higher restenosis rates. Patients who develop restenosis within the first year of surgery warrant closer follow up.

KEYWORDS

Carotid Artery Stenosis; Carotid Endarterectomy; Stents; Vascular Graft Restenosis

Introduction

The immediate and long-term success of carotid interventions is significantly influenced by the patency of the carotid artery1. The North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria define carotid stenosis as ≥50% reduction in lumen diameter at the site of initial intervention2. The incidence of restenosis following carotid interventions is up to 37%3. The rates differ significantly due to lack of consensus on the definition of restenosis, the imaging modality used for detection and duration of the follow-up period[3].

The incidence of restenosis is highest in the first year following surgery4. Intimal hyperplasia, smooth muscle cell growth and thrombus formation contribute to early restenosis[5]. Restenosis occurring several years after intervention is usually due to progression of atherosclerosis[5].

Many studies have reported on a variety of risk factors for carotid artery restenosis3-12. The predictive value of individual risk factors in the incidence of restenosis remains limited[5].

The incidence of restenosis-related symptoms varies from 0 to 8% with risk of stroke ranging from 0.1 to 10%3, 8. The appearance of neurological symptoms is influenced by the timing and degree of stenosis with early (<30 days) and low-grade lesions (stenosis<30%) having a lower incidence[8].

There is lack of consensus on the management of restenosis. Surgery for restenosis has a high risk of serious complications including perioperative stroke and cranial nerve injury compared to primary intervention[13, 14]. These risks must be weighed against the therapeutic benefit of stroke prevention.

Objectives

We aim to assess restenosis rates following carotid interventions and to identify factors influencing restenosis. Our primary endpoint is the incidence of restenosis and the time to restenosis following carotid revascularisation surgery. Secondary endpoints include:

- Risk factors contributing to restenosis
- Reintervention rates
- Stroke and stroke free survival
- Overall survival

Methods

Patients and Data

A retrospective series of all patients undergoing carotid surgery at our tertiary vascular centre from July 2003 to May 2016 were reviewed.

The Galway Clinical Research Ethics Committee approved our study. Individual informed consent was not specifically required due to the nature of this specific analysis.

Data was collected from our prospectively collated database (Vascubase™, Version 5.2, Consensus Medical Systems Inc., Richmond, BC, Canada), patients' case notes and our institutional patient administration system. Imaging details were collected from our Picture Archiving and Communication System and reviewed in an unblinded manner by a radiologist and the surgical team.

The Society for Vascular Surgery (SVS) Carotid Reporting Standards were used as a guideline for data collection15. Demographics, risk factors, symptom and plaque status, and procedural details were analyzed.

Procedure
Patients underwent CEA, CAST or bypass. CEA was performed under general anaesthesia. using systemic heparinisation, intravenous prophylactic antibiotics and selective shunting. The arteriotomy was repaired either by direct closure or patching.

In eversion CEA, an oblique arteriotomy of the ICA at the carotid bulb was performed through which the carotid plaque was extirpated and the ICA was reimplanted into the carotid bulb.

Patients underwent CAST under local anesthesia. Access was gained either via the femoral, brachial or through direct carotid artery puncture.

Follow up
Post-operatively all patients were managed with dual antiplatelets (aspirin and clopidogrel) for 6 months and on aspirin alone thereafter. Patients were followed with DUS at 6 weeks post-operatively and then at 6-monthly intervals for the next 3 years. Beyond that, patients were followed with DUS on an annual basis until 10 years post-procedure.

Outcome Variables
The primary outcome of this analysis was defined according to the NASCET criteria as restenosis >50% occlusion of the carotid artery detected at any stage during follow-up on DUS. This correlates with a peak systolic velocity of >125 cm/second[16].

Regarding the secondary outcomes, univariate and multivariate analysis were performed to analyze factors associated with restenosis. Reintervention was defined as any ipsilateral carotid surgical procedure performed to rectify restenosis. Stroke was defined as any as any disabling or nondisabling, ischemic or hemorrhagic stroke, ipsilateral to the site of carotid surgery. The surgical team reviewed all cases and diagnosis was confirmed with magnetic resonance imaging or computed tomography scans. Mortality was defined as death that occurred due to any cause.

Statistical Analysis
All data was analyzed using IBM Statistical Package for the Social Sciences (SPSS) Statistics Version 22 (IBM corp., Armonk, NY, USA). All missing variables were coded and omitted from analysis. Continuous data was analyzed using t-tests or Mann-Whitney U where appropriate. Categorical data was assessed with chi-square and Fischer's exact analysis where suitable and an odds ratio was performed. Cox regression analysis was performed taking outcome measures (stroke, death, restenosis and reintervention) as dependent variables and entering the risk factors with significant p values ($p<0.05$) from univariate analysis as independent variables. All non-significant variables were then removed and cox regression analysis was repeated. The times to event endpoints (restenosis, reintervention, stroke, death) over a 10-year follow-up period were calculated using Kaplan-Meier survival estimates with significance assessed with a log rank test.

Results
Out of 9585 patients with carotid disease referred to our tertiary vascular centre over 12 years, 690 carotid interventions were performed (633 CEA, 54 CAST, 3 bypass). Within the full group of carotid revascularization procedures, 94 of 690 (13.6%) patients progressed to restenosis.

Follow-up information was available for 627 (90.9%) patients. There were 63 patients lost to follow-up. The mean follow-up time was 47.43±38.21 months with a median follow-up time of 43 months [IQR 13.5-74].

The median time to restenosis was 49.5 weeks [IQR 18-92]. Of the 94 cases, 88.3% occurred 1 year after the initial procedure (12% of the full cohort of carotid revascularization procedures), 7.4% occurred in the second year (1% of all carotid revascularisations) and 4.2% occurred in the long-term (0.57% of all carotid surgeries).

The 30-day stroke/death rate was 2.8% (n=19).
Demographics, baseline risk factors and clinical presentation were compared (Tables 1 and 2).

Gender
The primary outcome of restenosis >50% occurred significantly more often in females compared to males (20.5% vs. 10.3%, P<.001). Female gender had an odds ratio of 3.051 (95%-CI:1.856–5.016, P<.001) to develop restenosis compared to males. 10-year restenosis-free survival was 79.5% (46 of 224) in females and 90.0% (46 of 466) in males (log rank P<.001)(Figure 1). The mean time (±standard deviation) to restenosis was shorter in females (52.13+43.25 weeks) compared to males (58.70+42.55 weeks, P=.060, 95%-CI:-13.421-0.272).

Females had significantly higher reintervention rates compared to males (3.2% vs. 0.4%, P=.007). 10-year reintervention-free survival was 96.9% (7 of 224) in females and 99.6% (2 of 466) in males (log rank P=.003)(Figure 2). The mean time to reintervention was shorter in females (60.19+41.31 weeks) compared to males (63.80+41.61 weeks, P=.286, 95%-CI:-10.26–3.03). Secondary outcomes of overall stroke and mortality were not statistically significant between males and females (P=.130, .548), respectively. There was no significant difference in 10-year stroke-free survival and overall survival between females and males (log rank P=.493 and .338), respectively.

Age
Univariate analysis did not show a correlation between age and restenosis.

Hyperfibrinogenemia
The primary outcome (>50% restenosis) occurred significantly more often in patients with hyperfibrinogenemia than in patients with normal fibrinogen levels (18.5% vs. 10.1%, P=.003). Hyperfibrinogenemia group had an odds ratio of 2.032 to develop restenosis compared to the normal fibrinogen group (95%-CI:1.26-3.27). The receiver operating characteristics curve identified a fibrinogen level of 2.1950 as the cutoff point of correlation to restenosis. 10-year restenosis-free survival was 81.8% (44 of 242) in the hyperfibrinogenemia group and 89.9% (35 of 345) with normal fibrinogen levels (log rank P=.017)(Figure 3). However, the mean time to restenosis was longer in the hyperfibrinogenemia group (58.95+42.03 weeks) compared to normal fibrinogen levels (56.06+44.49 weeks, P=.429).

The secondary outcomes of reintervention and overall stroke were not statistically significant between the two groups (P=1.000 and P=0.053, respectively). The normal fibrinogen group had a significantly higher mortality rate (32.4% vs. 25.5%, P=.017).

Smoking Status, Hypertension and Diabetes
Smoking, hypertension, diabetes and hyperlipidaemia did not influence the primary outcome of restenosis (P=.491, .286, .193, .971 respectively). None of them affected the secondary outcomes of reintervention (P=1.000, .697, 1.000, .219), overall stroke (P=.808, .275, .772, .369) or mortality (P=.980, .305, .632, .583), respectively.

Symptomatic Status
Restenosis rate was not significant between the asymptomatic and symptomatic groups (P=.829).

Asymptomatic patients had significantly higher reintervention rates than symptomatic patients (2.4% vs. 0.3%, P=.024). 10-year reintervention-free survival was 97.6% (7 of 289) in asymptomatic patients and 99.7% (1 of 383) in symptomatic patients (log rank P=.020)(Figure 4). Secondary outcomes of overall stroke and mortality were not statistically different between the asymptomatic and symptomatic groups (P=.848, .618), respectively. There was no significant difference in 10-year stroke-free survival and overall survival between asymptomatic and symptomatic patients (log rank P.819 and .245), respectively.

Degree of Ipsilateral Stenosis
Restenosis rate was not significant between the <70% and >70% degree of ipsilateral stenosis groups (P=.494).

Reintervention was significantly higher in the <70% group compared to the >70% degree of ipsilateral stenosis (4.0% vs. 0.7%, P=.005). 10-year reintervention-free survival was 96.0% (5 of 126) in the <70%

group and 99.3% (4 of 540) in the >70% group (log rank P=.004). The mean time to reintervention was 60.77+41.47 weeks in the <70% group and 63.45+41.72 weeks in the >70% group (P=.516, 95%-CI:-10.78–5.41). Secondary outcomes of stroke and mortality were not significant between the two groups (P=.684, .670), respectively. Likewise, there is no significant difference in 10-year stroke-free survival and overall survival (log rank P=.669 and .947), respectively.

Outcomes of Restenosis

Out of 94 patients who developed restenosis, only 4 patients required reintervention. This was a higher reintervention rate compared to patients who would have required reintervention for any cause other than restenosis (4.3% vs. 0.8%, P=.007). Secondary outcomes of stroke (28.6% vs. 13.2%, P=.095) and mortality (10.6% vs. 14.6%, P=.161) were not statistically significant between patients with restenosis and those without, respectively. Other postoperative complications did not differ significantly between the groups.

All four patients requiring reintervention were asymptomatic at the time of the second procedure. The indication for reintervention in two patients was the development of a sinus from the carotid patch to the skin below the stitch, with a ruptured carotid patch in one patient. The other two patients had 90-99% and 60-70% asymptomatic stenosis, respectively. Post-operatively, one patient suffered an ipsilateral stroke within 24 hours and none had an MI or death. There were no other postoperative complications in these patients.

Out of 90 patients who did not undergo reintervention for restenosis, no patients suffered an ipsilateral stroke compared to 1 patient in the reintervention group (0% vs. 25.0%, P<.001). Twenty-one patients without reintervention died during ten year follow up, compared to none in the reintervention group (23.3% vs. 0%, P=.273). There were no incidences of MI in the without reintervention group.

Discussion

The incidence of restenosis is quite variable in the literature due to lack of acceptance on the definition of restenosis. In our study we used the NASCET criteria, as its lower threshold identifies more cases of restenosis compared to the ECST criteria.

Higher rates of restenosis are reported in earlier studies and may be partly explained by improvement in surgical technique over time. Earlier CEAs were commonly performed by primary closure. The smaller arterial diameter ensuing from this technique, compared to patch closure, increases the risk of restenosis[3, 6, 7]. This was quite obvious within our own cohort of patients, where CEA with primary closure had a restenosis rate of 18.9% and eversion technique had a restenosis rate of 18.2% compared to 12.7% in patch closure patients (P=.022).

Our 18.2% restenosis rate following eversion endarterectomy is higher than those reported in other studies[7,17,18]. The use of inferior techniques of balloon angioplasty and stenting performed in earlier endovascular carotid surgeries may account for the higher restenosis rates compared to the 1.9% at our institution[19].

Differences in follow-up duration between studies influence the variations in restenosis incidence rates. A systematic review of the literature by Frericks et al. reported a 10% risk of restenosis in the first year, 3% in the second and a long-term risk of 1% per year4. In our tertiary vascular referral centre, 13.6% of interventions resulted in restenosis, over a follow up period of 12 years. Of these 94 cases, 88.3% occurred 1 year after the initial procedure, 7.4% occurred in the second year and 4.2% occurred in the long-term.

In our study we found female gender to be an independent predictor of carotid restenosis, with an odds ratio of 3.051 (95%-CI:1.856–5.016, P<.001) to develop restenosis compared to males. Females may be at higher risk for restenosis due to a smaller arterial diameter of the carotid artery3. Other possible reasons include kinking of carotid vessels, sex-related differences in platelet function and hormonal causes[3].

There is a lack of consensus in current literature about the impact of increasing age on carotid restenosis. Several studies including our own have not found a statistically significant correlation between age and carotid restenosis3. Others, most notably EVA-3S trial, found increasing age to be significantly associated with restenosis [6,10].

Unlike CREST and several other studies, dyslipidemia and diabetes were not found to be independent predictors of restenosis in our study[5, 6,8].

We found hyperfibrinogenemia to be significantly associated with higher restenosis rates. A previous study found a nearly 6 times higher likelihood of restenosis in patients with hyperfibrinogenemia compared to those with normal fibrinogen levels (OR 5.83)[14]. Hyperfibrinogenemia is an independent risk factor for cerebrovascular atherosclerosis. It modifies the histological composition of atherosclerotic plaques that predisposes them to carotid thrombosis[14]. Immunohistochemical analysis of plaques from patients with hyperfibrinogenemia showed a high number of inflammatory cells in the shoulder and cap of the plaque, as well as reduced plaque thickness[14]. In turn, both inflammatory infiltration and decreased cap thickness are associated with carotid plaque thrombosis and rupture[14].

Our study identified the presence of contralateral stenosis and ASA grades 2 and 3 to be independent predictors of restenosis. Our literature review did not find any studies reporting on an association between ASA grades and restenosis. The higher the ASA grade, the more comorbidities the patient has and these comorbidities may correlate with the higher restenosis rates observed in these patients.[20]

There is a lack of consensus on the management of restenosis in the current literature. The incidence of patients with restenosis who require reintervention varies from 2 to 10%[11]. In our study, [4] of the [94] patients with restenosis required reintervention. Oszkinis et al. specify that patients with asymptomatic restenosis >80% and symptomatic stenosis >60% post-CEA require therapeutic intervention to reduce stroke risk[13]. All [4] patients requiring reintervention were asymptomatic at the time of the second procedure.

Studies have found that patients who develop restenosis have a 0.1 to 10% risk of stroke[3, 7]. Our study did not identify a significant increase stroke risk (1.1%) or mortality (22.3%) in patients with restenosis, compared to those who did not develop restenosis (2.2% and 29.5%, respectively).

Patients with restenosis had a higher reintervention rate, compared to those who had not developed a restenosis. Surgical intervention for restenosis has a higher risk of serious complications compared to primary intervention due to technical challenges of subsequent surgery1[1,13]. One study found complication rates to be almost two times higher after secondary intervention (10.9% vs. 5%)[13]. The incidence of cranial nerve injury is particularly higher and is attributed to a dense fibrotic tissue reaction, which creates a more difficult dissection[11]. They can be transient or cause significant disability and were found to have longer healing times[11]. In our study, 1 patient suffered a major ipsilateral stroke [24] hours after reintervention. There were no other postoperative complications. Ultimately, the higher risk of subsequent surgery must be weighed against the risk of developing neurological complications from the restenosis.

The duration of follow-up with DUS to detect restenosis remains uncertain. Our centre vigorously follows patients at 6 weeks post-operatively and then at 6-monthly intervals for the next 3 years following procedure. Beyond that, patients were followed with DUS on an annual basis until 10 years post-procedure. In our study, 1 of 94 patients with restenosis suffered an ipsilateral stroke. The CAVATAS trial found that patients who developed restenosis within 60 days of the procedure were at a significantly higher risk for progression to severe restenosis compared to patients without early restenosis[21]. The trial also found that patients who developed >70% restenosis within 1 year post-operatively had an increased risk of subsequent ipsilateral cerebrovascular events[21]. These observations combined with our own results may be helpful in selecting patients for long-term follow-up.

Conclusion

Female gender, contralateral stenosis 90-99% and ASA grades 2 and 3 are independent predictors of carotid restenosis. Hyperfibrinogenemia

and open procedures are significantly associated with higher restenosis rates. We would recommend patch closure due to its significantly lower restenosis rate. Age was not an independent predictor of restenosis, showing that elderly patients must not be discriminated against when determining suitability for carotid surgery. DUS surveillance is not recommended beyond two years of initial surgery, as restenosis rates are highest in the first postoperative year.

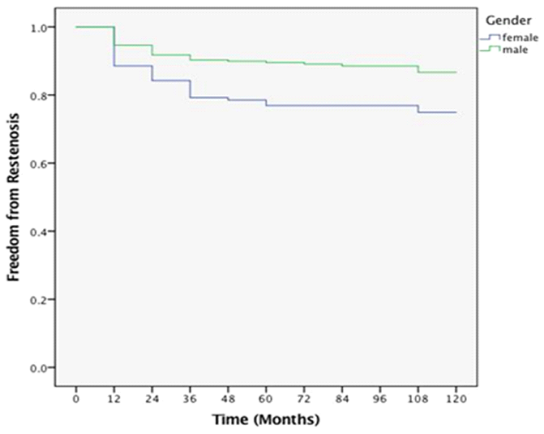
Tables 1. Vascular- Related Risk Factors and Clinical Presentation of Patients

Factor	No Restenosis	Restenosis	p Value	Odds Ratio	95% Confidence Interval	
Gender, female	46 (29.8)	178 (29.8)	<0.001	3.051	1.856	5.016
Age, <80	541 (91.2)	5 (94.6)	0.319	0.583	0.227	1.501
Smoking	210 (36.1)	31 (33.7)	0.649	0.931	0.588	1.475
Diabetes	114 (19.3)	22 (23.7)	0.323	1.279	0.761	2.149
Hypertension	447 (75.8)	68 (73.1)	0.582	0.885	0.540	1.451
Hyperfibrinogenaemia	198 (38.7)	45 (56.3)	0.003	2.032	1.262	3.272
Hyperlipidemia	460 (77.7)	73 (78.5)	0.864	1.064	0.626	1.809
Atrial fibrillation	74 (13.1)	12 (13.8)	0.854	1.048	0.544	2.019
Ischemic heart disease	204 (34.5)	28 (30.1)	0.404	0.851	0.532	1.360
Chronic renal disease	66 (11.1)	10 (10.8)	0.910	0.947	0.468	1.914
Chronic lung disease	135 (23)	21 (22.8)	0.977	0.977	0.579	1.647
Emergency procedure	184 (31.1)	35 (37.6)	0.212	1.309	0.832	2.059
Symptomatic	333 (56.7)	54 (58.7)	0.723	1.052	0.675	1.639
Ipsilateral stenosis, 90-99% 70-89% 50-69% <50%	278 (47.9) 196 (33.8) 87 (15) 19 (3.3)	45 (48.4) 28 (30.1) 16 (17.2) 4 (4.3)	0.842	0.829	0.485	1.419
Contralateral stenosis, Occluded 90-99% 70-89% 50-69% <50%	33 (5.7) 28 (4.8) 62 (10.7) 49 (8.4) 404 (69.4)	9 (9.7) 7 (7.5) 5 (5.4) 9 (9.7) 1 (1.1)	0.337	0.199	0.054	0.742
Plaque type, echolucent	88 (17.2)	14 (17.3)	0.309	0.919	0.501	1.683
Previous ipsilateral treatment	58 (9.9)	6 (6.5)	0.344	0.618	0.259	1.476
Previous contralateral treatment	78 (13.4)	17 (18.3)	0.207	1.427	0.801	2.540
Previous neck radiation	3 (0.5)	0 (0)	0.488	0.860	0.834	0.887
ASA Grade 1	16 (2.9)	2 (2.4)	0.001	0.727	0.109	4.849
ASA Grade 2	296 (54.3)	37 (44.6)	0.001	0.165	0.062	0.437
ASA Grade 3	220 (40.4)	35 (42.2)	0.001	0.226	0.085	0.602

2. Adverse Outcomes According to Procedure Type

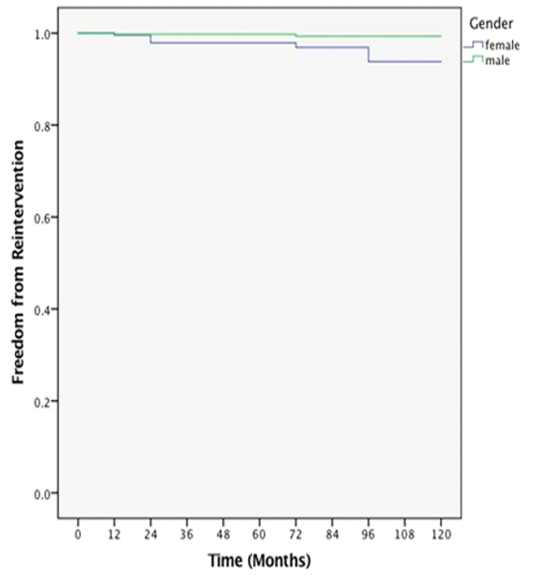
	Primary (n=111)	Patch (n=447)	Eversion (n=55)	Carotid Bypass (n=3)	CAST (n=54)	p Value
Restenosis	18.9 (21)	13.0 (58)	18.2 (10)	33.3 (1)	1.9 (1)	0.022
Reintervention	1.8 (2)	1.3 (6)	0 (0)	0 (0)	1.9 (1)	0.900
30 Day Stroke	0.9 (1)	0.7 (3)	1.8 (1)	0 (0)	1.9 (1)	0.855
5 Year Death	16.2 (18)	15.7 (70)	10.9 (6)	0 (0)	13.0 (7)	0.779

Figure 1



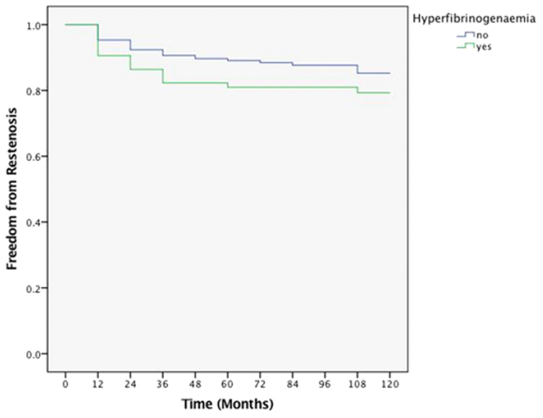
	0	12	24	36	48	60	72	84	96	108	120
F	209.5 ±0.02	164 ±0.03	135 ±0.03	110 ±0.03	97 ±0.03	84.5 ±0.03	70 ±0.03	53.5 ±0.03	38.5 ±0.04	25.5 ±0.04	11.5 ±0.09
M	428.5 ±0.01	360 ±0.01	311 ±0.01	265 ±0.02	229 ±0.02	195.5 ±0.02	159 ±0.02	125.5 ±0.02	94.5 ±0.02	61.5 ±0.02	23.5 ±0.04

Figure 2



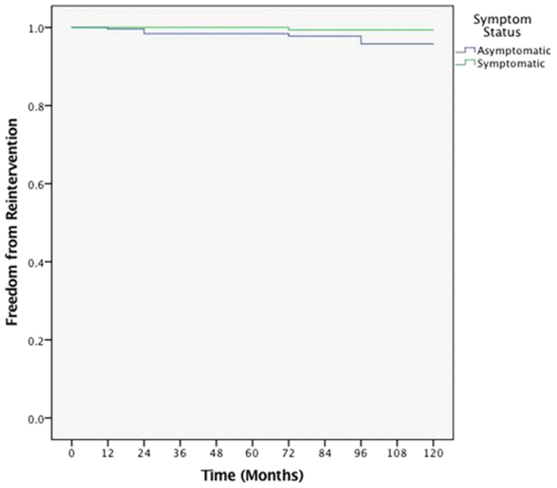
	0	12	24	36	48	60	72	84	96	108	120
F	211 ±0.00	183.5 ±0.01	155.5 ±0.01	134 ±0.01	116.5 ±0.01	99.5 ±0.01	79.5 ±0.01	62.5 ±0.01	44 ±0.01	29 ±0.01	11.5 ±0.01
M	430 ±0.00	380.5 ±0.00	340.0 ±0.00	294.5 ±0.00	254.5 ±0.00	218 ±0.01	176.5 ±0.01	139.5 ±0.01	103.5 ±0.01	68 ±0.01	25.5 ±0.01

Figure 3



	0	12	24	36	48	60	72	84	96	108	120
Yes	232.5 ±0.01	207.5 ±0.01	185 ±0.01	159.5 ±0.01	142 ±0.01	125 ±0.01	102 ±0.01	80 ±0.01	55 ±0.01	31 ±0.01	11 ±0.01
No	318 ±0.01	266.5 ±0.01	228.5 ±0.01	199 ±0.01	173 ±0.01	144.5 ±0.01	116 ±0.01	94.5 ±0.01	78 ±0.01	60.5 ±0.01	26 ±0.04

Figure 4



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