Incidence of End-Stage Renal Disease Following Bariatric Surgery in the Swedish Obese Subjects Study

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Abstract

Background—Obesity is a major public health problem leading to co-morbidities such as diabetes, hypertension and kidney failure. Bariatric surgery results in pronounced and maintained weight loss and prevention of obesity-related diseases and their complications. Most studies of bariatric surgery on kidney disease show improvements after surgery. However, long-term studies analyzing hard end-points are lacking. Here we report on the long-term effects of bariatric surgery compared to usual obesity care on incidence of end-stage renal disease (ESRD) alone and in combination with chronic kidney disease stage 4 (CKD4/ESRD).

Methods—4047 patients were included in the Swedish Obese Subjects (SOS) study. Inclusion criteria were age 37–60 years and BMI ≥34 in men and BMI ≥38 in women. Patients in the bariatric surgery group (N=2010) underwent banding (18%), vertical banded gastroplasty (69%) or gastric bypass (13%); controls (N=2037) received usual obesity care. In this analysis, patients were followed up for a median time of 18 years. The incidence of ESRD and CKD4 was obtained by crosschecking the SOS database with the Swedish National Patient Register.
Results—During follow-up, ESRD occurred in 13 patients in the surgery group and in 26 patients in the control group (adjusted hazard ratio (HR) = 0.27; 95% CI 0.12 – 0.60; p=0.001). The number of CKD4/ESRD events was 23 in the surgery group and 39 in the control group (adjusted HR = 0.33; 95% CI 0.18 – 0.62; p<0.001). In both analyses, bariatric surgery had a more favorable effect in patients with baseline serum insulin levels above median compared to those with lower insulin levels (interaction p=0.010). Treatment benefit of bariatric surgery was also greater in patients with macroalbuminuria at baseline compared to those without macroalbuminuria (interaction p<0.001).

Conclusions—Our study showed for the first time that bariatric surgery is associated with a long-term protection against ESRD and CKD4/ESRD.

Introduction

Overweight and obesity has during the last decades escalated to a global epidemic.(1, 2) Obesity is associated with serious conditions, such as diabetes and hypertension,(3–5) which contribute to development of chronic kidney disease (CKD) and kidney failure.(6) Additionally, obesity is an independent risk factor for initiation and progression of renal damage.(6–8)

Weight loss most likely plays an important role in prevention and reduced progression of CKD and kidney failure. Bariatric surgery is currently the most efficient way to achieve and maintain significant long-term weight loss.(9, 10) Recent studies have concluded that bariatric surgery attenuates diabetes mellitus and its microvascular complications such as nephropathy in patients with obesity and diabetes at baseline. (11–13) Several other studies have directly addressed the effects of bariatric surgery on kidney function. Most of these studies points towards an improvement in kidney function after bariatric surgery (14). However, several of these studies have been limited in either number of patients, short follow-up time, or both. The latest review of this topic clearly indicates the need for further well-powered long-term studies to establish if bariatric surgery can reverse CKD or delay progression to ESRD.(14)

In this study, we have examined the effects of bariatric surgery compared to usual obesity care on incidence of end-stage renal disease (ESRD). In a complementary analysis, we included chronic kidney disease stage 4 (CKD4) as a renal end-point alongside ESRD. CKD4 is the state of severe chronic kidney damage preceding ESRD. As renal function deteriorates to CKD4, specialist care is usually required, which makes the complementary CKD4/ESRD analysis clinically relevant. We have also investigated the association between risk factors for chronic kidney disease and the effect of bariatric surgery on the incidence of ESRD and CKD4/ESRD.

Methods

Seven regional ethics review boards (Gothenburg, Lund, Lindköping, Örebro, Karolinska Institute, Uppsala, Umeå) approved the study protocol. All patients provided written or oral informed consent. The study has been registered at ClinicalTrials.gov (NCT01479452).
Study participants

The Swedish Obese Subjects (SOS) study is an on-going, non-randomized, matched, prospective intervention study involving participation of 25 public surgical departments and 480 primary health care units in Sweden. The study design has been thoroughly accounted for in previous publications. In total, 4047 patients were recruited in this study between 1 September 1987 and 31 January 2001. Inclusion criteria were age between 37 and 60 years and a BMI of at least 34 kg/m\(^2\) for men and 38 kg/m\(^2\) for women. In the SOS study, according to intentions-to-treat principle, 2010 patients were included in the bariatric surgery group and 2037 patients were enrolled in the matched control group.

Intervention

In the surgery group, 266 patients were treated with gastric bypass (13.2%), 376 patients with non-adjustable or adjustable banding (18.7%) and 1365 patients with vertical banded gastroplasty (68.1%). The control group was given the customary non-surgical treatment of obesity offered at their primary health care center.

Examinations and data collection

Both groups had identical examinations at baseline and after 0.5, 1, 2, 3, 4, 6, 8, 10, 15 and 20 years. Centralized biochemistry was performed at baseline and after 2, 10, 15 and 20 years. A detailed account of data collection procedures has been provided in earlier publications.

Data on the incidence of diagnosed ESRD and CKD4 was obtained from the Swedish National Patient Register. The cut-off date for register linkage in the current report was 31 December 2013, resulting in a median follow up time of 18 years (interquartile range 14 to 21 years, maximum 26 years).

Patients were given clear and comprehensive instructions on how to collect 24 hours’ urine samples at home. Urinary albumin excretion rate (U-AER) was calculated on the basis of the 24 hours’ urine collection, expressed in mg per 24 hours. Urinary albumin-to-creatinine ratio (U-ACR) was calculated based on urinary albumin and creatinine concentrations.

Normoalbuminuria was defined as U-AER < 30 mg albumin/24h or, alternatively, U-ACR < 3.4 mg/mmol. Microalbuminuria was defined as 30 ≤ U-AER < 300 mg albumin/24h or, alternatively, 3.4 ≤ U-ACR < 34 mg/mmol. Macroalbuminuria was defined as U-AER ≥ 300 mg albumin/24h or, alternatively, U-ACR ≥ 34 mg/mmol. An estimate of renal function was derived from a value for estimated glomerular filtration rate (eGFR) calculated according to a four variable MDRD (Modification of Diet in Renal Disease) formula, where the race factor was not included. Impaired fasting glucose (IFG) was defined as fasting blood glucose of at least 90 mg/dl (5.0 mmol/L) and less than 110 mg/dl (6.1 mmol/L). Diabetes was defined by self-reported medication with antidiabetic drugs or by fasting blood glucose greater or equal to 110 mg/dl (6.1 mmol/L). Hypertension was defined as systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg or self-reported treatment with antihypertensive medication. The index of intraabdominal pressure and visceral adiposity was expressed by means of the sagittal diameter, measured as the
distance between the examination table and a carpenter’s level held horizontally across the abdomen at the level of the iliac crest. (18)

Outcomes

The primary end-point of the SOS study was overall mortality (9) and power calculations were performed based on this outcome. The secondary end-points were cardiovascular disease, (19) diabetes (10) and gall bladder disease. (20) Kidney disease was not a predefined endpoint. Here we define ESRD in accordance to the CDISC (Clinical Data Interchange Standards Consortium, Inc) criteria, namely:

- Diagnosed chronic kidney disease stage 5 (CKD5), end-stage renal disease, end-stage of chronic renal insufficiency and/or
- Treatment with chronic dialysis and/or
- Kidney transplantation.

Diagnosed chronic kidney disease stage 4 (CKD4) was added as a renal end-point to the above-mentioned ESRD criteria in a complementary CKD4/ESRD analysis. The complete list of the ICD-9, ICD-10 and procedure codes defining the renal outcomes of this study is presented in Supplementary Table 1.

Statistical analysis

The baseline characteristics were described using mean values with standard deviations. Evaluation of baseline differences between the treatment groups were performed using two-sided t-tests for continuous variables and Fisher’s exact test for categorical variables. Patients were followed up until any of the previously listed renal end-points defining ESRD or CKD4/ESRD, censoring, or until the cut-off date.

Time to renal event was compared between the surgery and the control groups using Kaplan-Meier estimates of cumulative incidence rates. The statistical differences in cumulative incidence was analyzed using the log-rank test. Cox proportional-hazards model with a single covariate was used to calculate the hazard ratio. Hazard ratios adjusted for sex and baseline diabetes status, hypertension, age, BMI, sagittal diameter, serum triglycerides and natural log transformed (ln-transformed) values of U-AER or U-ACR were calculated using a multivariate Cox regression model. Natural log transformation of U-AER and U-ACR values was carried out in the multivariate analyses in order to reduce the skewness in this data. Due to high correlation between U-AER and U-ACR, and their logarithmized values, accordingly, both could not be simultaneously included in the regression model. Hence, two separate calculations of adjusted hazard ratios were made, one using natural log-transformed U-AER, and one using natural log-transformed U-ACR as one of the variables.

The cumulative incidence of renal end-points in secondary subgroups defined in accordance to baseline parameters was calculated separately, and the association between the risk factors and the effect of bariatric surgery on ESRD and CKD4/ESRD was analyzed by introducing a corresponding interaction term to the Cox proportional hazard regression model. Dichotomous variables could attain one of the two values (e.g. male or female sex). All but two continuous variables were dichotomized based on median baseline values of the original
variables. U-AER and U-ACR were trichotomized based on above mentioned criteria for albuminuria. In total, 20 post hoc treatment interaction analyses were carried out and no correction for multiple testing was applied.

The numbers needed to treat to prevent end-stage renal disease in one patient at 10 years was calculated in different subgroups as the reciprocal of absolute risk difference between the surgery and the control groups.

The per protocol principle was applied in all analyses. In the per protocol analyses used in this study, 2007 patients were treated with bariatric surgery, whereas 2040 patients constituted the control group, owing to the fact that the bariatric surgery procedures that were planned for three patients included in the original surgery group were cancelled. During follow-up, patients were censored at the time of death or date of emigration. Two patients in the surgery group withdrew consent and were censored immediately after the date of inclusion to the study. In addition, control patients who underwent bariatric surgery and patients in the surgery group who underwent surgical re-instatement during follow-up, e.g. band removal, were identified using the National Patient Register and SOS questionnaires and they were censored at the time of surgery.

All p values were two-tailed and $p<0.05$ was considered to define statistical significance. Calculations were performed using Stata statistical package 12.1.

**Results**

**Baseline characteristics**

Detailed characteristics of study patients at baseline are presented in Table 1. Patients in the surgery group were slightly worse off as regards their metabolic condition with higher baseline mean values for BMI, sagittal diameter, body weight, systolic and diastolic blood pressure, and higher concentrations of serum insulin, cholesterol and triglycerides, compared to the control group. Risk factors for chronic kidney disease, such as diabetes, high blood glucose and hypertension, were also more pronounced in the patients in the surgery group, whereas eGFR was marginally higher than in control group.

**Incidence of ESRD and subgroup interaction analysis**

The cumulative incidence of ESRD in the control and surgery groups is shown in Figure 1. During follow-up, ESRD was observed in 26 patients in the control group, which corresponds to the incidence rate of 7.6 events (95% CI 5.2-11.1) per 10000 person years. Compared to the control group, the incidence of ESRD was lower in the bariatric surgery group, with 13 events during follow-up, corresponding to the incidence rate of 3.7 events (95% CI 2.1-6.4) per 10000 person years (log-rank $p = 0.019$; unadjusted hazard ratio = 0.46; 95% CI 0.24-0.60). Following adjustment for confounding baseline factors (sex, age, BMI, sagittal diameter, diabetes, hypertension, serum triglycerides and natural log-transformed U-AER, the hazard ratio was 0.27 (95% CI 0.12-0.60) (Table 2). Substituting natural log-transformed U-AER for natural log-transformed U-ACR in the regression model renders the adjusted hazard ratio of 0.28 (95% CI, 0.13-0.62) (Supplementary Table 2).
The cumulative incidence of ESRD stratified by different types of bariatric surgery is presented in Supplementary Figure 1. Compared to the control group, the hazard ratio of ESRD was 0.23 (1 event, 95% CI 0.03-1.70; p=0.151) in the banding subgroup; 0.59 (10 events, 95% CI, 0.28-1.22; p=0.151) in the vertical banded gastroplasty group; and 0 (0 events) in the gastric bypass group (log-rank p=0.093).

The incidence of ESRD in subgroups stratified in accordance to baseline parameters and interactions between the baseline risk factors and treatment effects are presented in Table 3. In the control group, male sex, baseline diabetes, baseline hypertension, elevated systolic blood pressure, higher levels of blood glucose, serum insulin and creatinine, along with micro- and macroalbuminuria were associated with higher incidence of ESRD (Table 3).

In general, bariatric surgery was associated with lower incidence rates of ESRD in baseline subgroups compared to usual care, with hazard ratios ranging from 0.15 to 0.97; the only exception among among smokers. Increased relative treatment benefit of bariatric surgery was observed in the subgroups with higher serum insulin (interaction p=0.010) and with macroalbuminuria (U-AER interaction p<0.001; U-ACR interaction p<0.001). Noteworthy, the lowest hazard ratios were observed in patients with macroalbuminuria at baseline (HR=0.19, 95%CI 0.06-0.60, and NNT = 8 for patients with baseline U-AER > 300 mg/24h; HR=0.15, 95% CI 0.04-0.57, and NNT = 5 for patients with baseline U-ACR > 34 mg/ mmol) (Table 3).

**Incidence of CKD4/ESRD**

The cumulative incidence graphs for the CKD4/ESRD event in the control and surgery group are shown in Figure 2. During follow-up, CKD4/ESRD was observed in 39 patients in the control group, which corresponded to the incidence rate of 11.4 events (95% CI 8.3-15.6) per 10000 person years. In the bariatric surgery group, the observed number of patients with incident CKD4/ESRD was 23, corresponding to the incidence rate of 6.5 events (95% CI 4.3-9.8) per 10000 person years, which was lower compared to the control group (log-rank p= 0.016; unadjusted hazard ratio = 0.53; 95% CI 0.32-0.89). Following adjustment for confounding baseline factors (sex, age, BMI, sagittal diameter, diabetes, hypertension, serum triglycerides and natural log-transformed U-AER), the hazard ratio was 0.33 (95% CI, 0.18-0.62) (Supplementary Table 3). Substituting natural log-transformed U-AER for natural log-transformed U-ACR in the regression analysis rendered the adjusted hazard ratio of 0.35 (95% CI, 0.19-0.64) (Supplementary Table 3).

The incidence of a CKD4/ESRD event in subgroups stratified by baseline risk factors, and interactions between risk factors and treatment are presented in Table 4. Generally, this interaction analysis rendered similar results as for the ESRD outcome. Increased treatment benefit of bariatric surgery compared to usual care was again observed in patients with higher serum insulin (interaction p=0.002), and with macroalbuminuria (U-AER interaction p<0.001; U-ACR interaction p<0.001) at baseline. The lowest hazard ratios were observed in patients with baseline U-AER > 300 mg/24h (HR=0.18, 95% CI 0.07-0.48, NNT = 6), and in those with baseline U-ACR > 34 mg/mmol (HR=0.14, 95% CI 0.04-0.44, NNT = 4), respectively (Table 4).
Discussion

The results of our study show that the long-term incidence of ESRD was reduced by over 70%; and the incidence of CKD4/ESRD was reduced by 65%, respectively, in the surgery group compared to the usual care control population. This highlights the possibility of weight-loss as a part of the long-term prevention strategy for kidney disease.

The analyses of the secondary subgroups showed that control patients with higher degree of metabolic disturbances at baseline generally were more prone to develop ESRD. In the high-risk control subgroups (male sex, diabetes, high systolic blood pressure, elevated levels of blood glucose, serum creatinine and urinary albumin at baseline) the incidence of ESRD was consistently higher than in corresponding low-risk control subgroups. This supports our previous findings, where the same factors (except S-creatinine) were found to significantly contribute to development of albuminuria. (22) In the current study, the risk reduction obtained for ESRD was also comparable to the risk reduction for albuminuria previously seen in the SOS study. (22)

In the risk factor-treatment interaction analysis, increased beneficial effects of bariatric surgery on prevention of ESRD were observed in patients with high serum insulin levels and macroalbuminuria at baseline. The same effects were seen in the complementary CKD4/ESRD analysis. The results of this interaction analysis were in line with our previous reports regarding factors predicting efficacy of bariatric surgery in prevention of various types of obesity-related disorders. This work, as well as our previous reports showed that in the SOS study baseline BMI is not a predictor of the effect of bariatric surgery, whereas different biochemical manifestations of disturbed glucose metabolism have repeatedly emerged as the factors that predicted benefits of bariatric surgery. (10, 19, 23) For instance, elevated baseline level of serum insulin was earlier shown to be a predictive factor in prevention of long-term cardiovascular events (19) and female-specific cancer. (23) Both elevated serum insulin and impaired fasting glucose at baseline were predictors for benefits of surgical obesity treatment in prevention of diabetes mellitus type 2. (10) Patients with prediabetes at baseline benefited more from bariatric surgery regarding long-term prevention of microvascular disease, compared to those with diabetes or normoglycemia. (24) Finally, in patients with obesity and diabetes at baseline, treatments with bariatric surgery resulted in the same total health care costs compared to the control population, although in the normoglycemic and prediabetes subgroups surgery was a more costly treatment option in regards to the total health costs. (25) Anew, our results raised the question whether guidelines for selecting patients for bariatric surgery need to be adapted to the new research findings and possibly include biochemical characteristics alongside or instead of BMI.

In the current study, macroalbuminuria was observed as a predictor of beneficial effects of bariatric surgery on prevention of ESRD and CKD4/ESRD. Following bariatric surgery, the incidence of ESRD was reduced by over 80% in patients with macroalbuminuria at baseline, with NNT to prevent one case of ESRD of 8 or 5 depending on whether macroalbuminuria was defined based on U-AER or U-ACR, respectively. Similar results were obtained for the incidence of the CKD4/ESRD. These results implied that bariatric surgery might have a
clinically relevant protective renal effect in obese patients with overt nephropathy and progressing renal damage.

One limitation of the SOS study is the fact that the study was not randomized due to the ethical considerations from 1980s related to the relatively high postoperative death rate (1-5%) following bariatric surgery. The study was not originally designed to address the issue of the effects of bariatric surgery on the incidence of chronic kidney damage and end-stage renal disease. However, to date this is the most comprehensive analysis of the association between bariatric surgery, CKD4 and ESRD. The major strengths lie in both the length of the follow-up time and the extensive study population. The length of the follow-up may be of particular importance since CKD4 and ESRD are late complications of obesity and obesity-related disorders, and usually take several years to develop. Our definitions of renal events include unambiguous and relevant register-based data. ESRD is defined in line with the latest criteria for ESRD proposed by the CDISC (Clinical Data Interchange Standards Consortium, Inc). The coverage of the data on the somatic disorders in the Swedish National Patient Register is 99% for inpatient care and 80% for specialist outpatient care.

In conclusion, bariatric surgery reduced the long-term incidence of ESRD by over 70% compared to conventional obesity treatment. The long-term incidence of clinically relevant obesity-related severe renal conditions that require specialist care, and include CKD4 and ESRD, was reduced by 65% following bariatric surgery. Elevated serum insulin and macroalbuminuria at baseline predicted relative benefits of bariatric surgery compared to conventional obesity treatment as regards prevention of ESRD and CKD4/ESRD. Thus, end-stage renal disease can now be added to the list of hazardous obesity-related health conditions that may be prevented by bariatric surgery.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Kaplan-Meier estimates of cumulative incidence of ESRD in the control group compared to the surgery group. Shaded areas in the graph represent 95% confidence intervals (CI) of the cumulative incidence. The x-axes are truncated at 22 years but all observations after 22 years were included in the analyses. HR=hazard ratio.
Figure 2.
Kaplan-Meier estimates of cumulative incidence of CKD4/ESRD in the control group compared to the surgery group. Shaded areas in the graph represent 95% confidence intervals (CI) of the cumulative incidence. The x-axes are truncated at 22 years but all observations after 22 years were included in the analyses. HR=hazard ratio.
Table 1
Baseline characteristics of study patients, showing mean values with standard deviations, where applicable.

|                          | Control       | Surgery       | p-value |
|--------------------------|---------------|---------------|---------|
| Age (years)              | 48.7±6.3      | 47.2±5.9      | <0.001  |
| Male gender (%)          | 29.1          | 29.2          | 0.917   |
| BMI (kg/m²)              | 40.1±4.7      | 42.4±4.5      | <0.001  |
| Sagittal diameter (cm)   | 27.4±3.7      | 28.9±3.7      | <0.001  |
| Body weight (kg)         | 114.7±16.5    | 120.9±16.6    | <0.001  |
| SBP (mmHg)               | 137.9±18.0    | 145±18.8      | <0.001  |
| DBP (mmHg)               | 85.2±10.7     | 89.9±11.1     | <0.001  |
| Hypertension (%)         | 63.9          | 78.4          | <0.001  |
| Blood glucose (mg/dL)    | 88.2±32.4     | 93.3±36.0     | <0.001  |
| IFG (%)                  | 14.2          | 15.1          | 0.476   |
| Insulin (mU/L)           | 18.0±11.4     | 21.5±13.7     | <0.001  |
| Diabetes (%)             | 12.9          | 17.2          | <0.001  |
| S-cholesterol (mg/dL)    | 221.8±41.6    | 225.7±43.3    | <0.001  |
| Triglycerides (mg/dL)    | 189.9±132.8   | 196.9±127.4   | <0.001  |
| HDL cholesterol (mg/dL)  | 52.4±13.4     | 52.4±12.5     | 0.845   |
| eGFR MDRD4 (mL/min/1.73 m²)| 92.4±14.6    | 93.4±14.5    | 0.025   |
| S-creatinine (μm/L)      | 69.6±9.6      | 69.2±8.8      | 0.201   |
| U-AER (mg/24h)           | 53.6±316.7    | 69.4±429.9    | 0.187   |
| U-ACR (mg/mmol)          | 3.4±16.6      | 4.4±31.5      | 0.199   |
| Daily smoking (%)        | 20.8          | 25.8          | <0.001  |

BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; IFG = impaired fasting glucose; HDL = high density lipoprotein; eGFR MDRD4 = estimated glomerular filtration rate according to four variable Modification of Diet in Renal Disease formula; U-AER = urinary albumin excretion rate; U-ACR = urinary albumin-to-creatinine ratio.
### Table 2

Adjusted hazard ratios for incidence of ESRD, calculated per standard deviation where applicable, using ln (U-AER) as one of the variables.

|                          | HR    | 95% CI      | p-value |
|--------------------------|-------|-------------|---------|
| Surgery, yes/no          | 0.27  | 0.12 - 0.60 | 0.001   |
| Sex, men/women           | 1.84  | 0.88 - 3.87 | 0.105   |
| Age, per 6.15 years      | 1.39  | 0.96 - 2.00 | 0.080   |
| BMI, per 4.74 kg/m²      | 0.92  | 0.62 - 1.37 | 0.676   |
| Sagittal diameter, per 3.74 cm | 1.18  | 0.84 - 1.65 | 0.332   |
| Diabetes, yes/no         | 2.05  | 0.94 - 4.50 | 0.072   |
| Hypertension, yes/no     | 2.26  | 0.65 - 7.87 | 0.201   |
| Triglycerides, per 1.48 mg/dL | 0.94  | 0.76 - 1.17 | 0.598   |
| ln (U-AER), per 1.11 unit | 2.27  | 1.78 - 2.91 | <0.001  |

BMI = body mass index; ln (U-AER) = natural log-transformed urinary albumin excretion rate.
Table 3

Incidence of ESRD, risk factor treatment interaction analyses and numbers needed to treat

| SURGERY | CONTROL | RELATIVE TREATMENT EFFECTS |
|---------|---------|-----------------------------|
|         | N Events | IR/10,000 95% CI | N Events | IR/10,000 95% CI | Log-rank p | HR 95% CI | p for HR | Interaction p* | NNT |
| TOTAL   | All      |                  |          |                  |            |          |          |          |             |     |
| Sex     |          |                  |          |                  |            |          |          |          |             |     |
| Female  | 1420     | 5                 | 2.0      | 0.8              | 4.8       | 1447     | 10        | 4.1      | 2.2          | 7.6  | 0.45 | 0.15 | 1.33 | 0.147 | 0.938 | 474 |
| Male    | 587      | 8                 | 8.0      | 4.0              | 16.0      | 593      | 16        | 16.2     | 9.9          | 26.4 | 0.001| 0.48 | 0.21 | 1.13 | 0.091 | 122 |
| Smoking |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| No      | 1487     | 11                | 4.1      | 2.3              | 7.5       | 1608     | 24        | 8.8      | 5.9          | 13.3 | 0.45 | 0.22 | 0.91 | 0.026 | 0.333 | 214 |
| Yes     | 518      | 2                 | 2.3      | 0.6              | 9.3       | 422      | 1         | 1.4      | 0.2          | 10.2 | 0.045| 1.48 | 0.14 | 1.588| 0.744 | –    |
| Diabetes|          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| No      | 1656     | 7                 | 2.4      | 1.1              | 5.0       | 1773     | 17        | 5.6      | 3.5          | 9.0  | 0.41 | 0.17 | 0.98 | 0.045 | 0.981 | 309 |
| Yes     | 344      | 6                 | 10.4     | 4.7              | 23.1      | 263      | 9         | 22.3     | 11.6         | 42.9 | <0.001| 0.41 | 0.14 | 1.18 | 0.097 | 84  |
| IFG     |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| No      | 1335     | 7                 | 2.9      | 1.4              | 6.1       | 1483     | 12        | 4.8      | 2.7          | 8.4  | 0.59 | 0.23 | 1.49 | 0.264 | –   | 548 |
| Yes     | 301      | 0                 | 0.0      |                  | 0.0       | 290      | 5         | 10.1     | 4.2          | 24.2 | 0.149| 0.00 | 0.00 | 0.00  | –   | 99  |
| Hypertension |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| No      | 433      | 0                 | 0.0      |                  | 0.0       | 737      | 3         | 2.5      | 0.8          | 7.6  | 0.00 | 0.00 | 0.00 | –    | –   | 406 |
| Yes     | 1573     | 13                | 4.7      | 2.7              | 8.1       | 1303     | 23        | 10.4     | 6.9          | 15.6 | 0.014| 0.43 | 0.22 | 0.85 | 0.015 | 175 |
| Age     |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| < 47.8  | 47.8     | 114               | 4        | 2.0               | 0.8       | 5.4      | 921      | 10       | 6.4      | 3.5          | 11.9 | 0.29 | 0.09 | 0.93 | 0.037 | 0.133 | 227 |
| > 47.8  | 47.8     | 903               | 9        | 5.8               | 3.0       | 11.2     | 1119     | 16       | 8.5      | 5.2          | 13.9 | 0.465| 0.66 | 0.29 | 1.49 | 0.320 | 368 |
| BMI     |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| < 40.8  | 40.8     | 793               | 4        | 2.9               | 1.1       | 7.7      | 1231     | 17       | 8.0      | 5.0          | 12.9 | 0.35 | 0.12 | 1.03 | 0.057 | 0.887 | 195 |
| > 40.8  | 40.8     | 1214              | 9        | 4.2               | 2.2       | 8.1      | 809      | 9        | 6.9      | 3.6          | 13.2 | 0.860| 0.56 | 0.22 | 1.43 | 0.236 | 377 |
| Sagittal diameter |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| < 28.0  | 28.0     | 991               | 2        | 1.1               | 0.3       | 4.5      | 1314     | 13       | 5.7      | 3.3          | 9.9  | 0.19 | 0.04 | 0.84 | 0.029 | 0.889 | 217 |
| > 28.0  | 28.0     | 1009              | 11       | 6.3               | 3.5       | 11.4     | 726      | 13       | 11.1     | 6.5          | 19.2 | 0.054| 0.52 | 0.23 | 1.17 | 0.114 | 206 |
| Body weight |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| < 116.0 | 116.0    | 883               | 2        | 1.3               | 0.3       | 5.1      | 1167     | 15       | 7.5      | 4.5          | 12.4 | 0.16 | 0.04 | 0.72 | 0.036 | 0.509 | 162 |
| > 116.0 | 116.0    | 1124              | 11       | 5.6               | 3.1       | 10.1     | 873      | 11       | 7.7      | 4.3          | 14.0 | 0.804| 0.68 | 0.29 | 1.58 | 0.366 | 474 |
| SBP     |          |                  |          |                  |            |          |          |          |              |      |      |      |      |      |      |     |
| < 140.0 | 140.0    | 1012              | 3        | 1.7               | 0.6       | 5.3      | 1310     | 9        | 4.1      | 2.1          | 7.9  | 0.41 | 0.11 | 1.50 | 0.177 | 0.638 | 422 |
| > 140.0 | 140.0    | 990               | 10       | 5.7               | 3.0       | 10.5     | 726      | 17       | 13.9     | 8.6          | 22.4 | 0.002| 0.38 | 0.17 | 0.83 | 0.014 | 121 |
| EVENT | N  | HR/10,000 | 95% CI | Log-rank p | HR | 95% CI | p for HR | Interaction p* | NNT |
|-------|----|-----------|--------|------------|----|--------|----------|--------------|-----|
| DBP **(mmHg)** | < | 88.0 | 829 | 2 | 1.4 | 0.4 | 5.6 | 1226 | 13 | 6.4 | 3.7 | 11.0 | 0.21 | 0.05 | 0.94 | 0.041 | 0.381 | 201 |
|   > | 88.0 | 1172 | 11 | 53 | 2.9 | 9.5 | 807 | 13 | 9.4 | 5.5 | 16.2 | 0.401 | 0.53 | 0.24 | 1.19 | 0.123 | 242 |
| B-glucose **(mg/dL)** | < | 81.1 | 930 | 5 | 3.0 | 1.3 | 7.3 | 1092 | 8 | 4.3 | 2.2 | 8.6 | 0.70 | 0.23 | 2.13 | 0.528 | 0.827 | 790 |
|   > | 81.1 | 1069 | 8 | 43 | 2.1 | 8.6 | 944 | 18 | 11.5 | 7.2 | 18.2 | 0.013 | 0.34 | 0.15 | 0.79 | 0.012 | 139 |
| S-insulin **(mU/L)** | < | 17.0 | 866 | 7 | 46 | 2.2 | 9.7 | 1155 | 9 | 4.6 | 2.4 | 8.8 | 0.97 | 0.36 | 2.60 | 0.951 | 0.000 | -31712 |
|   > | 17.0 | 1132 | 30 | 1.4 | 6.7 | 882 | 17 | 11.6 | 7.2 | 18.7 | 0.018 | 0.24 | 0.10 | 0.61 | 0.003 | 116 |
| Triglycerides **(mg/dL)** | < | 1.8 | 903 | 6 | 3.8 | 1.7 | 8.4 | 1120 | 7 | 3.7 | 1.8 | 7.8 | 0.96 | 0.32 | 2.84 | 0.935 | 0.174 | -15453 |
|   > | 1.8 | 1100 | 7 | 3.7 | 1.7 | 7.7 | 918 | 19 | 12.4 | 7.9 | 19.4 | 0.004 | 0.28 | 0.12 | 0.67 | 0.004 | 115 |
| HDL cholesterol **(mg/dL)** | < | 1.3 | 1002 | 6 | 3.4 | 1.5 | 7.5 | 1006 | 10 | 5.9 | 3.2 | 10.9 | 0.55 | 0.20 | 1.51 | 0.243 | 0.724 | 402 |
|   > | 1.3 | 919 | 7 | 4.4 | 2.1 | 9.2 | 973 | 10 | 6.1 | 3.3 | 11.4 | 0.866 | 0.67 | 0.26 | 1.76 | 0.418 | 576 |
| Total cholesterol **(mg/dL)** | < | 5.7 | 909 | 6 | 3.8 | 1.7 | 8.4 | 1122 | 11 | 5.9 | 3.3 | 10.7 | 0.60 | 0.22 | 1.61 | 0.308 | 0.348 | 470 |
|   > | 5.7 | 1094 | 7 | 3.6 | 1.7 | 7.6 | 916 | 15 | 9.5 | 5.8 | 15.8 | 0.307 | 0.36 | 0.15 | 0.88 | 0.026 | 169 |
| S-creatinine **(µmol/L)** | < | 68.7 | 1019 | 3 | 1.6 | 0.5 | 5.1 | 1006 | 8 | 4.6 | 2.3 | 9.2 | 0.34 | 0.09 | 1.26 | 0.105 | 0.593 | 338 |
|   > | 68.7 | 984 | 10 | 59 | 3.2 | 11.0 | 1032 | 18 | 10.7 | 6.7 | 16.9 | 0.023 | 0.53 | 0.24 | 1.15 | 0.107 | 212 |
| eGFR MDRD4 | < | 91.5 | 974 | 7 | 4.2 | 2.0 | 8.8 | 1047 | 15 | 8.7 | 5.2 | 14.4 | 0.47 | 0.19 | 1.15 | 0.098 | 0.352 | 222 |
|   > | 91.5 | 1029 | 6 | 3.3 | 1.5 | 7.3 | 991 | 11 | 6.5 | 3.6 | 11.7 | 0.302 | 0.47 | 0.17 | 1.27 | 0.135 | 313 |
| U-AER **(mg/24h)** | < | 3.0 | 1515 | 5 | 19 | 0.8 | 4.5 | 1646 | 11 | 3.9 | 2.2 | 7.1 | 0.44 | 0.15 | 1.28 | 0.132 | <0.001 | 487 |
|   > | 30-300 | 381 | 4 | 63 | 2.4 | 16.9 | 312 | 6 | 11.8 | 5.3 | 26.2 | 0.51 | 0.14 | 1.82 | 0.300 | 182 |
| U-ACR **(mg/mmol)** | < | 3.4 | 1679 | 5 | 17 | 0.7 | 4.0 | 1739 | 11 | 3.6 | 2.0 | 6.6 | 0.40 | 0.15 | 1.25 | 0.120 | <0.001 | 507 |
|   > | 3.4-34 | 228 | 5 | 13.5 | 5.6 | 32.4 | 207 | 7 | 22.1 | 106 | 46.5 | 0.34 | 0.17 | 1.72 | 0.299 | 115 |

**IFG** = impaired fasting glucose; **BMI** = body mass index; **SBP** = systolic blood pressure; **DBP** = diastolic blood pressure; **HDL** = high-density lipoprotein; **eGFR MDRD4** = estimated glomerular filtration rate according to four variable Modification of Diet in Renal Disease formula; **U-AER** = urinary albumin excretion rate; **U-ACR** = urinary albumin-to-creatinine ratio.

* Significant interaction p value indicates difference in relative treatment effects in the subgroups defined by baseline parameters.
|                  | SURGERY |                | RELATIVE TREATMENT EFFECTS |
|------------------|---------|----------------|---------------------------|
|                  | N Events IR/10,000 95% CI | N Events IR/10,000 95% CI | Log-rank p | HR 95% CI p for HR Interaction p² NNT |
| TOTAL            | All     | 2007           | 23 | 6.5 | 4.3 | 9.8 | 2040 | 39 | 11.4 | 8.3 | 15.6 | 0.53 | 0.32 | 0.89 | 0.017 | 207 |
| Sex              | Female  | 1420           | 30 | 4.0 | 2.1 | 7.4 | 1447 | 14 | 5.7 | 3.4 | 9.7 | 0.63 | 0.28 | 1.42 | 0.263 | 0.645 | 567 |
|                  | Male    | 587            | 13 | 13.0 | 7.5 | 22.3 | 593 | 25 | 25.3 | 17.1 | 37.4 | <0.001 | 0.30 | 0.25 | 0.97 | 0.041 | 81 |
| Smoking          | No      | 1487           | 19 | 7.2 | 4.6 | 11.2 | 1608 | 32 | 11.8 | 8.3 | 16.6 | 0.57 | 0.32 | 1.00 | 0.052 | 0.845 | 218 |
|                  | Yes     | 518            | 4  | 4.6 | 1.7 | 12.3 | 422 | 6  | 8.7 | 3.9 | 19.3 | 0.521 | 0.48 | 0.14 | 1.69 | 0.256 | 248 |
| Diabetes         | No      | 1656           | 14 | 4.8 | 2.8 | 8.1 | 1773 | 24 | 7.9 | 5.3 | 11.8 | 0.56 | 0.29 | 1.09 | 0.087 | 0.389 | 316 |
|                  | Yes     | 344            | 9  | 15.6 | 8.1 | 29.9 | 263 | 15 | 37.4 | 22.5 | 62.0 | <0.001 | 0.35 | 0.15 | 0.81 | 0.014 | 46 |
| IFG              | No      | 1355           | 12 | 5.0 | 2.8 | 8.8 | 1483 | 17 | 6.7 | 4.2 | 10.8 | 0.30 | 0.34 | 1.45 | 0.336 | 0.251 | 577 |
|                  | Yes     | 301            | 2  | 3.8 | 0.9 | 15.1 | 290 | 7  | 14.1 | 6.7 | 29.6 | 0.086 | 0.25 | 0.05 | 1.21 | 0.085 | 97 |
| Hypertension     | No      | 433            | 1  | 1.3 | 0.2 | 9.6 | 737 | 4  | 3.3 | 1.2 | 8.7 | 0.39 | 0.04 | 3.47 | 0.398 | 0.867 | 516 |
|                  | Yes     | 1573           | 22 | 7.9 | 5.2 | 12.0 | 1303 | 35 | 15.8 | 11.4 | 22.1 | 0.002 | 0.47 | 0.28 | 0.80 | 0.005 | 126 |
| Age (years)      | < 47.8 | 1104           | 7  | 3.6 | 1.7 | 7.4 | 921 | 11 | 7.1 | 3.9 | 12.8 | 0.45 | 0.18 | 1.16 | 0.100 | 0.273 | 284 |
|                  | > 47.8 | 903            | 16 | 10.3 | 6.3 | 16.9 | 1119 | 28 | 14.9 | 10.3 | 21.6 | 0.028 | 0.66 | 0.36 | 1.22 | 0.187 | 217 |
| BMI (kg/m²)      | < 40.8 | 793            | 8  | 5.8 | 2.9 | 11.6 | 1231 | 23 | 10.9 | 7.2 | 16.3 | 0.52 | 0.23 | 1.15 | 0.105 | 0.638 | 197 |
|                  | > 40.8 | 1214           | 15 | 7.0 | 4.2 | 11.7 | 809 | 16 | 12.2 | 7.5 | 19.9 | 0.490 | 0.50 | 0.25 | 1.02 | 0.058 | 193 |
| Sagittal diameter (cm) | < 28.0 | 991            | 4  | 2.3 | 0.9 | 6.1 | 1314 | 18 | 7.9 | 5.0 | 12.6 | 0.27 | 0.09 | 0.80 | 0.018 | 0.363 | 176 |
|                  | > 28.0 | 1009           | 19 | 10.9 | 6.9 | 17.1 | 726 | 21 | 18.0 | 11.8 | 27.7 | 0.003 | 0.53 | 0.28 | 0.99 | 0.045 | 140 |
| Body weight (kg) | < 116.0 | 883           | 3  | 1.9 | 0.6 | 6.0 | 1167 | 20 | 10.0 | 6.4 | 15.4 | 0.18 | 0.05 | 0.62 | 0.006 | 0.539 | 124 |
|                  | > 116.0 | 1124          | 20 | 10.2 | 6.6 | 15.8 | 873 | 19 | 13.4 | 8.5 | 20.9 | 0.238 | 0.69 | 0.36 | 1.29 | 0.240 | 318 |
| SBP (mmHg)       | < 140.0 | 1012          | 6  | 3.4 | 1.5 | 7.7 | 1310 | 12 | 5.5 | 3.1 | 9.6 | 0.59 | 0.22 | 1.58 | 0.296 | 0.732 | 496 |
|                  | > 140.0 | 990           | 17 | 9.6 | 6.0 | 15.5 | 726 | 27 | 22.1 | 15.2 | 32.2 | <0.001 | 0.40 | 0.22 | 0.73 | 0.003 | 80 |
|                  | N  | Events | IR/10,000 | 95% CI | N  | Events | IR/10,000 | 95% CI | Log-rank p | HR   | 95% CI | p for HR | Interaction p | NNT  |
|------------------|----|--------|-----------|--------|----|--------|-----------|--------|------------|-------|--------|----------|---------------|------|
| **DBP** (mmHg)   |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 88.0           | 880| 829    | 3.5       | 1.5    | 8  | 8226   | 9.3       | 6.0    | 14.6       | 0.35  | 0.13   | 0.95     | 0.040          | 0.306|
| < 1172           | 880| 1172   | 18        | 5.4    | 13.7| 807     | 14.5      | 9.3    | 22.4       | 0.255 | 0.56   | 0.30     | 1.06           | 0.075|
| **B-glucose (mg/dL)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 81.1           | 811| 930    | 7         | 4.3    | 2.0 | 8992    | 6.5       | 3.7    | 11.4       | 0.63  | 0.25   | 1.59     | 0.326          | 0.533|
| < 1069           | 811| 1069   | 16        | 8.6    | 5.3 | 944     | 17.3      | 11.8   | 25.2       | 0.002 | 0.45   | 0.24     | 0.84           | 0.012|
| **s-insulin (μU/L)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 17.0           | 170| 866    | 11        | 7.3    | 4.0 | 1155    | 5.6       | 3.1    | 10.1       | 1.22  | 0.53   | 2.82     | 0.036          | 0.002|
| < 1132           | 170| 1132   | 12        | 6.0    | 3.4 | 882     | 19.1      | 13.2   | 27.7       | <0.001| 0.29   | 0.15     | 0.57           | <0.001|
| **Triglycerides (mmol/L)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 1.8            | 1.8| 903    | 12        | 7.5    | 4.3 | 1120    | 4.8       | 2.5    | 9.1        | 1.47  | 0.62   | 3.47     | 0.036          | 0.101|
| < 1100           | 1.8| 1100   | 11        | 5.7    | 3.2 | 918     | 19.6      | 13.7   | 28.0       | <0.001| 0.27   | 0.14     | 0.55           | <0.001|
| **HDL cholesterol (mmol/L)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 1.3            | 1.3| 1002   | 10        | 5.6    | 3.0 | 1006    | 13.5      | 9.0    | 20.3       | 0.39  | 0.19   | 0.82     | 0.013          | 0.093|
| < 1913           | 1.3| 1913   | 13        | 8.2    | 4.7 | 973     | 6.1       | 3.3    | 11.4       | 0.084| 1.24   | 0.55     | 2.82           | 0.067|
| **Total cholesterol (mmol/L)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 5.7            | 5.7| 909    | 12        | 7.6    | 4.3 | 1142    | 9.2       | 5.7    | 14.7       | 0.76  | 0.36   | 1.59     | 0.467          | 0.280|
| < 1094           | 5.7| 1094   | 11        | 5.7    | 3.2 | 916     | 14.0      | 9.2    | 21.3       | 0.316| 0.38   | 0.19     | 0.79           | 0.009|
| **s-creatinine (μmol/L)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 68.7           | 68.7| 819    | 8         | 4.4    | 2.2 | 8006    | 6.9       | 3.9    | 12.2       | 0.59  | 0.24   | 1.44     | 0.245          | 0.253|
| < 984            | 68.7| 984    | 15        | 8.9    | 5.4 | 932     | 16.0      | 11.0   | 23.3       | 0.004| 0.52   | 0.28     | 0.98           | 0.042|
| **eGFR MDRD4**   |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 91.5           | 91.5| 974    | 10        | 6.0    | 3.2 | 1047    | 12.2      | 7.9    | 18.7       | 0.46  | 0.22   | 0.99     | 0.047          | 0.335|
| < 1029           | 91.5| 1029   | 13        | 7.1    | 4.1 | 991     | 10.6      | 6.7    | 16.8       | 0.373| 0.62   | 0.31     | 1.27           | 0.093|
| **U-AER (mg/mmol)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 3.0            | 3.0| 1515   | 10        | 3.7    | 2.0 | 8646    | 5.3       | 3.2    | 8.8        | 0.65  | 0.29   | 1.43     | 0.276          | <0.001|
| < 300            | 3.0| 300    | 381       | 7      | 11.5| 312     | 23.6      | 13.4   | 41.6       | 0.44  | 0.17   | 1.12     | 0.085          | 0.79 |
| **U-ACR (mg/mmol)** |    |        |           |        |    |        |           |        |            |       |        |          |               |      |
| < 3.4            | 3.4| 1679   | 10        | 3.4    | 1.8 | 1759    | 6.3       | 4.0    | 9.9        | 0.49  | 0.23   | 1.06     | 0.070          | <0.001|
| < 228            | 3.4| 228    | 9         | 24.3   | 12.7| 207     | 31.7      | 17.1   | 59.0       | 0.68  | 0.28   | 1.67     | 0.399          | 0.135|

IFG = impaired fasting glucose; BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL = high density lipoprotein; eGFR MDRD4 = estimated glomerular filtration rate according to four variable Modification of Diet in Renal Disease formula; U-AER = urinary albumin excretion rate; U-ACR = urinary albumin-to-creatinine ratio.

* Significant interaction p value indicates differences in relative treatment effects in the subgroups defined by baseline parameters.