This year’s European Association for the Study of Diabetes (EASD) meeting, held in Berlin, Germany, hosted more than 15,000 medical professionals from 130 countries from October 1 to 4. We review key sessions on an association between diuretics and amputations, specific diabetes drugs and cardiovascular disease, an appetite suppressant drug and obesity, a dual GIP/GLP-1 receptor agonist, long-term testosterone therapy, and two high-interest non-drug sessions on low-calorie sweeteners and on adverse effects of gastric bypass surgery.

**Association of Diuretics Use and Amputations in Patients With Type 2 Diabetes: A Hypothesis Driven From CANVAS Warning**

- Louis Potier, MD, Department of Diabetology, Endocrinology and Nutrition, Bichat Hospital, Assistance Publique-Hôpitaux de Paris, Paris, France

The use of diuretics in individuals with type 2 diabetes (T2D) is associated with a significantly increased risk of serious lower limb problems with the potential to lead to amputation, according to an analysis of data from SURDIAGENE, a French observational cohort that includes T2D patients enrolled from 2002 until 2012.

The analysis was spurred by the observation that T2D patients taking the SGLT2 inhibitor canagliflozin to reduce blood glucose had higher limb amputation risk in the CANVAS trial. This study was based on the hypothesis that amputations reported in CANVAS could have been driven when SGLT2 inhibitors like canagliflozin induce hypovolemia. If so, then diuretics might also raise amputation risks through the same mechanism.

SURDIAGENE included 1,459 subjects, 670 of whom were taking diuretics. Investigators assessed lower limb events (LLEs) such as amputations (LEAs) and lower extremity revascularizations (LLRs, which are angioplasties or bypasses of blocked or damaged blood vessels to prevent amputations) after an average follow-up of seven years. Follow-up was continued until the first instance of an LLE, a death, or a cut-off date of December 31, 2015. The authors used propensity score matching, matching each patient using diuretics to a comparable non-user patient.

Dr. Potier reported that LLEs occurred in 85 (13%) diuretic users and in 57 (7%) non-users. Among the 1,074 patients included in the matched cohort, those using diuretics had an almost doubled risk (75% higher) of LLE than non-users. Further analysis revealed a large increase in the risk of LEA (2.3 times greater in diuretic users than in non-users). A small increase in LLRs (1.3 times greater in users) was not statistically significant.

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Dr. Potier concluded, “Among patients with type 2 diabetes treated with diuretics, there was a significant and independent increase in the risk of lower limb events, coming predominantly from a rise in lower extremity amputations. Diuretics should be used cautiously in patients with type 2 diabetes at risk of amputations.”

Dr. Potier urged further confirmatory studies and noted that the hypovolemia hypothesis may explain the LEA increase observed with SGLT2 inhibitors.

**Albiglutide and Cardiovascular Outcomes in Patients With Type 2 Diabetes and Cardiovascular Disease (Harmony Outcomes): A Double-Blind, Randomized, Placebo-Controlled Trial**

- John V. McMurray, MD, British Heart Foundation Cardiovascular Research Centre, University of Glasgow, Glasgow, United Kingdom

In patients with type 2 diabetes (T2D) and cardiovascular disease, albiglutide was superior to placebo with respect to major adverse cardiovascular events, in results from the randomized, double-blind, placebo-controlled Harmony Outcomes trial. Albiglutide, Dr. McMurray said, is a glucagon-like peptide 1 (GLP-1) receptor agonist that lowers glucose levels.

While some drugs in the GLP-1 class (e.g., liraglutide and semaglutide) have been shown to reduce the risk of major adverse cardiovascular events in patients with T2D, others (e.g., lixisenatide and exenatide) have not. Harmony Outcomes investigators enrolled 9,463 subjects at 610 sites in 28 countries, assigning them to once-weekly subcutaneous injections of albiglutide (30 mg–50 mg) or matching placebo in addition to standard care. The trial hypothesis was that albiglutide would be non-inferior to placebo for the primary outcome of the first occurrence of cardiovascular death, myocardial infarction (MI), or stroke.

After a median follow-up of 1.6 years, the primary combined outcome occurred in 338 of 4,731 patients (7.1%; 4.6 events per 100 person-years) in the albiglutide group and in 428 of 4,732 patients (9.0%; 5.9 events per 100 person-years) in the placebo group (hazard ratio [HR], 0.78 [95% CI, 0.68, 0.90]; P < 0.001). Among the primary outcome components, MI rates per 100 person-years were significantly lower in the albiglutide group (3.26 vs. 2.43; HR, 0.75 [95% CI, 0.61, 0.90]; P = 0.003). While per 100 person-year rates were numerically lower for stroke and cardiovascular death, the differences were not statistically significant. A prespecified subgroup analysis showed consistent benefits across groups for albiglutide in major adverse cardiovascular events (MACE), but similar rates for all-cause death (196 events for albiglutide; 205 for placebo; P = 0.644).

Rates of acute pancreatitis (10 albiglutide patients and 7 placebo patients), pancreatic cancer (6 and 5 patients, respectively), medullary thyroid carcinoma (no cases in either group), and other serious adverse events did not differ significantly.
between the two groups.

Dr. McMurray stated, “These are impressive findings, with a reduction in risk at least as large as that obtained with traditional cardiovascular drugs and clearly an important addition to the therapeutic approaches available to tackle this problem.”

The Harmony Outcomes lead author Stefano Del Prato, of the Department of Clinical & Experimental Medicine at the University of Pisa in Italy, commented, “We are very excited by these results, which add to the evidence that certain GLP-1-receptor agonists reduce cardiovascular events in patients with type 2 diabetes. This new therapeutic approach offers physicians a further means of reducing the most common and deadly complication faced by our patients with type 2 diabetes.”

The authors concluded that evidence-based GLP-1-receptor agonists should therefore be considered as part of a comprehensive strategy to reduce the risk of cardiovascular events in patients with T2D.

**Effect of Lorcaserin on Prevention and Remission of Type 2 Diabetes in Overweight and Obese Patients (CAMELLIA-TIMI 61): A Randomized, Placebo-Controlled Trial**

- Erin A. Bohula, MD, Brigham and Women’s Hospital, the Thrombolysis in Myocardial Infarction (TIMI) Study Group, Boston, Massachusetts, and Harvard University, Cambridge, Massachusetts

Lorcaserin, an appetite-suppressant selective agonist of the serotonin (5HT)-2C receptor, decreases the risk of developing diabetes and increases high blood-sugar remission rates. It also reduces the risk of kidney complications due to diabetes in obese and overweight patients, Dr. Bohula noted in an oral presentation.

In a recent presentation of CAMELLIA-TIMI 61 results, lorcaserin facilitated modest but sustained weight loss without an increased risk of major adverse cardiovascular events in obese or overweight patients at high cardiovascular risk. Lorcaserin’s long-term impact on diabetes prevention or remission, however, remains unknown. The randomized, double-blind trial tested lorcaserin or a placebo on a background of lifestyle modification in 12,000 overweight or obese patients with or at high risk for atherosclerotic vascular disease at 473 centers in eight countries. All patients had a body mass index (BMI) of at least 27 kg/m² and either established cardiovascular disease (with or without diabetes) or diabetes and at least one other cardiovascular risk factor. Subjects were randomized double-blind 1:1 to lorcaserin 10 mg twice daily or a placebo. All of them received advice on diet and exercise. For this analysis, the prespecified endpoint of incident diabetes was assessed in patients with prediabetes at baseline. Other prespecified outcomes for efficacy included the remission of hyperglycemia, achievement of normal serum glucose, and a reduction in diabetic microvascular complications. Hypoglycemia was the main safety concern.

After one year, weight loss was statistically significant for patients with baseline diabetes (2.6 kg), pre-diabetes (2.8 kg) and normoglycemia (3.3 kg). Incident diabetes with lorcaserin was reduced by 19% in patients with prediabetes (8.5% vs. 10.3%). The rate of achievement of normoglycemia in patients with prediabetes was numerically higher with lorcaserin (9.2% vs. 7.6%), and the rate of remission of hyperglycemia in patients with diabetes was significantly higher by 21% (7.1% vs. 6.0%) as compared with placebo.

A composite of microvascular events including incident microalbuminuria, diabetic retinopathy, or neuropathy was reduced by 21% in those patients with diabetes (10.1% vs. 12.4%). In patients with diabetes at baseline, severe hypoglycemia with serious complications was rare, but more common with lorcaserin (12 events vs. 4 events) with borderline statistical significance. In patients with diabetes, lorcaserin reduced glycated hemoglobin (HbA1c) by 0.3% compared with placebo at one year, from a mean baseline of 7.0%.

Dr. Bohula concluded, “Lorcaserin is effective for weight loss, and in contrast to many other obesity medications to date has proven safe for major adverse cardiovascular events, including cardiovascular death, myocardial infarction, or stroke.” The findings of the present study, she added, “… reinforce the notion that modest, durable weight loss can improve cardiometabolic health and support the role of lorcaserin as an adjunctive therapy in chronic weight management and metabolic health.”

According to Drs. Xabier Unamuno and Gema Frühbeck, of the University of Navarra in Pamplona, Spain, the overall magnitude of the effects of lorcaserin might seem moderate to some physicians. Also, the resulting weight loss might be disappointing, particularly if it does not lower the risk of cardiovascular disease, and evidence exists that effective weight management delivered in the primary care setting can bring about sustained remission in T2D. They suggested that physicians might prefer to prescribe lorcaserin on a temporary basis (e.g., for 6 to 12 months) to identify patients who respond well and for whom treatment should be continued.

**Cardiovascular and Renal Microvascular Outcome Study With Linagliptin in Patients With Type 2 Diabetes Mellitus (CARMELINA)**

- Bernard Zinman, MD, University of Toronto, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Toronto, Canada

In CARMELINA, when linagliptin 5 mg once-daily was added to standard of care, it demonstrated a similar cardiovascular safety profile to placebo, thus meeting the trial’s primary endpoint. The study was conducted among adults with type 2 diabetes (T2D) at high risk for heart and/or kidney disease at 600 sites in 27 countries, Dr. Zinman said in his oral session. Linagliptin is a one-dose, once-daily DPP-4 inhibitor that has been shown to significantly reduce serum glucose in patients with T2D. “Heart disease,” Dr. Zinman noted, “is a major complication and the leading cause of death for people living with type 2 diabetes.” CARMELINA was designed to assess linagliptin’s impact on cardiovascular and renal safety in this population. The primary endpoint was time to first occurrence of the 3-P MACE (cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke). The key secondary endpoint was the first occurrence of sustained end-stage kidney disease
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(ESKD), death due to kidney disease, or a sustained decrease in eGFR from a baseline of ≥ 40% compared to placebo.

The CARAMELINA population, Dr. Zinman pointed out, 62.3% of whom have kidney disease (eGFR < 60 ml/min/1.73 m²), represents a previously understudied group. The primary endpoint, after a median duration of 2.2 years, was reported at similar rates in both groups, 12.4% (n = 434) of the linagliptin group compared to 12.1% (n = 420) in the placebo group. The secondary renal endpoint was also reported at similar rates, 9.4% (n = 327) in the linagliptin group compared to 8.8% (n = 306) in the placebo group. Among the prespecified microvascular outcomes, microvascular composite outcome significantly favored linagliptin ([Hazard Ratio]HR, 0.86; P = 0.0032) as did albuminuria progression (HR, 0.86; P = 0.0034). Hospitalization for heart failure, another secondary endpoint, was reported at similar rates for linagliptin and placebo (6.0% and 6.5%, respectively). An increase in the risk of hospitalization for heart failure has been observed in some other cardiovascular outcome trials in diabetes. Dr. Zinman cited the SAVOR-TIMI 53, EXAMIE, and TECOS trials, which had HRs favoring placebo of 1.27, 1.19, and 1.0, respectively. The HR in CARAMELINA favored linagliptin (HR, 0.90).

No new safety findings for linagliptin were observed, with no increases for hypoglycemia, including among the most susceptible patients (e.g., insulin background and reduced eGFR). “The overall safety profile, including kidney outcomes, in this high-risk patient population was reassuring,” commented Dr. Zinman.

He concluded, “In this patient population, linagliptin demonstrated cardiovascular safety for atherosclerotic cardiovascular events, with neutral effects on hospitalization for heart failure and kidney outcomes.”

Efficacy and Safety of LY3298176, a Novel Dual GIP and GLP-1 Receptor Agonist, in Patients With Type 2 Diabetes: A Randomized, Placebo-Controlled, and Active Comparator-Controlled Phase 2 Trial

• Juan Pablo Frias, MD, Diabetes Center Bochum-Hattingen, St. Josef Hospital, Ruhr-University Bochum, Bochum, Germany

In individuals with type 2 diabetes (T2D), results of a phase 2b clinical trial showed the investigational dual glucose-dependent insulinomimetic polypeptide (GIP) and GLP-1 receptor agonist (GLP-1 RA) LY3298176 as producing strong and clinically meaningful blood sugar reduction and weight loss.

Dr. Frias reported that the weekly dual GIP and GLP-1 receptor agonist integrates the action of both incretins into a single novel molecule, aiming to build upon the clinical benefits seen with a selective GLP-1 RA. In the double-blind, randomized study, T2D patients were randomly assigned (1:1:1:1:1:1) to receive either once-weekly subcutaneous LY3298176 (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1.5 mg), or placebo for 26 weeks. Assignment was stratified by baseline HbA1c, metformin use, and body mass index (BMI). Entry criteria allowed adults with T2D for at least six months (HbA1c 7.0–10.5%, inclusive), a BMI of 23–50 kg/m², and with disease that was inadequately controlled with diet and exercise alone or with stable metformin therapy. A change in HbA1c from baseline to 26 weeks was the primary efficacy outcome.

Investigators assigned 318 patients (53% male) to one of six treatment groups. At baseline, the mean age was 57 years, BMI was 32.6 kg/m², duration from diagnosis of diabetes was nine years, and HbA1c was 8.1%.

The primary analysis showed a robust dose response compared to placebo throughout the entire dose range of GIP/GLP-1 RA. At 26 weeks, changes in HbA1c with LY3298176 were dose-dependent and had not plateaued. From baseline with LY3298176 they were –1.06% for 1 mg, –1.73% for 5 mg, –1.89% for 10 mg, and –94% for 15 mg, compared with –0.06% for placebo.

Also, at doses from 5 mg to 15 mg, glycemic control and weight loss were significantly increased compared with treatment with dulaglutide (1.5 mg). Sixteen (30%) of 53 patients treated with 15 mg of LY3298176 reached normoglycemia (defined as HbA1c < 5.7%) compared with only one (2%) of 54 patients treated with dulaglutide. In the 15-mg LY3298176 group, 24.5% of patients lost at least 15% of their body weight compared to only 1.9% of patients on dulaglutide. Gastrointestinal (GI) side effects were more frequent with LY3298176, but hypoglycemia rates were similar. GI events included nausea (20% [5 mg], 22% [10 mg], and 40% [15 mg]), diarrhea (24% [5 mg and 10 mg] and 32% [15 mg]), and vomiting (8% [5 mg], 16% [10 mg], and 26% [15 mg]), which were mild to moderate and generally temporary, most often occurring during the titration period. Dulaglutide 1.5 mg had a similar side-effect profile to previous studies.

In addition, pulse rates were not raised by treatment with LY3298176, unlike with the GLP-1 and glucagon co-agonist MEDI0382, which has been associated with an increase of six to eight beats per minute.

Commenting in The Lancet, Drs. Michael Stumvoll and Matthias Tschöp wrote, “...these new observations indicating superior benefits of a twincretin approach suggest that these treatment approaches could contribute to efforts to reduce the rising prevalence of obesity and type 2 diabetes.” They also reported that despite the small but significant competitive edge of this twincretin over a classic GLP-1 monoaogistant, it was too early for any comprehensive clinical conclusion or recommendation.

Improvement of Type 2 Diabetes in Hypogonadal Men with Long-Term Testosterone Therapy (TTh) Is Sustained for up to 10 Years Compared to Untreated Controls

• Farid Saad, MD, Bayer AG, Berlin, Germany

In men with low testosterone who have type 2 diabetes (T2D), long-term testosterone therapy (TTh) can improve their disease and reverse its progress. It can also induce significant weight loss, Dr. Saad reported, in a poster presentation of results from a study conducted among 805 hypogonadal men.

Numerous experimental and clinical studies have shown beneficial effects of TTh in hypogonadal men with T2D. In an ongoing registry study in a urological setting, 311 men with...
T2D were analyzed as a subgroup, with the aim of determining the effect of long-term TTh on hypogonadal men. Among them, 141 chose to receive TTh and were given 1,000-mg injections of testosterone undecanoate every 12 weeks. The remaining group of 170 men who did not wish to receive TTh acted as the control group.

Follow-up (one to four times per year) included weight and waist measurements along with fasting blood glucose and HbA1c. By the end of the 10-year follow-up period, average fasting blood glucose levels had decreased in the testosterone group from 7.7 to 5.3 mmol/L, while in the control group, they had risen from 6.3 to 8.2 mmol/L. Average levels of HbA1c also fell in the testosterone group, from 9.0% to 5.9%, and increased in the control patients from 7.8% to 10.6%.

Average insulin doses among the 61 men in the testosterone group who relied on insulin decreased significantly, falling from an average of 34 to 20 units per day. Members of the untreated control group saw their average insulin dose rise from 31 to 42 units per day. Advantages in weight and waist size were also observed among those receiving testosterone. The average weight of testosterone group members decreased from 113 kg to 91 kg at the end of the 10-year study period, and their average waist size dropped from 113 cm to 100 cm. In the control group, weight and waist circumference remained stable.

While no patients in the control group reached target HbA1c levels of 6.5% or 7.0%, in the testosterone group, 80.1% achieved the 6.5% target and 90.8% reached the 7.0% HbA1c level by the time of the last measurement. Dr. Saad pointed out that those who did not reach their targets were men who had been treated with testosterone for the shortest duration.

A common but unsubstantiated fear of increased prostate cancer rates was not supported, with rates actually doubled in the untreated controls. Dr. Saad also noted, “A substantially elevated hematocrit occurred very rarely in this study and was always transient…. There was not a single heart attack or stroke in the testosterone-treated group, events one may associate with an increase in hematocrit.”

In conclusion, Dr. Saad noted, “Long-term testosterone therapy can support diabetes treatment in hypogonadal men with T2D. Its use improved control of blood glucose.” He observed also that some men went into remission from T2D, some of them after as many as 10 years of testosterone therapy.

Low-Calorie Sweeteners Disrupt the Gut Microbiome in Healthy Subjects in Association With Impaired Glycemic Control

• Richard Young, MD, Adelaide Medical School and the Centre of Research Excellence in Translating Nutritional Science to Good Health, University of Adelaide, Australia

New research identifies mechanisms through which the consumption of low-calorie sweeteners (LCS) can lead to impaired regulation of glucose levels. Prior research, Dr. Young said in an oral presentation, has indicated that a regular high intake of beverages sweetened with LCS is linked to an increased risk of developing type 2 diabetes (T2D). The underlying mechanisms, however, remain unknown. Dr. Young and colleagues’ other recent investigations have shown that adding LCS to the diets of healthy non-diabetic subjects for two weeks was enough to cause a clinically relevant increase in responses to glucose consumption. Specifically, it showed augmented glucose absorption (serum 3-O-methyl glucose [3-OMG]) and attenuated release of glucagon-like peptide-1 (GLP-1) to contribute to dysglycemia. That research raised the likelihood that gut dysbiosis contributes to abnormalities in serum glucose in humans, as has been shown in rodents.

Investigators recruited 29 non-diabetic subjects with an average age of 30 years and an average BMI of 24 kg/m², and randomized them to either a placebo (n = 15) or an LCS combination of 92 mg of sucralose and 52 mg of acesulfame-K (n = 14). The dose, equivalent to drinking around 1.5 liters of diet beverage per day, was given as capsules taken three times daily over two weeks. Analyses (shotgun metagenomic sequencing) of the types and species of microorganisms were conducted on stool samples before and after treatment.

Dr. Young reported that LCS-treated subjects exhibited a greater variation in fecal microbiota composition, along with a significant reduction in the health-associated bacterium Eubacterium cylindroides and an increased abundance of 11 opportunistic gut pathogens, including Klebsiella, Porphyromonas, and Finegoldia (all P ≤ 0.001). A decrease in beneficial and fermentative Bifidobacterium, Lactobacillus, and Bacteroides populations correlated with augmented glucose absorption (3-OMG); a decrease in Butyribrio populations correlated with attenuated GLP-1 release (P ≥ 0.37; P ≤ 0.05). Investigators also identified shifts in the abundance of microbial genes involved in sucrose degradation and pyruvate metabolism correlated with a deterioration in glucose regulation in LCS-treated subjects.

Dr. Young concluded, “Our findings support the concept that such sweeteners worsen blood sugar control in healthy subjects by disrupting the regulation of glucose uptake and disposal, as well as [causing] changes in the balance of gut bacteria. This highlights the clinical relevance of dietary low-calorie sweetener patterns to overall blood sugar control.”

Pros and Cons of Gastric Bypass Surgery in Obese Individuals With Type 2 Diabetes: Nationwide, Matched, Observational Cohort Study

• Vasileios Liakopoulos, MD, Department of Molecular and Clinical Medicine, University of Gothenburg, Gothenburg, Sweden

While gastric bypass (GBP) surgery offers obvious benefits in obese individuals with type 2 diabetes (T2D), serious possible adverse events require monitoring and potentially, treatment, according to Dr. Liakopoulos.

Although prior research into GBP efficacy is extensive, studies looking at long-term complication incidence are limited, said Dr. Liakopoulos in his oral session, and patients with T2D are underrepresented in them. Such information would help inform patient selection and follow-up care. Dr. Liakopoulos sought to evaluate the long-term effects of GBP in obese patients with T2DM, in particular regarding the risks of postoperative complications.

Dr. Liakopoulos’ research matched obese T2D patients who
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had undergone GBP from the Scandinavian Obesity Surgery Registry, the National Diabetes Register, and the Swedish national databases with those who had not been treated surgically for obesity. Matching was based on sex, age, and body mass index (BMI), and paired 5,321 T2DM patients who underwent a GBP operation, and 5,321 control subjects who did not. Follow-up extended up to nine years, and investigators assessed clinical benefits as well as early postoperative and long-term adverse effects.

The mean age was approximately 48 years and BMI (kg/m²) was 42.0 and 40.9 in the GBP and control groups, respectively. Results favored the GBP group significantly across important outcomes: all-cause mortality (49% decrease; \( P < 0.0001 \)), cardiovascular disease (34% decrease; \( P = 0.0014 \)), fatal cardiovascular disease (\( P < 0.0001 \)), acute myocardial infarction (\( P = 0.0010 \)) and congestive heart failure (50% decrease; \( P < 0.0001 \)). Other factors significantly favoring the GBP group were rates for hyperglycemia (\( P < 0.0001 \)), amputation (\( P = 0.0432 \)), renal disease (42% decrease; \( P < 0.0001 \)), and cancer (\( P = 0.0257 \)).

However, these benefits arrived accompanied by a range of associations and/or adverse events, Dr. Liakopoulos said. Psychiatric disorders were 33% more likely in the bypass group (\( P = 0.0008 \)), and alcoholism was nearly three times as likely (hazard ratio [HR], 2.90; \( P < 0.0001 \)). Malnutrition was more common (HR, 2.81; \( P < 0.0001 \)), as was anemia (HR, 1.92; \( P = 0.0005 \)). Furthermore, a wide range of gastrointestinal adverse events was significantly more common in the GBP group (all \( P < 0.0001 \)): additional gastrointestinal surgery (HR, 3.33), abdominal pain (HR, 5.52), gallstone/pancreatitis (HR, 2.49), gastrointestinal ulcer and reflux (HR, 5.42), hernia (HR, 2.75), bowel obstruction (HR, 9.47), gastrointestinal leakage (HR, 5.42), plastic surgery (HR, 19.85), wound complications (HR, 3.45), and bleeding (HR, 6.87).

Pointing out study limitations, Dr. Liakopoulos noted that it was not randomized, and outpatient visits to primary care physicians were not tallied. Its strengths included the fact that nationwide coverage of T2D and bypass surgery afforded high-quality data that could form a basis for generalizations.

“This nationwide study,” Dr. Liakopoulos said, “confirms the benefits but also describes the variety of adverse effects after bariatric surgery in obese persons with type 2 diabetes.” He concluded, “In order to maximize the benefit and minimize the risk of unfavorable results after bariatric surgery, a thorough and long-term follow-up and support of these patients appears vital. Better selection of patients for such surgery could also improve results.”