Circulation

ORIGINAL RESEARCH ARTICLE

Association of Metabolic Surgery With Major Adverse Cardiovascular Outcomes in Patients With Previous Myocardial Infarction and Severe Obesity

A Nationwide Cohort Study

BACKGROUND: The number of patients with myocardial infarction and severe obesity is increasing and there is a lack of evidence how these patients should be treated. The aim of this study was to investigate the association between metabolic surgery (Roux-en-Y gastric bypass and sleeve gastrectomy) and major adverse cardiovascular events in patients with previous myocardial infarction (MI) and severe obesity.

METHODS: Of 566 patients with previous MI registered in the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry undergoing metabolic surgery and registered in the nationwide Scandinavian Obesity Surgery Registry, 509 patients (Roux-en-Y gastric bypass n=465; sleeve gastrectomy n=44) could be matched 1:1 to a control with MI from SWEDEHEART, but no subsequent metabolic surgery regarding sex, age (±3 years), year of MI (±3 years), and body mass index (±3). The 2 groups were well matched, except for a lower proportion of reduced ejection fraction after MI (7% versus 12%), previous heart failure (10% versus 19%), atrial fibrillation (6% versus 10%), and chronic obstructive pulmonary disease (4% versus 7%) in patients undergoing metabolic surgery.

RESULTS: The median (interquartile range) follow-up time was 4.6 (2.7–7.1) years. The 8-year cumulative probability of major adverse cardiovascular events was lower in patients undergoing metabolic surgery (18.7% [95% CI, 15.9–21.5%] versus 36.2% [33.2–39.3%], adjusted hazard ratio, 0.44 [95% CI, 0.32–0.61]). Patients undergoing metabolic surgery had also a lower risk of death (adjusted HR, 0.45 [95% CI, 0.29–0.70]; MI, 0.24 [0.14–0.41]) and new onset heart failure, but there were no significant differences regarding stroke (0.91 [0.38–2.20]) and new onset atrial fibrillation (0.56 [0.31–1.01]).

CONCLUSIONS: In severely obese patients with previous MI, metabolic surgery is associated with a low risk for serious complications, lower risk of major adverse cardiovascular events, death, new MI, and new onset heart failure. These findings need to be confirmed in a randomized, controlled trial.

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ORIGINAL RESEARCH ARTICLE

Clinical Perspective

What Is New?

- In this observational matched-cohort study of 1018 obese individuals with previous myocardial infarction, metabolic surgery is associated with a significantly lower risk of MACE, as well as death and new myocardial infarction alone.

What Are the Clinical Implications?

- If these results are confirmed by a randomized, control trial, severely obese patients with a previous myocardial infarction can be suggested to undergo metabolic surgery as a secondary prevention.

There is a well-established association between obesity, type 2 diabetes mellitus (T2D), and cardiovascular disease (CVD).[1] With the increasing prevalence of obesity there is an expected increase in obese patients with T2D and CVD.[2,3] There is abundant evidence for treating obesity and T2D with metabolic surgery.[4–6] In patients with severe obesity and T2D, observational studies suggest that metabolic surgery reduces both macro- and microvascular complications.[7,8] Although the effect of surgery on CVD is less studied than T2D, there is evidence that metabolic surgery is more effective than nonsurgical treatment in preventing myocardial infarction (MI), stroke, heart failure, and cardiovascular mortality[9–12] in patients with severe obesity.

Despite the relatively established effect of metabolic surgery as primary prevention of CVD, there is minimal available data on the use of metabolic surgery for secondary prevention of CVD.[13,14] The "obesity paradox," which suggests a lower mortality risk with higher body mass index (BMI) in patients with established CVD, has led to some hesitation regarding the benefit of weight loss in this population. However, the association between BMI and outcome in patients with CVD appears to be U-shaped, with a higher risk in those with severe obesity (BMI>35.)[15,16] In one of the first studies to assess the feasibility of metabolic surgery as a secondary prevention strategy in cardiovascular disease, 21 patients with a MI before surgery were identified.[17] These patients were compared with 14 patients with previous MI in the conventionally treated cohort. The authors found that the surgery appeared safe and that patients who underwent surgery had significant reductions in risk factors.

The aim of the current study was to investigate the association between metabolic surgery and major adverse cardiovascular events (MACE) in patients with MI and obesity, utilizing large, well-established Swedish nationwide registries.

METHODS

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure, owing to restriction in the Swedish research ethics law. This observational matched cohort study was conducted using a register linkage between the SWEDEHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) registry, SOReg (Scandinavian Obesity Surgery Registry), the Swedish National Patient Register, the Swedish Prescribed Drug Register, and the Swedish Population Register, using the unique personal identity number assigned to each Swedish resident. The datasets generated and analyzed during this study are not publicly available owing to Swedish ethical restrictions. The study was approved by the Regional Ethical Committee in Stockholm (Dnr: 2018/2500-32) and conducted according to the Declaration of Helsinki. Swedish national databases do not require informed consent from each participant. The linkage was approved by the National Board of Health and Welfare and the SOReg and SWEDEHEART steering groups.

The SWEDEHEART registry is a national registry including almost all patients hospitalized for acute MI and admitted to a coronary care unit or other specialized facility in Sweden. In the acute coronary care part of the registry, >100 variables are collected prospectively including admission logistics, patient demographics, risk factors, past medical history, medical treatment before admission, electrocardiographic changes, biochemical markers, clinical investigations, medical treatment in hospital, interventions, hospital outcome, diagnoses, and medication at discharge. Follow-up data are limited to 1 year after MI in a subset of patients. SOReg is a nationwide registry for metabolic surgery containing nearly all patients (99%) undergoing metabolic surgery at 1 of 40 participating centers in Sweden since 2007. Data are entered into SOReg before and at the time of surgery, and at 6 weeks and 1, 2, 5, and 10 years after surgery; however, loss to 3 to 5 years follow-up is about 50%, and therefore, data beyond 2 years is less reliable.

Study Population, Covariates, and Intervention

By linking the SWEDEHEART and SOReg registries, patients who had undergone metabolic surgery in 2007 to 2018 after an MI registered in SWEDEHEART between 1995 to 2018 were identified. These patients were then matched 1:1 (without replacement, optimal) regarding sex, age (±3 years), year of MI (±3 years), and BMI (±3) to a control with MI registered in SWEDEHEART, with no subsequent metabolic surgery, and who was alive at the time of surgery of the case. The matching ratio was chosen after considering precision and balance (1:3 matching ratio did not improve balance or precision). Follow-up started the date of metabolic surgery for the case and the control.

Data regarding the last MI before metabolic surgery or start of follow-up was obtained from the SWEDEHEART registry, including type of MI, treatment, and left ventricular ejection fraction (LVEF). Baseline data, such as risk factors (including BMI), previous cardiovascular disease, and other

previous disease were obtained both from the SWEDEHEART registry and the National Patient Register, which includes all *International Classification of Diseases* (*ICD*) 10 codes for all admissions and emergency room visits to Swedish hospitals since 1987 and for all outpatient visits to specialists since 2005. The *ICD* codes are listed in Table I in the Data Supplement. Medical treatment was obtained from the Swedish Prescribed Drug Register, including all dispensed drugs in Sweden since 2005. Except for BMI, smoking status, and data regarding last MI, all covariates were updated with the most recently available information at the time of surgery or start of follow-up using data from the National Patient Register and the Swedish Prescribed Drug Register.

The surgical technique for laparoscopic gastric bypass is highly standardized in Sweden with a majority being an antecolic, antegastric, Roux-en-Y gastric bypass (RYGB) with a small (<25 mL) gastric pouch, an alimentary limb of 100 cm, and a biliopancreatic limb of 50 cm.[18] The sleeve gastrectomy (SG) is less standardized, but routinely performed using a 32 to 36 Fr bougie, starting resection no more than 5 cm from the pylorus, ending 1 cm lateral to the angle of His. Surgical complications were classified according to the Clavien–Dindo classification of postoperative complications.[19] A complication graded as ≥3b (ie, a complication requiring intervention under general anesthesia, resulting in organ failure or death) was considered to be a serious postoperative complication.

Outcome

Patients were followed up to 8 years after surgery or after the start of follow-up. The primary outcome was MACE, defined as first occurrence of death (all-cause, the databases lack information on specific causes of death), or readmission with MI (*ICD* code I21 or I22 as primary or secondary diagnosis) or stroke (subarachnoid bleeding [I60], intracerebral bleeding [I61], ischemic stroke [I63], or stroke not specified as ischemia or bleeding [I64] as primary or secondary diagnosis). Secondary outcomes were each part of primary outcome as separate outcomes (death, readmission with MI, and readmission with stroke), admission with not previously known atrial fibrillation (I48 as primary or secondary diagnosis), and admission because of previously unknown heart failure (I50 as primary diagnosis). Furthermore, the clinical outcome after surgery and number of serious complications after surgery was assessed. The rate of clinical remission for T2D, hypertension, dyslipidemia, and sleep apnea after surgery was defined as discontinuing pharmacological treatment (continuous positive airway pressure for sleep apnea) after surgery. Date of death was obtained from the Swedish Population Register, including the vital status of all Swedish residents. Admissions and *ICD* codes were obtained from the Swedish National Patient Register, which has been thoroughly validated.[20]

Statistical Methods

Descriptive continuous variables are presented as means±SD or as medians with interquartile range and categorical variables are presented as counts and proportions (%). Differences in proportions between independent groups were evaluated with χ^2 or Fisher exact test as appropriate. Kaplan–Meier survival curves were used to illustrate the outcome in patients undergoing metabolic surgery and in nonsurgical controls. Comparison was made by the log-rank test. Outcomes are also given as incident rates per 100 person-years with 95% CI and as cumulative incidence with 95% CI at 8 years of follow-up. After matching cases undergoing metabolic surgery with controls and updating with the most recent information about comorbidities at the time of surgery or start of follow-up (as previously described), the balance between cases and controls was evaluated by calculating the standardized difference which is a measure of difference in units of the pooled standard deviation (Table 1). We considered a standardized difference of >0.1 as residual imbalance and adjusted for those covariates in a Cox regression model with shared frailty to account for correlation among pairs. In model 1, we only adjusted for an imbalance in matching variables, ie, BMI (as a cubic spline with 3 knots). In model 2, we adjusted also for other residual imbalances, ie, current smoking, hypertension, chronic kidney disease, previous peripheral artery disease, heart failure, atrial fibrillation, chronic obstructive pulmonary disease, cancer diagnosis within the last 3 years, and medical treatment with aspirin, P2Y12-receptor blockers, and statins. There were no missing values for these variables and therefore no need for imputation. We performed 3 different sensitivity analyses. First, because a large proportion of patients with missing LVEF (n=290 [28%]), we performed a separate analysis also including LVEF in a complete case analysis regarding the primary end point. Second, we performed a propensity score matching analysis. In this analysis, the 1018 cases and controls were again matched on an estimated propensity score of being treated using a caliper of 0.05. The propensity score was estimated using a logistic regression analysis, including all variables in Table 1 except for LVEF (because of large proportion of missing). The balance between groups was checked by calculating the standardized difference. The analysis was then performed as a Cox regression (with shared frailty) with metabolic surgery as a predictor. Third, the same propensity score matching analysis was performed, but only included individuals with known LVEF. For all Cox regression analyses, the proportional hazard assumption was tested using the Schoenfeld residual test. IBM SPSS version 25 (IBM, Armonk, NY) and Stata version 14.0 (StataCorp, College Station, TX) were used for statistical analyses.

RESULTS

Between January 1995 and May 2018, there were 331 394 patients with MI and who were registered in SWEDEHEART at least once. During 1995 to 2009, 76 713 (37%) patients had a BMI registered, of which 3043 (4.0%) had a BMI >35 kg/m^2, and during 2010 to 2018, 112 846 (92%) patients had a BMI registered, of which 6288 (5.6%) had a BMI >35 kg/m^2. Out of 331 394 patients, 566 underwent metabolic surgery and were registered in SOReg between 2007 to 2018, and 509 cases could be matched to a control using age, sex, BMI, and year of MI (Figure 1). The 2 groups were well matched, except for a lower proportion of reduced LVEF after MI (7% versus 12%), previous heart failure (10% versus 19%), atrial fibrillation (6% versus 10%), and chronic obstructive pulmonary disease (4% versus

Table 1. Characteristics of Metabolic Surgery Patients and Nonsurgical Control Patients at the Time of Matching

	Cases (N=509)		Controls (N=509)		Standardized difference
Demography and BMI					
Age, mean (SD)	53.0	(7.0)	53.2	(7.4)	–0.028
Men, n (%)	291	(57.2)	291	(57.2)	0
BMI, mean (SD)	40.6	(4.4)	39.7	(4.7)	0.198
Other risk factors					
Smokers at last MI, n (%)	246	(48.5)	219	(43.0)	0.107
Hypertension, n (%)	332	(65.5)	365	(71.7)	-0.134
Diabetes, n (%)	209	(41.1)	229	(45.0)	-0.079
Chronic kidney function, n (%)	34	(6.7)	51	(10.0)	-0.120
Last MI					
Time since MI to surgery or start of follow-up, years mean (SD)	4.8	(3.5)	4.6	(3.7)	0.056
ST-elevation myocardial infarction, n (%)	203	(39.9)	194	(38.1)	0.037
Angiography performed, n (%)	442	(86.8)	440	(86.4)	0.012
PCI performed, n (%)	363	(71.3)	341	(67.0)	0.093
CABG performed, n (%)	18	(3.5)	16	(3.1)	0.022
LVEF determined, n (%) (n=500/507)	392	(78.4)	400	(78.9)	–0.012
LVEF<40%, n (%) (n=350/378)	24	(6.9)	46	(12.2)	–0.181
Previous cardiovascular disease					
Previous >1 myocardial infarction, n (%)	82	(16.1)	91	(17.9)	–0.048
Previous stroke, n (%)	19	(3.7)	21	(4.1)	–0.021
Previous peripheral artery disease, n (%)	10	(2.0)	22	(4.3)	–0.132
Previous heart failure, n (%)	53	(10.4)	97	(19.1)	–0.247
Previous atrial fibrillation, n (%)	29	(5.7)	49	(9.6)	–0.147
Previous other disease					
Previous chronic obstructive pulmonary disease, n (%)	22	(4.3)	37	(7.3)	–0.129
Previous cancer <3years, n (%)	3	(0.6)	16	(3.1)	–0.186
Medication					
Aspirin, n (%)	441	(86.6)	421	(82.7)	0.109
P2Y12-rec blockade, n (%)	65	(12.8)	97	(19.1)	-0.173
β-Blockade, n (%)	437	(85.9)	421	(82.7)	0.088
ACEI/ARB, n (%)	401	(78.8)	386	(75.8)	0.072
Statins, n (%)	440	(86.4)	412	(80.9)	0.149

ACEI/ARB indicates angiotensin converting enzyme inhibitor/angiotensin II receptor blocker; BMI, body mass index; CABG, coronary artery bypass graft; LVEF, left ventricle rejection fraction; MI, myocardial infarction; and PCI, percutaneous coronary intervention.

7%) in patients undergoing metabolic surgery. The standardized difference was >0.1 in another 9 covariates, indicating a residual imbalance (Table 1).

Surgery, Effect on Weight, Clinical Outcome, and Adverse Events

RYGB was used in 465 (91%) cases and SG in 44 (9%). Follow-up regarding postoperative complications within 30 days from surgery was registered in 502 patients (99%). Type and degree of complication are listed in Tables II and III in the Data Supplement. A postoperative complication occurred in 42 patients (8.4%), with 19 (3.8%) classified as having serious complications. There were no differences regarding baseline characteristics when those with or without postoperative complications were compared Table IV in the Data Supplement. There was no significant difference in total complication rates between RYGB or SG (39 [8.4%] after RYGB, versus 4 [10.0%] after SG; *P*=0.77), or serious

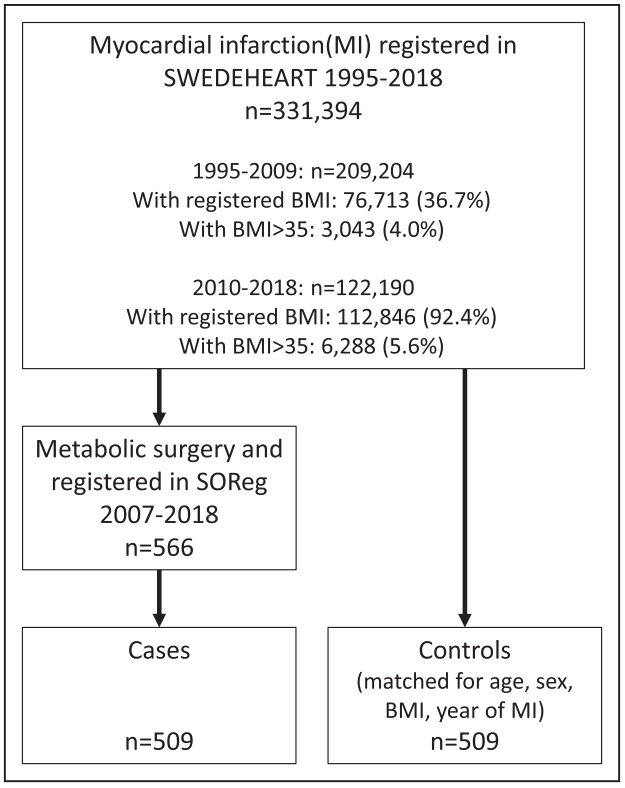

Figure 1. Flow chart of subject identification and inclusion.

complication rates (17 [3.7%] versus 2 [5.0%]; *P*=0.66). One patient died within 30 days of surgery because of a cardiovascular event secondary to massive postoperative bleeding (30-day mortality rate, 0.2%).

At surgery, the median (interquartile range [IQR]) weight and BMI were 118 (107–131) kg and 40 (37–43) kg/m^2. At 1-year follow-up in 453 patients, the median (IQR) weight and BMI were 85 (76–96) kg and 29 (26–32) kg/m^2, indicating a total weight loss of 28% (23–34%). At 2-year follow-up in 315 patients, the median (IQR) weight, BMI, and total weight loss from before surgery (84 [75–95] kg, 28 [26–31] kg/m^2, and 29% [22–34%]) were similar to 1 year after surgery.

Glycosylated hemoglobin A1c improved after surgery. The median (IQR) before surgery was 45 (39–58) mmol/mol; at 1 year after surgery, 37 (34–43) mmol/mol; and 2 years after surgery, 39 (39–46) mmol/mol. Clinical remission of diabetes was seen for 111 patients at 1 year (52.3%), and 74 patients at 2 years (51.0%). Corresponding remission numbers for other cardiometabolic comorbidities were: hypertension (1 year [n=95], 24.7%; 2 years [n=58], 21.6%), dyslipidemia (1 year [n=110], 35.6%; 2 years [n=58], 29.0%), and sleep apnea (1 year [n=76], 66.1%; 2 years [n=53], 67.1%).

Long-Term Outcome

The median (IQR) follow-up time was 4.6 (2.7–7.1) years. The incident rate and the 8-year cumulative probability of MACE was lower in patients undergoing metabolic surgery (1.48 [1.14–1.92] versus 3.68 [3.09–4.39] per 100 person-years and 18.7% [95% CI, 15.9–21.5%] versus 36.2% [33.2–39.3%]; Table 2; Figure 2). After adjusting for differences in baseline characteristics, metabolic surgery was still associated with a lower risk of MACE (adjusted HR, 0.44 [95% CI, 0.32–0.61]). Patients undergoing metabolic surgery had also a significant lower risk of death (adjusted HR, 0.45 [95% CI, 0.29–0.70]; Figure 3A) and MI (0.24 [0.14–0.41]; Figure 3B), but there were no significant differences regarding stroke (0.91 [0.38–2.20]; Figure 3C and Figure IA in the Data Supplement) and new onset atrial fibrillation (0.56 [0.31–1.01]; Figure 4A and Figure IB in the Data Supplement). In the univariable analysis, surgery was also associated with lower risk of new onset heart failure (adjustment not possible because of few events; Figure 4B and Figure IC in the Data Supplement). When LVEF after the last MI was also included as a sensitivity analysis, the association between surgery and MACE remained almost unchanged (HR, 0.47 [95% CI, 0.31–0.71]). In the propensity score matching analysis, the distribution of propensity score was similar in cases and controls (Figure II in the Data Supplement), and there was a good balance regarding covariates with small standardized differences (Table V in the Data Supplement). The estimates were similar to those in the main analyses (Table VI in the Data Supplement). This was also the case when only cases with known LVEF were included in the propensity score matching analysis (Tables VII and VIII in the Data Supplement).

DISCUSSION

This study suggests that metabolic surgery in severely obese patients with previous MI is associated with a low risk of serious complications and a substantially better cardiovascular long-term outcome compared with no surgery. Compared with controls matched for age, sex, BMI, and year of MI, patients undergoing metabolic surgery had less than half the long-term risk of the composite of all-cause death, MI, or stroke, all-cause death alone, and MI alone. They also had a lower risk of being readmitted because of new-onset heart failure. When adjusting for differences regarding baseline characteristics, the results remained unchanged.

Obesity is continuously increasing in prevalence and its association with cardiovascular disease is well established. Obesity acts through the development of risk factors, such as hypertension, dyslipidemia, and glucose intolerance or T2D, but may also act independently through promotion of systemic inflammation, increased sympathetic tone, and induction of a more hypercoagulable state.[21]

In patients with established cardiovascular disease, the association between obesity and outcome has

Table 2. Crude and Adjusted Association Between Surgery and Outcome

	Incident rate (95% CI) per 100 person-years				Cumulative incidence (95% CI) at 8 years				Model 1		Model 2	
	Metabolic surgery		Nonsurgical controls		Metabolic surgery		Nonsurgical controls		HR	(95% CI)	HR	(95% CI)
Death, MI or stroke	1.48	(1.14–1.92)	3.68	(3.09–4.39)	18.7	(15.9–21.5)	36.2	(33.2–39.3)	0.37	(0.27–0.52)	0.44	(0.32–0.61)
Death	0.77	(0.54–1.10)	1.92	(1.52–2.43)	11.7	(9.2–14.2)	21.4	(18.7–24.1)	0.36	(0.23–0.56)	0.45	(0.29–0.70)
MI	0.46	(0.29–0.72)	1.47	(1.13–1.92)	5.4	(4.0–6.8)	17.9	(15.4–20.4)	0.22	(0.13–0.36)	0.24	(0.14–0.41)
Stroke	0.28	(0.15–0.50)	0.38	(0.23–0.63)	3.5	(2.4–4.6)	5.4	(3.6–6.9)	0.68	(0.31–1.49)	0.91	(0.38–2.20)
New onset atrial fibrillation	0.54	(0.34–0.83)	0.85	(0.59–1.22)	8.7	(6.3–11.1)	9.9	(8.0–11.8)	0.46	(0.29–0.91)	0.56	(0.31–1.01)
New onset HF	0.11	(0.04–0.29)	0.34	(0.19–0.62)	2.0	(0.9–3.1)	4.9	(3.3–6.5)	–	–	–	–

Model 1: Adjusting for body mass index. Model 2: Adjusting for body mass index, smoking, hypertension, chronic kidney disease, peripheral artery disease, previous heart failure, atrial fibrillation, chronic obstructive pulmonary disease, cancer disease within 3 years, and treatment with aspirin, P2Y12–rec blockade, and statins. HF indicates heart failure; HR, hazard ratio; and MI, myocardial infarction.

been less clear and many studies have even suggested an obesity paradox, because a higher BMI have been associated with a better outcome.[15,22–24] These studies have been partly contradicted by one study showing that abdominal obesity, measured as waist circumference is independently associated with worse outcome in MI patients.[25] Also, severe obesity, defined as BMI >35, has been associated with cardiovascular mortality in a previous meta-analysis.[15] This uncertainty, together with the fact that persistent weight loss is difficult to achieve, has resulted in less focus on weight and obesity in post-MI care. Also, although the metabolic surgery in this study, in line with previous studies, was shown to reduce weight[26] and lead to improvement in T2D,[4] hypertension,[27] and hyperlipidemia[28] in severely obese patients, the method has been rarely used in post-MI patients because of concerns that the beneficial effects would not outweigh the risk of perioperative complications and long-term side effects. These concerns were recently supported by an observational study comparing severely obese patients with and without previous cardiovascular disease who underwent metabolic surgery. In that study, patients with previous cardiovascular risk had a higher risk of both early (within 30 days) and late major adverse cardiocerebral events (HR, 2.18 [95% CI, 1.45–3.28]).[29] In another recent observational cohort study, patients with a history of coronary artery bypass graft or percutaneous coronary intervention who underwent metabolic surgery were matched with coronary artery bypass graft and percutaneous coronary intervention patients that did not undergo metabolic surgery. The all-cause mortality was not significantly different. This was also true for the rate of cardiac death and MI.[30] From these perspectives, our

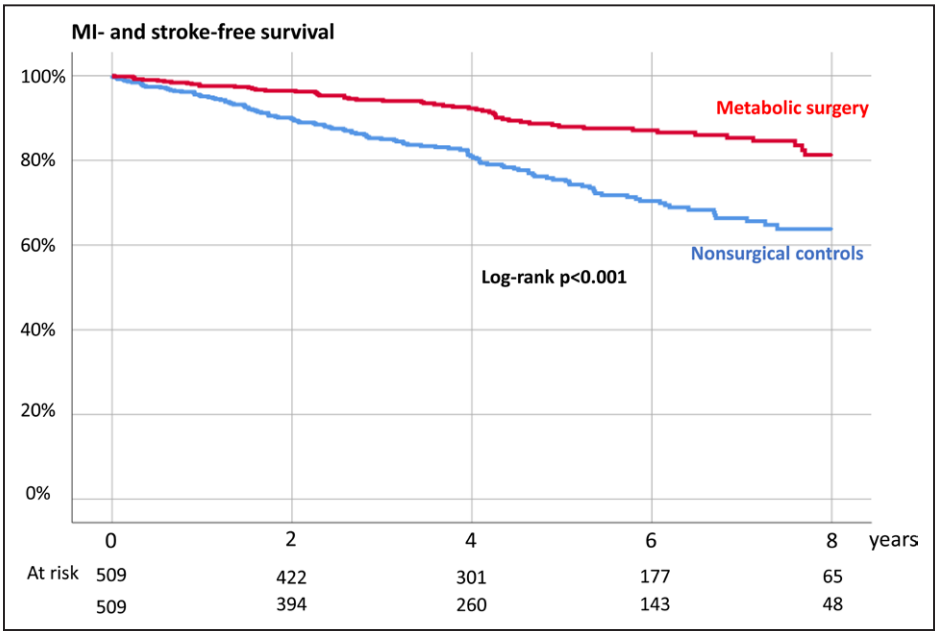

Figure 2. Myocardial infarction (MI) and stroke-free survival in patients with previous MI with and without metabolic surgery (unadjusted Kaplan-Meier survival curves).

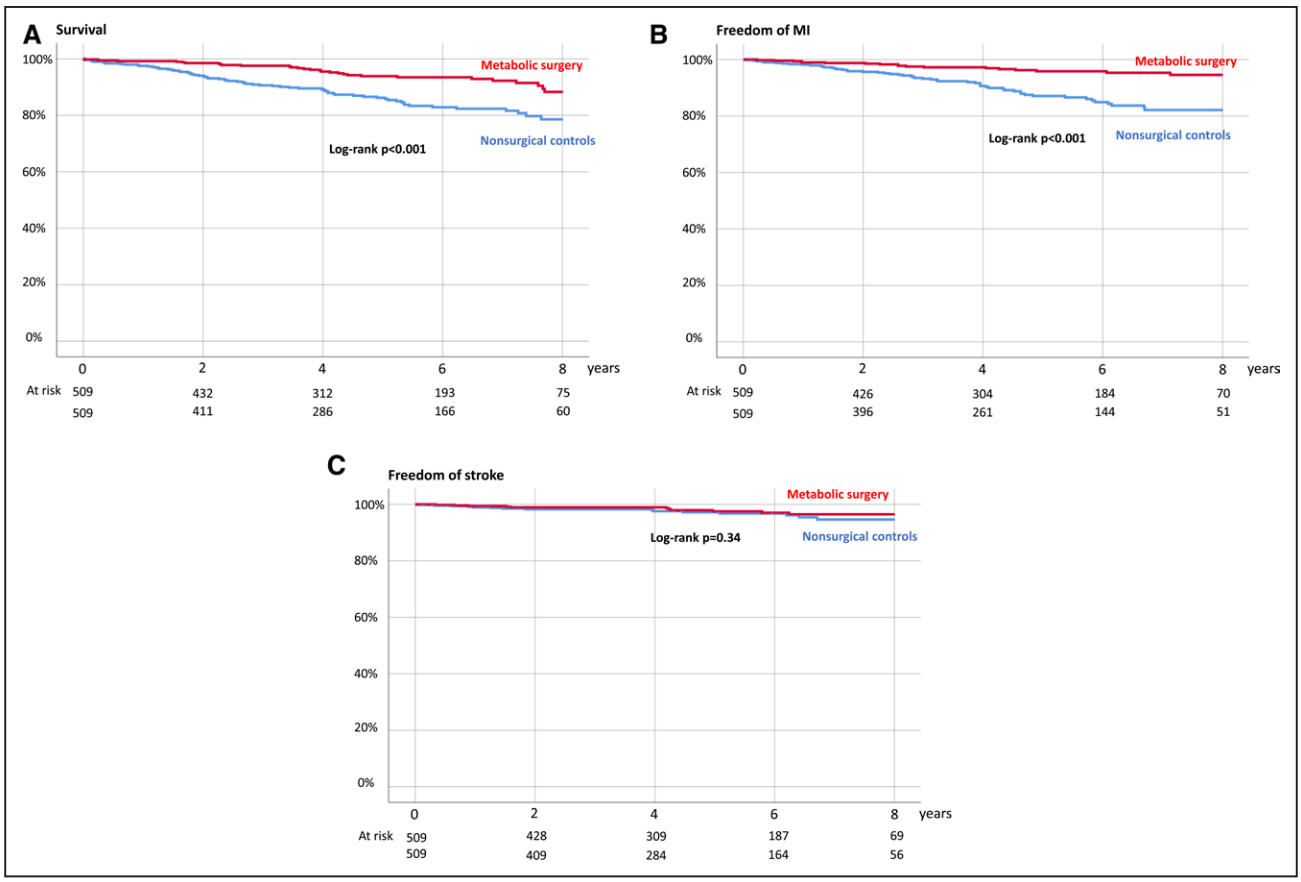

Figure 3. Outcomes in patients with previous myocardial infarction with or without metabolic surgery.
Overall survival (**A**), freedom of myocardial infarction (MI; **B**), and freedom of stroke (**C**) in patients with previous MI with and without metabolic surgery (unadjusted Kaplan–Meier survival curves).

study fills an important knowledge gap. The rate of serious complications after the surgery was similar to that seen in patients without previous MI.[31] Overall, our data indicate that metabolic surgery may be an important secondary prevention strategy in the growing population of severely obese individuals with established coronary artery disease.

In the absence of randomized, controlled trials examining primary prevention by metabolic surgery on MACE, there are some observational studies that have demonstrated an association between metabolic surgery and a lower rate of MACE. Aminian et al[32] recently reported a significant difference in favor of metabolic surgery for an extended MACE outcome (adjusted HR, 0.61 [95% CI, 0.55–0.69]) in patients with severe obesity and T2D (90% primary prevention). Similarly, Moussa et al[33] reported that patients who had undergone bariatric surgery had a significantly lower occurrence of MACE (HR, 0.41 [95% CI, 0.27–0.62]) compared with unoperated severely obese patients. In a matched cohort study of severely obese patients with T2D, metabolic surgery was associated with a lower incidence of macrovascular events at 5 years (HR, 0.60 [95% CI, 0.42–0.86]), and a lower incidence of coronary artery disease (HR, 0.64 [95% CI, 0.42–0.99]).[7] The same researchers have also demonstrated lower incidence of microvascular disease after metabolic surgery.[34]

Few studies have so far assessed cardiovascular outcomes after metabolic surgery in patients with preexisting cardiovascular disease.[13,14,32] Previous metabolic surgery seems to be associated with a protective effect on survival after MI and stroke. In a recent paper, mortality after MI or stroke in patients with or without previous metabolic surgery was studied. The authors found that the patients who had undergone metabolic surgery previous to the MI or stoke had a lower mortality rate (odds ratio [OR], 0.62 [95% CI, 0.44–0.88]) than matched controls without previous metabolic surgery.[35]

It seems unlikely that weight loss alone is the driving force behind the observed association between surgery and lower risk of MACE in this study. A large proportion of patients that underwent metabolic surgery in this study had clinical remission of T2D, hypertension, and dyslipidemia. In the Look AHEAD (Action for Health in Diabetes) trial, a weight loss of 6% after a 9-year long intensive lifestyle intervention in patients with T2D was not associated with a reduction of MACE.[36] This is in contrast also to a recently published study where MACE was significantly reduced after bariatric surgery in patients with T2D.[32] Thus, we suggest that the observed

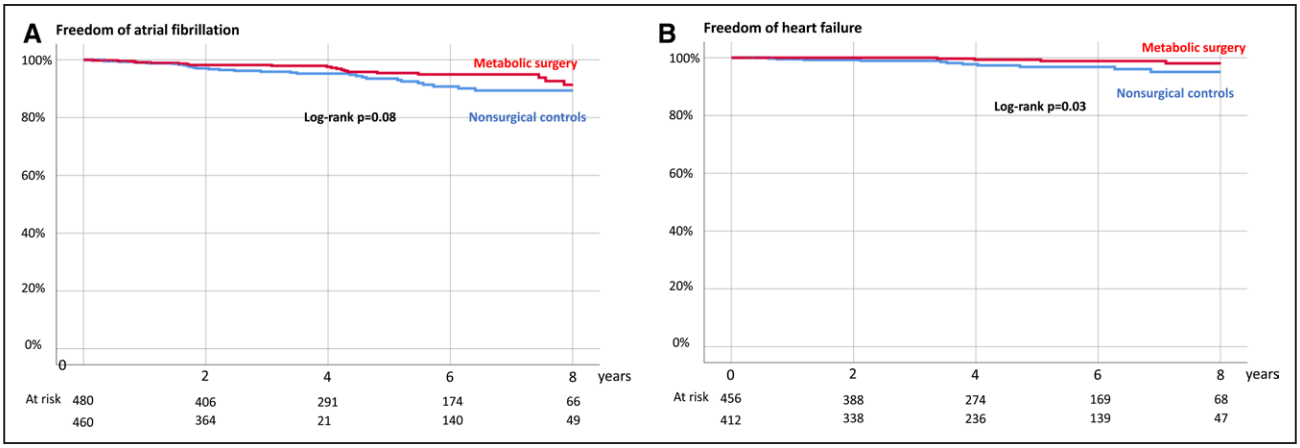

Figure 4. Outcomes in patients with previous myocardial infarction with or without metabolic surgery.
Freedom of new onset atrial fibrillation (**A**) and freedom of new onset heart failure (**B**) in patients with previous myocardial infarction with and without metabolic surgery (unadjusted Kaplan-Meier survival curves).

benefit of metabolic surgery on MACE is caused not only by a larger and more sustainable weight loss, but also by other cardiometabolic effects of metabolic surgery.[37] This is, in turn, related to the alterations in gastrointestinal anatomy and physiology seen after metabolic surgery. One such alteration is changes in the release of gastrointestinal peptides. Postprandial plasma concentrations of glucagon-like peptide-1 are significantly increased after modern metabolic surgery.[38] Glucagon-like peptide-1 receptor agonist treatment in patients with T2D showed a significant 10% relative risk reduction in primary outcome (cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke) in a recent meta-analysis.[39] This suggests that increased plasma concentrations of glucagon-like peptide-1 may contribute to the observed association between metabolic surgery and MACE in the current study. However, the degree to which glucagon-like peptide-1 is responsible for the cardiometabolic successes after metabolic surgery is under debate.[40]

We found a lower risk of new onset heart failure after metabolic surgery in patients with MI. Although this finding should be interpreted with caution because further adjustment was not possible, this is in line with previous reports that also have demonstrated a significantly reduced risk of heart failure after metabolic surgery compared with controls.[11,12,14,32]

This study has several limitations. This is an observational study. Thus, despite extensive matching and subsequent adjustments, we cannot exclude that it still exists residual confounding. We, therefore, need to be cautious regarding causality. The study database did not include any falsification end point, ie, an end point that is known to be unrelated to metabolic surgery, which could have been supportive of unbiased analyses. The study lacks data regarding socioeconomic status. We did not have available data on weight development and other biomarkers beyond 2 years in the surgical cohort, and had no follow-up weight data or other biomarkers in the control group, limiting the comparison between the groups with regard to weight development and the resolution of comorbid disease. However, weight loss and changes in biomarkers after metabolic surgery are durable,[37] which is not expected in the control group. Data on the remission of comorbid disease after metabolic surgery are based on clinical data (discontinuation of pharmacological treatment or discontinuation of continuous positive airway pressure treatment), which may result in an overestimation of remission rates. The study lacks data on causes of death. However, the validity of such data outside clinical trials with adjudication of each event can be questioned. Because of the predominance of gastric bypass in our cohort, we were unable to address any differences between RYGB and SG. Also, as complications that might be associated with previous MI were low, the power was low to assess if the timing between the MI and the metabolic surgery was of importance for the occurrence of complications. As with all registry studies, coding errors may exist. On the other hand, this study was based on large nationwide registers with high validity and degree of completeness.

In conclusion, this study suggests that in severely obese patients with a previous MI, metabolic surgery was associated with a low risk for serious complications, and lower risk of MACE, death, new MI, and new onset heart failure compared with no surgery. These findings need to be confirmed in a randomized, controlled trial.

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Disclosures

Dr Ottosson reports advisory board Johnson and Johnson and Vifor Pharma. Johnson and Johnson and Vifor Pharma has not had any knowledge, input, or previous information of the study or study design. The other authors report no conflicts.

Supplemental Materials

Data Supplement Figures I and II
Data Supplement Tables I–VIII

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