Clinical Factors Associated With Remission of Obesity-Related Comorbidities After Bariatric Surgery

Ida J. Hatoum, ScD; Robin Blackstone, MD; Tina D. Hunter, PhD; Diane M. Francis, MPH; Michael Steinbuch, PhD; Jason L. Harris, PhD; Lee M. Kaplan, MD, PhD

IMPORTANCE Little is known about comorbidity remission after bariatric surgery during typical clinical care across diverse and geographically distributed populations.

OBJECTIVE To estimate the improvement in obesity-related comorbidities after bariatric surgery and to identify clinical factors associated with these responses using a large representative population of patients.

DESIGN, SETTING, AND PARTICIPANTS This retrospective cohort study included all patients (N = 33 718) with a recorded Current Procedural Terminology code for Roux-en-Y gastric bypass (RYGB) or adjustable gastric banding (AGB) in the MarketScan Commercial Claims and Encounters Medicare Supplemental Databases from January 1, 2005, to June 30, 2010, and who had continuous enrollment from 6 months or more before to 12 months after surgery.

MAIN OUTCOMES AND MEASURES Comorbidities before and after surgery were identified using both diagnoses (from International Classification of Diseases, Ninth Revision [ICD-9] codes) and prescription drug fills. Remission was based on a record of the comorbidity within 6 months before surgery, without record of the condition 18 months after surgery, using both ICD-9 codes and medication fills, as applicable. Multivariable logistic regression models were developed to identify factors associated with remission of diabetes and hypertension.

RESULTS Among the 33 718 patients, 13 comorbidities with at least 1% prevalence before surgery were identified. Both RYGB and AGB led to statistically and clinically significant reductions in these comorbidities; remission rates for all comorbidities were higher after RYGB than AGB. For comorbidities that could be defined using both ICD-9 and prescription drug fill codes, prevalence was higher before and lower after surgery when measured by fill codes. Diagnoses using ICD-9 codes, but not prescription fill codes, increased in the 3 months before surgery. In multivariable logistic regression models for remission of diabetes mellitus after RYGB and AGB, age (RYGB: odds ratio [OR], 0.976; 95% CI, 0.965-0.988 and AGB: OR, 0.982; 95% CI, 0.971-0.933), procedure year (RYGB: OR, 1.11; 95% CI, 1.012-1.218 and AGB: OR, 1.185; 95% CI, 1.039-1.351), preoperative insulin use (RYGB: OR, 0.14; 95% CI, 0.114-0.171; AGB: OR, 0.174; 95% CI, 0.131-0.230), preoperative sulfonylurea use (RYGB: OR, 0.616; 95% CI, 0.505-0.752 and AGB: OR, 0.449; 95% CI, 0.357-0.566), and other antidiabetic medication use (RYGB: OR, 0.747; 95% CI, 0.568-0.981 and AGB: OR, 0.506; 95% CI, 0.359-0.715) were significantly associated with response after both procedures. For remission of hypertension, age (RYGB: OR, 0.964; 95% CI, 0.957-0.972 and AGB: OR, 0.968; 95% CI, 0.959-0.977), number of preoperative antihypertensive medications (RYGB: OR, 0.104; 95% CI, 0.067-0.161 and AGB: OR, 0.239; 95% CI, 0.140-0.408), and preoperative diuretic use (RYGB: OR, 1.729; 95% CI, 1.462-2.045 and AGB: OR, 1.648; 95% CI, 1.380-1.967) were significantly associated with response after both procedures.

CONCLUSIONS AND RELEVANCE Analysis of a large, representative administrative database confirmed established predictors and revealed novel variables associated with comorbidity remission after bariatric surgery. Incorporating these factors into clinical tools to assess an individual patient’s risk-to-benefit profile for these procedures could enhance patient selection and the overall use of surgery for the treatment of obesity and metabolic disease.

Published online October 14, 2015.
Obesity is a major public health issue, with more than 1 billion people overweight or obese worldwide.\(^1\) In the United States, more than one-third of adults are obese\(^2\) and annual expenditures for obesity-related health care, including care for type 2 diabetes mellitus (T2DM), heart disease, hypertension, gastroesophageal reflux disease (GERD), depression, obstructive sleep apnea, osteoarthritis, and obesity-related cancers, are estimated at $200 billion.\(^3\)-\(^7\)

While behavioral and pharmacological treatments for obesity can lead to modest weight loss with some improvement in obesity-related comorbidities, these approaches are frequently ineffective over the long-term.\(^8\) Bariatric surgery leads to greater sustained weight loss than behavioral and pharmacologic therapies, particularly in cases of severe obesity.\(^9\)-\(^13\) In addition to the weight loss benefits of bariatric surgery, studies have shown that bariatric procedures result in dramatic improvements in obesity-related comorbidities, far beyond what has been reported with nonsurgical weight loss therapies.\(^14\)-\(^16\)

The rates of improvement have been shown to vary by procedure type, with Roux-en-Y gastric bypass (RYGB) generally resulting in greater improvement in metabolic comorbidities than adjustable gastric banding (AGB).\(^9\),\(^17\),\(^18\)

While many patients experience complete remission of comorbidities after bariatric surgery, others do not. In large meta-analyses, an average of 78% of patients with T2DM had remission of their T2DM after bariatric surgery, with 82% and 55% of RYGB and AGB patients with T2DM showing T2DM remission by 2 years after surgery, respectively.\(^17\) Similarly, 68% and 43% of patients with hypertension showed resolution of hypertension after RYGB and AGB, respectively.\(^9\) To assess the risk-to-benefit profile of this procedure for an individual patient, it is necessary to identify factors that may indicate which patients will likely improve or resolve their comorbidities after surgery.

A limited number of factors have been identified in restricted sets of patients as predictive of resolution of T2DM and hypertension, including weight and severity/duration of disease.\(^9\)-\(^23\) Therefore, it would be beneficial to identify additional predictors that apply to the broader population. The objectives of the current study were to estimate the rates of resolution and improvement in obesity-related comorbidities after bariatric surgery and to identify factors associated with these responses using a large representative population of patients.

### Methods

#### Study Population

Participant data were derived from the nationally representative Truven Health Analytics MarketScan Commercial Claims and Encounters and Medicare Supplemental Databases (eAppendix in the Supplement).\(^24\) The primary study population included 33,718 bariatric surgery patients who were admitted between January 1, 2005, and June 30, 2010, from a total of 103,000 patients with a Current Procedural Terminology (CPT) code of interest for bariatric surgery (eAppendix in the Supplement). Eligibility criteria for the primary cohort included (1) bariatric surgery defined by a restricted list of 5 CPT codes (eTable 1 in the Supplement); (2) a single bariatric surgery CPT code of interest on the date of the index procedure; (3) age 21 years or older on the day of surgery; (4) continuous health care and prescription drug enrollment for at least 6 months before and 12 months after the index procedure; (5) no record of bariatric or revisional surgery before the index procedure; and (6) no International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code for cancer or benign neoplasm of the esophagus, stomach, pancreas, or small intestine within 6 months before the index procedure (eTable 2 in the Supplement). Sleeve gastrectomy was excluded from these analyses owing to the small number of sleeve gastrectomies performed during the study. Detailed reasons for other exclusions are summarized in eTable 3 in the Supplement. An exemption from review was granted for this study by the New England Institutional Review Board because the data source consisted solely of deidentified patient data.

#### Obesity and Covariate Characterization

Morbid obesity was determined using ICD-9 code 278.01. Additional diagnoses were determined using ICD-9 codes after grouping ICD-9 codes using medical and surgical expertise and by prescription fills using therapeutic class codes for those comorbidities with an associated therapeutic drug class (eTable 4 in the Supplement). They were assessed over sequential 3-month intervals from 6 months before the index bariatric procedure until 12 months after surgery. Any diagnosis with at least 1% prevalence within the year before bariatric surgery was selected as a comorbid condition of interest for follow-up in the primary analyses (eAppendix and eTable 5 in the Supplement). Thirteen comorbidities met this criterion (eTable 6 in the Supplement).

#### Statistical Analyses

To determine which patients had remission or improvement of T2DM and hypertension and remission of hyperlipidemia, GERD/hiatal hernia, sleep apnea, and shortness of breath, we analyzed data from patients with 21 months of follow-up information and a CPT code for laparoscopic RYG or laparoscopic AGB. Remission of each of these conditions was defined as a record of the comorbidity within 6 months before surgery (baseline), but no record of the same condition between 15 and 21 months (18-month time point) after surgery. Remission for both T2DM and hypertension was defined as a change from medication use to no medication use, as determined by drug prescription fills from an associated therapeutic class. Univariate confidence intervals were calculated at 6, 12, and 18 months after surgery for the mean percentage resolution of the comorbid conditions.

Multivariable analytical models were developed to test the effect of RYG and AGB on both the reduction and remission of T2DM and hypertension. Separate logistic regression models were fitted for each type of surgery. The dependent variables for 18-month outcomes were defined as follows: hypertension remission defined by no prescription refills; hypertension reduction defined by a reduction from multiple medication classes to a single class or no medication and by...
Results

Medical Coding Practices for Obesity
Nearly all patients (99.5%) had an ICD-9 code for morbid obesity recorded within 3 months before surgery, up to and including the day of surgery, while less than 34% had the code recorded more than 3 months before or after surgery (eFigure 1 in the Supplement). Codes for more specific body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) ranges were recorded for less than half of the patients in the 3 months before surgery and rarely used outside of that time frame.

Prevalence of Comorbidities Before and After Bariatric Surgery
Trends in comorbidity prevalence before and after bariatric surgery for the 13 studied comorbidities, based on ICD-9 coding, are depicted in the Figure, and comorbidity prevalence estimates, based on ICD-9 coding and medication use, in the 3- to 6-month period before and 9- to 12-month period after the index bariatric procedure are summarized in eTable 6 in the Supplement. Because coding of comorbidities was dramatically increased on the day of surgery for all conditions, the day of surgery was not included in trend analyses. There was an increase in the prevalence of ICD-9 coding for comorbidities in the 3 months immediately preceding surgery (Figure; eFigure 1 and eFigure 2 in the Supplement), but there was no similar increase in medication use (eFigure 2 in the Supplement). With the exception of abdominal pain and antianxiety medications, the prevalence of all comorbidities analyzed decreased after bariatric surgery (Figure; eTable 6 in the Supplement).

Comparison of RYGB and AGB Procedures 18 Months After Bariatric Surgery
Of 33 718 patients who met the inclusion criteria, 19 909 underwent RYGB (60%) and 13 809 underwent AGB (40%). Of these, 10 767 patients with RYGB and 7832 patients with AGB had sufficient follow-up to analyze response at 18 months after surgery. Baseline characteristics are presented in Table 1. Remission rates were both statistically and clinically significant for all 13 comorbidities after each procedure, ranging from 23% (depression after AGB) to 96% (shortness of breath after RYGB) (Table 2). Remission rates were significantly higher after RYGB than after AGB for T2DM, GERD, hyperlipidemia, and hypertension.
Multivariable logistic regression models were fitted for 18-month remission and reduction end points in patients who underwent RYGB or AGB and who had T2DM or hypertension at baseline, as defined by medication use. Stepwise regression of potential predictors identified significant factors associated with full or partial remission of T2DM and hypertension (Table 3 and Table 4, respectively; eTable 5 in the Supplement). In all models, the odds of improvement after bariatric surgery decreased with advancing age (all P < .006). The specific therapeutic class of anti-diabetic medication was highly significant in indicating T2DM remission, with patients with insulin-dependent T2DM having the lowest odds of remission (odds ratio, 0.140; 95% CI, 0.114-0.171; P < .001 for RYGB; odds ratio, 0.174; 95% CI, 0.131-0.230; P < .001 for AGB). Similarly, in hypertension models, several of the therapeutic classes of hypertension medication were significant. In particular, severity based on the number of different hypertension therapeutic classes for which a patient filled prescriptions was highly significant (all P < .003). The odds of hypertension remission after surgery decreased with increasing number of drug classes. The odds of reduction were higher for patients taking multiple hypertension drug classes than those on a single class, in part because reduction in hypertension was defined by a decrease in the number of hypertension drug classes.

### Discussion

Using a large representative medical claims database, we confirmed several established factors and identified several novel factors that are associated with T2DM and hypertension remission after bariatric surgery. We also identified patterns in medical coding practice that may have potentially important methodological implications for future studies using claims databases, including an increase in diagnostic coding in the 3 months before surgery using ICD-9 codes but no increase in prescription drug fills, and a substantially more rapid fall in prescription drug fills than ICD-9 code use after surgery.

We observed that with the exception of abdominal pain, depression, and anxiety, the prevalence of all comorbidities investigated decreased rapidly after bariatric surgery.
Abbreviations: AGB, adjustable gastric banding; Dx, diagnosis from Rx, prescription drug fill; RYGB, Roux-en-Y gastric bypass.

Remission rates for T2DM, hypertension, hyperlipidemia, sleep apnea, and GERD were significantly greater after RYGB than after AGB, an outcome that has been seen previously.9,17 Similar to what was observed in this study, previous studies in claims databases have found rapid and marked decreases in T2DM, hypertension, and hyperlipidemia medication use associated with resolution, because of the nature of the administrative claims database, we were unable to assess BMI or patient laboratory values directly. Finally, we found that RYGB leads to a significantly greater reduction in medication use than AGB; therefore, it would be beneficial for future studies to explicitly determine the relative costs of each procedure.

Preoperative insulin use was the factor most strongly associated with failing to resolve T2DM, a finding consistent with previous studies of T2DM resolution among bariatric surgery patients.19-21 However, it should be noted that despite failing to exhibit full remission of T2DM, overall medication use in this population is decreased. This is consistent with previous studies that have shown that even patients with severe T2DM can reduce the use of insulin after surgery.19-21 Previous studies have consistently demonstrated that patients with more severe and less well-controlled T2DM, as determined by insulin use,19,21 hemoglobin A1c level,19,21,22 fasting glucose level,19,21,22 and/or longer duration of disease20-22 are less likely to experience full remission of T2DM after bariatric surgery. Furthermore, in a clinical trial of T2DM remission after RYGB, patients with less well-controlled T2DM had a lower rate of remission28 than was seen in a separate trial that examined patients with less severe T2DM at baseline.29 Taken together, these findings underscore the potential value of using bariatric surgery in patients with T2DM earlier in the course of disease progression. Notably, however, patients later in the course of the disease may also see dramatic improvement in T2DM with substantial long-term benefit despite not experiencing complete remission. Other studies have found that visceral obesity,21 baseline BMI,19,22 and sleep apnea, and GERD were significantly greater after RYGB than AGB, an outcome that has been seen previously.9,17 Taken together, these findings underscore the potential value of using bariatric surgery in patients with T2DM earlier in the course of disease progression. Notably, however, patients later in the course of the disease may also see dramatic improvement in T2DM with substantial long-term benefit despite not experiencing complete remission. Other studies have found that visceral obesity,21 baseline BMI,19,22 and fasting C-peptide levels30 are associated with T2DM response to surgery. While we also found that age was associated with resolution, because of the nature of the administrative claims database, we were unable to assess BMI or patient laboratory values directly. Finally, we found that rates of T2DM remission were greater after RYGB than AGB, which is consistent with findings from previous clinical studies.9 This difference in remission rates likely reflects the distinct mechanisms of action of the 2 procedures.

Associated with failure to resolve hypertension was whether the patient was taking hypertension medications from multiple therapeutic classes, a single class, or not taking any hypertension medications at the time of surgery. This metric is likely an indicator of the severity and/or degree of control of the patient’s hypertension before surgery. To date, remission of hypertension after bariatric surgery has been less fully examined than remission of T2DM, but one previous study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Remission</th>
<th>Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AGB (n = 814a)</td>
<td>RYGB (n = 2371a)</td>
</tr>
<tr>
<td></td>
<td>OR 95% CI</td>
<td>P Value</td>
</tr>
<tr>
<td>Female vs male</td>
<td>NS NS</td>
<td>NS</td>
</tr>
<tr>
<td>Age</td>
<td>0.982 0.971-0.993</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Procedure year</td>
<td>1.185 1.039-1.351</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>No. of baseline drug types</td>
<td>0.743 0.660-0.837</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Dx of baseline congestive heart failure</td>
<td>NS NS NS NS NS NS NS NS NS NS NS</td>
<td>0.575 0.357-0.826</td>
</tr>
<tr>
<td>Dx of baseline ischemic heart disease</td>
<td>NS NS NS NS NS NS NS NS NS NS NS</td>
<td>0.746 0.560-0.992</td>
</tr>
<tr>
<td>Rx for antihyperlipidemic at baseline</td>
<td>NS NS NS NS NS NS NS NS NS NS NS</td>
<td>0.697 0.559-0.869</td>
</tr>
<tr>
<td>Rx for antiangiecty at baseline</td>
<td>1.543 1.087-2.189</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Rx for β-blocker at baseline</td>
<td>NS NS</td>
<td>NS</td>
</tr>
<tr>
<td>Rx for insulin at baseline</td>
<td>0.174 0.131-0.230</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rx for sulfonylureas at baseline</td>
<td>0.449 0.357-0.566</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Rx for miscellaneous antidiabetic agent at baseline</td>
<td>0.506 0.359-0.715</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviations: AGB, adjustable gastric banding; Dx, diagnosis from International Classification of Diseases, Ninth Revision codes; NS, not significant; OR, odds ratio; Rx, prescription drug fill; RYGB, Roux-en-Y gastric bypass.

a Among individuals with baseline diabetes mellitus (AGB: n = 1813; RYGB: n = 3035).

b Number of patients with remission/reduction.
found that a longer duration of hypertension before surgery was associated with a decreased likelihood of postoperative remission. Other studies have also identified vitamin D depletion and lower attained BMI, which could not be examined in this study, as potential factors associated with hypertension remission.

There was a sharp increase in ICD-9 code use immediately before and on the day of bariatric surgery. This increased coding behavior likely reflects more comprehensive coding at the time of surgery or hospital admission, rather than a true spike in incidence before surgery. These observations suggest a need for caution in making direct comparisons between different periods relative to the day of a major medical event or across data sets where the timing of data collection may vary. In contrast to the observed pattern in diagnosis code use, no spike in medication use was noted just before the index surgery. In addition, the observed decrease in T2DM was more pronounced when determined by medication fills than by diagnosis codes, indicating the possibility that there is a tendency to continue reporting diagnosis codes for chronic conditions, even in the presence of a clinical remission. Taken together, these results suggest that for comorbidities with an associated therapeutic drug class, medication use may be a more sensitive marker of change in both the prevalence and severity of disease and its response to intervention. The discrepancy between prescription fills and diagnosis codes was particularly pronounced for depression and anxiety. It is possible that the medications used to treat depression and anxiety are also used for a broader range of psychiatric disorders. This may also be the case for other classes of medications, including those used for hypertension. Future research is necessary to determine whether diagnosis codes are truly more specific markers of such disorders.

In the present study, 26% of individuals with depression and 48% of individuals with anxiety had remission of their disorder after RYGB. It is possible that the relatively low rate of remission for these psychiatric illnesses may be affected by certain preoperative and postoperative clinical protocols. For example, many treatment centers advise patients to continue medications for depression indefinitely, which would artificially raise drug fill–defined prevalence estimates for these diseases. Further research is needed to determine whether the sustained level of drug fills for medications to treat depression and anxiety may be inflated by practice patterns. Despite the relatively low rate of remission, the population prevalence of these disorders remained stable when defined by...
prescription drug fills. The observed prevalence of depression and anxiety medication use after surgery thus reflects both continued and incident disease. Previous studies have identified an increase in certain psychiatric illnesses, including alcohol abuse, after bariatric surgery. It is possible that for some illnesses, the ability to self-medicate with food has been lost after surgery, which may lead to the development of alternate coping mechanisms.

There are well-recognized benefits and limitations of using administrative databases for evaluating clinical outcomes. The presence of each condition examined was determined using ICD-9 codes and/or prescription drug fills during the normal course of clinical care. Thus, both disease definition and the clinical decision to use medication were not standardized across all patients. Provider- or center-specific treatment protocols that affect the continuation and/or discontinuation of certain medications could alter the apparent prevalence of disease. Some medications are used to treat multiple conditions, so drug fills may be an imprecise measure of a particular disease target. Prescription drug fill data are a proxy for use; these data alone do not allow us to draw conclusions about an individual’s adherence to the prescribed medication. However, these concerns are somewhat mitigated because in this study, we primarily analyzed change in medication use. Despite these limitations, administrative claims databases have been shown to offer efficiency, generalizability, validity, and completeness of prescription drug data. In the current study, baseline prevalence of comorbidities and rates of resolution were comparable with what has been seen in clinical studies, indicating that these databases offer the potential to extend similar analyses to other comorbidities and complications. Further, as the use of sleeve gastrectomy and other surgical therapies for obesity increase, the methods used here offer the ability to assess the comparative effectiveness of various procedures in real-world conditions.

Conclusions

We identified both established and novel predictors of comorbidity remission after bariatric surgery. As claims databases accrue follow-up on large numbers of additional patients, we may be able to identify factors that are associated with adverse outcomes and additional factors of comorbidity resolution for RYGB, AGB, and other emerging surgical and endoscopic bariatric procedures. Given the large and representative nature of administrative databases, the findings from this and other similar studies may help identify subsets of patients in whom more intensive or specialized clinical intervention may be indicated.

REFERENCES
15. Rubino F, Kaplan LM, Schauer PR, Cummins DE; Diabetes Surgery Summit Delegates. The Diabetes Surgery Summit
Obesity is a negative predictor of remission of type 2 diabetes. \cite{16,17}

Fasting blood glucose, HbA1c, and medication status were examined in five models using HbA1c, fasting blood glucose, and medication status. \cite{18}

Stubbs RS. A model for predicting the resolution of obesity-related comorbid conditions and life-changing improvements in quality of life from near-miraculous benefits to null, or even negative, effects. For example, weight loss from bariatric surgery can range from more than 100% excess body weight loss in hyperresponders to weight gain in some nonresponders, with standard deviations often exceeding mean weight loss. \cite{19}

Similarly, health outcomes range from complete resolution of comorbid conditions and life-changing improvements in quality of life to tragic adverse events, including addiction, disability, and suicide. \cite{20-22}

Aarts EO, Janssen J, Janssen IMC, Berends FJ, Telting D, de Boer H. Preoperative fasting plasma C-peptide level may help to predict diabetes remission following bariatric surgery. \cite{23}

Surgical variables were associated with remission of diabetes mellitus and hypertension, including age and several measures of preoperative medication use, which is likely a proxy for disease severity.

Hatinou et al. \cite{24} reaffirmed the relative improvements in comorbid conditions after Roux-en-Y gastric bypass compared with adjustable gastric banding and demonstrated that medication use similarly declines much more after bariatric surgery.