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ELSEVIER

Insulin degludec reduced hypoglycaemia vs U100 insulin glargine in separate trials in types 1 and 2 diabetes

In the two separate SWITCH 1 and 2 trials in types 1 and 2 diabetes, insulin degludec reduced hypoglycaemia vs insulin glargine U100.

These results of the SWITCH 1 and 2 trials were reported at the 76th Scientific Sessions of the American Diabetes Association, from June 10–14. ▸3

Long-term effects of neighbourhood deprivation on diabetes risk

The Lancet Diabetes & Endocrinology

This is an interesting study design, and the results provide further evidence that socioeconomic factors are significant contributors to diabetes risk. ▸3

Liraglutide reduces CV outcomes in patients with type 2 diabetes

The New England Journal of Medicine

Liraglutide appears to be superior to placebo for reducing events and deaths from cardiovascular causes in patients with type 2 diabetes. ▸6

Cardiovascular effects of SGLT-2 inhibitors in type 2 diabetes

The Lancet Diabetes & Endocrinology

The available data provide a strong rationale to expect benefit from use of SGLT2 inhibitors in patients with type 2 diabetes at high risk of cardiovascular events ▸8

Portion-controlled prepackaged foods promote weight loss

Obesity

Overweight and obese patients who followed meal plans that include portion-controlled prepackaged foods lost more weight and fat than those who followed meal plans involving self-selection of foods. ▸15

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Insulin degludec reduced hypoglycaemia vs U100 insulin glargine in separate trials in types 1 and 2 diabetes

Continued from page 1.

SWITCH 1 in type 1 diabetes

Athena Philis-Tsimikas, MD, of the Scripps Whittier Diabetes Institute, San Diego, California, explained that SWITCH 1 was a 64-week, double-blind, treat-to-target crossover trial that randomised 501 adults with type 1 diabetes and at least one factor associated with increased risk of developing hypoglycaemia to once-daily insulin degludec or insulin glargine U100, both with mealtime insulin aspart for 32 weeks (16-week titration, 16-week maintenance), followed by crossover to insulin glargine U100 or insulin degludec for an additional 32 weeks with the same titration and maintenance schedule.

Dr Philis-Tsimikas remarked, "I am so pleased that this was a randomised, double-blind design. This design is difficult to employ in trials of the newer insulins, but it provides a very strong methodology and clear insights into the differences between groups".

The primary objective was to confirm noninferiority in terms of the number of severe (requiring third-party aid, all externally adjudicated) or blood glucose-confirmed (<3.11 mmol/L) symptomatic hypoglycaemic episodes during the maintenance periods. Other endpoints included haemoglobin A_{1c}, fasting plasma glucose, and adverse events.

Treatment with insulin degludec vs insulin glargine U100 resulted in significantly lower rates of severe or blood glucose-confirmed symptomatic hypoglycaemia, severe or blood glucose-confirmed symptomatic nocturnal hypoglycaemia (00:01–05:59), and severe hypoglycaemia for the maintenance and total treatment periods.

> "It is very difficult to achieve a haemoglobin A1c level consistently below 7% in a high-risk population with type 1 diabetes. Our study not only achieved that goal but demonstrated lower rates of severe and symptomatic hypoglycaemia as well. The results were remarkable.

Insulin degludec was superior to insulin glargine U100 in as much as a lower proportion of patients experienced severe hypoglycaemia during the maintenance and total treatment periods.

Haemoglobin A_{1c} noninferiority of insulin degludec vs insulin glargine U100 was confirmed in both treatment periods (means, week 32: 6.95 vs 6.92%; week 64: 6.95 vs 6.97%). Adverse event rates were similar for insulin degludec vs insulin glargine U100.

Dr Philis-Tsimikas concluded that, in this population of patients with type 1 diabetes, insulin degludec significantly reduced the rates and proportions of severe hypoglycaemia and the rates of blood glucose-confirmed symptomatic overall and nocturnal hypoglycaemia vs insulin glargine U100.

She added, "It is very difficult to achieve a haemoglobin A_{1c} level consistently below 7% in a high-risk population with type 1 diabetes. Our study not only achieved that goal but demonstrated lower rates of severe and symptomatic hypoglycaemia as well. The results were remarkable".

SWITCH 2 in type 2 diabetes

Carol H. Wysham, MD, of the Rockwood Clinic, Spokane, Washington, explained that SWITCH 2 was a randomised, 2 x 32-week, double-blind, treat-to-target crossover trial of insulin degludec vs insulin glargine U100 in patients with type 2 diabetes at high risk of hypoglycaemia.

Adults (n=721) with type 2 diabetes were randomised 1:1 to once-daily insulin degludec/insulin glargine U100 followed by crossover to insulin glargine/insulin degludec. Each treatment period was composed of a 16-week titration and 16-week maintenance period.

Patients had been treated with basal insulin ± oral antidiabetic drugs excluding sulfonylurea/meglitinides, and were at increased risk of developing hypoglycaemia based on pretrial risk factors.

The primary endpoint was the number of severe (requiring third-party assistance and external adjudication) or blood glucose-confirmed (<3.11 mmol/L) symptomatic hypoglycaemic events in the maintenance periods.

Treatment with insulin degludec resulted in significantly lower rates of severe or confirmed symptomatic hypoglycaemia and severe or confirmed symptomatic nocturnal hypoglycaemia (occurring 00:01–05:59) vs insulin glargine U100.

The proportion of patients experiencing severe hypoglycaemia in the maintenance periods was 1.6% for insulin degludec vs 2.4% for insulin glargine U100 (difference not significant). Severe hypoglycaemia rates were significantly lower with insulin degludec than with insulin glargine U100 in the total treatment period.

Haemoglobin A_{1c} reductions with insulin degludec were noninferior to insulin glargine U100. Adverse event rates were similar between insulin degludec and insulin glargine.

Dr Wysham concluded that, compared to insulin glargine U100, insulin degludec resulted in a consistent reduction in hypoglycaemia in this cohort of patients with type 2 diabetes at high risk of hypoglycaemia.

Editor's pick

JOURNAL SCAN

Long-term effects of neighbourhood deprivation on diabetes risk

The Lancet Diabetes & Endocrinology

Take-home message

- The authors of this study used national data from a government-associated quasi-random assignment of refugees to various neighbourhoods in Sweden to evaluate the effects of socioeconomic deprivation on diabetes risk. They found that refugees assigned to higher deprivation areas had a higher risk of diabetes.
- This is an interesting study design, and the results provide further evidence that socioeconomic factors are significant contributors to diabetes risk.

BACKGROUND Although studies have shown associations between neighbourhood quality and chronic disease outcomes, such associations are potentially confounded by the selection of different types of people into different neighbourhood environments. We sought to identify the causal effects of neighbourhood deprivation on type 2 diabetes risk, by comparing refugees in Sweden who were actively dispersed by government policy to low-deprivation, moderate-deprivation, or high-deprivation neighbourhoods.

METHODS In this quasi-experimental study, we analysed national register data for refugees who arrived in Sweden aged 25–50 years, at a time when the government policy involved quasi-random dispersal of refugees to neighbourhoods with different levels of poverty and unemployment, schooling, and social welfare participation. Individuals in our sample were assigned to a neighbourhood categorised as high deprivation (≥1 SD above the mean), moderate deprivation (within 1 SD of the mean), or low deprivation (≥1 SD below the mean). The primary outcome was new diagnosis of type 2 diabetes between Jan 1, 2002, and Dec 31, 2010. We used multivariate logistic and linear regressions to assess the effects of neighbourhood deprivation on diabetes risk, controlling for potential confounders affecting neighbourhood assignment and assessing effects of cumulative exposure to different neighbourhood conditions.

FINDINGS We included data for 61386 refugees who arrived in Sweden during 1987–91 and who were assigned to one of 4833 neighbourhoods. Being assigned to an area deemed high deprivation versus low deprivation was associated with an increased risk of diabetes (odds ratio [OR] 1,22, 95% CI 1.07–1.38; P = 0.001). In analyses that included fixed effects for assigned municipality, the increased diabetes risk was estimated to be 0·85 percentage points (95% CI –0·030 to 1.728; P = 0.058). Neighbourhood effects grew over time such that 5 years of additional exposure to high-deprivation versus low-deprivation neighbourhoods was associated with a 9% increase in diabetes risk.

INTERPRETATION This study makes use of a pre-existing governmental natural experiment to show that neighbourhood deprivation increased the risk of diabetes in refugees in Sweden. This finding has heightened importance in the context of the current refugee crisis in Europe.

Long-term effects of neighbourhood deprivation on diabetes risk: quasi-experimental evidence from a refugee dispersal policy in Sweden. *Lancet Diabetes Endocrinol* 2016 Jun 01;4(6)517-524, JS White, R Hamad, X Li, et al.

New drugs and devices listing

THERAPEUTIC GOODS ADMINISTRATION www.tga.gov.au

Avanafil (Spedra), A Menarini – Erectile dysfunction
Cobimetinib (Cotellic), Roche – Unresectable or metastatic melanoma
Idarucizumab (rch) (Praxbind), Boehringer Ingelheim Reversal agent for dabigatran
Evolocumab (rch) (Repatha), Amgen Primary hypercholesterolaemia and homozygous familial hypercholesterolaemia
Follitropin alfa (rch) (Afolia/Bemfola), Finox Biotech Australia For the treatment of infertility.
Eltrombopag (Revolade), Novartis – Severe aplastic anaemia (SAA)
Ibrutinib (Imbruvica), Janssen-Cilag Small lymphocytic lymphoma (SLL), mantle cell lymphoma
Liraglutide (Saxenda), Novo Nordisk – For chronic weight management.
Enzalutamide (Xtandi), Astellas Pharma Metastatic castration-resistant prostate cancer

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Sumatriptan (Imigran FDT), Aspen
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Adrenal gland tumours linked to ADHD diagnosis

BY JESSICA CRAIG

Paediatric patients diagnosed with pheochromocytomas (PHEO) or paragangliomas (PGL) were nearly three times as likely to also carry a diagnosis of attention deficit hyperactivity disorder (ADHD), compared to paediatric patients without PHEO or PGL, investigators reported.

In addition, in 33% of the patients with PHEO and PGL, ADHD symptoms were resolved following surgical removal of the tumour.

PHEO and PGL are rare tumours of the adrenal gland. About 10% of PHEO and PGL cases occur in patients younger than 18 years. PHEOs form inside the adrenal gland in the adrenal medulla while PGLs form outside the adrenal gland. Both tumours cause excess secretion of epinephrine and noradrenaline resulting in high blood pressure, headaches, weight loss, excess sweating, anxiety, and depression. These tumours are most often surgically removed or treated with medication. Chemotherapy and radiation therapy have not been as effective in treating PHEO or PGL.

ADHD is a neurodevelopment disorder characterised by a pattern of inattention and hyperactivity or impulsivity. ADHD is associated with catecholamine dysregulation; the function of catecholamine receptors is impaired by either excess or deficient stimulation. ADHD has a prevalence of 7.2% in children aged 4–18.

In addition to the overlap in symptoms, "the stimulants used to treat ADHD may exacerbate the symptoms of the PHEO/PGL and potentially lead to a hypertensive crisis ... Amphetamines, the most widely used ADHD medication class, lead to release of stored catecholamines from vesicles, block reuptake of noradrenaline and dopamine, and block catecholamine degradation," wrote Dr M. Batsis of the Eunice Kennedy Shriver National Institute of Child Health and Human Development and her associates (*Horm Metab Res* 2016 May 12. doi: 10.1055/s-0042-106725).

"I noticed that a lot of patients with the same story as follows: [parents] went to their paediatrician when their child started having feelings of anxiety or their heart was racing. And these symptoms were attributed to ADHD, and the child was started on medications. It wasn't until later symptoms – an abdominal mass or a hypertensive crisis – that the patient was ultimately found out to have a pheochromocytoma," Dr Maya Lodish, a paediatric endocrinologist and coauthor of the paper, said in an interview.

"In hindsight, it just was not picked up. ADHD medications in no way affect tumour growth. The substances that these tumours release are stimulants. Endocrine tumours release catecholamine which are naturally occurring hormones we release under stress. When you add on top of that a stimulant medication [to treat ADHD] that may cause the nervous system to go into overdrive," she said.

Due to the rarity of PHEO and PGL, their association with ADHD has not been well characterised. The purpose of this study was to therefore better assess the relationship between ADHD and PHEO/PGL development.

Investigators recruited 43 paediatric patients aged 6–17 who had been diagnosed with PHEO or PGL. Twenty-one percent (n = 9) of patients with PHEO/PGL carried a diagnosis of ADHD, compared to 7.2% in the general population (P = 0.0328).

Prior to the surgical removal of the tumours, eight of the nine patients had elevated levels of noradrenaline (n = 7), dopamine (n = 3), epinephrine (n = 1), metanephrine (n = 5) and/or normetanephrine (n = 7). In the remaining patient, levels were not measured.

Following the surgical removal of the tumours, three of the nine patients experienced both a resolution of their ADHD-related symptoms and a drop or normalisation of their catecholamine and metanephrine levels. Two of those three patients showed no clinical signs of recurrent tumours while the third is under evaluation for a small pelvic lesion.

"These tumours are very rare and the vast majority of patients with ADHD are not affected by them, but they do occur. There are other organic conditions with the same symptoms – drug abuse, medications, Graves disease. If the child has symptoms attributed to ADHD and high blood pressure or family history of endocrine tumours then it is important to have a full organic workup to measure other causes of hypertension prior to starting stimulant medication," Dr Lodish said.

"My observation is that, and a lot of articles out there would agree, diagnoses of ADHD are on the rise and the prescribing of ADHD medication is also on the rise. I hope this is a bit of a wake-up call to practitioners that what's common is common but there are some rare [conditions] to be aware of and so don't have a knee jerk reaction to prescribing a medication for symptoms believed to be attributed to ADHD," she said. ■

The Division of Intramural Research at the Eunice Kennedy Shriver National Institute of Child Health and Human Development supported the study. The investigators had no disclosures to report.

FRONTLINE MEDICAL NEWS

RF ablation successfully treats focal adrenal tumours

BY DANIEL M. KELLER

Radiofrequency ablation is a safe and effective procedure for treating focal adrenal tumours in patients who are poor surgical candidates or who refuse adrenalectomy. With a short treatment time and minimal hospital stay, RF ablation can provide rapid clinical and biochemical improvement.

Dr Lima Lawrence, an internal medicine resident at the University of Illinois at Chicago/Advocate Christ Medical Centre in Oak Lawn, presented a case report and a review of the literature during an oral abstract session at the annual meeting of the American Association of Clinical Endocrinologists. The patient was a 65-year-old woman who presented with weight gain, decreased energy, and muscle weakness. On physical exam, she was hypertensive, anxious, obese, and had prominent supraclavicular fat pads. Salivary cortisol and overnight dexamethasone suppression tests were both elevated, and ACTH levels were depressed, confirming the diagnosis of a cortisol-secreting tumour causing adrenal Cushing's syndrome. Computed tomography (CT) surveillance showed a progressively enlarging right-sided adrenal mass. A peritoneal biopsy revealed a low-grade serous neoplasm of peritoneal origin.

Her medical history included type 2 diabetes, uncontrolled hypertension, mixed connective tissue disease, depression, and total abdominal hysterectomy with bilateral salpingo-oophorectomy for ovarian cancer.

Dr Lawrence said the patient had been scheduled for adrenalectomy, but it was not performed because of an intraoperative finding of peritoneal studding from what turned out to be metastatic ovarian cancer. Therefore, she underwent CT-guided radiofrequency (RF) ablation of the adrenal mass using a 14-gauge probe that heated a 3.5-cm ablation zone to 50–60°C for 8–10 minutes to achieve complete tumour necrosis.

The patient showed dramatic "clinical and biochemical improvement," Dr Lawrence said. The patient had no procedural complications and no blood loss and was observed for 23 hours before being discharged home. A CT scan 8 weeks later showed a slightly decreased mass with marked decreased radiographic attenuation post-contrast from 30.2 Hounsfield Units (HU) preoperatively to 17 HU on follow-up.

Potential adverse outcomes using RF ablation include a risk of pneumothorax, haemothorax, and tumour seeding along the catheter track, but this last possibility can be mitigated by continuing to heat the RF probe as it is withdrawn.

Published evidence supports use of RF ablation. "To date there have been no randomised clinical trials comparing the safety, efficacy, and survival benefits of adrenalectomy vs radio frequency ablation," she said. It may not be feasible to do a randomised trial. But a review of the literature generally supports the efficacy of the technique although the publications each involved a small series of patients, Dr Lawrence said in an interview.

A 2003 series (*Cancer* 2003;97:554-60) of 15 primary or metastatic adrenal cell carcinomas that were unresectable or were in patients who were not surgical candidates showed nonenhancement and no growth in 8 (53%) at a mean follow-up of 10.3 months. Eight of the 12 tumours of 5 cm or smaller had complete loss of radiographic enhancement and a decrease in size.

From a retrospective series of 13 patients with functional adrenal neoplasms over 7 years, there was 100% resolution of biochemical abnormalities and clinical symptoms at a mean follow-up of 21.2 months. One small pneumothorax and one limited haemothorax occurred, neither of which required hospital admission. There were two instances of transient, self-remitting hypertension associated with the procedures (*Radiology* 2011;258:308–16).

In 2015, one group of investigators followed 11 patients for 12 weeks postprocedure. Eight of nine patients with Conn's syndrome attained normal serum aldosterone levels. One with a nodule close to the inferior vena cava had incomplete ablation. Two of two Cushing's patients had normal cortisol levels after the procedure (*J Vasc Interv Radiol* 2015;26:1459–64).

A retrospective analysis of 16 adrenal metastases showed that 13 (81%) had no local progression over 14 months after ablation. In two of three functional adrenal neoplasms, clinical and biochemical abnormalities resolved (*Eur J Radiol* 2012.81:1717–23).

A retrospective series of 10 adrenal metastases showed that one recurred at 7 months after image-guided thermal ablation, with no recurrence of the rest at 26.6 months. There was no tumour recurrence for any of the cases of metastatic disease localised to the RF ablation site (*J Vasc Interv Radiol* 2014;25:593–8).

Results were somewhat less good in a retrospective evaluation of 35 patients with unresectable adrenal masses over 9 years. Although 33 of 35 (94%) lost tumour enhancement after the initial adrenal RF ablation, there was local tumour progression in 8 of 35 (23%) patients at a mean follow-up of 30.1 months (*Radiology* 2015;277:584–93).

Finally, Dr Lawrence discussed a systematic literature review on adrenalectomy vs stereotactic ablative body radiotherapy (SABR) and percutaneous catheter ablation (PCA) in the treatment of adrenal metastases: 30 papers on adrenalectomy on 818 patients; 9 papers on SABR on 178 patients; and 6 papers on PCA, including RF ablation, on 51 patients. The authors concluded that there was "insufficient evidence to determine the best local treatment modality for isolated or limited adrenal metastases." Adrenalectomy appeared to be a reasonable treatment for suitable patients. SABR was a valid alternative for nonsurgical candidates, but they did not recommend PCA until more long-term outcomes were available (*Cancer Treat Rev* 2014;40:838–46).

Dr Lawrence concurred, based on her case study and literature review. She said RF ablation "offers patients a minimally invasive option for treating focal adrenal tumours" and is a "safe and effective procedure … in patients who are poor surgical candidates or refuse adrenalectomy." More long-term follow-up studies are needed before RF ablation could replace adrenalectomy, she noted. ■

FRONTLINE MEDICAL NEWS

Accuracy of gene test for thyroid nodules questioned

BY RICHARD MARK KIRKNER

Biopsy results from a commercially available genetic test for ruling out malignancy of thyroid nodules may not provide reliable answers to clinicians and patients.

When fine-needle aspiration biopsy of thyroid nodules comes back inconclusive, clinicians have increasingly utilised the Afirma gene expression classifier (GEC) to rule out malignancy, but a retrospective analysis of almost 200 patients with indeterminate biopsy results along with a pooled analysis of 11 previous studies has raised questions about the negative predictive value of the test.

"The Afirma GEC test has substantial variability in performance," said Dr Zaid Al-Qurayshi of Tulane University, New Orleans, who reported the results at the annual meeting of the American Association of Endocrine Surgeons. "This variability cannot be explained based on differences in prevalence alone, but may also be the result of intrinsic test properties."

The Afirma GEC measures the expression of 167 genes to more precisely determine the cancer risk of an indeterminate biopsied thyroid nodule and avoid unnecessary surgery. The test costs approximately US$4,800 per nodule.

The researchers undertook the study in light of an American Thyroid Association (ATA) statement last year that concluded that test results are predicated on the clinician knowing the prevalence of malignancy within each indeterminate cytologic category at his/her own institution. Without this information, the performance of the diagnostic tests may vary substantially (*Thyroid* 2015;25:760–8).

The single-centre, retrospective cohort analysis included 192 patients with 210 indeterminate biopsy results, 145 of whom had surgery with 154 thyroid nodules. With a malignancy prevalence of 45%, the expected negative predictive value (NPV) of the test was estimated to be 85%, Dr Al-Qurayshi said. However, the actual observed NPV was 69%. "If the prevalence was assumed to be 25%, the expected NPV was estimated to be 94%, while the observed NPV would have been 85%," Dr Al-Qurayshi said.

The researchers calculated the expected NPV by adopting the sensitivity and specificity rates of the test as reported in previous studies, while they calculated the observed NPV based on the actual negative rate among the Tulane cohort, Dr Al-Qurayshi said.

Dr Al-Qurayshi and colleagues then compared their results with pooled data from 11 other studies of the Afirma GEC. The pooled data analysis included 1,303 patients and yielded a malignancy prevalence of 31.1%, with a range of 29–35%, and a pooled NPV of 92%, with a range of 87–96%, Dr Al-Qurayshi said.

"A lot of previously published studies took the sensitivity and specificity that were previously reported for granted, and now we are showing this sensitivity is all over the place," Dr Al-Qurayshi said. "Now, we don't know which is the true one, and we need a larger clinical trial first to determine the true properties. Then we can ask how the prevalence in one's institution is affecting the performance of the test."

In an interview, Dr Emad Kandil, senior study coauthor, also of Tulane, said the 69% NPV of the Tulane cohort puts the diagnostic scenario "back to ground zero, which is similar to what we had prior to the use of the new commercially available genetic tests." He added, "A larger, randomised trial of the Afirma GEC test should answer those questions."

The seminal study for the Afirma GEC, authored by Dr Erik Alexander of Brigham and Women's Hospital, Boston, in 2012, reported a 92% NPV with the test (*N Engl J Med* 2012;367:705–15).

"The first thought was that they had different results because their population was different," Dr Al-Qurayshi said. "The ATA statement noted that it is the clinician's responsibility to determine if this test is appropriate for their population or not, but the performance of the test doesn't just depend on the population property, but it also depends on the intrinsic testing properties." ■

Dr Kandil disclosed that he has been a primary investigator in the ENHANCE mutlicentre study of the Afirma GEC. The other coauthors had no financial disclosures.

FRONTLINE MEDICAL NEWS

Starting with combination diabetes therapy beats initial monotherapy

BY DANIEL M. KELLER

Whether to start a patient with newly diagnosed type 2 diabetes mellitus on combination therapy or monotherapy should be based on experimentation and observation rather than expert opinion, according to Dr Alan Garber, president of the American College of Endocrinology and professor of medicine, biochemistry, and molecular and cellular biology at Baylor College of Medicine in Houston.

Monotherapy for type 2 diabetes with stepwise addition of other antihyperglycaemic agents has long been the accepted way to initiate therapy in this population. Beginning in the 1990s, investigators began to compare the efficacy of monotherapy with combination therapy, first with metformin and glyburide alone or together, and then testing metformin in combination with glipizide, rosiglitazone, and sitagliptin, he said.

For metformin and glyburide, each agent alone lowered glycated haemoglobin (HbA_{1c}), compared with placebo, but adding one to the other enhanced lowering. Combining the two drugs had the greatest benefit for higher HbA_{1c} entry levels (e.g., HbA_{1c} strata of 9–9.9% or 10% or greater vs less than 8%). At the highest-entry HbA_{1c} levels, half doses of each of metformin and glyburide (250 mg/1.25 mg, respectively) were more efficacious than full doses of each (500 mg/2.5 mg). "This is called drug sparing," he said.

In a trial of metformin and rosiglitazone, the combination was superior to either alone, producing significantly greater mean reductions in HbA_{1c} and in fasting plasma glucose (FPG) at 32 weeks from their respective baselines, again, with greater reductions for higher-entry HbA_{1c} levels. The combination was also better than either drug alone in the speed of reducing HbA_{1c} or FPG, and in the final attained levels.

The combination of metformin and a sulfonylurea presents a risk of hypoglycaemia, but Dr Garber said the results are "much cleaner" using combinations of metformin with agents such as a thiazolidinedione, a dipeptidyl peptidase-4 inhibitor, or a sodium/glucose cotransporter-2 inhibitor.

Also noteworthy are findings from the EDICT (Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes) trial using insulin-sensitizing and insulin-secreting agents metformin/pioglitazone/exenatide in combination vs escalating doses of metformin with sequential addition of a sulfonylurea and glargine insulin to treat patients with newly diagnosed type 2 diabetes. Over 2 years, the subjects receiving combination therapy had lower HbA_{1c}, a mean weight loss, compared with weight gain, in the sequential therapy group, and a 7.5-fold lower rate of hypoglycaemia, compared with the sequential treatment group (*Diabetes Obes Metab* 2015;17:268–75).

Although the agents used in the two treatment strategies were not strictly equivalent, "it's clear that testing multiple therapeutic mechanisms tends to produce better outcomes than fewer therapeutic mechanisms," Dr Garber said. The conclusions are fairly straightforward. "Look for evidence to support what strategies you want to use for your patients' care."

Using the Kaiser Permanente database, investigators found that the mean time of having an HbA_{1c} above 8% was 3 years before a second agent was added, and the mean HbA_{1c} was 9%. Many people have ascribed this sort of delay to a problem with the physician. But Dr Garber said it is more related to patients, who often resist prescriptions for more drugs. So starting with two drugs may produce better efficacy faster as well as overcome the psychological issues of trying to add another one later (*Am J Manag Care* 2003;9:213–7).

Session moderator Dr Daniel Einhorn, medical director of the Scripps Whittier Diabetes Institute in La Jolla, California, raised the possibility of "subtraction therapy, where you start with three agents no matter what, and then if things go well, you subtract. And so you reverse the situation that Alan discussed." In the patient's view, "you have a celebration that night instead of a wake," he said.

Dr Garber has received honoraria or consulting fees as a member of the advisory boards of Novo Nordisk, Janssen, and Merck. Dr Einhorn is on the scientific advisory boards of Eli Lilly, Novo Nordisk, Janssen, Boehringer Ingelheim, Sanofi, and Adocia, is a consultant for Halozyme, Glysens, Freedom-Meditech, and Epitracker, and has research funding from Lilly, Novo, Janssen, AstraZeneca, Mannkind, Freedom-Meditech, Merck, Sanofi, and Boehringer Ingelheim.

FRONTLINE MEDICAL NEWS

JOURNAL SCAN

Liraglutide reduces CV outcomes in patients with type 2 diabetes

The New England Journal of Medicine

Take-home message

- In a study of 9340 patients with type 2 diabetes followed for a median of 3.8 years, only 13% of patients treated with liraglutide experienced the primary outcome, the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke, compared with 14.9% of those receiving placebo (P < 0.001 for noninferiority; P = 0.01 for superiority). Deaths from cardiovascular causes were also reduced with liraglutide (4.7% vs 6.0%; P = 0.007), as was the rate of deaths due to any cause (P = 0.02). Gastrointestinal events were the most common adverse events leading to the discontinuation of liraglutide.
- Liraglutide appears to be superior to placebo for reducing events and deaths from cardiovascular causes in patients with type 2 diabetes.

BACKGROUND The cardiovascular effect of liraglutide, a glucagon-like peptide 1 analogue, when added to standard care in patients with type 2 diabetes, remains unknown.

METHODS In this double-blind trial, we randomly assigned patients with type 2 diabetes and high cardiovascular risk to receive liraglutide or placebo. The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke. The primary hypothesis was that liraglutide would be noninferior to placebo with regard to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% confidence interval of the hazard ratio. No adjustments for multiplicity were performed for the prespecified exploratory outcomes.

RESULTS A total of 9340 patients underwent randomisation. The median follow-up was 3.8 years. The primary outcome occurred in significantly fewer patients in the liraglutide group (608 of 4668 patients [13.0%]) than in the placebo group (694 of 4672 [14.9%]) (hazard ratio, 0.87; 95% confidence interval [CI], 0.78 to 0.97; P < 0.001 for noninferiority; P = 0.01 for superiority). Fewer patients died from cardiovascular causes in the liraglutide group (219 patients [4.7%]) than in the placebo group (278 [6.0%]) (hazard ratio, 0.78; 95% CI, 0.66 to 0.93; P = 0.007). The rate of death from any cause was lower in the liraglutide group (381 patients [8.2%]) than in the placebo group (447 [9.6%]) (hazard ratio, 0.85; 95% CI, 0.74 to 0.97; P = 0.02). The rates of nonfatal myocardial infarction, nonfatal stroke, and hospitalisation for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group. The most common adverse events leading to the discontinuation of liraglutide were gastrointestinal events. The incidence of pancreatitis was nonsignificantly lower in the liraglutide group than in the placebo group.

CONCLUSIONS In the time-to-event analysis, the rate of the first occurrence of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke among patients with type 2 diabetes mellitus was lower with liraglutide than with placebo.

Liraglutide and cardiovascular outcomes in type 2 diabetes *N Engl J Med* 2016; [EPub ahead of print], SP Marso, GH Daniels, K Brown-Frandsen, et al.

US FDA panel recommends two new combo injectables for diabetes

BY KARI OAKES

In back-to back advisory committee hearings, the US Food and Drug Administration received recommendations for approval of two new combination medications to treat type 2 diabetes. The two medications each combine long-lasting insulin with a glucagon-like peptide-1 (GLP-1) receptor agonist in a once-daily injectable fixed-dose combination.

On May 24, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) voted unanimously to approve the fixed-dose combination of liraglutide and insulin degludec (individually marketed as Victoza and Tresiba, respectively, by Novo Nordisk). The new combination was referred to as IDegLira in the sponsor's clinical trials.

The following day, the EMDAC recommended in a 12–2 vote to approve Sanofi-Aventis' new fixed-dose combination of lixisenatide and insulin glargine, also indicated as an add-on to lifestyle management for type 2 diabetes. The sponsor's proposed name for this combination is iGlarLixi.

For both products, most committee members felt that the combo would most benefit patients who were already on either insulin or a GLP-1 agonist (though the second day's panel noted that data were lacking on patients transitioning from a GLP-1 agonist to Sanofi-Aventis' lixisenatide/glargine combo). "I tend to agree with many of the people who have gone before me that the population of patients this should be used in are those that are on one of these two injectable medications already and in particular I think the GLP-1 agonist," said Dr Marie Gelato, professor of medicine at Stony Brook University, New York, who voted in favour of the liraglutide/degludec combination medication.

A concern common to discussion on both days was that some patients with diabetes and a higher body mass might not be able to benefit from these medications, since each one caps insulin dosing.

Other themes common to both days' deliberations among the largely overlapping panels included the need for fine-tuning the dosing apparatus, labelling, patient interface, and nomenclature for these novel devices. For Dr Robert Smith, panel chair and professor of endocrinology at Brown University, Providence, Rhode Island, his vote on the second day should be "considered contingent on accomplishing those things adequately."

Most of the endocrinologists on the committees noted that they personally felt more comfortable beginning a single agent, and probably tended to tinker with patients' regimens fairly frequently at least during the initial period of diabetes management. However, the committees on both days felt that having the fixed-dose combination agent available might be a particularly useful tool for family practice physicians and those practicing general internal medicine.

Since the proposed lixisenatide/glargine combination would be dispensed as one of two pens, each with a different dose range of lixisenatide, the second day's panel spent more time in discussion of the potential for confusion or misdosing with two choices.

"It's incumbent upon the sponsor to make it easier for the doctor. I have confidence that they will work out the delivery system," said Dr Peter Wilson, explaining his rationale for voting for approval of the lixisenatide/glargine combo despite some reservations about the device and delivery system, "I think this will be a boon for the patients," added Dr Wilson, professor of medicine and public health at Emory University, Atlanta.

Lixisenatide, marketed as Lyxumia in Australia and elsewhere by Sanofi-Aventis, is pending FDA approval, so it received some additional attention during the committee hearing for lixisenatide/glargine. Though it would be the sixth GLP-1 agonist on the US market, committee members did not voice concerns that it would be a "me too" drug; rather, said Dr Wilson, "It provides yet another choice. ... Choice is very important for physicians and for patients."

During Sanofi-Aventis' and the FDA's presentations, safety data, especially as interpreted by the FDA, seemed to indicate a slightly elevated risk of significant allergic reactions with lixisenatide compared with placebo. However, conceded the FDA's clinical reviewer Dr Suchitra Balakrishnan, the postmarketing surveillance program for lixisenatide was "a larger program, which may have contributed to more events occurring."

Earlier concerns about lixisenatide's cardiovascular safety have been largely assuaged after publication late last year of results from the ELIXA trial (*N Engl J Med* 2015; 373:2247–57) that showed no increased risk – but no benefit – for those with type 2 diabetes taking lixisenatide.

IDegLira and iGlarLixi are not registered in Australia.

FRONTLINE MEDICAL NEWS

Subclinical hypothyroidism: Treat or not?

BY ROXANNE NELSON

The benefits of treating subclinical hypothyroidism with low-dose levothyroxine may outweigh the harms of delaying treatment until the condition has become symptomatic, requiring higher doses, according to one of the authors of a "Beyond the Guidelines" assessment of this controversy.

Last year, the US Preventive Services Task Force issued guidelines and updated its 2004 recommendations, which essentially stated that there is no evidence to support treating subclinical hypothyroidism. In their own guidelines, the American Association of Clinical Endocrinologists and American Thyroid Association have instead advocated aggressive case-finding and recommend screening individuals who may be a high risk. These societies also argue that subclinical hypothyroidism can have an adverse effect on cardiovascular outcomes and therefore it merits case-findings.

In the June 6, 2016 issue of the *Annals of Internal Medicine* (doi: 10.7326/M16-0857), experts from Beth Israel Deaconess Medical Centre in Boston offered differing perspectives on the issue, as to whether or not subclinical hypothyroidism should be treated.

They gave their viewpoints in the context of a case study:

Mrs C is a 60-year-old woman who has experienced mild symptoms such as fatigue and constipation for about 10 years, and has a family history of "thyroid problems." In 2012, her TSH level was slightly elevated (5.8 uIU/L), and in 2013, she reported fatigue, although her TSH level was similar (5.9 uIU/L) to the year before.

Her free thyroxine (T4) was normal (11.97 pmol/L), and given the stability of her TSH level, treatment was not initiated. Recently, she reported weight gain, intermittent constipation, and persistent fatigue. Currently she is being treated for hyperlipidaemia with atorvastatin 10 mg daily as well as for cervical radiculitis. Two of her three sisters receive thyroid medication, and recently, her blood pressure was 136/79 mmHg with a heart rate of 77 beats per minute. Her weight had increased by 9 pounds, to 156 pounds (body mass index, 29.6 kg/m^2). Her thyroid examination was normal, and her TSH measurement was 6.5 uIU/ML and free T4 was 12.87 pmol/L.

Dr Pamela Hartzband noted that there is an "evidence base suggesting that patients like Mrs C may benefit with respect to both morbidity and mortality," given her family history and elevated cholesterol levels. TSH is a sensitive indicator of primary hypothyroidism, and given that the patient's levels have gradually increased, this is significant and suggests early thyroid failure. That said, in "reviewing the evidence for benefit of treatment, there are not only conflicting data but also conflicting interpretation[s] of the same data by different experts," according to Dr Hartzband.

However, subclinical hypothyroidism has been associated with a greater risk for both cardiovascular morbidity and mortality in some but not all prospective population-based studies.

Symptom relief is the primary goal for patients, and Mrs C has described symptoms that are suggestive of hypothyroidism including fatigue, constipation, scalp hair loss, and weight gain and elevated TSH. There is a "paucity of evidence" demonstrating improvement with treatment of subclinical hypothyroidism. And while harms associated with treatment can also be a concern, there is remarkably limited evidence for harms related to the treatment of subclinical hypothyroidism, noted Dr Hartzband of the division of endocrinology and metabolism and medical director of the Thyroid Biopsy Clinic at Beth Israel Deaconess Medical Centre, Boston.

There is, however, speculation that patients might develop hyperthyroidism from being given excessive doses of levothyroxine, but this can be avoided by initiating treatment of subclinical hypothyroidism with low-dose levothyroxine (25–50 mcg).

Overall, when weighing the benefits and harms of treatment in this case, Dr Hartzband would consider offering Mrs C a trial of levothyroxine. The reasoning is that based on family history, she is at increased risk for thyroid disease and was appropriately tested by measuring TSH. In addition, levothyroxine could lower her cholesterol levels and risk for heart disease, and she might be able to reduce or even discontinue her statin therapy.

"I believe that for Mrs C the potential for benefit outweighs potential risk," wrote Dr Hartzband. "If she does not feel better and if cholesterol is not improved, then levothyroxine could be stopped until her TSH rises further."

Dr Carol K. Bates of the division of general medicine and primary care at Beth Israel Deaconess Medical Centre, Boston, leaned more toward holding back on treatment. For one thing, since there is a diurnal variation in TSH, the patient's TSH values might have been normal if measured in the afternoon instead of the morning.

As far as the risk of heart disease, where much of the treatment debate is focused, she pointed out that while there is an association between congestive heart failure, coronary artery disease, and subclinical hypothyroidism, Mrs C only has a mildly increased TSH.

There have also been arguments that treating subclinical hypothyroidism could lower cholesterol levels. Mrs C started on a statin in 2003 when her TSH was 3.5 and thus euthyroid. Any efforts to lower cholesterol might be done by adjusting her statin dose rather than adding levothyroxine.

Both over- and undertreatment with thyroid hormone replacement are common, she pointed out, and overtreatment has been associated with an increased risk for hip and major osteoporotic fracture, as well as increasing the risk for atrial fibrillation. She also noted that there is harm in medicalising a normal condition, as the upper range of TSH is arbitrarily set based upon population data.

In the case of Mrs C, Dr Bates would explain that there is no risk for heart disease given the degree of thyroid dysfunction and, especially, that her goal of weight loss and symptom relief likely won't happen.

If she did wish to be treated, Dr Bates would also start her on a low dose. "If she were to embark on treatment, I would suggest monitoring her weight and symptoms," she wrote. "While many authorities would recommend treatment at a calculated full replacement dose, my experience suggests that this risks overtreatment, and I would recommend starting at 25 to 50 mcg." ■

FRONTLINE MEDICAL NEWS

Beloranib reduces weight in Prader-Willi syndrome, but concerns remain

BY BRIAN HOYLE

Prader-Willi syndrome patients lost more than 4% of their body weight over a 26-week period with the investigative antiobesity drug beloranib, compared with a similar gain in patients taking placebo, in the phase III bestPWS trial.

Hunger-related behaviour was also reduced, along with total and LDL cholesterol levels and other cardiometabolic risk factors, lead investigator Dr Merlin G. Butler reported at the annual meeting of the Endocrinology Society.

However, because of concerns over venous thromboembolic events in patients on beloranib, the trial was halted before all patients reached 26 weeks of treatment.

"BestPWS is the first phase III clinical trial to show statistically and clinically significant weight loss and improvement in hyperphagia-related behaviours in PWS [Prader-Willi syndrome] patients. The reduction in hyperphagia-related behaviours in the beloranib-treated groups represents a clinically meaningful benefit to patients," Dr Butler said.

Beloranib is a novel, first-in-class injectable molecule that works by inhibiting MetAP2, an enzyme that modulates the activity of cellular processes that are important in the control of metabolism. Its benefits in preclinical studies and a phase II trial in reducing body weight and decreasing hyperplasia fuelled optimism regarding the therapeutic value in Prader-Willi syndrome, the most common genetic cause of morbid obesity. Although rare, Prader-Willi syndrome is life threatening and life limiting, with most of those affected dying before the age of 50.

"There are currently no treatment options for the intractable obesity and hyperphagia in Prader-Willi syndrome," said Dr Butler of the University of Kansas Medical Centre, Kansas City, Kansas.

In the bestPWS trial, 107 patients were randomised 2:1 to receive twice-weekly subcutaneous injections of beloranib or placebo

for 26 weeks: 36 received 1.8 mg and 37 received 2.4 mg of beloranib, and 34 received placebo. Seventy-four patients completed the treatment. The coprimary efficacy endpoints were improvement in hyperphagia-related behaviours and reduction in body weight. Secondary endpoints included improvements in total body fat mass, lipids, and, as markers of cardiometabolic risk, total cholesterol and LDL cholesterol levels.

Baseline demographic and clinical characteristics were comparable in the three trial arms, with an average age of 20 years, average body mass index of 40 kg/m^2, average body weight of 100 kg, average fat mass of 51 kg, and average Hyperphagia Questionnaire for Clinical Trials (HQ-CT) total score of 16.9.

Patients in the placebo arm displayed an increase in body weight of about 4% over the 26-week trial. In contrast, patients treated with beloranib lost weight (4.1% and 5.3% in the 1.8-mg and 2.4-mg arms, respectively; both $P < 0.0001$, compared with placebo). The weight loss in the two treatment arms did not differ significantly. Beloranib was also associated with improvements in body composition, total cholesterol, and LDL cholesterol, high-sensitivity C-reactive protein, leptin, and adiponectin, compared with placebo.

Both beloranib doses also appreciably reduced hunger-associated behaviours, with reductions of 6.7–7.4 points with beloranib, compared with a reduction of 0.4 with placebo.

Adverse events most commonly included injection-site bruising, aggression, and hyperphagia; they were generally mild and transient.

There were five serious adverse events. Those that occurred in the treatment arms were psychiatric disorders, which are common background comorbidities in Prader-Willi patients, and so are not necessarily treatment related. In the bestPWS trial, two deep vein thrombosis events and two fatal pulmonary embolism events occurred. After the first pulmonary embolism death, the trial was discontinued; at that point, 27 randomised patients had not completed the full 26-week course.

Overall, 11 venous thrombotic events, including pulmonary embolism, deep vein thrombosis, and superficial thrombophlebitis, have occurred in the roughly 400 patients who have so far received beloranib in the course of its development, including the adverse events in the bestPWS trial. None of these events has occurred in those receiving placebo.

Even in light of these sobering events, Dr Butler said he remains optimistic. "In addition to the reduction in body weight and decrease in excessive eating behaviours previously reported from this study, [these data] demonstrate important reductions in cardiometabolic risk factors and further support a strong rationale for continued evaluation of beloranib as a potential treatment for Prader-Willi syndrome," said Dr Butler.

Beloranib is currently on clinical hold while the potential for a prothrombotic effect of beloranib and a heightened risk for Prader-Willi syndrome patients are assessed, Dr Butler said. ■

Dr Butler disclosed study funding by Zafgen, the manufacturer of Beloranib.

FRONTLINE MEDICAL NEWS

JOURNAL SCAN

Cardiovascular effects of SGLT-2 inhibitors in type 2 diabetes

The Lancet Diabetes & Endocrinology

Take-home message

- The authors of this systematic review and meta-analysis of 6 regulatory submissions and 57 clinical trials, including a total of over 70,000 participants, evaluated the association between use of SGLT2 inhibitors and cardiovascular outcomes. SGLT2 inhibitors reduced the risk of major cardiovascular events, cardiovascular death, heart failure, and death from any cause. There was a 30% increase in non-fatal stroke that was statistically significant. The association between SGLT2 inhibitors and genitourinary infection was confirmed, but variability was found in the rates of other adverse events in the scientific literature compared with regulatory data.
- The authors provide a comprehensive update on cardiovascular and adverse events in patients treated with SGLT-2 inhibitors. They confirm the results of the EMPA-REG trial and suggest that the protection against cardiovascular events may extend to other drugs in this class, although the effects observed were heavily influenced by the large amount of data available for empagliflozin.

This meta-analysis of cardiovascular outcomes with SGLT-2 inhibitors included 57 prospective randomised trials with MACE (major adverse cardiac events of cardiovascular mortality, nonfatal myocardial infarction, and nonfatal stroke) as the primary outcome. For the safety assessment, 6 regulatory submissions were included.

The CV outcomes in this meta-analysis (primary 3-point and 4-point MACE, CV mortality, all-cause mortality) are almost entirely driven by the results of the EMPA-REG OUTCOMES trial. The studies with other agents are small, and they are not primarily CV outcome trials.

The safety analyses using the regulatory data and clinical trial statistics both show the increased risk for genital infections. Other adverse events appear to have different incidence and risk in the regulatory data and in the clinical trials. Urinary tract infections and episodes of volume depletion were increased in the regulatory data yet not observed in clinical trials. In contrast, kidney disease was reduced in the clinical trials but not impacted in the regulatory observations. The differences are likely due to the larger number of events in the clinical trial data as well as the placebo-controlled design of the majority of included clinical trials.

This "meta-analysis," in which the majority of the data comes from one randomised controlled trial with one drug, shows the limitation of drawing conclusions about the efficacy and safety of other agents. Consequently, it would not be appropriate to draw any conclusions about the possibility of a class effect of SGLT-2 inhibitors on CV outcomes from this analysis.

BACKGROUND In patients with type 2 diabetes, sodium-glucose cotransporter-2 (SGLT2) inhibitors are known to reduce glucose concentrations, blood pressure, and weight, but to increase LDL cholesterol and the incidence of urogenital infections. Protection against cardiovascular events has also been reported, as have possible increased risks of adverse outcomes such as ketoacidosis and bone fracture. We aimed to establish the effects of SGLT2 inhibitors on cardiovascular events, death, and safety outcomes in adults with type 2 diabetes, both overall and separately for individual drugs.

METHODS In this systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Library, and websites of US, European, and Japanese regulatory authorities from Jan 1, 1950, to Sept 30, 2015, for data from prospective randomised controlled trials assessing the effects of SGLT2 treatment compared with controls. We excluded duplicate reports, trials of compound drugs, trials that lasted 7 days or fewer, trials that did not report on outcomes of interest, and articles that presented pooled trial data for which the individual trials could not be identified. We extracted data in duplicate using a standardised approach. The primary outcome was major adverse cardiovascular events. Secondary outcomes were cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, admission to hospital for unstable angina, heart failure, and all-cause mortality. We estimated summary relative risks with fixed-effects meta-analysis, with the I(2) statistic used to estimate heterogeneity of results beyond chance.

FINDINGS The analyses included data from six regulatory submissions (37 525 participants) and 57 published trials (33 385 participants), which provided data for seven different SGLT2 inhibitors. SGLT2 inhibitors protected against the risk of major adverse cardiovascular events (relative risk 0.84 [95% CI 0.75–0.95]; P = 0.006), cardiovascular death (0.63 [0.51–0.77]; P < 0.0001), heart failure (0.65 [0.50–0.85]; P = 0.002), and death from any cause (0.71 [0.61–0.83]; P < 0.0001). No clear effect was apparent for non-fatal myocardial infarction (0·88 [0·72–1·07]; P = 0.18) or angina (0.95 [0.73–1.23]; P = 0.70), but we noted an adverse effect for non-fatal stroke (1.30 [1.00–1.68]; P = 0.049). We noted no clear evidence that the individual drugs had different effects on cardiovascular outcomes or death (all I(2)<43%). Safety analyses showed consistent increased risks of genital infections (regulatory submissions 4.75 [4.00–5.63]; scientific reports 2.88 [2.48–3.34]), but findings for some safety outcomes varied depending on whether analyses were based on data extracted from regulatory submissions or trials reported in the scientific literature.

INTERPRETATION These data suggest net protection of SGLT2 inhibitors against cardiovascular outcomes and death. The efficacy results were driven by findings for empagliflozin (the only SGLT2 inhibitor for which data from a dedicated long-term cardiovascular safety trial have been reported), although results for the other drugs in the class were not clearly different. Adverse events were more difficult to quantify than was efficacy, with the effects of individual drugs in the class seeming to differ for some safety outcomes. Results from ongoing studies will be crucial to substantiate these findings across the drug class, but the available data provide a strong rationale to expect benefit from use of SGLT2 inhibitors in patients with type 2 diabetes at high risk of cardiovascular events.

Effects of sodium-glucose cotransporter-2 inhibitors on cardiovascular events, death, and major safety outcomes in adults with type 2 diabetes: a systematic review and meta-analysis. *Lancet Diabetes Endocrinol* 2016;4:411–419, JH Wu, C Foote, J Blomster, et al.

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More than 15,000 leading physicians, scientists and health care professionals from around the world attended this year's American Diabetes Association's Scientific Sessions to unveil cutting-edge research, treatment recommendations and advances toward a cure for diabetes. PracticeUpdate reporters share these highlights.

Bariatric surgery reduces the incidence of retinopathy and nephropathy in obese patients with type 2 diabetes

Bariatric surgery has been found to be associated with reduced long-term incidence of complications affecting the eyes and kidneys in both patients with screen-detected and established type 2 diabetes. This conclusion, based on results of outcome of a prospective controlled trial comparing bariatric surgery and usual care was presented at the ADA 2016.

Kajsa Sjöholm, PhD, of the University of Gothenburg, Sweden, explained that bariatric surgery often causes diabetes remission in obese patients, especially in newly diagnosed diabetes.

Dr Sjöholm and colleagues have previously reported that bariatric surgery also reduces the incidence of overall macrovascular and microvascular complications in the Swedish Obese Subjects study, a prospective controlled trial comparing bariatric surgery and usual care.

The investigators have now analysed the effects of bariatric surgery on retinopathy, nephropathy and neuropathy, traced in nationwide registers, in Swedish Obese Subjects study patients with screen-detected (n = 246) and established type 2 diabetes (n = 357, mean duration 5.2 years) followed for up to 26 years.

Bariatric surgery reduced the incidence of retinopathy in patients with screen-detected type 2 diabetes [incidence rate 6.3 and 19.2 per 1000 person years in the surgery and control groups, respectively; hazard ratio 0.27 (0.15–0.50), P < 0.001] and established type 2 diabetes [incidence rate 25.9 and 46.9 per 1000 person years in the surgery and control groups, respectively; hazard ratio 0.51 (0.37–0.70), P < 0.001].

The incidence of nephropathy was also reduced by bariatric surgery in both subgroups [screen-detected type 2 diabetes: incidence rate 3.8 and 9.7 per 1000 person years in the surgery and control groups, respectively; hazard ratio 0.37 (0.17–0.81), P = 0.012; established type 2 diabetes: incidence rate 18.8 and 9.6 per 1000 person years in the surgery and control groups, respectively; hazard ratio 0.48 (0.30–0.77), P = 0.002].

Complications affecting nerves were few and no difference in their incidence between the surgery and control groups was observed [screen-detected type 2 diabetes: incidence rate 2.1 and 3.3 per 1000 person years in the surgery and control groups, respectively; established type 2 diabetes: incidence rate 4.3 and 6.8 per 1000 person years in the surgery and control groups, respectively].

> "Bariatric surgery reduced the incidence of retinopathy in patients with screen-detected type 2 diabetes and established type 2 diabetes.

Dr Sjöholm concluded that bariatric surgery was shown to be associated with reduced long-term incidence of complications affecting the eyes and kidneys both in patients with screen-detected and established type 2 diabetes. ■

> Bariatric surgery was shown to be associated with reduced longterm incidence of complications affecting the eyes and kidneys both in patients with screen-detected and established type 2 diabetes. >10

> The 'carbohydrate-first' pattern showed marked fluctuation in postprandial glucose levels in contrast to very stable glucose levels with the 'carbohydrate- last' pattern. >11

> SORELLA 1: SAR342434 was as effective and well tolerated as insulin lispro in patients with type 1 diabetes. >12

Food order impacts postprandial glucose and insulin excursions significantly

Food order has been found to exert a significant impact on postprandial glucose and insulin excursions and may be an effective strategy to attenuate postprandial glucose spikes and glycaemic variability in patients with type 2 diabetes. This conclusion, based on results of a follow-up study to a pilot trial of a carbohydrate-last meal order.

Alpana P. Shukla, MD, of Weill-Cornell Medical School, New York, explained that in a previous pilot study using a typical Western meal, she and colleagues demonstrated that ingestion of protein and vegetables before carbohydrate leads to lower postprandial glucose and insulin excursions up to 120 minutes than eating carbohydrate first in a meal.

"Standard nutritional counselling regarding carbohydrate consumption in diabetes," Dr Shukla noted, "focuses on how much and what not to eat. Our previous pilot study suggested that the temporal sequence of carbohydrate consumption during a meal impacts glucose levels following a meal."

She continued, "In this follow-up study, we sought to validate those initial findings and gain further insight into the effect of food order on postprandial glycaemic response."

In this follow up study, the investigators sought to examine the effect of food order on postprandial plasma glucose and insulin excursions in the setting of three commonly followed meal patterns with extended follow-up to 180 minutes, to capture delayed effects of food order on glycaemia.

Seven overweight/obese subjects (body mass index 25–40 kg/m^2) with type 2 diabetes (haemoglobin A_{1c} ≤8%) who were taking metformin were studied using a within-subject crossover design.

After a 12-hour fast, subjects were randomly assigned to an isocaloric meal with the same composition on three separate days in one of the following food orders:

1. Carbohydrate(bread) followed 10 minutes later by protein (chicken) and vegetables
2. Protein and vegetables followed 10 minutes later by carbohydrate
3. All meal components eaten together as a sandwich

Blood was sampled for measurement of glucose and insulin at baseline and at 30-minute intervals up to 180 minutes after the meal.

Incremental areas under the curve for glucose (0–180) were similar, though the carbohydrate-first meal pattern demonstrated greater glycaemic variability with a higher peak at 60 minutes and lower nadir at 180 minutes.

The average incremental glucose peak following ingestion of protein and vegetables first was 51% and 45% lower than eating carbohydrate first or eating all meal components together as a sandwich, respectively.

The incremental area under the curve 0–180 for plasma insulin was significantly lower when vegetables and protein were consumed first followed by carbohydrate vs other meal conditions.

Dr Shukla concluded that food order has been found to exert a significant impact on postprandial glucose and insulin excursions. Food order may be an effective strategy to attenuate postprandial glucose spikes and glycaemic variability in patients with type 2 diabetes, with implications for improving insulin sensitivity.

"The 'carbohydrate-first' pattern," she noted, "showed marked fluctuation in postprandial glucose levels in contrast to very stable glucose levels with the 'carbohydrate- last' pattern."

She continued, "This was clinically very relevant in that glycaemic variability is associated with increased risk of diabetes- related complications. The insulin response was remarkable and suggests that the optimal food order (protein and vegetables first) may positively impact insulin sensitivity."

Dr Shukla asserted, "The effect of initial carbohydrate consumption on postmeal glucose spikes was not significantly reduced when all meal components were consumed to together."

"This issue needs further study," she added, "with a larger sample size. The project is ongoing at our Centre. We are investigating the hormonal mechanisms underlying the effect of food order on glycaemia. Further research is also needed in larger numbers of patients with different meal patterns and meal compositions to assess the feasibility and effectiveness of this intervention across different populations."

Red grape cell supplementation improves major parameters of type 2 diabetes

Twelve weeks of red grape cell consumption by patients with type 2 diabetes has been shown to reduce haemoglobin A_{1c}, improve insulin sensitivity, influence clock gene expression significantly.

Julio Wainstein, MD, of E. Wolfson Medical Centre, Tel Aviv, Israel, explained that disrupted clock genes mRNA expression in white blood cells is associated with type 2 diabetes. Resveratrol, a natural polyphenol, exerts potent modulatory effects on clock gene expression and has been linked to glycaemic regulation.

The effects of red grape cells (a resveratrol polyphenol complex), on glycaemic control and clock gene (Bmal1, Clock, Per2, Cry1, and Rev-erbα) mRNA expression have not been explored in type 2 diabetes.

Dr Wainstein and colleagues set out to evaluate the impact of red grape cell supplementation on haemoglobin A_{1c}, plasma glucose, insulin, C-peptide and clock gene mRNA expression in white blood cells.

> Further study is needed to elucidate the best dosage and whether red grape cells might be useful as adjuvant therapy to achieve glycaemic control in type 2 diabetes.

Thirty-three patients with type 2 diabetes age 63.7 ±7.1 years, body mass index 30.28 ± 4.58 kg/m^2, and haemoglobin A_{1c} 7.76% ± 0.78% were randomised for 12 weeks to either supplementation with red grape cells 1000 mg daily or placebo.

All patients underwent a meal test (520 kilocalories, 29.4 g protein; 50.2 g carbohydrate; 44.7 g fat) at baseline and at the end of the study.

After 12 weeks, greater reduction of haemoglobin A_{1c} was observed for red grape cells, –0.55% ± 0.05% (from 7.85% ± 1.01% to 7.30% ± 0.75%, P = 0.0353) than for placebo, –0.16% ± 0.15% (from 7.67% ± 0.55% to 7.51% ± 0.52%, not significant).

Reduction of haemoglobin A_{1c} was 29% greater with red grape cells than placebo. Within a subgroup with higher haemoglobin A_{1c} at baseline (7.5% to 10.1%), reduction of haemoglobin A_{1c} was –1.21% with red grape cells and –0.39% with placebo (P < 0.0247).

Compared to placebo, the area under the curve (0–240 minutes) for plasma glucose and insulin showed non-significant changes, while C-peptide was reduced more, by 27.2% with red grape cells vs placebo (P = 0.0409).

As a result, estimated insulin sensitivity calculated from fasting glucose and C-peptide rose by 40.6% with red grape cells vs placebo (P < 0.0137).

Postprandial mRNA expression of the clock genes showed non-significant changes in the transcription factors Bmal1 and Clock, while the repressor genes Per2, Cry1, and Rev-erbα, were significantly depressed (P < 0.05) with red grape cells vs placebo

Dr Wainstein concluded that after 12-weeks of red grape cell supplementation in patients with type 2 diabetes, haemoglobin A_{1c} was improved, insulin sensitivity improved, and clock gene expression influenced significantly.

Further study is needed to elucidate the best dosage and whether red grape cells might be useful as adjuvant therapy to achieve glycaemic control in type 2 diabetes.

SAR342434 is equally safe and effective as insulin lispro + insulin glargine in type 1 diabetes

Six-month, interim results of a multicentre phase 3 comparative trial have demonstrated that SAR342434 is as effective and well-tolerated as insulin lispro in patients with type 1 diabetes.

Satish K. Garg, MD, of the University of Colorado, Aurora, explained that SAR342434 was developed as a biosimilar, rapid-acting follow-on insulin to Humalog (insulin lispro) with similar pharmacokinetics and pharmacodynamics between the two insulins in a phase 1 clamp study.

> "We observed no difference in hypoglycaemia nor in hypersensitivity reactions between the two groups.

Dr Garg and colleagues compared the efficacy and safety of SAR342434 and insulin lispro in patients with type 1 diabetes using GLA100 (Lantus) as basal insulin. In this 6-month randomised, controlled, open-label study (SORELLA 1), 507 patients from the US, Europe, and Japan were randomised 1:1 to a multiple daily injection regimen of SAR342434 or insulin lispro while using once-daily Lantus.

The SAR342434 or insulin lispro dose was adjusted to achieve a 2-h postprandial glucose level of 6.66–8.88 mmol/L, while avoiding hypoglycaemia.

The recommended target for fasting and preprandial glucose was 4.44–7.21 mmol/L. The primary endpoint was haemoglobin A_{1c} change (noninferiority margin of 0.3%) from baseline to week 26 (tested for noninferiority of SAR342434 vs insulin lispro) with secondary endpoints including seven-point self-monitored plasma glucose profiles.

SAR342434 was noninferior to insulin lispro for change in haemoglobin A_{1c}, with similar postprandial glucose excursions and insulin dosages. No difference was observed in the percentage of patients reporting hypoglycaemia (severe hypoglycaemia: SAR342434 7.9%; insulin lispro 7.5).

Safety profiles, including adverse events, hypersensitivity events, and injection site reactions, were similar for SAR342434 and insulin lispro. "A similar percentage of patients developed anti-insulin antibodies in both groups," Dr Garg noted.

Dr Garg concluded that in these interim, 6-month results, SAR342434 was as effective and well tolerated as insulin lispro in patients with type 1 diabetes. "We observed no difference in hypoglycaemia nor in hypersensitivity reactions between the two groups."

"One-year data will be complete in September of this year," he added. ■

An insulin balanced infusion system stabilises blood-sugar in a hospital setting

Admetsys, a first-in-kind artificial pancreas for hospital care, leverages adaptive learning algorithms to counterbalance insulin and glucose levels.

Timothy Valk, MD, of Advanced Metabolic Systems, Orlando, Florida, explained that he and colleagues set out to assess the clinical applicability of Admetsys to normalise and continue to stabilise glucose levels. They also wanted to demonstrate system safety and performance under extraordinary circumstances and validate the system's performance over prolonged periods, he noted.

Pulsatile infusions of insulin and/or glucose were delivered intravenously by the Admetsys system to 43 hospitalised patients with diabetes.

Extended trial protocols for blood glucose stabilisation were carried out, each successive protocol using a more refined version of the system's physical components. The first protocol employed automated sensing, then high-precision syringe pumps, and finally, integrated power management. All studies were US FDA-approved.

Ninety-seven percent of patients were controlled, with blood glucose levels between 4.44 and 6.94 mmol/L. Mean time to normoglycaemia was 2.5 h and hypoglycaemia <3.89 mmol/L did not occur. Once brought to normoglycaemic levels, and unless intentionally destabilised, blood glucose levels remained ideal. Normoglycaemia was preserved despite 43.8% of attempts to destabilise it.

A consistent, effective normalisation of glucose levels was achieved irrespective of initial level. The system maintained and restored control during endogenous and exogenous stress events, with an absence of hypoglycaemia. Variability was reduced and precise glucose control attained.

Dr Valk concluded that abnormal glucose levels were controlled in this cohort of hospitalised diabetes patients, under stressful conditions and without hypoglycaemia. The data constitute the basis for planned closed-loop clinical trials of Admetsys in hospitalised diabetes patients undergoing major surgery. ■

A hybrid closed-loop system proves safe and effective for home use in type 1 diabetes

A hybrid closed loop system has been proven safe, acceptable, and associated with improved glucose control during extended at-home use in patients with type 1 diabetes.

Richard M. Bergenstal, MD, of the International Diabetes Centre at Park Nicollet, Minneapolis, Minnesota, explained that he and colleagues evaluated a hybrid closed loop insulin delivery system was evaluated to establish its safety for unsupervised use in patients ≥14 years of age. The system included the Medtronic MiniMed 670G pump, 4th-generation sensors, and a control algorithm.

Patients calibrated the sensor periodically and gave mealtime and correction boluses as needed. A 2-week run-in (baseline) phase was followed by a 3-month study phase of the hybrid closed loop system at home and supervised hotel settings for five nights followed by an optional continued-access program.

Data were available from 124 patients with type 1 diabetes (55 male) with a mean age of 37.8±16.46 years (30 age ≤21 years) and duration of diabetes 21.7 ± 13.65 years. Sensor glucose and haemoglobin A_{1c} values from baseline and study phases were compared. Hybrid closed loop mode was used for a median 87.2% interquartile range 75.0% to 91.7%) of the time after first start.

Higher percentages of sensor glucose 3.94–9.99 mmol/L, lower percentages of sensor glucose ≤3.89 mmol/L, and lower percentages of sensor glucose ≤2.77 mmol/L were observed during 24 h and at night ($P < 0.001$ for each) in the study phase vs baseline. Mean haemoglobin A_{1c} decreased from 7.4 ± 0.9% to 6.9 ± 0.6% ($P < 0.001$). Sensor glucose variability measured by coefficient of variation decreased from 0.38 to 0.35 ($P < 0.001$).

No diabetic ketoacidosis, severe hypoglycaemia, or serious device-related adverse event was observed during 12,389 patient-days. At study end, 99 patients entered the continued-access program.

Dr Bergenstal concluded that a hybrid closed loop system was proven safe, acceptable, and associated with improved glucose control during extended at-home use in patients with type 1 diabetes. "It was gratifying to see the overwhelming patient and family peace of mind when using the system," he added. ■

The MiniMed 670G is not registered in Australia.
The MiniMed 640G (pictured) is the latest advance in insulin pump technology available in Australia.

Metabolic syndrome in type 1 diabetes is a prelude to escalating costs and complications

A high risk of incident albuminuria has been observed in patients with type 1 diabetes and metabolic syndrome.

Per-Henrik Groop, MD, of the University of Helsinki, Finland, explained that he and colleagues in the Finnish Diabetic Nephropathy Study performed their analysis of published metabolic subtypes of type 1 diabetes. The study included type 1 diabetes patients (2059 men, 1924 women) from the Finnish Diabetic Nephropathy Study, a national prospective cohort.

Five subtypes were created in 2008 according to 28 biochemical measures collected between 1999 and 2007: good glycaemic control (subtype A), high high-density-lipoprotein cholesterol (subtype B), advanced kidney disease (subtype C), metabolic syndrome (subtype D), and low cholesterol (subtype E).

Outpatient medication records were extracted from the Social Insurance Institution starting from 1994. Primary endpoints were prescription costs for diabetes drugs, cardiovascular drugs, and other drugs.

Kidney disease was defined as microalbuminuria (30 mg/24 h < urinary albumin excretion ratio <300 mg/24 h), macroalbuminuria (urinary albumin excretion rate >300 mg/24 h), or end-stage renal disease (dialysis or transplant).

The secondary endpoint was progression from normal urinary albumin excretion rate (incident albuminuria). The lowest total cost was observed for subtypes A (good glycaemic control) and E (low cholesterol).

The advanced kidney disease subtype (subtype C) showed 3.6-fold cost and the metabolic syndrome (subtype D) 2.4-fold cost compared to subtype A ($P < 0.001$). Costs were 1.3-fold higher in men for subtypes C ($P = 0.004$) and D ($P = 0.03$) compared to women. Diabetes drug costs were 1.2-fold higher for subtype C in both sexes ($P < 0.001$).

Dr Groop concluded that a high risk for incident albuminuria (odds ratio 4.5, $P < 0.001$) was observed for metabolic syndrome (subtype D) when compared to subtype A (good glycaemic control).

Eighteen women had the metabolic profile of advanced kidney disease (subtype C) but normal urinary albumin excretion rate at baseline, with up to 14-fold risk for progression into albuminuria.

The results highlight the role of the metabolic syndrome in type 1 diabetes as a prelude to escalating drug costs and complications. ■

Levemir® insulin detemir (rys)

NovoRapid® insulin aspart (rys)

My type of treatment[2,3]

PBS information: NovoRapid® is listed on the PBS as a drug for the treatment of diabetes mellitus. Levemir® is listed as a restricted benefit for type 1 diabetes.

Levemir® is indicated for once- and twice-daily use in type 1 and type 2 diabetes[2]

Please review Product Information before prescribing. The Product Information can be accessed at www.novonordisk.com.au

Levemir® (insulin detemir (rys)). Indication: Treatment of diabetes mellitus. **Contraindications:** Hypersensitivity to insulin detemir or excipients. **Precautions:** Inadequate dosing may lead to hyperglycaemia and DKA. Hypoglycaemia may occur if dose too high in relation to requirements (see full PI). For subcutaneous administration only. Avoid I.M. administration. I.V. administration may result in a severe hypo. Mixed with other insulins the action profile of either or both may change. Do not use in infusion pumps. Do not add to infusion fluids. When thiazolidinediones (TZDs) are used in combination with insulin, patients should be observed for signs and symptoms of congestive heart failure, weight gain and oedema; discontinuation of TZDs may be required. No clinical experience during lactation. *Children:* Levemir can be used in children. Clinical trial experience is available in children with type 1 diabetes aged 2 years and over (see 'Clinical Trials' in full PI). *Pregnancy:* Category A. Levemir can be considered during pregnancy. Clinical trial experience is available in pregnant women with type 1 diabetes (see 'Clinical Trials' in full PI). **Interactions:** Oral antidiabetic drugs (OADs), octreotide, lanreotide, monoamine oxidase inhibitors, nonselective beta-adrenergic blocking agents, angiotensin converting enzyme inhibitors, salicylates, alcohol, anabolic steroids, alpha-adrenergic blocking agents, quinine, quinidine, sulphonamides, oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide, asparaginase, nicotinic acid, oxymetholone and danazol. Studies do not suggest clinically relevant albumin binding interactions between insulin detemir and fatty acids or other protein-bound drugs. **Adverse Effects:** Hypoglycaemia, injection site reaction. **Dosage and Administration:** For type 1 diabetes, use in combination with rapid- or short-acting insulin. For type 2 diabetes, use alone or in combination with bolus insulin, OADs, or as add-on therapy to liraglutide. Administer once- or twice-daily as part of a basal-bolus regimen, depending on needs. Adjust dose individually. In combination with OADs or as add on therapy to liraglutide, where optimisation of blood glucose control is not achieved with once daily injection, consideration should be given to adding a mealtime bolus injection of short-/rapid-acting insulin, or to transferring the patient to a pre-mixed insulin (October 2013). **NovoRapid® (insulin aspart (rys)). Indication:** Treatment of diabetes mellitus. **Contraindications:** Hypoglycaemia. Hypersensitivity to insulin aspart or excipients. **Precautions:** Inadequate dosing or discontinuation of treatment may lead to hyperglycaemia and diabetic ketoacidosis. Where blood glucose is greatly improved, e.g. by intensified insulin therapy, patients may experience a change in usual warning symptoms of hypoglycaemia, and should be advised accordingly. The impact of the rapid onset of action should be considered in patients where a delayed absorption of food might be expected. When thiazolidinediones (TZDs) are used in combination with insulin, patients should be observed for signs and symptoms of congestive heart failure, weight gain and oedema; discontinuation of TZDs may be required. Insulin administration may cause insulin antibodies to form and, in rare cases, may necessitate adjustment of the insulin dose. *Pregnancy:* Category A. Insulin aspart can be used in pregnancy (see 'Clinical Trials' in full PI). *Children:* NovoRapid® can be used in children. Clinical experience is available in children aged 2 years and over (see 'Clinical Trials' in full PI). *Elderly:* No safety issues were raised in elderly patients with type 2 diabetes (mean age 70 years) in a PK/PD trial but careful glucose monitoring may be necessary in elderly patients (see 'Clinical Trials' in full PI). **Interactions:** Oral hypoglycaemic agents, octreotide, lanreotide, monoamine oxidase inhibitors, non-selective beta-adrenergic blocking agents, angiotensin converting enzyme (ACE) inhibitors, salicylates, alcohol, anabolic steroids, alpha-adrenergic blocking agents, quinine, quinidine, sulphonamides, oral contraceptives, thiazides, glucocorticoids, thyroid hormones, sympathomimetics, growth hormone, diazoxide, asparaginase, nicotinic acid. **Adverse Effects:** Hypoglycaemia. **Dosage and Administration:** Dosage as determined by physician. NovoRapid® should be administered immediately before a meal, or when necessary after the start of a meal. Discard the needle after each injection. NovoRapid® can be used subcutaneously, intravenously or (10mL vial only) via continuous subcutaneous insulin infusion ('CSII'). (July 2014).

References: 1. Korytkowski M *et al. Clin Ther* 2005; 27(Suppl. B):S89–S100. 2. Levemir® Approved Product Information. 3. NovoRapid® Approved Product Information.

Novo Nordisk Pharmaceuticals Pty Ltd. ABN 40 002 879 996. Level 3, 21 Solent Circuit, Baulkham Hills, NSW 2153. NovoCare® Customer Care Centre (Australia) 1800 668 626. www.novonordisk.com.au. AU/LM/0116/0004f. INK2552-07_CEN. March 2016.

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Phentermine-topiramate shows best chance of weight loss at 1 year

BY BIANCA NOGRADY

The combination weight-loss drug phentermine plus topiramate is associated with the highest odds of individuals being able to lose 5% of their body weight within 1 year, according to a meta-analysis comparing outcomes and adverse events for orlistat, lorcaserin, naltrexone-bupropion, phentermine-topiramate, and liraglutide.

Researchers analysed 28 randomised placebo- or active-controlled clinical trials involving a total of 29,018 participants and found those who took phentermine-topiramate had a ninefold greater likelihood of achieving a 5% weight loss by 1 year than did those on placebo, according to a paper published in the June 14 issue of *JAMA*.

Liraglutide showed the second-highest odds of achieving a 5% weight loss at 1 year (odds ratio, 5.54), followed by naltrexone-bupropion (OR, 3.96), lorcaserin (OR, 3.10), and orlistat (OR, 2.70).

Nearly one-quarter of individuals on placebo achieved at least a 5% weight loss by 1 year, compared with three-quarters of individuals taking phentermine-topiramate, 63% of those taking liraglutide, 55% taking naltrexone-bupropion, 49% taking lorcaserin, and 44% taking orlistat (*JAMA* 2016;315:2424–34. doi: 10.1001/jama.2016.7602).

> "Ultimately, given the differences in safety, efficacy, and response to therapy, the ideal approach to weight loss should be highly individualised, identifying appropriate candidates for pharmacotherapy, behavioural interventions, and surgical interventions.

Of those on placebo, only 9% achieved at least a 10% weight loss at 1 year, compared with 54% of patients taking phentermine-topiramate, 34% of patients on liraglutide, 30% of patients on naltrexone-bupropion, 25% of those taking lorcaserin, and 20% of those taking orlistat.

Phentermine-topiramate was also associated with the greatest weight loss, compared with placebo, with patients losing a mean of 8.8 kg vs 5.2 kg with liraglutide, 5 kg with naltrexone-bupropion, 3.2 kg with lorcaserin, and 2.6 kg with orlistat.

While all active drugs were associated with a higher rate of discontinuation because of adverse events than was seen with placebo, liraglutide was associated with the greatest risk of discontinuation, compared with placebo, followed by naltrexone-bupropion, phentermine-topiramate, orlistat, and then lorcaserin.

Dr Rohan Khera of the department of internal medicine at the University of Iowa, Iowa City, and coauthors wrote that pharmacologic treatment decisions should consider coexisting medical conditions that might influence for or against a particular choice for weight loss.

"For example, liraglutide may be a more appropriate agent in people with diabetes because of its glucose-lowering effects," they wrote. "Conversely, naltrexone-bupropion in patients with chronic opiate or alcohol dependence may be associated with neuropsychiatric complications.

"Ultimately, given the differences in safety, efficacy, and response to therapy, the ideal approach to weight loss should be highly individualised, identifying appropriate candidates for pharmacotherapy, behavioural interventions, and surgical interventions." ■

Two study authors were supported by a grant from the National Library of Medicine or the National Institute of Diabetes and Digestive and Kidney Diseases. One author reported receiving funding, participating on advisory committees, and serving as a consultant with a range of pharmaceutical manufacturers, as well as being a cofounder of Liponexus. Another author reported research support from NovoNordisk for research on liraglutide. No other disclosures were reported.

FRONTLINE MEDICAL NEWS

Obesity continues to trend up among women over the past decade

BY AMY KARON

Four in 10 women in the United States are obese, 1 in 10 women has a body mass index above 40 kg/m², and significantly more women are obese than a decade ago, according to a large study published June 7 in *JAMA*.

In contrast, obesity rates among men in the United States have remained stable since 2005, said Dr Katherine Flegal of the National Centre for Health Statistics. "Other studies are needed to determine the reasons for these trends," she and her associates wrote.

Between 1980 and 2000, obesity rates in the United States rose significantly among both men and women. Between 2000 and 2004, rates rose significantly for men, but not women. Rates then leveled off for both sexes through 2012. To further explore these trends, Dr Flegal and her associates calculated the prevalence of obesity (BMI greater than 30 kg/m²) and class 3 obesity (BMI greater than 40 kg/m²) for 2638 men and 2817 women aged 20 and up during 2013–2014, the most recently available 2-year data period from the National Health and Nutrition Examination Survey (NHANES). The researchers also examined trends in obesity since 2005, based on NHANES data from 21,013 adults (*JAMA* 2016 Jun 7. doi: 10.1001/jama.2016.6458).

About 38% of adults in the United States were obese during 2013–2014 (95% confidence interval, 36–40%), including about 40% of women and 35% of men, the researchers found. A total of 7.7% of adults had a BMI of at least 40, including 5.5 % of men and 9.9% of women.

During the decade from 2005 through 2014, the prevalence of obesity among women rose significantly from 35.6% to 41.1% (P = 0.004), even after the investigators adjusted for age, race and Hispanic origin, smoking status, and education. Among men, the adjusted prevalence of obesity remained about 35% during this time period. Likewise, the adjusted prevalence of class 3 obesity (BMI of at least 40) rose significantly for women (P = 0.01), but not for men.

Black women also were significantly more likely to be obese or severely obese, compared with non-Hispanic white women in the study, the investigators found. Among men, current smokers were less likely to be obese than never smokers, and women with education beyond high school were less likely to be obese than women who had not finished high school. ■

The investigators reported no funding sources and had no disclosures.

FRONTLINE MEDICAL NEWS

JOURNAL SCAN

Trends in obesity prevalence among children and adolescents

The Journal of the American Medical Association

Take-home message

- This study investigated the trends in obesity (BMI > 95th percentile on the CDC BMI-for-age growth charts) and extreme obesity (BMI > 120% of the 95th percentile on the CDC BMI-for-age growth charts) in 40,780 children and adolescents between 1988 to 1994 and 2013 to 2014. From 2011 to 2014, the prevalence of obesity in children and adolescents ages 2 to 19 was 17.0%, and the prevalence of extreme obesity was 5.8%. When the researchers analysed obesity trends by age group, they found that obesity increased for all age groups between 1988 to 1994 and 2005 to 2006. Among children aged 2 to 5, obesity decreased between 2003 to 2004 and 2013 to 2014 (13.9% to 9.4%), but researchers did not observe any significant changes between 2005 to 2006 and 2013 to 2014 in the other age groups.
- This is a comprehensive analysis of children and adolescents showing that obesity has decreased among children aged 2 to 5 years in the last decade, but other age groups have not seen the same reduction in obesity prevalence.

IMPORTANCE Previous analyses of obesity trends among children and adolescents showed an increase between 1988–1994 and 1999–2000, but no change between 2003-2004 and 2011–2012, except for a significant decline among children aged 2 to 5 years.

OBJECTIVES To provide estimates of obesity and extreme obesity prevalence for children and adolescents for 2011–2014 and investigate trends by age between 1988–1994 and 2013–2014.

DESIGN, SETTING, AND PARTICIPANTS Children and adolescents aged 2 to 19 years with measured weight and height in the 1988–1994 through 2013–2014 National Health and Nutrition Examination Surveys.

EXPOSURES Survey period.

MAIN OUTCOMES AND MEASURES Obesity was defined as a body mass index (BMI) at or above the sex-specific 95th percentile on the US Centers for Disease Control and Prevention (CDC) BMI-for-age growth charts. Extreme obesity was defined as a BMI at or above 120% of the sex-specific 95th percentile on the CDC BMI-for-age growth charts. Detailed estimates are presented for 2011-2014. The analyses of linear and quadratic trends in prevalence were conducted using 9 survey periods. Trend analyses between 2005–2006 and 2013–2014 also were conducted.

RESULTS Measurements from 40,780 children and adolescents (mean age, 11.0 years; 48.8% female) between 1988–1994 and 2013–2014 were analysed. Among children and adolescents aged 2 to 19 years, the prevalence of obesity in 2011–2014 was 17.0% (95% CI, 15.5–18.6%) and extreme obesity was 5.8% (95% CI, 4.9–6.8%). Among children aged 2 to 5 years, obesity increased from 7.2% (95% CI, 5.8–8.8%) in 1988–1994 to 13.9% (95% CI, 10.7–17.7%) (P<0.001) in 2003–2004 and then decreased to 9.4% (95% CI, 6.8–12.6%) (P=0.03) in 2013–2014. Among children aged 6 to 11 years, obesity increased from 11.3% (95% CI, 9.4–13.4%) in 1988–1994 to 19.6% (95% CI, 17.1–22.4%) (P<0.001) in 2007–2008, and then did not change (2013–2014: 17.4% [95% CI, 13.8–21.4%]; P=0.44). Obesity increased among adolescents aged 12 to 19 years between 1988–1994 (10.5% [95% CI, 8.8–12.5%]) and 2013–2014 (20.6% [95% CI, 16.2–25.6%]; P<0.001) as did extreme obesity among children aged 6 to 11 years (3.6% [95% CI, 2.5–5.0%] in 1988–1994 to 4.3% [95% CI, 3.0–6.1%] in 2013–2014; P=0.02) and adolescents aged 12 to 19 years (2.6% [95% CI, 1.7–3.9%] in 1988–1994 to 9.1% [95% CI, 7.0–11.5%] in 2013–2014; P<0.001). No significant trends were observed between 2005–2006 and 2013–2014 (P value range, 0.09–0.87).

CONCLUSIONS AND RELEVANCE In this nationally representative study of US children and adolescents aged 2 to 19 years, the prevalence of obesity in 2011–2014 was 17.0% and extreme obesity was 5.8%. Between 1988–1994 and 2013–2014, the prevalence of obesity increased until 2003–2004 and then decreased in children aged 2 to 5 years, increased until 2007–2008 and then levelled off in children aged 6 to 11 years, and increased among adolescents aged 12 to 19 years.

Trends in obesity prevalence among children and adolescents in the United States, 1988–1994 through 2013–2014. *JAMA* 2016;315:2292–2299, CL Ogden, MD Carroll, HG Lawman, et al.

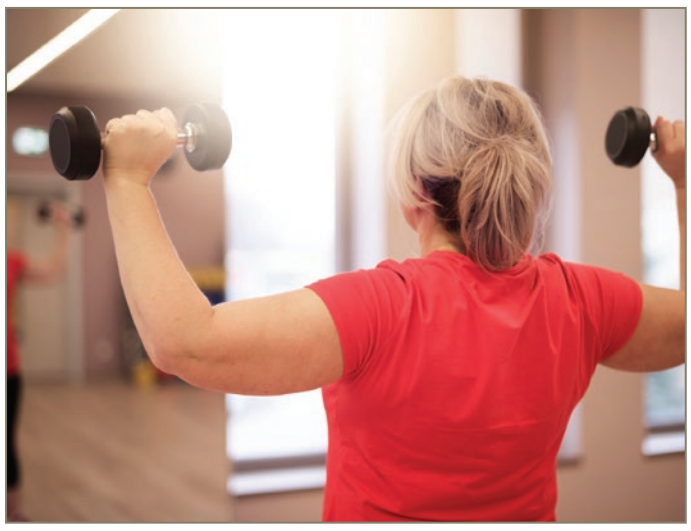
EXPERT OPINION

What have we learned about obesity from "The Biggest Loser" show?

BY DR ERIC RAVUSSIN AND DR MARTICA HEANER

Recently, the journal *Obesity* published the long-awaited results from a long-term study on some of the contestants from The Biggest Loser televised weight-loss competition.[1] As a result of a front-page feature about this study in the New York Times, the story of The Biggest Loser contestants' struggles against weight loss relapse went viral, triggering online and offline discussions among obesity researchers as well as the general public.

Typically, weight-loss stories, such as those depicted in The Biggest Loser, are portrayed as resounding successes. The "before's" depict people with out-of-control eating habits and sedentary lifestyles who are severely overweight. They typically experience an "aha!" moment where they learn to manage their behaviours and beat their biology. After a period of disciplined diet and exercise, their "after" moments show a dramatically weight-reduced and more confident individual. But the "after-after" depictions uncover a darker outcome, one where weight-loss maintenance is difficult, if possible at all.



So, what are the lessons to be learned from what we know now that can help those people struggling to maintain a healthy weight in the modern toxic environment that encourages them to eat more and move less – and gain weight – at every turn?

The only piece of good news from this study is that an overweight or obese individual who is struggling to control his/her body weight can finally be excused for not trying hard enough. Society and health professionals, too, can stop blaming the victims. Laziness is clearly not a factor in the weight regain seen in The Biggest Loser contestants. In fact, it may be challenging to find a more dedicated group of individuals. Studies designed to further understand the biology behind obesity are necessary to improve the treatment of this deleterious disease until we design public health policies to reverse part of the toxic environment.

The insights from published studies on weight loss and weight-loss maintenance are:

- Weight loss, and even dramatic weight loss, is possible. But the kind of weight loss occurring in The Biggest Loser contestants is almost impossible to maintain long term when the individuals return to their former environment – away from the 24/7 support system of fitness, nutrition, psychological, and medical staff on the TV series. Of the average 58.3 kg lost in 30 weeks, 70% was regained over the next 6 years. However, the average final weight was still 12% lower than before the completion, which may seem like a failure in terms of weight-loss success, but is probably still of value and clinically important for health benefits.
- The major drivers for weight regain are due to physiological responses to weight loss: a) the persistence of a very low resting metabolic rate (RMR; 700 kcal/day in absolute value and 500 kcal/day after adjusting for the lost weight); b) the lower energy cost of all weight-bearing activities; and c) the likely persistence of decreased orexigenic signals in concert with increased anorexic hormones.
- Other drivers for weight regain are extrinsic but may have a psychological component. Post weight loss, The Biggest Loser contestants likely experience a diminution of the heavy-duty regimen that led to the dramatic weight loss in the first place. When contestants returned home, even if they tried to watch what they ate and keep up regular workouts, they were more prone to slip-ups.
- From many studies in which RMR was measured before and after weight loss, it is clear that this metabolic adaptation to lower levels is proportional to the amount of weight loss. So, this reduction will be much less with more moderate weight loss.
- For persons with overweight or obesity seeking definitive improvements in their metabolic health, a weight loss of 5%, 10%, or 15% is recommended. With this smaller degree of weight loss, patients are unlikely to experience the extreme calorie handicaps that lead to weight regain that were observed in The Biggest Loser Instead, they might see only a small deficit in RMR of 50 to 150 kcal/day.
- Since moderate and realistic weight-loss recommendations yield important health benefits, the focus should now shift from striving for dramatic amounts of weight loss toward achieving moderate weight loss, with a stronger emphasis on weight-loss maintenance. To be successful, it is of the utmost importance to continue the lifestyle changes implemented during the weight loss, including medications if indicated. Also, continuing with proven behaviours, such as weighing frequently and initiating a long-lasting lifestyle change to increase physical activity, is key to success. Surgery should only be recommended if the level of obesity is increasing a person's health risks and if all other strategies have failed.

1. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition [published online May 2, 2016]. *Obesity* doi: 10.1002/oby.21538.

PRACTICEUPDATE

Diet inclusive of healthy fats does not lead to weight gain

Olive oil and nut diet groups had lower increase in waist circumference than low-fat diet group

An eating plan that includes healthy fats such as olive oil and nuts isn't likely to cause weight gain, according to a study published online June 6 in *The Lancet Diabetes & Endocrinology*.

The study included 7447 women and men in Spain, aged 55 to 80. The participants ate one of three eating plans: an unrestricted-calorie Mediterranean diet rich in olive oil; an unrestricted-calorie Mediterranean diet rich in nuts; or a low-fat diet meant to avoid all dietary fat. All of the participants had type 2 diabetes or three or more cardiovascular risk factors. More than 90 percent were overweight or obese.

After 5 years, total fat intake fell from 40.0 to 37.4 percent in the low-fat diet group, and rose in both Mediterranean diet groups, from about 40 to 42 percent. The percentage of proteins and carbohydrates decreased in both Mediterranean diet groups. Participants lost an average of 0.88 kg per person in the olive oil group, 0.60 kg in the low-fat diet group, and 0.40 kg in the nut group. The low-fat group had an increase in waist circumference of 1.2 cm per person, the olive oil group saw an increase of 0.85 cm, and the nut group had the smallest increase of 0.37 cm.

"Energy density and total caloric contents can be similarly misleading. Rather, modern scientific evidence supports an emphasis on eating more calories from fruits, nuts, vegetables, beans, fish, yogurt, phenolic-rich vegetable oils, and minimally processed whole grains; and fewer calories from highly processed foods rich in starch, sugar, salt, or trans-fat," Dr Dariush Mozaffarian from the School of Nutrition Science & Policy at Tufts University in Boston, writes in an accompanying commentary. "Dietary guidelines should be revised to lay to rest the outdated, arbitrary limits on total fat consumption. Calorie-obsessed caveats and warnings about healthier, higher-fat choices such as nuts, phenolic-rich vegetable oils, yogurt, and even perhaps cheese, should also be dropped."

HEALTHDAY

JOURNAL SCAN

Portion-controlled prepackaged foods promote weight loss

Obesity

Take-home message

- The goal of this study was to evaluate the efficacy of providing overweight and obese individuals with prepackaged meals to encourage weight and fat loss. Researchers randomised 183 participants (58% female, 42% male) to either self-selected food or portion-controlled prepackaged entrees. Participants in the prepackaged food group had a greater decrease in weight and fat after 12 weeks compared with the control group (8.6% vs 6.0% and 5.7% vs 4.4%; P < 0.05).
- Overweight and obese patients who followed meal plans that include portion-controlled prepackaged foods lost more weight and fat than those who followed meal plans involving self-selection of foods.

OBJECTIVE Providing portion-controlled prepackaged foods in a behavioural counselling intervention may promote more weight and fat loss than a standard self-selected diet.

METHODS The primary aim was to test whether providing portion-controlled prepackaged lunch and dinner entrées within a behavioural weight loss intervention promotes greater weight loss at 12 weeks compared to self-selected foods in adults with overweight/obesity. Other aims were to examine effects on biological factors, fitness, and meal satisfaction. One-half of those assigned to prepackaged entrées were provided items with a higher protein level (>25% energy) as an exploratory aim.

RESULTS Participants (n = 183) had a baseline weight of 95.9 (15.6) kg (mean [SD]) and BMI of 33.2 (3.5) kg/m^2) . Weight data at 12 weeks were available for 180 subjects. Weight loss for regular entrée, higher protein entrée, and control groups was 8.6 (3.9)%, 7.8 (5.1)%, and 6.0 (4.4)%, respectively (P<0.05, intervention vs control). Intervention participants lost more body fat than controls (5.7 [3.4] vs 4.4 [3.3] kg, P<0.05).

CONCLUSIONS A meal plan incorporating portion-controlled prepackaged entrées promotes greater weight and fat loss than a standard self-selected diet, with comparable meal satisfaction. Initial weight loss predicts long-term weight loss so these results are relevant to likelihood of longer term success.

Randomized clinical trial of portion-controlled prepackaged foods to promote weight loss
Obesity 2016;24:1230–1237, CL Rock, SW Flatt, B Pakiz, et al.

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