Cardiovascular Outcomes in Patients With Type 2 Diabetes and Obesity: Comparison of Gastric Bypass, Sleeve Gastrectomy, and Usual Care

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OBJECTIVE

To determine which one of the two most common metabolic surgical procedures is associated with greater reduction in risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus (T2DM) and obesity.

RESEARCH DESIGN AND METHODS

A total of 13,490 patients including 1,362 Roux-en-Y gastric bypass (RYGB), 693 sleeve gastrectomy (SG), and 11,435 matched nonsurgical patients with T2DM and obesity who received their care at the Cleveland Clinic (1998–2017) were analyzed, with follow-up through December 2018. With multivariable Cox regression analysis we estimated time to incident extended MACE, defined as first occurrence of coronary artery events, cerebrovascular events, heart failure, nephropathy, atrial fibrillation, and all-cause mortality.

RESULTS

The cumulative incidence of the primary end point at 5 years was 13.7% (95% CI 11.4–15.9) in the RYGB groups and 24.7% (95% CI 19.0–30.0) in the SG group, with an adjusted hazard ratio (HR) of 0.77 (95% CI 0.60–0.98, $P = 0.04$). Of the six individual end points, RYGB was associated with a significantly lower cumulative incidence of nephropathy at 5 years compared with SG (2.8% vs. 8.3%, respectively; HR 0.47 [95% CI 0.28–0.79], $P = 0.005$). Furthermore, RYGB was associated with a greater reduction in body weight, glycated hemoglobin, and use of medications to treat diabetes and cardiovascular diseases. Five years after RYGB, patients required more upper endoscopy (45.8% vs. 35.6%, $P < 0.001$) and abdominal surgical procedures (10.8% vs. 5.4%, $P = 0.001$) compared with SG.

CONCLUSIONS

In patients with obesity and T2DM, RYGB may be associated with greater weight loss, better diabetes control, and lower risk of MACE and nephropathy compared with SG.

More than 10 small randomized clinical trials (RCTs) have shown that metabolic surgery is superior to usual medical therapy for diabetes control and modifying cardiometabolic risk factors in patients with type 2 diabetes mellitus (T2DM) and

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obesity (1–5). Furthermore, >30 large comparative cohort studies have consistently reported reduction in risk of mortality after metabolic surgery (6–9). The majority of these RCTs and large observational studies have only examined the favorable effects of Roux-en-Y gastric bypass (RYGB). Currently, sleeve gastrectomy (SG), a relatively new procedure, is the most commonly performed metabolic surgical procedure worldwide (10,11). However, long-term data on efficacy of SG for macro- and microvascular complications of T2DM and mortality are limited.

Guiding patients toward the most appropriate metabolic surgical procedure for treatment of chronic diseases of obesity, T2DM, and their adverse events is crucial for improving outcomes. The surgical risk, impact of each procedure on body weight and comorbidities, coexistence of other medical and mental conditions, and patient behavioral factors, values, and goals are important considerations in choosing the most appropriate metabolic surgical procedure (12,13). One factor that may help in decision-making would be understanding the differential impact of each surgical procedure on the risk of major adverse cardiovascular events (MACE) and mortality. This important consideration has not been studied yet.

RESEARCH DESIGN AND METHODS

This is a secondary analysis of a matched-cohort study that originally reported association of metabolic surgery with lower risk of MACE in adult patients with obesity and T2DM (6). The main aim of the current study is to determine which metabolic surgical procedure (RYGB vs. SG) is associated with greater risk reduction in development of MACE. In addition, since there are limited data on the effects of SG on cardiovascular health, the second aim of this study is to examine the association of each metabolic surgical procedure separately with risk of MACE and mortality.

A retrospective observational study on patients who received treatment within the Cleveland Clinic Health System between 1 January 1998 and 31 December 2017 with follow-up through 31 December 2018 was performed. The Cleveland Clinic's institutional review board approved the study as minimal risk research using data collected for routine clinical practice for which the requirement for informed consent was waived.

Details of the study protocol, enrollment criteria, construction of study cohorts, and statistical analysis have previously been published (6). The ICD-9, ICD-10, and Current Procedural Terminology (CPT) procedure codes that were used to extract data from the electronic health records (EHR) are summarized in Supplementary Tables 1 and 2.

Study Cohorts

A total of 2,287 adult patients with T2DM and BMI $\geq$30 kg/m^2 who underwent metabolic surgery and did not have a history of solid organ transplant, severe heart failure, or active cancer were identified. Among the 2,287 surgical patients of the original cohort, 1,362 RYGB and 693 SG cases are included in the current analysis. Patients who underwent adjustable gastric banding (n = 109), duodenal switch (n = 5), or conversion of primary SG and RYGB to other procedures (n = 118) were not included.

Enrollment criteria were implemented for identification of the nonsurgical patients who received usual care for T2DM and obesity. Each surgical patient was matched with a propensity score to five nonsurgical patients based on the index date, age at index date, sex, BMI at index date, location (Ohio vs. Florida), insulin use, and presence of diabetes end-organ complications (composite of coronary artery disease, heart failure, cerebrovascular disease, peripheral vascular disease, neuropathy, nephropathy, or requiring dialysis), resulting in 11,435 nonsurgical patients (6).

End Points

As described in the original study (6), the primary end point was the incidence of extended MACE, defined as first occurrence of any of six outcomes including all-cause mortality, coronary artery events (unstable angina, myocardial infarction, or coronary intervention/surgery), cerebrovascular events (ischemic stroke, hemorrhagic stroke, or carotid intervention/surgery), heart failure (diastolic and systolic), atrial fibrillation, and nephropathy (at least two measures of estimated glomerular filtration rate [eGFR] <60 mL/min), with the first occurrence after the index date recorded as the event date (see Supplementary Table 1 for definitions and codes). A secondary composite end point included three-component MACE (all-cause mortality, myocardial infarction, and ischemic stroke).

All patients were included in the assessment of the composite primary and secondary end points. However, the conditions or events that a patient had at baseline were omitted from the count toward the composite end points in follow-up. For example, in a patient with history of ischemic stroke before the index date, having a code for stroke after the index date was not considered an event for composite end points. However, development of myocardial infarction in this patient after the index date would count toward the composite end points (6).

Other secondary end points included the six individual components of the primary end point including coronary artery events, cerebrovascular events, heart failure, atrial fibrillation, nephropathy, and all-cause mortality. Death information was obtained from a combination of local EHR, Social Security, and state death indices. For assessment of individual secondary end points, patients who already had these conditions prior to the index date were eliminated from subsequent risk evaluation only for that specific outcome.

Other Outcomes

Weight, glycated hemoglobin (HbA_{1c}), and dates of prescription orders for diabetes and cardiovascular drugs were collected from the EHR for comparison of groups. Data on nutritional, endoscopic, radiologic, and surgical interventions until last follow-up were also compared between surgical procedures to serve as surrogates of surgical adverse events.

Statistical Analysis

Baseline data are expressed as median (interquartile range [IQR]) and number (%). Doubly robust estimation combining the propensity score and outcome regression was used to compare the outcomes between three study groups head-to-head.

Cause-specific event rates per 100 patient-years of follow-up starting from

the index date were estimated for each outcome within each study group. Cumulative incidence estimates (Kaplan-Meier method) 5 years after the index date with 95% CIs for each outcome were calculated.

Fully adjusted Cox proportional hazards regression models were generated for two composite and six individual study outcomes. Regression analyses were performed for all of the factors used in the matching process as well as a larger range of potential confounding variables (all variables in Table 1). Therefore, any imbalances in the observed potential confounders that remained after the matching process were controlled for by the statistical analysis. The proportional hazards assumptions for the treatment variable were tested based on weighted residuals.

To address missing values, within each outcome data set, we imputed missing values at baseline (Table 1) with multiple imputation by chained equations (MICE) to create five imputed data sets. Predictive mean matching, logistic regression, and polytomous logistic regression were used for numeric, binary, and categorical variables, respectively. Imputation-corrected SEs of model estimates and contrasts were obtained with Rubin's formula (6, 14).

The Wald test was used for comparing mean changes in weight loss and HbA_{1c}, two-sample proportions test for comparing proportions of patients on diabetes and cardiovascular medications, and log-rank test for comparing interventions between the study groups at 5 years of follow-up.

A significance level of 0.05 for two-sided comparisons was considered statistically significant, and 95% CIs were reported where applicable. Because of the potential for a type 1 error due to multiple comparisons, findings should be interpreted as exploratory. All analysis was done in the R statistical programming language (version 3.5.0).

RESULTS

A total of 13,490 patients including 1,362 RYGB, 693 SG, and 11,435 matched nonsurgical patients were included in the analysis. The median BMI of RYGB, SG, and control group was 45.3, 44.7, and 42.6 kg/m^2, respectively. In total, 4.3% of patients had a BMI between 30 and 34.9 kg/m^2.

The distribution of 37 baseline covariates was well balanced after matching among the RYGB, SG, and nonsurgical patient study groups (Table 1) including median HbA_{1c} level (7.1% vs. 7.0% vs. 7.1%) and eGFR (91.3 vs. 90.4 vs. 91.9 mL/min) and percentage taking insulin (33.7% vs. 34.2% vs. 33.3%), cholesterol-lowering medications (52.6% vs. 51.5% vs. 52.5%), and renin-angiotensin system inhibitors (60.6% vs. 61% vs. 62.1%), respectively. Compared with RYGB patients, SG patients were older (54.6 vs. 51.2 years) and had higher rates of some comorbidities at baseline including heart failure (14.3% vs. 7.7%), history of myocardial infarction (3.3% vs. 1.9%), history of atrial fibrillation (9.1% vs. 5.2%), chronic obstructive pulmonary disease (11.1% vs. 8.4%), and nephropathy (9.8% vs. 6.9%). Conversely, the frequency of smoking (8.9% vs. 4.8%) and BMI $\geq$40 kg/m^2 (77.5% vs. 71.7%) was higher among patients receiving RYGB compared with SG. The median follow-up time for RYGB, SG, and nonsurgical patients was 4.0 years (IQR 1.3–7.0), 2.0 years (IQR 0.7–4.1), and 4.0 years (IQR 2.1–6.1), respectively.

Primary Composite End Point

The cumulative incidence of the primary end point at 5 years was 13.7% (95% CI 11.4–15.9) in the RYGB group and 24.7% (95% CI 19.0–30.0) in the SG group, with an adjusted hazard ratio (HR) of 0.77 (95% CI 0.60–0.98, $P = 0.035$) (Fig. 1*A* and Table 2). The cumulative incidence of the primary end point at 5 years was 30.4% (95% CI 29.4–31.5) in the nonsurgical group. Both metabolic surgical procedures were associated with a significantly lower cumulative incidence of the primary end point at 5 years compared with usual care: HR 0.53 (95% CI 0.46–0.61, $P < 0.001$) after RYGB and HR 0.69 (95% CI 0.56–0.85, $P < 0.001$) after SG (Fig. 1*A* and Table 2).

Secondary Composite End Point

The cumulative incidence of three-component MACE at 5 years was 6.4% (95% CI 4.8–8.0) in the RYGB group and 11.8% (95% CI 7.6–15.8) in the SG group, with an adjusted HR of 0.81 (95% CI 0.57–1.16, $P = 0.258$) (Fig. 1*B* and Table 2). The cumulative incidence of three-component MACE at 5 years was 15.5% (95% CI 14.7–16.4) in the nonsurgical group. Both metabolic surgical procedures were associated with significantly lower cumulative incidence of three-component MACE at 5 years in comparison with usual care: HR 0.53 (95% CI 0.43–0.65, $P < 0.001$) after RYGB and HR 0.65 (95% CI 0.48–0.88, $P = 0.006$) after SG (Fig. 1*B* and Table 2).

Secondary Individual End Points

RYGB was associated with a significantly lower cumulative incidence of nephropathy at 5 years compared with SG (2.8% vs. 8.3%, respectively) (HR 0.47 [95% CI 0.28–0.79, $P = 0.005$]). Although the 5-year cumulative incidences of the other five individual end points were lower after RYGB, the fully adjusted HRs were not significantly different in comparison of RYGB and SG (Fig. 2, Table 2, and Supplementary Table 3).

Compared with usual care, RYGB was associated with a significantly lower incidence of five out of six individual end points and SG was associated with a significantly lower incidence of three out of six individual end points. The incidence for these end points and adjusted HRs are reported in Table 2 and Supplementary Table 3. The proportional hazards assumption was satisfied for the primary and secondary composite outcomes and individual outcomes (see Supplementary Table 4 for *P* values testing the proportional hazards assumption).

Change in Status of Obesity, Diabetes, and Medications

Both metabolic surgical procedures were associated with a significant reduction in weight and HbA_{1c} level in comparisons with the control group ($P < 0.001$ for all four comparisons at 5 years). Patients who underwent RYGB on average had 9.7%-points greater weight loss (95% CI 9.3–10.1, $P < 0.001$) and a 0.31% lower HbA_{1c} level (95% CI 0.16–0.47, $P < 0.001$) at 5 years compared with SG patients (Fig. 3 and Supplementary Table 5).

Patients after RYGB and SG required significantly less diabetes and cardiovascular medication compared with those who received usual care. Furthermore, use of noninsulin diabetes medications, renin-angiotensin system blockers, lipid-lowering therapies, and aspirin was significantly lower after the

Table 1—Characteristics of patients at the index date

Baseline variable	RYGB (*N* = 1,362)	SG (*N* = 693)	Nonsurgical control (*N* = 11,435)
Demographic data			
Index year	2012 (2010, 2014)	2014 (2012, 2016)	2013 (2011, 2015)
Sex			
Female	908 (66.7)	439 (63.3)	7,339 (64.2)
Male	454 (33.3)	254 (36.7)	4,096 (35.8)
Age (years)	51.2 (43.1, 58.4)	54.6 (44.6, 62.8)	54.8 (46.2, 62.5)
BMI (kg/m^2)	45.3 (40.7, 51.5)	44.7 (39.3, 52.5)	42.6 (39.4, 47.2)
BMI category (kg/m^2)			
30–34.9	58 (4.3)	30 (4.3)	495 (4.3)
35–39.9	249 (18.3)	166 (24)	2,595 (22.7)
≥40	1,055 (77.5)	497 (71.7)	8,345 (73)
Weight (kg)	126.8 (112, 147)	125.6 (108.4, 149.4)	120.2 (106.8, 136.5)
Race			
White	1,066 (78.3)	492 (71)	7,994 (69.9)
Black	239 (17.5)	156 (22.5)	2,804 (24.5)
Other	23 (1.7)	27 (3.9)	234 (2)
Missing	34 (2.5)	18 (2.6)	403 (3.5)
Annual zip code income ($)	49,664 (39,730, 61,278)	50,925 (41,013, 63,445)	48,732 (36,951, 61,512)
Missing	29 (2.1)	34 (4.9)	125 (1.1)
Smoking status			
Never	724 (53.2)	383 (55.3)	5,615 (49.1)
Former	480 (35.2)	261 (37.7)	4,012 (35.1)
Current	121 (8.9)	33 (4.8)	1,607 (14.1)
Missing	37 (2.7)	16 (2.3)	201 (1.8)
Location			
Ohio	1,231 (90.4)	390 (56.3)	9,834 (86)
Florida	131 (9.6)	303 (43.7)	1,601 (14)
Medical history			
Hypertension	1,165 (85.5)	587 (84.7)	8,565 (74.9)
Dyslipidemia	1,042 (76.5)	483 (69.7)	7,457 (65.2)
Peripheral neuropathy	139 (10.2)	84 (12.1)	1,203 (10.5)
Heart failure	105 (7.7)	99 (14.3)	1,342 (11.7)
Coronary artery disease	129 (9.5)	81 (11.7)	1,104 (9.7)
COPD	114 (8.4)	77 (11.1)	1,188 (10.4)
Nephropathy	94 (6.9)	68 (9.8)	1,219 (10.7)
Atrial fibrillation	71 (5.2)	63 (9.1)	701 (6.1)
Peripheral arterial disease	66 (4.8)	47 (6.8)	755 (6.6)
Myocardial infarction	26 (1.9)	23 (3.3)	211 (1.8)
Cerebrovascular disease	18 (1.3)	19 (2.7)	358 (3.1)
Ischemic stroke	17 (1.2)	13 (1.9)	298 (2.6)
Dialysis	5 (0.4)	8 (1.2)	78 (0.7)
Clinical and laboratory data			
HbA_{1c}			
%	7.1 (6.3, 8.4)	7 (6.4, 8)	7.1 (6.4, 8.4)
mmol/mol	54 (45, 68)	53 (46, 64)	54 (46, 68)
Missing	88 (6.5)	50 (7.2)	1,288 (11.3)
Systolic blood pressure (mmHg)	136.7 (126, 147.3)	141.3 (130.8, 151.2)	130.2 (121, 142)
Missing	0 (0)	0 (0)	54 (0.5)
Diastolic blood pressure (mmHg)	72 (65.5, 79.7)	71.2 (65, 78)	78 (70, 84)
Missing	0 (0)	0 (0)	54 (0.5)
eGFR (mL/min)[a]	91.3 (74, 107.9)	90.4 (69.8, 111.5)	91.9 (72.5, 111.9)
Missing	0 (0)	1 (0.1)	432 (3.8)
HDL (mg/dL)	43 (36, 51)	45 (38, 51.5)	43 (36, 51)
Missing	378 (27.8)	346 (49.9)	3,512 (30.7)
LDL (mg/dL)	93 (72, 116)	91 (71, 116)	93 (72, 118)
Missing	121 (8.9)	56 (8.1)	2,947 (25.8)
Triglycerides (mg/dL)	150 (104, 216.5)	139 (96, 197.5)	146 (103, 208)
Missing	87 (6.4)	46 (6.6)	1,816 (15.9)
UACR (mg/g)	14 (6, 39.8)	14.2 (4.8, 39.8)	14 (5, 43)
Missing	532 (39.1)	353 (50.9)	4,224 (36.9)

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Table 1—Continued

Baseline variable	RYGB (*N* = 1,362)	SG (*N* = 693)	Nonsurgical control (*N* = 11,435)
Medication history			
Noninsulin diabetes medication	1,139 (83.6)	553 (79.8)	9,253 (80.9)
0	223 (16.4)	140 (20.2)	2,182 (19.1)
1	628 (46.1)	351 (50.6)	5,218 (45.6)
2	362 (26.6)	148 (21.4)	2,929 (25.6)
3+	149 (10.9)	54 (7.8)	1,106 (9.7)
Insulin	459 (33.7)	237 (34.2)	3,806 (33.3)
Lipid-lowering medications	716 (52.6)	357 (51.5)	5,998 (52.5)
Renin-angiotensin system inhibitors[b]	825 (60.6)	423 (61)	7,102 (62.1)
Other antihypertensive medications	973 (71.4)	501 (72.3)	8,066 (70.5)
Aspirin	451 (33.1)	216 (31.2)	4,627 (40.5)
Warfarin	99 (7.3)	66 (9.5)	943 (8.2)

Data are *n* (%) or median (IQR). COPD, chronic obstructive pulmonary disease; UACR, urinary albumin-to-creatinine ratio. [a]eGFR was estimated using the MDRD study equation. [b]Including ACE inhibitors and angiotensin-receptor blockers.

RYGB compared with SG (Fig. 4 and Supplementary Table 6).

Adverse Events After Metabolic Surgery

The cumulative incidence of different interventions after RYGB and SG is shown in Fig. 5 and reported in Supplementary Table 7. More patients 5 years after RYGB required upper endoscopy (45.8% vs. 35.6%, $P < 0.001$) and abdominal surgical procedures (10.8% vs. 5.4%, $P = 0.001$) compared with patients after SG.

CONCLUSIONS

Findings of this study indicate that RYGB and SG were separately associated with a significant reduction in risk of MACE and all-cause mortality compared with usual care among patients with T2DM and a BMI $\geq$30 kg/m^2. Furthermore, during 5 years of follow-up, RYGB compared with SG was associated with a greater reduction in body weight, HbA_{1c}, use of medications to treat diabetes and cardiovascular diseases, and risk of six-component MACE. Among the individual components of MACE in this study, protective effects of RYGB versus SG were more prominent for risk of nephropathy than other end points. Nonetheless, more patients required endoscopic and abdominal surgical procedures after RYGB compared with SG.

In current practice, RYGB and SG account for >95% of metabolic surgical procedures performed in patients with T2DM (10,11). Despite the well-known metabolic effects of RYGB, SG has become a more popular procedure worldwide in the last several years, largely because of the relative ease of performing the procedure and fewer short- and long-term complications after SG (12,15–17). To date, there are only a few RCTs directly comparing long-term metabolic effects of RYGB with SG (3,18,19). These small trials were not primarily designed and adequately powered to specifically compare the impact of RYGB and SG on T2DM-related end

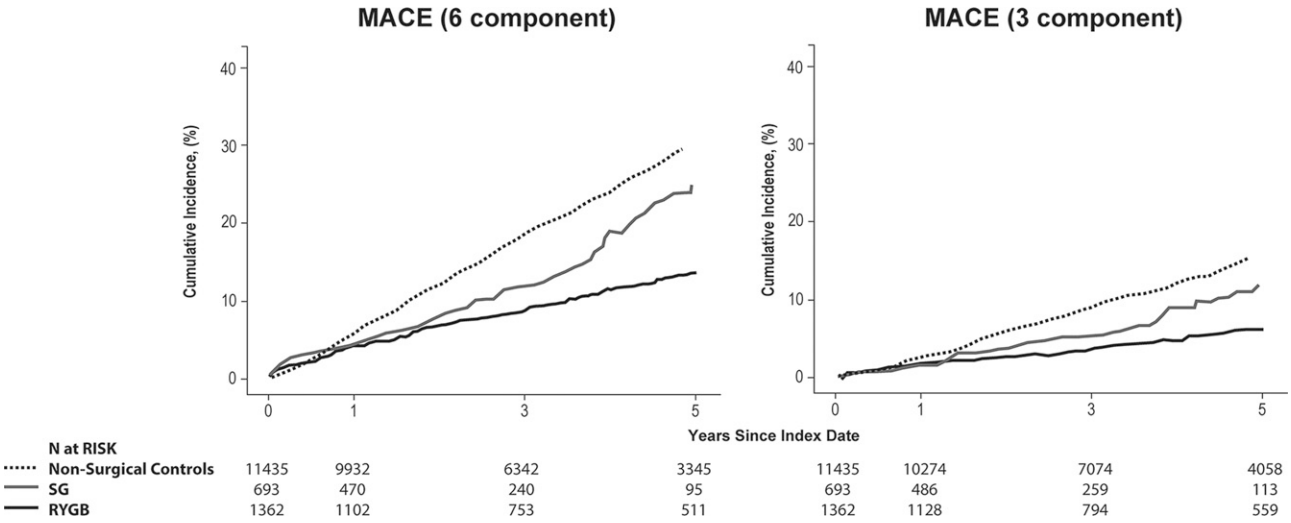

Figure 1—Five-year cumulative incidence estimates (Kaplan-Meier) for two composite end points. The primary end point was the incidence of extended MACE (composite of six outcomes), defined as first occurrence of coronary artery events, cerebrovascular events, heart failure, atrial fibrillation, nephropathy, and all-cause mortality, with the first occurrence after the index date recorded as the event date. The secondary composite end points included three-component MACE (all-cause mortality, myocardial infarction, and ischemic stroke), with the first occurrence after the index date recorded as the event date.

Table 2—Cumulative incidence estimates (%) and fully adjusted HRs from Cox models for each outcome stratified by treatment

	Cumulative incidence at 5 years, % (95% CI)				
	RYGB	SG	Nonsurgical control	HR (95% CI)	*P*
Primary	13.7 (11.4–15.9)	24.7 (19.0–30.0)	30.4 (29.4–31.5)		
RYGB vs. SG				0.77 (0.60–0.98)	0.035
RYGB vs. control				0.53 (0.46–0.61)	<0.001
SG vs. control				0.69 (0.56–0.85)	<0.001
Secondary composite	6.4 (4.8–8.0)	11.8 (7.6–15.8)	15.5 (14.7–16.4)		
RYGB vs. SG				0.81 (0.57–1.16)	0.258
RYGB vs. control				0.53 (0.43–0.65)	<0.001
SG vs. control				0.65 (0.48–0.88)	0.006
All-cause mortality	3.9 (2.6–5.1)	4.5 (2.0–6.9)	10.1 (9.4–10.8)		
RYGB vs. SG				0.99 (0.60–1.66)	0.983
RYGB vs. control				0.51 (0.39–0.67)	<0.001
SG vs. control				0.52 (0.33–0.81)	0.004
Heart failure	2.9 (1.7–4.1)	5.3 (1.8–8.7)	10.7 (10.0–11.5)		
RYGB vs. SG				0.79 (0.45–1.39)	0.416
RYGB vs. control				0.32 (0.23–0.44)	<0.001
SG vs. control				0.40 (0.25–0.66)	<0.001
Coronary artery disease	2.7 (1.5–3.8)	7.1 (3.9–10.2)	7.1 (6.4–7.7)		
RYGB vs. SG				0.63 (0.38–1.05)	0.077
RYGB vs. control				0.56 (0.41–0.77)	<0.001
SG vs. control				0.89 (0.58–1.37)	0.606
Cerebrovascular disease	1.6 (0.7–2.5)	3.6 (0.9–6.2)	3.3 (2.8–3.7)		
RYGB vs. SG				0.70 (0.34–1.45)	0.340
RYGB vs. control				0.59 (0.38–0.92)	0.019
SG vs. control				0.85 (0.46–1.56)	0.593
Nephropathy	2.8 (1.6–4.0)	8.3 (4.1–12.3)	9.1 (8.3–9.9)		
RYGB vs. SG				0.47 (0.28–0.79)	0.005
RYGB vs. control				0.32 (0.23–0.45)	<0.001
SG vs. control				0.68 (0.45–1.05)	0.081
Atrial fibrillation	4.2 (2.9–5.6)	6.0 (2.5–9.4)	7.9 (7.3–8.6)		
RYGB vs. SG				1.30 (0.76–2.22)	0.340
RYGB vs. control				0.76 (0.57–1.00)	0.054
SG vs. control				0.58 (0.36–0.94)	0.027

HRs (95% CIs) and *P* values from adjusted Cox models comparing the relative instantaneous risk of each outcome among the study groups. When *P* value is <0.05, the "left" group is at a lower instantaneous risk of the outcome than the "right" group when the HR is <1. We included all baseline variables in Table 1 to adjust for potential confounding.

points. In the Surgical Treatment And Medications Potentially Eradicate Diabetes Efficiently (STAMPEDE) trial, 150 patients with T2DM were randomized to intensive medical therapy alone or intensive medical therapy plus RYGB or SG. Five years after enrollment, RYGB led to greater weight loss (~5 kg greater) compared with SG. However, the RCT did not show a difference in improvement of T2DM, hypertension, lipid profile, and quality of life indices in comparisons of RYGB with SG. At the end of the study, 45% of RYGB patients vs. 25% of SG patients were not taking any diabetes medications ($P < 0.05$) (3). In the SLEEVE versus byPASS (SLEEVEPASS) RCT and the Swiss Multicenter Bypass or Sleeve Study (SM-BOSS), 101 (42%) and 54 (26%) enrolled patients with severe obesity had T2DM at baseline, respectively. After 5 years, both RCTs reported no significant differences between RYGB and SG in remission of diabetes, improvement of HbA_{1c}, and fasting glucose, although they were primarily designed to compare weight loss, and not T2DM-related end points, after two surgical procedures (18,19). There is only one RCT comparing RYGB and SG with T2DM remission at 1 year after surgery as the primary end point. In this trial on 109 patients who were randomly assigned to RYGB ($n = 54$) or SG ($n = 55$), RYGB was superior to SG for remission of T2DM at 1 year after surgery (relative risk 1.57 [95% CI 1.14–2.16], $P = 0.005$) (13).

In the current study, the greater and more sustained weight loss after RYGB compared with SG (10% difference in total weight loss at 5 years) could have meaningful physiologic effects. Similarly, in a recent retrospective observational cohort study from 41 health systems in the U.S. on nearly 5,000 patients, the average weight loss at 5 years was 71 lb (26% total body weight loss) after RYGB and 52 lb (19% total body weight loss) after SG (20). Although weight loss drives many of the metabolic improvements after bariatric surgery, the relative contribution of weight-independent mechanisms remains an area of active investigation. Current evidence suggests that RYGB may lead to greater weight-independent metabolic and neurohormonal

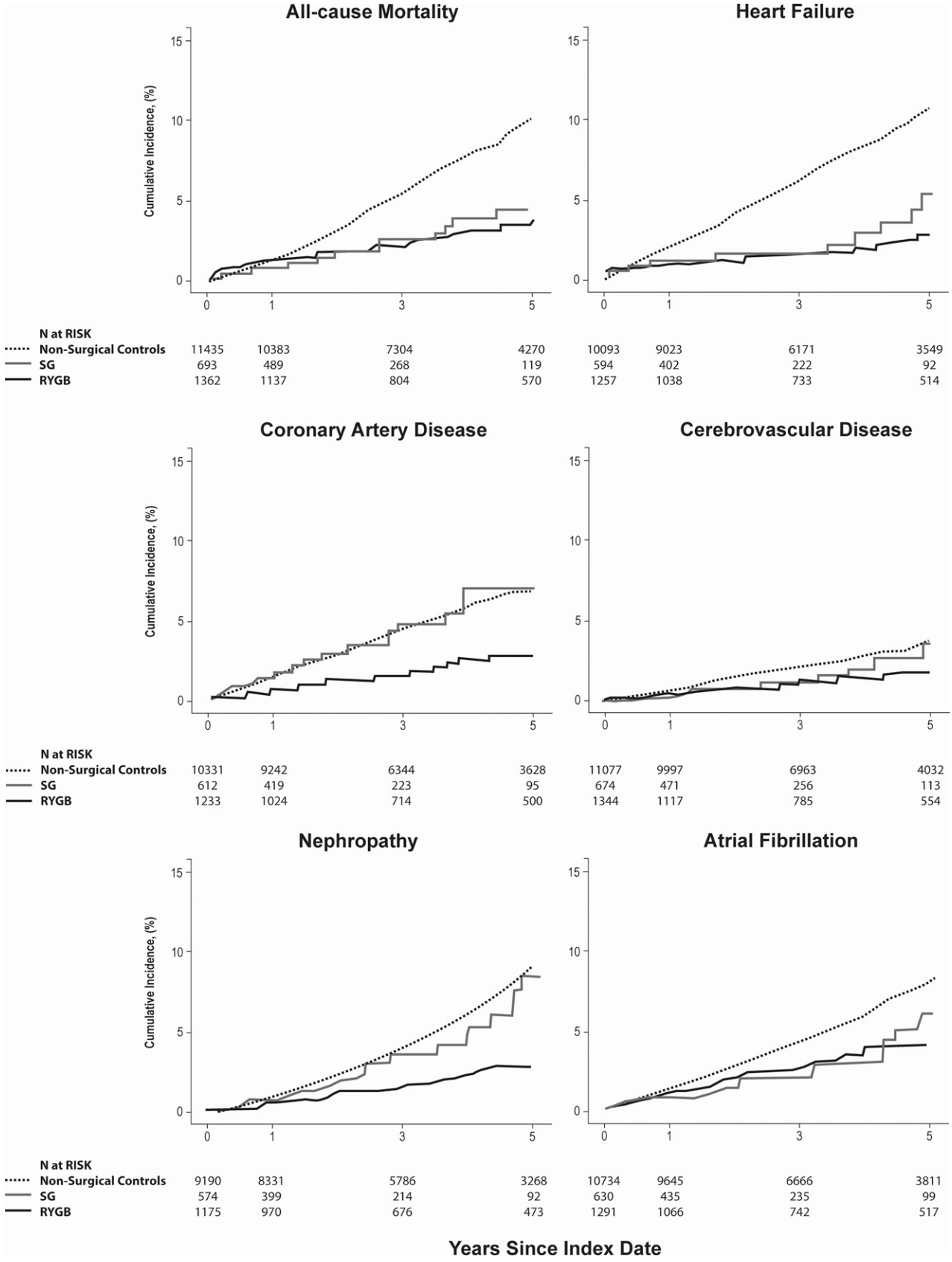

Figure 2—Five-year cumulative incidence estimates (Kaplan-Meier) for six individual end points. For each five individual outcomes (except all-cause mortality), any patient with a history of that outcome prior to the index date was eliminated from risk assessment only for that outcome.

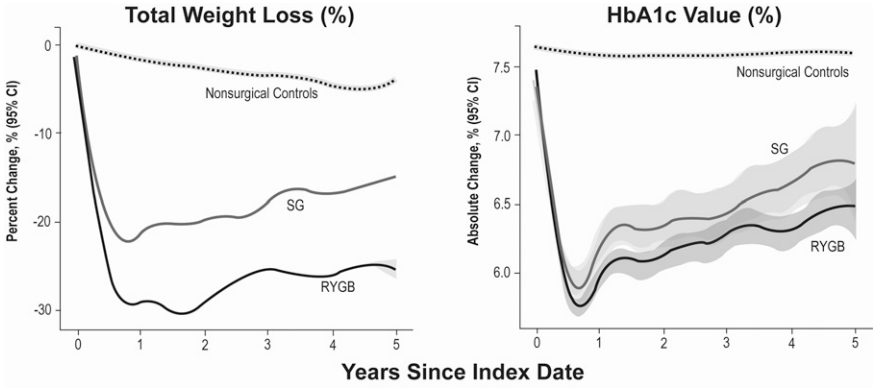

Figure 3—Mean trend curves of weight loss and HbA_{1c} over 5 years of follow-up. Figure displays smoothed mean trends of percent weight lost from baseline and absolute HbA_{1c} values (%) in three study groups during follow-up. Statistical comparisons between the study groups are reported in Supplementary Table 5.

benefits compared with SG (21,22). This constellation of favorable weight loss–dependent and weight-independent changes may explain better diabetes control, less medication use, and reduced risk of MACE after RYGB.

The combination of obesity, T2DM, and hypertension has a large negative impact on kidney integrity and function (23,24). Among the six individual secondary end points, RYGB was associated with 53% lower risk of nephropathy compared with SG. Although the exact explanation of this observation remains for future studies, this finding supports other evidence showing that the risk of nephropathy is extremely sensitive to weight changes and diabetes control (25–28). Despite no reduction in cardiovascular outcomes, findings of the Look AHEAD (Action for Health in Diabetes) randomized trial suggest that among patients with T2DM, intensive life modifications significantly decrease the risk of chronic kidney disease (26). Furthermore, in large clinical trials the impact of intensive glucose control has been more prominent on the risk of nephropathy than the risk of cardiovascular events (27,28). The relative contributions of weight loss, diabetes and blood pressure control, altered adipokine levels, decreased inflammation, and gut hormone signaling toward improving nephropathy risk and progression are yet to be elucidated (29–31). As shown in Table 2 and Fig. 2, we also observed some evidence of lower risk of coronary artery events favoring RYGB compared with SG (HR 0.63 [95% CI 0.38–1.05]), which did not reach conventional levels of statistical significance ($P = 0.08$). Both surgical groups had comparable effects for other secondary individual end points including all-cause mortality. Overall, there has been substantial evidence to support the improvement of cardiovascular risk after metabolic surgery. Because of the close association between diabetes and cardiovascular disease, it is also clear that greater metabolic improvements, particularly diabetes remission, lead to greater reduction in long-term cardiovascular risk (6–9).

The safety profile of metabolic surgery has remarkably improved in the last two decades (32–34). Consistent with prior studies (15–17,20), the current study showed fewer complications after SG compared with RYGB. The need for more reinterventions long-term after RYGB compared with SG has previously been documented and is primarily related to ulceration or stricture formation at the gastrojejunostomy and bowel obstructions. Although development of new gastroesophageal reflux disease or worsening of existing gastroesophageal reflux is a well-known adverse effect of SG (35), in the current study, similar to findings of prior studies (15–17), we found a lower rate of upper endoscopy in follow-up after SG compared with RYGB. Shorter operative time, lack of a gastrointestinal anastomosis, maintaining nutritional flow through an intact pylorus and small intestine, and unaltered gut absorption may contribute to a better safety profile of SG (12,15–17,20). In the field of metabolic surgery, gastrointestinal bypass procedures are generally associated with more weight loss and greater metabolic benefits but at a cost of higher surgical and nutritional complications and reintervention rates (12,36,37). There also appears to be a dose-response relationship between the length of the intestinal bypass, particularly the biliopancreatic limb, and the magnitude and duration of metabolic improvement (38,39).

Several factors should be considered when the patient and medical team make a shared decision about the most appropriate metabolic surgical procedure (12). The current study shows that while both RYGB and SG are safe, effective, and durable operations, RYGB is associated with greater metabolic effects and greater reduction in risk of MACE and nephropathy. Overall, RYGB outperforms SG in achieving diabetes remission (40). Conversely, SG may be a better choice in patients with higher surgical risk, when there is limited intra-abdominal working space to perform more complex operations due to extreme obesity or complex abdominal wall hernias, in patients with certain small bowel diseases (e.g., Crohn disease, or history of multiple bowel resections), in solid organ transplant patients or in patients requiring psychotropic polypharmacy (because of possible lesser effect on absorption of medications), and in active smokers and patients dependent on chronic nonsteroidal anti-inflammatory drugs (to avoid risk of anastomotic ulceration of RYGB) (12,41). Notably, the recommended nutritional surveillance in short- and long-term follow-up after RYGB and SG is similar (42).

This study has several limitations. First, the study cohorts were derived from the original study, where investigators comprehensively

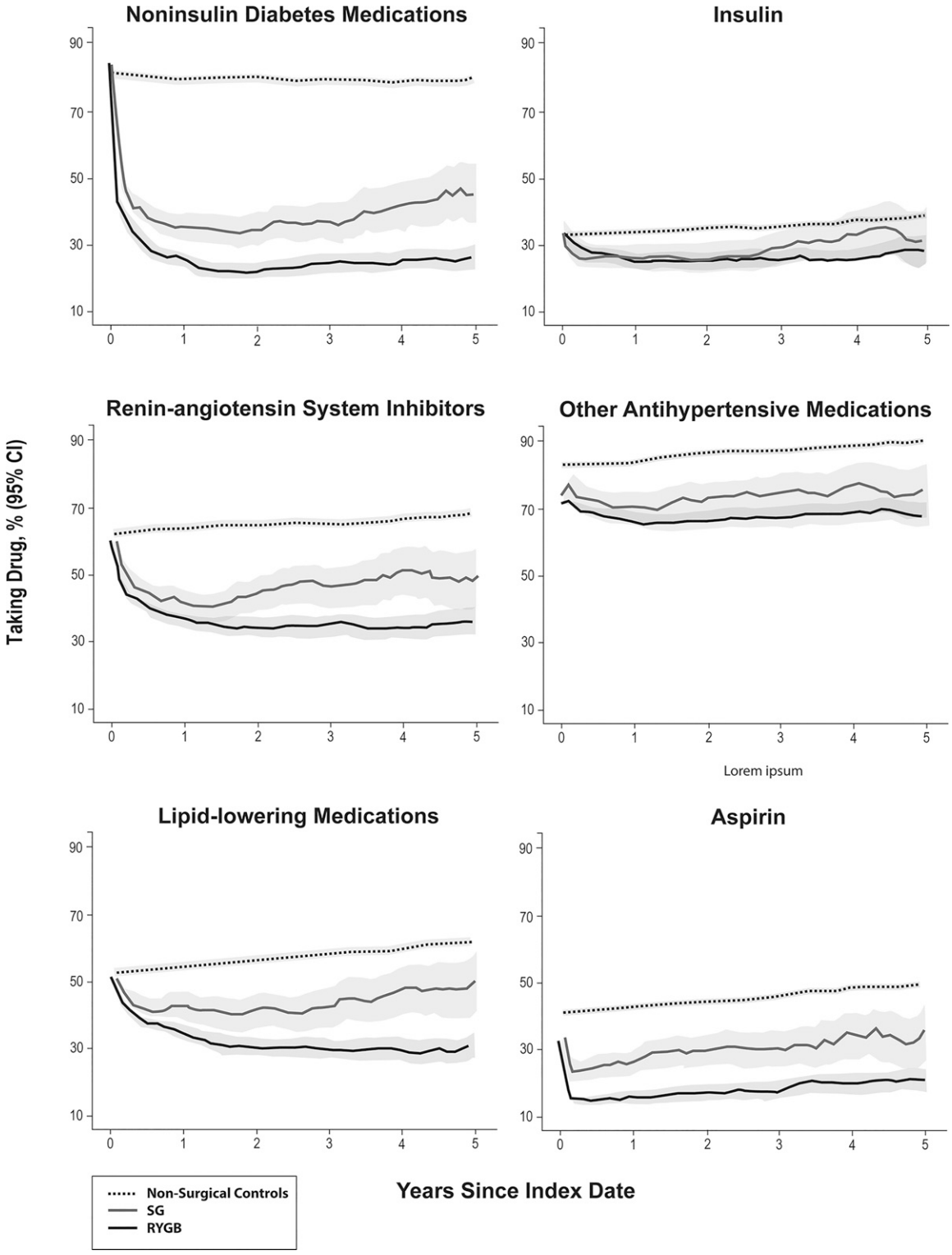

Figure 4—Proportions of patients taking diabetes and cardiovascular drugs over 5 years of follow-up. The proportion of patients on each drug was computed every one-tenth of a year starting at the index date through 5 years of follow-up. Displayed are the proportions over time with 95% point-wise CIs by surgical and nonsurgical patients. Statistical comparisons between the study groups are reported in Supplementary Table 6.

matched a surgical group with a nonsurgical group (6), which was not specifically designed to match and compare RYGB and SG subgroups. The propensity score matching was originally done to obtain a sample from a group of clinically valid comparators for the surgical patients—not to control for differences in every patient characteristic between RYGB and SG subgroups. The intention of the regression adjustment was to be the main method of actual statistical

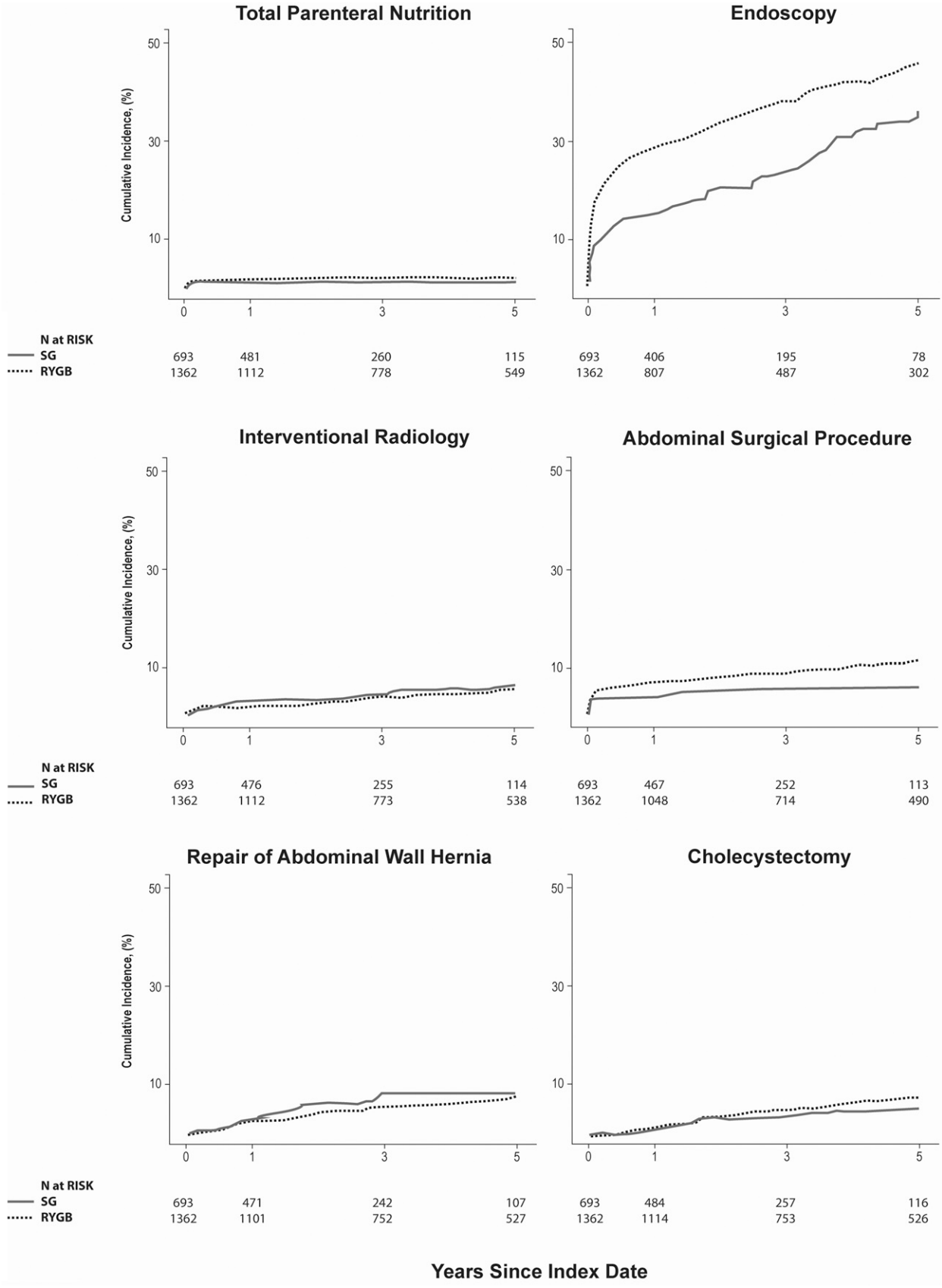

Figure 5—Five-year cumulative incidence estimates (Kaplan-Meier) for interventions after RYGB and SG. More patients after RYGB than after SG required upper endoscopy (45.8% vs. 35.6%, $P < 0.001$) and abdominal surgical procedures (10.8% vs. 5.4%, $P = 0.001$). Cumulative incidences and statistical comparisons are reported in Supplementary Table 7. Abdominal surgical procedure does not include repair of abdominal wall hernia or cholecystectomy.

adjustment for comparison of three study groups in order to control any imbalances that remained after the matching process. Nonetheless, residual measured or unmeasured confounders could have influenced findings of this retrospective observational study. Second, the SG group has a relatively smaller sample size and shorter follow-up time compared with other groups. Nonetheless, those were adequate to provide enough power to show differential impact of surgical procedures (favoring RYGB) on the primary composite end point of study. If this study could not show any difference in the primary end point between two surgical procedures, one valid argument would be lack of enough power due to smaller sample size and shorter follow-up time of the SG group than of the RYGB group. More studies with larger sample size, longer follow-up time, and higher number of events are needed to assess whether RYGB and SG have significantly different rates of "individual" cardiovascular end points beyond six-component MACE and nephropathy. In the current study, the HR for five of six individual cardiovascular end points favored RYGB compared with SG, although the upper 95% CI was <1 only for the nephropathy outcome. Particularly, the adjusted HR of coronary artery events for RYGB versus SG was 0.63 (95% CI 0.38–1.05), which did not reach conventional levels of statistical significance ($P = 0.08$). Third, coding errors, misclassification, and misdiagnosis can occur in EHR-driven data. Fourth, the causes of death could not be determined. Fifth, to analyze the status of diabetes and cardiovascular medications, prescription orders for medications were assessed, which does not necessarily equate to actual medication use. Sixth, surgical adverse events that did not lead to intervention were not analyzed. Indications and diagnoses associated with interventions were not collected. Seventh, a small percentage of nonsurgical patients received newer diabetes medications including glucagon-like peptide 1 receptor agonists and sodium–glucose cotransporter 2 inhibitors that could be associated with significant cardiovascular benefits (6).

Although cardiovascular and survival benefits of RYGB have been reported, the current study is among the first in the literature to show lower risk of MACE and mortality after SG compared with usual care. The findings of this large retrospective study also provide evidence suggesting that RYGB in patients with obesity and T2DM may be associated with greater weight loss, better diabetes control, and lower risk of six-component MACE and nephropathy compared with SG. However, given the nature of the study, these data should be considered hypothesis generating and not conclusive.

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