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Lessons from the trials

# STAMPEDE: Bariatric surgery gains more evidence based support

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## ABSTRACT

Diabetes mellitus (DM) and obesity are associated with significant morbidity and mortality. Recent large-scale trials of intensive medical management for obesity and diabetes have been disappointing. Observational studies and small-scale trials of bariatric surgery on DM patients have shown promising results. The effects of sleeve gastrectomy and gastric bypass in a larger cohort of patients with DM and obesity was tested in the STAMPEDE trial over a 3-year follow-up.

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## INTRODUCTION

Bariatric surgery is often used to treat morbidly obese patients. Moreover, observational studies and small-randomized trials have shown improvement in patients with diabetes mellitus after bariatric surgery. The STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) trial<sup>1,2</sup> is, to-date, the largest randomized trial and has the longest follow-up.

## THE STUDY

A single-center study that randomized patients with uncontrolled type 2 diabetes mellitus (and obesity) to either intensive medical therapy, or medical therapy following sleeve gastrectomy, or gastric bypass. A 12-month follow-up was initially reported in the *New England Journal of Medicine* in 2012,<sup>1</sup> and more recently, the 3-year outcome was simultaneously presented at the 63<sup>rd</sup> Annual Scientific Session of the American College of Cardiology in Washington, DC, USA and published in the *New England Journal of Medicine*.<sup>2</sup> 150 patients were enrolled from March 2007 through January 2011. Eligibility criteria included an age of 20 to 60 years, a glycated hemoglobin level of more than 7%, and a body-mass index (BMI, the weight in kilograms divided by the square the height in meters) of 27 to 43. Patients were randomized in a 1:1:1 ratio, to one of the three study groups; intensive medication therapy, gastric bypass or sleeve gastrectomy. Patients were followed-up for 3 years and the primary outcome was a glycated hemoglobin level of  $\leq 6\%$ , with or without the use of diabetes mellitus medications. Secondary endpoints included levels of fasting plasma glucose, fasting insulin, lipids, and high-sensitivity C-reactive protein (CRP), weight loss, blood pressure, adverse events and changes in medications.

## RESULTS

Nine patients withdraw from the trial immediately after randomization or during the initial 6 months (8 patients in the medical-therapy group and 1 patient who did not undergo sleeve gastrectomy because of severe anemia); 4 patients were lost to follow-up. The remaining 137 patients (91.3%) were evaluated in the 3-year assessment of safety and efficacy. The mean ( $\pm$  SD) was  $48 \pm 8$  years and the mean BMI was  $36.5 \pm 3.5$ , 68% were women and 74% were white. The mean glycated hemoglobin was  $9.3 \pm 1.5\%$ , and the average duration of diabetes was  $8.3 \pm 5.1$  years, with 43% requiring insulin at baseline. There were no significant differences between the study groups at baseline.

At 3 years, the targeted HbA1C  $\leq 6\%$  was achieved in 5% of patients in the medical therapy group compared to 38% of those in the gastric-bypass group ( $P < 0.001$ ) and 24% of those in the sleeve-gastrectomy group ( $P = 0.01$ ). The mean percentage reductions in weight from baseline were greater in the gastric bypass group ( $24.5 \pm 9.1\%$ ) and the sleeve-gastrectomy group ( $21.1 \pm 8.9\%$ ), as compared with a reduction of  $4.2 \pm 8.3\%$  in the medical group ( $P < 0.001$ ). Of the patients with baseline albuminuria, a return to normal values at 3 years occurred in 62% in the gastric bypass group, 80% in the sleeve-gastrectomy group and 25% in the medical-therapy group. In regards to quality of life, there were significant improvements in five of eight mental and physical domains among patients in the gastric-bypass group and two of eight domains among patients in the sleeve-gastrectomy group, as compared with the medical-therapy group. The decrease in triglyceride levels and increase in high-density lipoprotein (HDL) cholesterol levels in the surgical groups, as compared with intensive medical therapy, were sustained at 3 years. There were no significant differences in blood pressure among the three study groups, although there was a significant reduction in the number of medications needed to treat hyperlipidemia and hypertension in the surgical groups. There were no significant differences among the three groups in maximal carotid intima-media thickness at baseline or at 24 months. Additional surgical interventions were required in four patients in the first year, including laparoscopic procedures for blood-clot evacuation, assessment of nausea and vomiting, and cholecystectomy after gastric bypass and jejunostomy for feeding access to treat gastric leak after sleeve gastrectomy. There were no late surgical complications. There were also no excessive weight loss or hypoalbuminuria and no life-threatening complications or deaths in any of the groups.

## DISCUSSION

The 3-year outcome results of the current trial extend the earlier observations of the same trial (12-month follow-up) and are consistent with the observations obtained from smaller trials (see Table 1).<sup>3-7</sup> To-date, 6 randomized controlled trials compared bariatric surgery to medical therapy,

Table 1. Review of published randomized bariatric surgery trials.

Investigators/ year	No of patients/ centers	DM	Baseline BMI	Randomization	Endpoint (Primary)	Endpoint (Secondary)	Follow-up (months)	Outcome
O'Brien <sup>3</sup>	80/2	No*	~33.5	Gastric banding vs. medical care.	Weight change.	Health, Quality of life, Side effects of treatment.	24	The surgical group had lost 21.6% of initial weight, and the nonsurgical group had lost 5.5% of initial weight. 4 patients required laparoscopic revision of the gastric band.
Dixon <sup>4</sup>	60/3	Yes	~37	Conventional medical/behavioral therapy or laparoscopic banding plus medical therapy.	Remission of DM.	Δ HbA1c, weight, BP, waist, lipids.	24	DM remission 73% in the surgical group vs. 13 % medical group. Greater % of weight loss and lower baseline HbA1c in the surgical group.
Mingrone <sup>5</sup>	60/1	Yes	≥35	Roux-en-Y gastric bypass, biliopancreatic diversion, or standard medical therapy.	Remission of DM.	Δ FPG, HbA1c, body weight, waist circumference, BP, and lipids.	24	Surgical complications; 4 patients (minor). DM remission: 75% for gastric bypass and 95% for bilio- pancreatic diversion, no re- missions for medical therapy.
Ikramuddin <sup>6</sup>	120/4	Yes	34	Intensive-medical management (IMM) vs. IMM plus Roux-en-Y gastric bypass.	<7% HbA1c, LDL < 100 mg/dL, SBP < 130	No of medications required achieving endpoint. Weight loss	12	Primary endpoint (49% surgical vs. 19% medical). Secondary endpoints- fewer medications and greater weight loss. Surgical complications; 4 peri-operative complications and 6 late postoperative complications, 1 cardiac event (brain anoxia).
Liang <sup>7</sup>	108/1	Yes + HT	> 28	Usual care (A) vs. Usual care and exenatide (B) vs. Roux-en-Y gastric bypass (C).	Change in cardiac function.	Assess changes in metabolic parameters.	12	Left ventricular mass index was significantly improved in groups B & C, pts in-group C had greater degree of improvement vs.usual care. DM remission 90% @, vs, none in the other groups
Schauer <sup>1,2</sup>	150/1	Yes	~36	Gastric bypass,gastric sleeve vs. medical therapy.	HbA1c ≤6%,	Δ FPG, HbA1c, lipids, and high-sensitivity C-reactive protein, BP and change of medications.	36	Primary endpoint (5% medical, 38% gastric bypass & 21.1% in the sleeve gastrectomy group). Quality of life measures were significantly better in the surgical groups. 4 early and 0 late surgical complications.

~ = Approximately, Δ = change, HbA1c = hemoglobin A1 C, BP = blood pressure, SBP = systolic blood pressure, FPG = fasting plasma glucose, LDL = LDL cholesterol, HT = hypertension, \* = metabolic syndrome.

4 in patients with diabetes mellitus and 1 in patients with metabolic syndrome. The total number of patients enrolled in these trials (including STAMPEDE) was only 578 patients and the types of surgical techniques used varied among the trials (gastric banding, sleeve gastrectomy, or gastric bypass.)

The current study extends those previous observations in a larger cohort of patients and over longer time follow-up. More than, 3 years after randomization, bariatric surgery as compared with intensive medical therapy alone was associated with superior and sustained glycemic control and weight reduction. Analysis of secondary endpoints, including BMI, body weight, waist circumference and levels of triglycerides, and HDL cholesterol, also showed favorable results at 3 years in the surgical groups, as compared with the group receiving intensive medical therapy alone.

### WHAT WE HAVE LEARNED?

STAMPEDE trial was a positive study demonstrating the safety and efficacy of bariatric surgery up to three years from the time of randomization among obese diabetic patients, resulting in improved glycemic control and weight reduction. The study has two main limitations, the small sample size (although to-date it enrolled the largest number of patients among published randomized trials) and the duration of follow-up to detect differences in incidence of diabetes complications, such as myocardial infarction, stroke or death. However, the protocol of the trial specifies further follow-up at 5 years for all patients. Trials including larger numbers of patients and over longer-time periods are needed to confirm these earlier findings. Moreover, bariatric surgery was performed in one highly specialized hospital by very experienced operators resulting in very low complications rates, with these excellent surgical outcomes can be replicated by wider group of surgeons need to be monitored.

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