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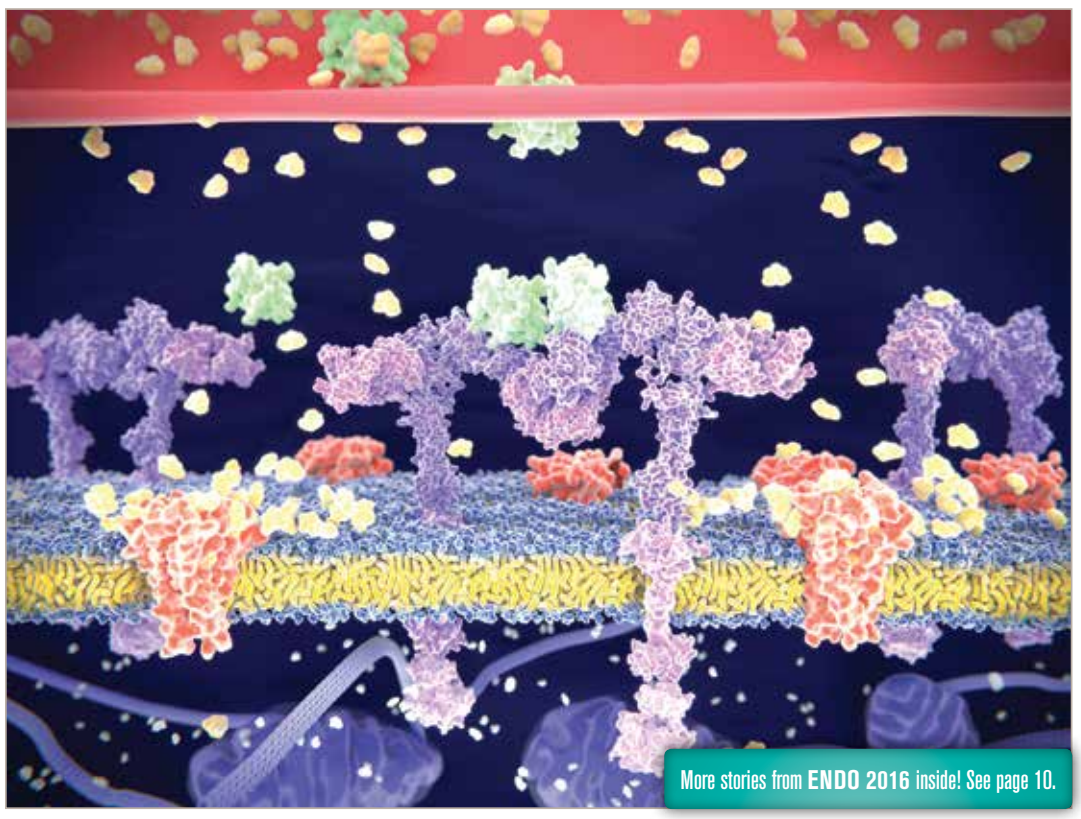
Clinical Endocrinology News

Vol. 9 • No. 1 • 2016 *The Leading Independent Newspaper from Elsevier* AUSTRALIAN EDITION

Bionic glucagon delivery improved hypoglycaemia control in T1D patients

BY BRIAN HOYLE
Frontline Medical News
At ENDO2016, Boston



More stories from **ENDO 2016** inside! See page 10.

A wearable, closed-loop bionic pancreas system that automatically delivers glucagon has been found to improve hypoglycaemia control in patients with type 1 diabetes.

A double-blind, randomised, placebo-controlled, cross-over study (NCT02181127) has demonstrated the value of automated injection of glucagon in establishing glycaemic regulation in adult patients with type 1 diabetes. "Automated glucagon delivery reduces hypoglycaemia and increases time in range without an increase in mean glucose, with no difference in insulin dose," said Dr Laya Ekhlaspour of Massachusetts General Hospital, Boston.

Glycaemic regulation can be problematic in young adults with type 1 diabetes, whose blood glucose levels can fall below 3.89 mmol/L for over 2 hours daily, even with glycaemic control using conventional insulin pump therapy. The typical response to hypoglycaemia – supplying glucose in a quickly digested form – is a short-term solution and is not effective during sleep.

Dr Ekhlaspour and her colleagues surmised that a closed-loop system comprising a wearable bionic pancreas system that automatically delivers glucagon could reduce the incidence and severity of hypoglycaemia when used along with the conventional insulin therapies of multiple daily injection (MDI) or continuous subcutaneous insulin infusion (CSII).

Of 31 subjects screened, 27 were eligible in terms of the frequency of hypoglycaemia, but 5 were excluded because of scheduling problems, leaving 22 patients. The participants, adults with type 1 diabetes, had blood glucose levels below 3.33 mmol/L on average at least twice a week, and some periods with blood glucose below 2.77 mmol/L.

In addition to self-administered insulin (CSII or MDI), the subjects also received glucagon or placebo for 24 hours at a time using the automated wearable bionic pancreas system. In the 2-week study, the subjects (mean age 42 years; mean duration of diabetes 25 years) were randomised to receive glucagon or placebo for a total of 7 days each. The subjects were not told which preparation they were receiving.

The primary outcome of area over the curve (AOC) under 3.33 mmol/L was reduced by 75% on days when glucagon was supplied (47.23 mmol/L/min), compared with days when placebo was supplied (189.48 mmol/L/min), a significant difference. The difference in AOC was even more pronounced at night (6.49 vs 72.65 mmol/L/min).

The percentage of subjects with blood glucose of 3.89–9.99 mmol/L was significantly greater on days when glucagon was administered than when placebo was given (69% vs 62%). Subjects spent 74% less time with blood glucose under 3.33 mmol/L on days when glucagon was supplied, compared with placebo (1.2% vs 4.7%).

Symptomatic hypoglycaemia episodes were significantly fewer for glucagon, compared with placebo (0.6 vs 1.2). The need for oral carbohydrates was reduced when glucagon was provided (1.3 vs 1.9 interventions per day). Nausea severity rankings for glucagon and placebo on the visual analog scale were similar.

Androgen deprivation therapy linked to depression

BY NEIL OSTERWEIL
Frontline Medical News
From the Journal of Clinical Oncology

Men on androgen deprivation therapy for prostate cancer are at significantly increased risk for depression, a risk that increases with duration of therapy, investigators report.

A review of Surveillance, Epidemiology, and End Results (SEER) US Medicare data on nearly 79,000 men older than 65 years with a diagnosis of prostate cancer showed that those who received androgen deprivation therapy (ADT) had a 23% increased risk for depression, compared with men who were not on ADT, reported Kathryn T. Dinh of Harvard Medical School, Boston, and her colleagues.

"We observed a significantly increased risk of depression and inpatient psychiatric treatment in men treated with ADT for prostate cancer, as well as a duration-response effect such that more ADT was linked to an increasing risk of depression and inpatient and outpatient psychiatric treatment. The possible psychiatric effects of ADT should be recognised by physicians and discussed with patients before initiating treatment," they wrote (*J Clin Oncol* 2016 Apr 11. doi: 10.1200/JCO.2015.64.1969).

Although ADT has been identified in some studies as a risk factor for clinical depression, evidence for such a relationship has been spotty, the investigators said, prompting them to conduct a population-based retrospective study to get a better handle on the issue.

They reviewed SEER Medicare data on 78,552 men older than 65 years with a diagnosis of stage I–III prostate cancer treated with ADT from 1992 through 2006, excluding from the sample those patients who had a psychiatric diagnosis within the past 12 months.

Ms Dinh and her associates found that the 33,882 patients (43%) who received ADT had a significantly higher 3-year cumulative incidence of depression than patients who did not have ADT (7.1% vs 5.2%, $P < 0.001$), and a significantly higher proportion had either inpatient psychiatric treatment (2.8% vs 1.9%, $P < 0.001$) or outpatient psychiatric therapy (3.4% vs 2.5%, $P < 0.001$).

In proportional hazard models controlling for demographic and clinical factors, receipt of ADT was associated with adjusted hazard ratios of 1.23 for depression and 1.29 ($P < 0.001$ for both) for inpatient psychiatric treatment. There was no significant increase in risk for outpatient psychiatric treatment in this analysis, however.

In addition, the longer patients that were on ADT, the greater the risk for depression. The risk of depression was 12% for patients treated for 6 months or less, 26% for those on ADT for 7–11 months, and 37% for those on ADT for at least 1 year.

"The impact of ADT on depression may plausibly occur via deregulation of neurochemicals, such as serotonin, in addition to the well-described physical effects," Ms Dinh and her associates wrote.

Side effects of ADT that can impair quality of life also may contribute to clinical depression, they noted.

The study was supported by charitable grants and internal institutional sources. One investigator reported consulting or advisory roles with Medivation, GenomeDx, and Ferring. Three of the other ten coauthors also reported financial disclosures.

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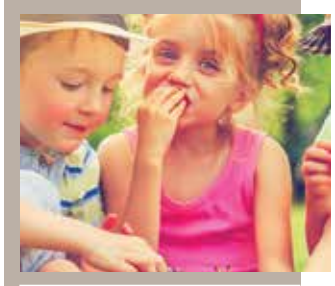

NEWS

Only 'early' oestradiol limits atherosclerosis progression

BY MARY ANN MOON
Frontline Medical News
From the New England Journal of Medicine

Hormone therapy – oestradiol with or without progesterone – only limits the progression of subclinical atherosclerosis if it is initiated within 6 years of menopause onset, according to a report published online March 30 in the *New England Journal of Medicine*.

The "hormone-timing hypothesis" posits that hormone therapy's beneficial effects on atherosclerosis depend on the timing of initiating that therapy relative to menopause. To test this hypothesis, researchers began the ELITE study (Early versus Late Intervention Trial with Estradiol) in 2002, using serial noninvasive measurements of carotid-artery intima-media thickness (CIMT) as a marker of atherosclerosis progression.

Several other studies since 2002 have reported that the timing hypothesis appears to be valid, wrote Dr Howard N. Hodis of the Atherosclerosis Research Unit, University of Southern California, Los Angeles, and his associates.

Their single-centre trial involved 643 healthy postmenopausal women who had no diabetes and no evidence of cardiovascular disease at baseline, and who were randomly assigned to receive either daily oral oestradiol or a matching placebo for 5 years. Women who had an intact uterus and took active oestradiol also received a 4% micronised progesterone vaginal gel, while those who had an intact uterus and took placebo also received a matching placebo gel.

The participants were stratified according to the number of years they were past menopause: less than 6 years (271 women in the "early" group) or more than 10 years (372 in the "late" group).

A total of 137 women in the early group and 186 women in the late group were assigned to active oestradiol, while 134 women in the early group and 186 women in the late group were assigned to placebo. As expected, serum oestradiol levels were at least 3 times higher among women assigned to active treatment, compared with those assigned to placebo.

The primary outcome – the effect of hormone therapy on CIMT progression – differed by timing of the initiation of treatment. In the "early" group, the mean CIMT progression rate was decreased by 0.0034 mm per year with oestradiol, compared with placebo.

In contrast, in the "late" group, the rates of CIMT progression were not significantly different between oestradiol and placebo, the investigators wrote (*N Engl J Med* 2016;374:1221-31. doi: 10.1056/NEJMoa1505241).

This beneficial effect remained significant in a sensitivity analysis restricted only to study participants who showed at least 80% adherence to their assigned treatment. The benefit also remained significant in a post-hoc analysis comparing women who took oestradiol alone against those who took oestradiol plus progestogen, as well as in a separate analysis comparing women who used lipid-lowering and/or hypertensive medications against those who did not.

The findings add further evidence in favour of the hormone timing hypothesis. The effect of oestradiol therapy on CIMT progression was significantly modified by time since menopause (P = 0.007 for the interaction), the researchers wrote.

Cardiac computer tomography (CT) was used as a different method of assessing coronary atherosclerosis in a subgroup of 167 women in the early group (88 receiving oestradiol and 79 receiving placebo) and 214 in the late group (101 receiving oestradiol and 113 receiving placebo). The timing of oestradiol treatment did not affect coronary artery calcium and other cardiac CT measures. This is consistent with previous reports that hormone therapy has no significant effect on established lesions in the coronary arteries, the researchers wrote.

The ELITE trial was funded by the USNational Institute on Aging. Dr Hodis reported having no relevant financial disclosures; two of his associates reported ties to GE and TherapeuticsMD.

Childhood obesity rates may fall if trend continues

BY ABIGAIL CRUZ
Frontline Medical News
From Pediatrics

Children aged 2–5 years were less likely to be obese than older children in 2003–2004; however, the results were reversed in 2011–2012, according to Ashley Wendell Kranjac, Ph.D., of Rice University, Houston, and Robert L. Wagmiller, Ph.D., of Temple University, Philadelphia.

Previous research showed that in the United States, the obesity rate in children aged 2–5 years decreased from 14% in 2003–2004 to 8% in 2011–2012. The sample study using data from the US National Health and Nutrition Examination Survey (NHANES) created by the investigators included 926 children from 2003 to 2004 (498 girls and 428 boys) and 974 children from 2011 to 2012 (482 girls and 492 boys), totalling 1900 children.

Although age and time are factors of the decreasing obesity rate, there are multiple other components that ultimately determined the researchers' statistics. Factors such as race, gender, a child's health characteristics, and activity are just a few, and these all were included as Blinder-Oaxaca regression decomposition techniques were used to assess the change in obesity over time. "The fact that older children were more likely to be obese than younger children in 2003–2004, but not in 2011–2012, has further implications," Dr Kranjac and Dr Wagmiller said.

"If this association between age and obesity persists as these children advance into middle and late childhood, sizable reductions in obesity rates at later stages of childhood can be expected, as well as significant declines in the overall rate of childhood obesity over time," the investigators concluded.

Read more about the study at *Pediatrics* (2016. doi: 10.1542/peds.2015-2096).

NEW DRUGS AND DEVICES LISTING

Newly Listed	Indication
Therapeutic Goods Administration (TGA) tga.gov.au	
Follitropin alfa (rch) *Afolia/Bemfola*, Finox Biotech Australia	In adult women: For the treatment of anovulatory infertility in women who have been unresponsive to clomiphene citrate or where clomiphene citrate is contraindicated. Controlled ovarian hyperstimulation in women undergoing assisted reproductive technologies In adult men: indicated with concomitant human chorionic gonadotrophin (hCG) therapy for the stimulation of spermatogenesis in gonadotrophin-deficient men in whom hCG alone is ineffective.
Eltrombopag *Revolade*, Novartis Pharmaceuticals	For the treatment of adult patients with severe aplastic anaemia (SAA) who have had an insufficient response to immunosuppressive therapy.
Liraglutide *Saxenda*, Novo Nordisk	Indicated as an adjunct to a reduced calorie diet and increased physical activity for chronic weight management in adult patients with an initial Body Mass Index (BMI) of • greater than or equal to 30 kg/m^2 (obese); or • greater than or equal to 27 kg/m^2 to less than 30 kg/m^2 (overweight) in the presence of at least one weight related comorbidity, such as dysglycaemia (pre-diabetes and type 2 diabetes mellitus), hypertension, dyslipidaemia, or obstructive sleep apnoea.
Pharmaceutical Benefit Scheme (PBS) pbs.gov.au	
Nadroparin, *Fraxiparine*, Aspen	For prophylaxis and treatment of deep vein thrombosis.
Rituximab, *Mabthera* SC, Roche	For patients with CD20 positive, B-cell non-Hodgkin's lymphoma.
Sumatriptan, *Imigran* FDT, Aspen	For the relief of migraine.
Trastuzumab, *Herceptin* SC, Roche	For the treatment of HER2-positive breast cancer.

Please consult the full Product Information before prescribing.

Clinical Endocrinology News
AUSTRALIAN EDITION

Managing Editor Anne Neilson anne.neilson@elsevier.com
Editor Carolyn Ng carolyn.ng@elsevier.com
Designer Jana Sokolovskaja j.sokolovskaja@elsevier.com
Commercial Manager Fleur Gill fleur.gill@elsevier.com
Account Manager Stephen Yue s.yue@elsevier.com

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The news and information in CLINICAL ENDOCRINOLOGY NEWS (Australian edition) is sourced from CLINICAL ENDOCRINOLOGY NEWS (US edition) published by Frontline Medical News.

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ISSN: 1835-6125

CLINICAL ENDOCRINOLOGY NEWS, Australian Edition is published by Elsevier Australia, ABN 70 001 002 357
475 Victoria Avenue
Chatswood NSW 2067, Australia
Locked Bag 7500
Chatswood DC NSW 2067

EMED041601

Fibrosis still key to predicting NAFLD mortality

BY SARA FREEMAN
Frontline Medical News
At the International Liver Congress 2016, Barcelona

Although a new histological scoring system was able to predict mortality from non-alcoholic fatty liver disease (NAFLD), fibrosis remains the key predictor of whether an individual is likely to die decades later.

Patients with severe NAFLD, as determined by having a high steatosis, activity, and fibrosis (SAF) score, were more than twice as likely to die than those with mild-to-moderate disease up to 41 years later.

However, when a sensitivity analysis was performed to adjust for fibrosis stage or exclude patients with stage 3–4 fibrosis, the hazard ratio for mortality was no longer significant.

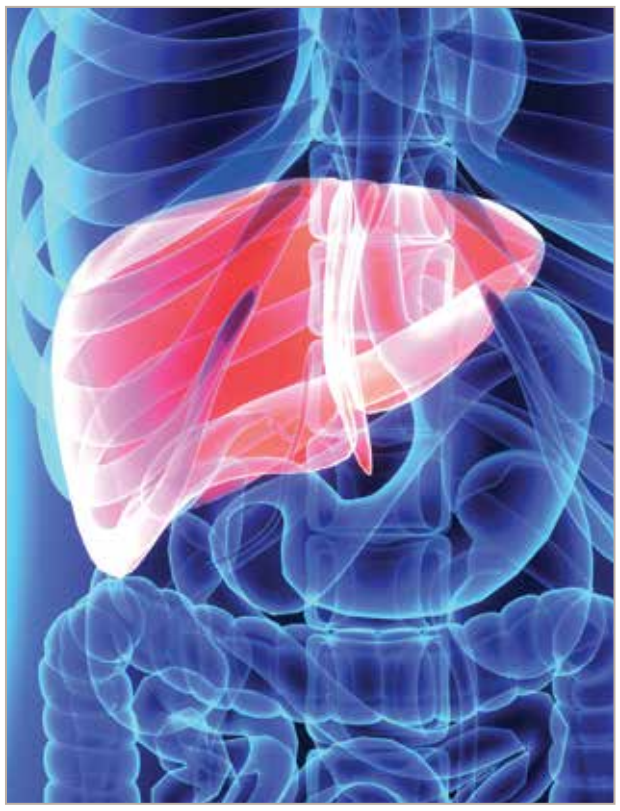
"Severe SAF score was associated with increased mortality, but this largely depended on fibrosis stage," Dr Hannes Hagström of the Karolinska Institutet in Stockholm reported at the International Liver Congress.

Although it is known that the more severe the disease the more likely the risk for death, assessing the severity of NAFLD can be challenging for clinicians because it is a continuum of disease, he explained. "NAFLD is the most prevalent liver disease globally with a prevalence of around 25%; it is very heterogeneous and makes prognostication difficult." This has implications for including people in trials and for determining what the clinical endpoints should be, as well as making it difficult to determine the outlook for individual patients.

There are several histological scoring systems developed over the years trying to help with this issue, including the Brunt score, the NAFLD activity score (NAS), and fibrosis stage.

While the latter has previously been shown to be a robust marker for mortality, the NAS has been criticised, Dr Hagström noted. This is because the effect of steatosis may be overestimated and because NAS does not measure fibrosis. Thus, there is a need for new means to risk-stratify patients and one relatively new method is the SAF score.

The SAF score was developed to evaluate the severity of fatty liver lesions, originally in morbidly obese individuals (*Hepatology* 2012 Oct;56:1751–9). Using this score, the extent of fatty accumulation in the liver can be assessed, with a score of 0 signifying that steatosis is present in less than 5% of the liver and a score of 3 signifying that more than two-thirds of the liver is affected. NAFLD activity is determined on a scale of 0 to 4 by assessing the degree of ballooning and lobular inflammation. Finally, the score looks at the extent of fibrosis, rating it from 0 (not present) to 4 (cirrhosis).



The aim of the study was to examine the impact of this score on overall mortality in a previously published (*Hepatology* 2015 Mar;61:1547–54) cohort of patients with long follow-up, Dr Hagström explained at the meeting sponsored by the European Association for the Study of the Liver (EASL). Data on 139 patients with biopsy-proven NAFLD were obtained from a historical cohort of patients who had undergone liver biopsy between 1974 and 1994. Their biopsies were reclassified using the SAF score and the presence of nonalcoholic steatohepatitis was also determined using the FLIP algorithm and the NAS score. Data on causes of death were taken from a national Swedish population register. At baseline, 35 patients had mild, 35 had moderate, and 69 had severe NAFLD.

After a median follow-up of 25 years, ranging from 2 to 41 years, 74 patients died. Of these deaths, 45 occurred in patients with severe NAFLD, representing 65% of the severe NAFLD group. Half (n = 18; 51%) of the patients with moderate NAFLD and just under one-third (n = 11; 31%) of those with mild NAFLD had also died. The median time to death was 18 years after liver biopsy.

Dr Hagström reported that cardiovascular causes were the main cause of mortality, in 21% of patients; extrahepatic malignancy caused 12% of deaths, 7% of deaths were liver related, and 13% were due to other reasons. Patients with severe NAFLD identified by a high SAF score were more than two and a half times more likely to die than those with mild NAFLD, with a hazard ratio of 2.65 (P = 0.02). Patients with moderate NAFLD were no more likely than those with mild liver disease to die (HR = 1.23; P =0 .84). Data had been adjusted for gender, body mass index, and for the presence of type 2 diabetes.

HRs for mortality comparing high with low SAF scores after adjusting for fibrosis stage and excluding patients with fibrosis stages 3–4 were a respective 1.85 (P = 0.18) and 1.94 (P = 0.15). In a press statement issued by EASL, Dr Laurent Castera of Hôpital Beaujon in Paris noted that these data were an important step forward for the medical community in being able to identify the patients who are most at risk of death from NAFLD. Dr Castera, who is the secretary general of EASL, noted that these long-term study data also demonstrated the importance of having sufficient follow-up periods for patients with NAFLD.

In an interview after his presentation Dr Hagström also emphasised the importance of long-term follow-up of patients.

"The clinical importance of this is that it is most important for clinicians to look at fibrosis stage, and I think to have to follow these patients a little bit more," he said. "You can't just do a liver biopsy, say 'you just have steatosis, you don't have NASH [nonalcoholic steatohepatitis], [so] you are fine'," he added. Equally, it is not possible to say that because NASH is not present that patients won't advance in the future. Patients need to be followed up for a long period of time.

"Fibrosis is the most important thing, both for clinicians and for patients," Dr Hagström said.

Dr Hagström has been a consultant to Novo Nordisk. Dr Castera had no relevant financial disclosures.

New ACC consensus guidance addresses nonstatin therapies

BY SHARON WORCESTER
Frontline Medical News
At ACC 16, Chicago

A new American College of Cardiology expert consensus decision pathway for the use of nonstatin therapies to lower cholesterol in high-risk patients addresses situations not covered by an evidence-based 2013 guideline on managing atherosclerotic cardiovascular disease risk.

Like the 2013 guideline (the 2013 American College of Cardiology/American Heart Association Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Disease Risk in Adults), the new guidance emphasises the importance of a healthy lifestyle, but also addresses the use of two monoclonal antibodies-proprotein convertase subtilisin/kexon 9 (PCSK9) inhibitors-approved for certain patient groups since the 2013 guideline was released, as well as other nonstatin therapies, including ezetimibe and bile acid sequestrants.

"At the time [the 2013 guideline was published] the only really good outcomes data ... were for statin medication and there were no data from clinical trials that showed additional benefit of medications over and above being on the maximally tolerated dose of a statin," according to Dr Donald M. Lloyd-Jones, a professor at Northwestern University, Chicago and chair of the writing committee for the new guidance. "However, since 2013, a number of trials have been published that actually move the field forward in our understanding of which patients might benefit from adding nonstatin therapy on top of effective statin therapy."

The guidance was developed to address gaps in care until the guidelines can be updated, which will likely take a few years.

Based on findings from recent studies, including the IMPROVE IT trial, which examined ezetimibe as statin add-on therapy after acute coronary syndromes, the HPS2-THRIVE study, which examined use of niacin in high-risk patients, and short-term outcomes studies of PCSK9 inhibitors, which have been shown to dramatically reduce low-density lipoprotein cholesterol levels beyond the lowering provided by statin therapy, the committee developed algorithms for the four main high-risk statin benefit patient groups:

- Adults aged 21 years and older with clinical atherosclerotic cardiovascular disease (ASCVD), on statin for secondary prevention.
- Adults aged 21 years and older with LDL-C greater than or equal to 4.92 mmol/L not due to secondary modifiable causes, on statin for primary prevention.
- Adults aged 40–75 years without ASCVD but with diabetes and LDL-C of 1.81–4.9 mmol/L, on statin for primary prevention.
- Adults aged 40–75 years without clinical ASCVD or diabetes, with LDL-C of 1.81–4.9 mmol/L and an estimated 10-year risk for ASCVD of at least 7.5%, on statin for primary prevention.

The guidance suggests a number of steps to take with patients who fail to achieve treatment goals (such as addressing treatment adherence, intensifying lifestyle modifications, using a high-intensity stain, and evaluating for statin intolerance), and lists "clinician-patient discussion factors" to consider for each of a number of patient scenarios (including the potential benefits and risks associated with nonstatin therapies, as well as patient preferences).

Included for each of the patient scenarios is an algorithm for which nonstatin therapies to use in which order, building on the "rock-solid confidence" that for the four statin benefit groups, statins remain the starting point, Dr Lloyd-Jones said.

In general, ezetimibe for those patients who are not achieving the types of reduction in LDL or the amount of risk reduction desired, "should probably be the first choice," he said.

Bile acid sequestrants can be considered in those who are ezetimibe intolerant and who have triglycerides less than 3.39 mmol/L.

PCSK9 inhibitors are suggested for consideration only in very high-risk patients with ASCVD or with the familial hypercholesterolaemia phenotype who are still not achieving the goal (ideally, a 50% reduction in LDL cholesterol), he said.

The committee did not recommend use of niacin, stating that there is no clear indication for the routine use of niacin preparations as additional nonstatin therapies due to an unfavourable risk-benefit profile.

Additionally, PCSK9 inhibitors are not recommended in any primary prevention scenarios, he noted.

Dr Neil J. Stone, chair of the 2013 guideline writing committee, said the new guidance provides a useful tool for clinicians, extending, in a practical way, the current guideline as the field awaits the long-term outcomes data for PCSK9 inhibitors.

Despite some backlash in the wake of the 2013 guideline, which marked a move away from specific cholesterol treatment targets to a cardiovascular disease risk-based approach, the cardiovascular risk calculation formula introduced in that guideline has been shown to be useful and accurate, said Dr Stone, also of Northwestern University.

"[The new guidance] is simply an amplification and extension of the guideline," he said, adding that "it's about a risk discussion, not automatic treatment."

Dr Lloyd-Jones and Dr Stone each reported having no disclosures.

NEWS

Prepsychosis links with elevated metabolic syndrome

BY MITCHEL L. ZOLER
Frontline Medical News
At the European Congress of Psychiatry, Madrid

Untreated people at high risk for developing psychosis also showed an increased prevalence of certain components of metabolic syndrome in data collected from 163 German study participants, a finding that gives new insight into the well-documented but poorly delineated link between schizophrenia and metabolic syndrome.

"The findings point out that a high risk for schizophrenia implies a certain risk for patients to develop metabolic syndrome independent of treatment effects," said Dr Joachim Cordes, a psychiatrist at the LVR Clinic of the Heinrich-Heine University in Düsseldorf, Germany. He assumed that genetic factors underlie the shared risk some people face for both developing schizophrenia and metabolic syndrome. "I think there is a direct connection between schizophrenia and metabolic syndrome, an inherent factor like a genetic factor," Dr Cordes said in an interview. This understanding should influence how patients with newly diagnosed schizophrenia or those at risk for psychosis are managed, he added.

Dr Cordes's report was one of several at the meeting sponsored by the European Psychiatric Association that examined different facets of the complex links that tie schizophrenia to metabolic syndrome, an association that already had lots of evidence, including a recent meta-analysis (*Schizophr Bull* 2013 March;39[2]:306-18).

He used data collected on 163 people enrolled in the PREVENT study and at high risk for a first psychotic episode. Run at nine German centres, PREVENT primarily tested very early intervention with drug and behavioural therapy to improve outcomes. Dr Cordes took data collected from these prepsychosis, high-risk patients to assess their prevalence of metabolic syndrome and of the various individual features that define metabolic syndrome, using a definition published by the American Heart Association and the US National Heart, Lung, and Blood Institute (*Circulation* 2005 Oct 18;112[17]:2735–52). He compared these metabolic syndrome rates with the general German population, using data from 35,869 randomly selected German adults in more than 1500 German primary care practices, the German Metabolic and Cardiovascular Risk Project (GEMCAS).

The findings showed a 9.2% prevalence of metabolic syndrome in the prepsychosis group and a 7.4% rate among the general adult population, Dr Cordes reported. Among men in the prepsychosis group, the metabolic syndrome definers with the largest increments in prevalence were low HDL, in 21% of the prepsychosis people and in 12% of the general population, and elevated blood glucose in 11%, compared with 6%. Among women, the metabolic syndrome definers with the greatest between-group differences were elevated waist circumference, in 30% of those with prepsychosis, compared with 17% in the general population, and low HDL in 19%, compared with 14%.

This apparently inherent link between a tendency toward psychosis and schizophrenia and a tendency to develop features of metabolic syndrome suggests that patients with newly diagnosed schizophrenia need a preventive approach to weight management, Dr Cordes said. He also suggested prescribing antipsychotic medications that pose the lowest risk for causing further metabolic derangements in patients.

A second report at the meeting came from an assessment of cognitive function and its relationship to metabolic syndrome in 54 women diagnosed with schizophrenia and on stable treatment. The schizophrenia patients with metabolic syndrome, nearly half of the total group, performed significantly worse than those without metabolic syndrome in tests of verbal memory, executive function, and attention and processing speed, findings that support an increased incidence of selective cognitive impairment in patients with schizophrenia and metabolic syndrome, said Dr Adela C. Botis, a psychiatrist and researcher at the University of Medicine and Pharmacy in Cluj-Napoca, Romania.

Dr Botis and her associates studied 54 women diagnosed with schizophrenia who had remitted symptoms for at least 6 months on stable antipsychotic treatment. Using the metabolic syndrome definition of the International Diabetes Federation 25 (46%) had metabolic syndrome, and the other 29 (54%) did not. These numbers document the high prevalence of metabolic syndrome in schizophrenia patients.

A multivariate analysis identified demographic and metabolic factors that significantly linked with decrements in several cognitive domains. Economic status and living situation linked with deficits in verbal memory; elevated systolic blood pressure significantly linked with worsened attention and processing speed; high body mass index linked with loss of motor speed; and less education significantly linked with all these increments as well as four other domains.

A third report used a post-hoc analysis of data from two separate trials to show that treatment with a relatively new antipsychotic drug, lurasidone, produced less metabolic syndrome, compared with risperidone or extended-release quetiapine, said Dr Andrei Pikalov, head of global medical affairs at Sunovion Pharmaceuticals, the company that markets Latuda. Lurasidone received approval for treating schizophrenia in 2010.

He took data from two studies designed to assess lurasidone's efficacy for treating adults with schizophrenia for 12 months, compared with either risperidone in a study with 621 patients, or with quetiapine XR in a study with 292 patients. He applied the same metabolic syndrome definition used by Dr Cordes to clinical measurements taken at baseline and after 12 months on treatment.

The results showed that treatment with lurasidone produced less than half the rate of new metabolic syndrome cases, compared with risperidone, a statistically significant difference, and less than two-thirds the rate of quetiapine XR, a difference that did not reach statistical significance.

Dr Cordes said he has been a speaker for Servier. Dr Botis had no disclosures. Dr Pikalov is an employee of Sunovion, which markets lurasidone.

Early biopsy predicts levonorgestrel IUD response in endometrial cancer

BY M. ALEXANDER OTTO
Frontline Medical News
At the Annual Meeting on Women's Cancer, San Diego

Endometrial pathology findings at 3 months predicted response to levonorgestrel-releasing IUD treatment for complex atypical hyperplasia or grade 1 endometrial cancer at the MD Anderson Cancer Center in Houston.

Twenty-nine of 32 women (91%) who responded by 12 months showed stromal, glandular, or other endometrial changes indicating an effect at 3 months, vs only 3 of 9 nonresponders (33%) ($P < 0.001$). There were no differences in responders versus nonresponders in median age (47 vs 56 years, $P = 0.2$) or body mass index (45 vs 55 kg/m^2, $P = 0.16$).

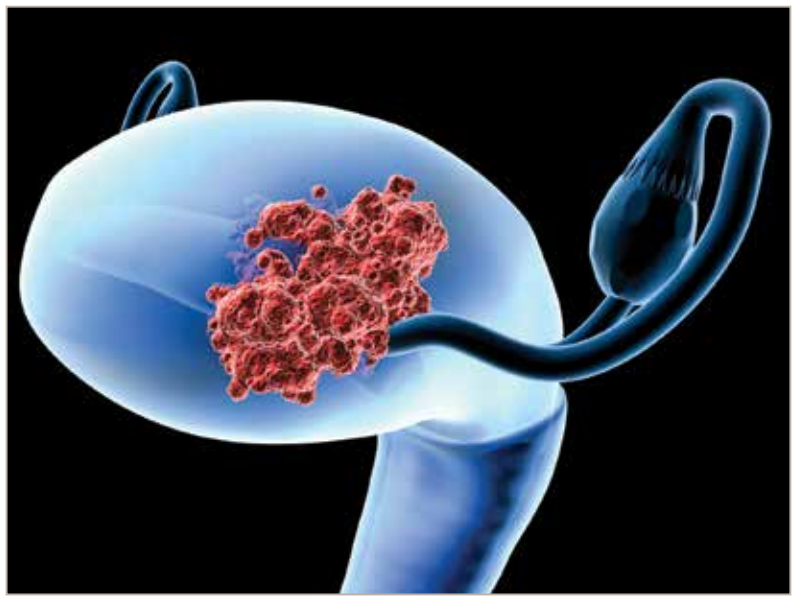
The finding addresses an "unmet need" for markers of response to levonorgestrel-releasing IUD therapy. "You can look at [early] pathology" and have an idea how patients will do, Dr Shannon Westin, a study investigator who is with the department of gynaecologic oncology at MD Anderson, said at the annual meeting of the Society of Gynecologic Oncology.

Twenty-seven of 29 women (93%) with complex atypical hyperplasia (CAH) responded completely to the IUD, meaning they had normal endometrium or hyperplasia without atypia at 12 months. The response rate for endometrial cancer was 67%; 7 of 12 women had a complete response, and an 8th was diagnosed at 12 months with CAH, indicating a partial response. The rest of the patients remained stable or progressed.

Endometrial biopsies were performed every 3 months; the team also did molecular testing on tumours from 20 patients. Baseline protein Ki67 – a marker of proliferation – was significantly higher in nonresponders. Expression of several oestrogen-induced genes was higher in responders.

Patients opted for the IUD to retain fertility or because obesity or comorbidities precluded surgery. Exclusion criteria included prior treatment for CAH or endometrial cancer, evidence of extrauterine spread, or levonorgestrel IUD contraindications, such as uterine infection.

Adverse events – primarily irregular bleeding and cramping – were mild and tended to resolve by 12 months. Treatment had little effect on measures of social, mental, and physical function. About half of the patients were white, a third were Hispanic, and most of the remaining patients were black.



There was no external funding for the work. Dr Westin is a consultant for AstraZeneca, Medivation, Roche, Ovation, and Vermillion, and reported receiving research funding from AstraZeneca, Critical Outcomes Technologies, and Novartis.

Bisphenol S promotes fat accumulation, differentiation

BY MARY ANN MOON
Frontline Medical News
From Endocrinology

Bisphenol S (BPS), commonly used as a "safe" substitute for bisphenol A (BPA) in the manufacturing of plastics and other consumer products, induces lipid accumulation in, and differentiation of, human preadipocytes, indicating that it may have adverse effects on the endocrine system, according to a report published online March 22 in *Endocrinology*.

The findings suggest that BPS is not a harmless substitute for BPA and that more thorough toxicologic and epidemiologic studies are warranted regarding its effects on human health, said Jonathan G. Boucher and his associates at the Environmental Health Science and Research Bureau, Health Canada, Ottawa.

BPS is a close analogue of BPA and has been detected in many products, including paper receipts, canned foods and drinks, epoxy resins, and baby bottles, as well as in environmental samples such as indoor dust. It is known to exhibit oestrogenic activity and was suspected of involvement in lipid processes that also entail hormonal cues from glucocorticoids and insulin.

In a series of laboratory analyses, the investigators examined the effects of BPS on primary human preadipocytes harvested from the hips, thighs, and abdomens of normal-weight female donors aged 25–57 years. They confirmed that BPS has oestrogenic effects. They also reported for the first time that, "similar to BPA, BPS increases adipogenesis in human preadipocytes" by almost twofold and induces adipocyte differentiation, primarily by activating the adipogenic transcription factor PPARG (peroxisome proliferator-activated receptor-gamma).

"Further study is required to better understand potential hazards of widespread BPS exposure. The few reports available now indicate that BPS can affect endocrine function, as demonstrated by studies showing decreased testosterone, androstenedione, and cortisol levels in ex vivo and in vitro models," the investigators noted (*Endocrinol* 2016 Mar 22. doi:10.1210/en.2015-1872) .

Adjuvant endocrine therapy for premenopausal breast cancer patients should be individualised

BY SUSAN LONDON
Frontline Medical News
From the Journal of Clinical Oncology

Oncologists should take an individualised approach when making decisions about adjuvant endocrine therapies for premenopausal hormone receptor-positive, HER2-negative early breast cancer, suggests an analysis of a pair of randomised phase III trials published online in the *Journal of Clinical Oncology.*

Investigators led by Meredith M. Regan, Sc.D., of Dana-Farber Cancer Institute in Boston, analysed data from the TEXT (Tamoxifen and Exemestane Trial) and SOFT (Suppression of Ovarian Function Trial) trials of adjuvant endocrine therapies, comprising a total of nearly 5000 women.

> **TEXT and SOFT demonstrated that premenopausal women with hormone receptor-positive disease benefit, on average, from exemestane plus OFS versus tamoxifen with or without OFS.**

Results suggested that the absolute improvement in the 5-year breast cancer-free interval rate with exemestane plus ovarian function suppression (OFS) versus tamoxifen with or without OFS ranged from less than 1% in women with a lowest recurrence risk based on clinicopathologic factors to 10–15% in women with a highest risk.

"TEXT and SOFT demonstrated that premenopausal women with hormone receptor-positive disease benefit, on average, from exemestane plus OFS versus tamoxifen with or without OFS. However, individualised treatment decisions should weigh the benefits against the adverse effects and costs of these therapy options," the investigators wrote.

"In the absence of predictive biomarkers, consideration of a patient's prognosis, as illustrated by STEPP [Subpopulation Treatment Effect Pattern Plot] analysis of a composite measure of recurrence risk in the TEXT and SOFT populations, is integral to this decision making," they added.

In the SOFT trial, women were randomised to 5 years of tamoxifen alone (as an active comparator), tamoxifen plus OFS, or exemestane plus OFS. In the TEXT trial, women were randomised to 5 years of exemestane plus OFS or of tamoxifen plus OFS.

Dr Regan and colleagues based their analyses on a total of 4891 women. They assessed each patient's composite recurrence risk from a Cox model that included a set of conventional clinicopathologic factors: age, nodal status, tumour sise and grade, and oestrogen receptor, progesterone receptor, and Ki-67 expression levels. And they used STEPP methodology to assess the impact of endocrine therapy across groups having different risk.

The median duration of follow-up was 5.6 years in the SOFT trial and 6 years in the TEXT trial. Results showed that the 5-year breast cancer-free interval rate was 90.8% for the study cohort as a whole. But it ranged considerably from 98.6% for patients with composite risk in the lowest quartile to 77.5% for patients with composite risk in the highest quartiles, the investigators reported (*J Clin Oncol* 2016. doi: 10.1200/JCO.2015.64.3171).

In the SOFT population, patients who remained premenopausal after neoadjuvant or adjuvant chemotherapy had an absolute improvement of 5% or more in the 5-year breast cancer-free interval rate with exemestane plus OFS, compared with tamoxifen plus OFS or tamoxifen alone. The difference was 10%-15% for the subset at intermediate to high risk for recurrence.

In addition, a benefit of tamoxifen plus OFS over tamoxifen alone was evident in patients having the highest composite risk.

Among patients who were not given chemotherapy, who on average had the lowest composite recurrence risk, the 5-year breast cancer–free interval rate was excellent regardless of the endocrine therapy received.

In the TEXT trial population, the benefit of exemestane plus OFS over tamoxifen plus OFS in 5-year breast cancer-free interval rate ranged from 5% to 15%. Again, the patients who were not given chemotherapy, who had the lowest composite recurrence risk, fared well regardless of which endocrine therapy they received.

These findings should help guide clinical decisions in premenopausal women with hormone receptor-positive, HER2-negative breast cancer, both at the extremes of risk and in the scenario of intermediate risk, where factors such as patient preference, tolerance, and cost play a greater role, according to the investigators.

"Further follow-up of TEXT and SOFT patients is essential to guide patient care," they concluded. ■

NEWS

Antisclerostin osteoporosis drugs might worsen or unmask rheumatoid arthritis

BY JEFF EVANS
Frontline Medical News
From Science Translational Medicine

Antisclerostin monoclonal antibodies have shown their ability to increase bone density in phase II and III trials of men and women with osteoporosis but could potentially have the opposite effect in patients with rheumatoid arthritis or other chronic inflammatory diseases in which tumour necrosis factor-alpha (TNF-alpha) plays an important role, according to new research.

The new work, conducted by Corinna Wehmeyer, Ph.D., of the Institute of Experimental Musculoskeletal Medicine at University Hospital Muenster (Germany) and her colleagues, shows that the bone formation-inhibiting protein sclerostin is not expressed in bone only, as was previously thought, but is also expressed on the synovial cells of patients with rheumatoid arthritis (RA).

Dr Wehmeyer and her associates were surprised to find that inhibiting sclerostin in a human TNF-alpha transgenic mouse model of RA actually accelerated joint damage rather than prevented it, suggesting that sclerostin actually had a protective role in the presence of chronic TNF-alpha-mediated inflammation. They confirmed this by demonstrating that sclerostin inhibited TNF-alpha signalling in fibroblast-like synoviocytes and showing that blocking sclerostin caused less or little worsening of bone erosions in mouse models of RA that are more dependent on a robust T and B cell response accompanied by high cytokine expression within the joint, rather than damage driven by TNF-alpha.

"These findings strongly suggest that in chronic TNF-alpha-mediated inflammation, sclerostin expression is upregulated as part of an attempt to reestablish bone homeostasis, where it exerts protective functions," the authors wrote (*Sci Transl Med* 2016 Mar 16;8:330ra34. doi: 10.1126/scitranslmed.aac4351).

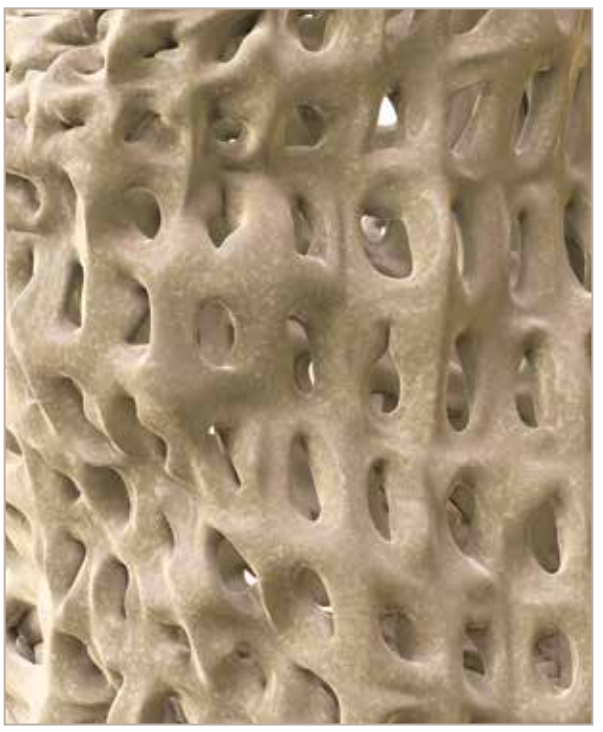
The research needs confirmation in humans with RA and potentially in other chronic inflammatory diseases in which TNF-alpha plays an important role. "Nevertheless, the preliminary data in three different models indicate that sclerostin antibody therapy could be contraindicated in patients with chronic TNF-alpha-dependent inflammatory conditions. The possibility of adverse pathological effects means that caution should be taken both when considering such treatment in RA or in patients with chronic TNF-alpha-dependent comorbidities. Thus, to translate these findings to patients, first strategies to use sclerostin inhibition should exclude inflammatory comorbidities and very thoroughly monitor inflammatory events in patients to which such therapies are applied," the researchers advised.

In an editorial, Dr Frank Rauch of McGill University, Montreal, and Dr Rick Adachi of the department of rheumatology at McMaster University, Hamilton, Ontario, wrote that antisclerostin "treatment might accelerate joint destruction, at least when the inflammatory process is not quelled first. Patients with established RA usually undergo anti-inflammatory treatment, and it is unclear whether sclerostin inactivation would be detrimental in this context. Mouse data suggest that antisclerostin treatment might bring about regression of bone erosions when combined with TNF-alpha inhibition. The new work mirrors the situation of patients who have unrecognised RA while on antisclerostin therapy or who develop RA while receiving this treatment" (*Sci Transl Med* 2016 Mar 16;8:330fs7. doi: 10.1126/scitranslmed.aaf4628).

Antisclerostin antibodies in trials

Trials of the antisclerostin monoclonal antibodies romosozumab and blosozumab have been successful in treating postmenopausal women and men with osteoporosis.

Romosozumab codevelopers UCB and Amgen reported that the biologic agent significantly reduced the rate of new vertebral fractures by 73% versus placebo at 12 months in the randomised, double-blind phase III FRAME (Fracture Study in Postmenopausal Women With Osteoporosis) study. In the 7180-patient trial, the reduction was 75% versus placebo at 24 months after both treatment groups had been transitioned to denosumab given every 6 months in the second year of treatment. Romosozumab also significantly lowered the relative risk of clinical fractures (composite of vertebral and nonvertebral fractures) by 36% at 12 months, but the difference was not statistically significant at 24 months.



In the initial 12-month treatment period, the most commonly reported adverse events in both arms (greater than 10%) were arthralgia, nasopharyngitis, and back pain. There were no differences in the proportions of patients who reported hearing loss or worsening of knee osteoarthritis. There were two positively adjudicated events of osteonecrosis of the jaw in the romosozumab treatment group, one after completing romosozumab dosing and the other after completing romosozumab treatment and receiving the initial dose of denosumab. There was one positively adjudicated event of atypical femoral fracture after 3 months of romosozumab treatment.

Phase III results from the 244-patient BRIDGE (Placebo-Controlled Study Evaluating the Efficacy and Safety of Romosozumab in Treating Men With Osteoporosis) trial found a significant increase in bone mineral density (BMD) at the lumbar spine at 12 months, which was the study's primary endpoint. Other significant increases in femoral neck and total hip BMD were detected at 12 months. Cardiovascular severe adverse events occurred in 4.9% of men on romosozumab and 2.5% on placebo, including death in 0.6% and 1.2%, respectively. At least 5% or more of patients who received romosozumab reported nasopharyngitis, back pain, hypertension, headache, and constipation. About 5% of patients who received romosozumab in each trial had injection-site reactions, most of which were mild.

A phase II trial of blosozumab in 120 postmenopausal women with low bone mineral density (mean lumbar spine T-score –2.8) showed that the drug increased BMD in the lumbar spine by 17.7% above baseline at 52 weeks, femoral neck by 8.4%, and total hip by 6.2%, compared with decreases of 1.6%, 0.6%, and 0.7%, respectively, with placebo (*J Bone Miner Res* 2015 Feb;30[2]:216–24). However, mild injection-site reactions were reported by up to 40% of women taking blosozumab, and 35% developed antidrug antibodies after exposure to blosozumab. Eli Lilly, its developer, is looking at possible ways to reformulate the drug before it moves to phase III.

The study in Science Translational Medicine was supported by the German Research Foundation. The authors had no competing interests to disclose.

STAMPEDE: Metabolic surgery bests medical therapy long term

BY SHARON WORCESTER
Frontline Medical News
At ACC16, Chicago

The superiority of metabolic surgery over intensive medical therapy for achieving glycaemic control in patients with type 2 diabetes was largely maintained at the final 5-year follow-up evaluation in the randomised, controlled STAMPEDE trial.

The 150 subjects, who had "fairly severe diabetes" with an average disease duration of 8 years, were randomised to receive intensive medical therapy alone, or intensive medical therapy with Roux-en-Y gastric bypass surgery or sleeve gastrectomy surgery. The primary endpoint of haemoglobin A_{1c} less than 0.06 was achieved in 5%, 29%, and 23% of patients in the groups, respectively. The difference was statistically significant in favour of both types of surgery, Dr Philip Raymond Schauer reported at the annual meeting of the American College of Cardiology.

Furthermore, patients in the surgery groups fared better than those in the intensive medical therapy group on several other measures, including disease remission (defied as HbA_{1c} less than 6% without diabetes medication), HbA_{1c} less than 0.07 (the American Diabetes Association target for therapy), change in fasting plasma glucose from baseline, and changes in high- and low-density lipoprotein cholesterol levels, said Dr Schauer, director of the Cleveland Clinic Bariatric and Metabolic Institute.

Patients in the surgery groups also experienced a significantly greater reduction in the use of antihypertensive medications and lipid-lowering agents, he added.

The "very dramatic drop" in HbA1c seen early on in the surgical patients was, for the most part, sustained out to 5 years, he said.

The results for both surgeries were significantly better than those for intensive medical therapy, but the results with gastric bypass were more effective at 5 years than were those for sleeve gastrectomy, he added, noting that the surgery patients had better quality of life, compared with the intensive medical therapy patients.

As for adverse events in the surgery groups, no perioperative deaths occurred, and while there were some surgical complications, none resulted in long-term disability, Dr Schauer said.

Anaemia was more common in the surgery patients, but was fairly mild. The most common complication was weight gain in 20% of patients, and the overall reoperation rate was 7%.

Of note, patients in the study had body mass index ranging from 27 to 43 kg/m^2, and those with BMI less than 35 had similar benefits as those with more severe obesity. This is important, as many insurance companies won't cover metabolic surgery for patients with BMI less than 35, he explained.

These findings represent the longest follow-up to date comparing the efficacy of the two most common metabolic surgery procedures with medical treatment of type 2 diabetes for maintaining glycaemic control or reducing end-organ complications. Three-year outcomes of STAMPEDE (Surgical Treatment and Medications Potentially Eradicate Diabetes Efficiently) were reported in 2014 (*N Engl J Med* 2014;370:2002–13).

The participants ranged in age from 20 to 60 years. The average HbA_{1c} was about 0.09, the average BMI was 36, and most were on at least three antidiabetic medications at baseline. Half were on insulin.

The findings are important, because of the roughly 25 million Americans with type 2 diabetes, only about half have good glycaemic control on their current medical treatment strategies, Dr Schauer said.

Though limited by the single-centre study design, the STAMPEDE findings show that metabolic surgery is more effective long term than intensive medical therapy in patients with uncontrolled type 2 diabetes and should be considered a treatment option in this population, he concluded, adding that multicentre studies would be helpful for determining the generalisability of the findings.

Dr Schauer reported receiving consulting fees/honoraria from Ethicon Endosurgery and The Medicines Company, and having ownership interest in Surgical Excellence.

Among hospitalised patients with diabetes, 25% have undiagnosed diabetic retinopathy

BY SHANNON AYMES
Frontline Medical News
From BMJ Diabetes Research and Care

The prevalence of undiagnosed diabetic retinopathy was 25% and that of sight-threatening diabetic retinopathy was 19% of an inpatient population of patients with diabetes, compared with the general population; researchers identified several barriers to ophthalmic care.

Diabetic retinopathy and sight-threatening diabetic retinopathy are estimated at a prevalence of 28.5% and 4.4%, respectively. In contrast, there is little research in to the prevalence of undiagnosed diabetic retinopathy or sight-threatening diabetic retinopathy in higher risk inpatients.

Dr Jessica Kovarik, who at the time of this research was with the UPMC Eye Center at the University of Pittsburgh, and her associates sought to identify the prevalence of undiagnosed diabetic retinopathy among inpatients with established diabetes as well as barriers to diabetic retinopathy examinations and treatment.

They conducted a cross-sectional analysis of diabetic patients admitted to an urban teaching hospital in Pittsburgh. Digital funduscopic images were obtained to determine the presence and severity of diabetic retinopathy and macular oedema. Questionnaires assessed barriers to ophthalmic examinations and demographics (*BMJ Open Diab Res Care* 2016;4:e000164 [doi: 10.1136/bmjdrc-2015-000164]).

In total, 113 patients were eligible and 5 were excluded from analysis of diabetic retinopathy prevalence due to an inability to take images or poor-quality images.

Among the patients, 61 were women, 83 were white, and 34 were aged 50–60 years. Most had health insurance (89%) and an ophthalmologist (64%), and most understood that diabetic retinopathy affects vision (91%). Further, patients reported a history of type 2 diabetes (96%), hypertension (85%), hyperlipidaemia (68%), renal disease (25%), peripheral vascular disease (55%), and coronary artery disease (52%).

Among those who had not had a dilated funduscopic examination within a year, barriers to screening examination included transportation issues, physical disability, too many appointments or being too sick, cost, lack of time or priority, or no visual impairment. Forty percent reported having an eye examination within the year and 5% reported never having an eye examination.

> Most inpatients in our population (91%) are aware of the ocular complications of diabetes, and many (64%) do have ophthalmologists, yet only a minority (40%) of patients are getting the recommended standard of care screening examinations.

The investigators identified 7 patients with clinically significant macular oedema (6%), 13 with proliferative diabetic retinopathy (12%), and 1 with severe (1%), 14 with moderate (13%), and 16 with mild nonproliferative diabetic retinopathy (15%). Overall, 44% of the patients had diabetic retinopathy, with 25% previously undiagnosed. Further, sight-threatening diabetic retinopathy was found in 19%, with 3.7% previously undiagnosed.

Finally, after multivariable analysis, a longer duration of diabetes (odds ratio, 1.08 per year; 95% confidence interval, 1.014–1.147; P = 0.017) and renal disease (OR, 3.86; 95% CI, 1.22–12.27; P = 0.022) was associated with diabetic retinopathy. Further, of the 17 patients admitted with osteomyelitis or a nonhealing diabetic ulcer, 15 (88.2%) had diabetic retinopathy.

"Curiously, most inpatients in our population (91%) are aware of the ocular complications of diabetes, and many (64%) do have ophthalmologists (more than any other subspecialty listed), yet only a minority (40%) of patients are getting the recommended standard of care screening examinations. Barriers that are unique to this high-risk population may explain this disparity," the authors wrote.

The study was funded by the National Institutes of Health, Eye and Ear Foundation of Pittsburgh, Clinical and Translational Science Institute, the University of Pittsburgh, and a grant from Research to Prevent Blindness. One of the researchers, Dr Jann Johnston, reported speaking for Medtronic, Lilly, and Sanofi.

New analysis bolsters metformin as first line in type 2 diabetes

BY WILLIAM PERLMAN
Frontline Medical News
From Annals of Internal Medicine

Patients with type 2 diabetes treated with metformin as a monotherapy are at a decreased risk for cardiovascular mortality when compared with those on sulfonylurea monotherapy, according to a report in the *Annals of Internal Medicine*.

Dr Nisa M. Maruthur and her associates conducted an update of a previous systematic literature review and meta-analysis to assess the comparative effectiveness and safety of metformin monotherapy and combination therapies including metformin with nonmetformin monotherapies in patients with type 2 diabetes. They focused on original, adult human experimental, and observational studies (*Ann Intern Med* 2016 Apr 19. doi: 10.7326/M15-2650).

Dr Maruthur and colleagues identified a total of 19,423 articles, of which 234 were found to meet the study inclusion criteria. The majority of the included studies were randomised, controlled trials, with 98 assessing all-cause mortality and macro- and microvascular outcomes.

On the basis of consistent findings from two randomised, controlled trials including 3199 total participants (ADOPT and SPREAD-DIMCAD), a lower risk for cardiovascular mortality was found for metformin monotherapy versus sulfonylurea monotherapy. For those on metformin monotherapy, 2 of the 1454 patients had a fatal MI and 7 of 156 patients died from cardiovascular disease. Three of 1441 patients on monotherapy with a sulfonylurea had a fatal MI and 11 of 148 patients died from cardiovascular disease.

The evidence from this systematic review supports current type 2 diabetes guidelines that recommend metformin as the first-line agent to treat adults, based on its beneficial effects on haemoglobin A_{1c}, weight, and cardiovascular mortality versus sulfonylureas, as well as its relative safety profile, Dr Maruthur of the department of medicine and epidemiology at Johns Hopkins University, Baltimore, and her coinvestigators said.

The study was funded by Agency for Healthcare Research and Quality. Several of the coauthors disclosed contracts with the funding source during the conduct of the study. The remaining coauthors disclosed no conflicts of interest.

Incretin-based diabetes drugs don't raise heart failure risk

BY MARY ANN MOON
Frontline Medical News
From the New England Journal of Medicine

Incretin-based antidiabetic drugs didn't raise the risk of hospitalisation for heart failure in an international observational study involving 1.5 million patients reported online March 24 in the *New England Journal of Medicine*.

The safety of dipeptidyl peptidase 4 (DPP-4) inhibitors such as sitagliptin, saxagliptin, and linagliptin, and of glucagon-like peptide–1 (GLP-1) analogues such as exenatide and liraglutide is controversial. Some clinical trials have reported these agents raise the risk of heart failure (HF) while others have found no increase in risk, but all of the studies are underpowered to settle the question, said Kristian B. Filion, Ph.D., of McGill University and the Center for Clinical Epidemiology, Lady Davis Research Institute, Jewish General Hospital, and his associates.

> Incretin-based drugs were not associated with an increased rate of hospitalisation for HF when compared with other antidiabetic drugs (hazard ratio, 0.82) among the roughly 1.4 million patients who had no history of HF at baseline.

They examined this issue by analysing data from several large cohorts of diabetes patients treated in routine clinical practice in the United States, Canada, and England. Their study population comprised 1,499,650 adults who began taking noninsulin antidiabetic drugs at or after the date that incretin-based agents entered the market. "With 3.2 million person-years of observations, we had the statistical power to robustly assess this important drug safety issue," the investigators said.

Patients taking DPP-4 inhibitors and GLP-1 analogues were compared with those taking non–incretin-based drugs such as biguanides, sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, meglitinides, and sodium-glucose cotransporter-2 inhibitors. A total of 29,741 patients were hospitalised for HF, for an overall rate of 9.2 events per 1000 person-years.

Incretin-based drugs were not associated with an increased rate of hospitalisation for HF when compared with other antidiabetic drugs (hazard ratio, 0.82) among the roughly 1.4 million patients who had no history of HF at baseline. Individually, neither DPP-4 inhibitors (HR, 0.84) nor GLP-1 analogues (HR, 0.95) were associated with an increased risk of hospitalisation for HF. These findings remained consistent through several subgroup and sensitivity analyses that categorised the data according to duration of exposure, presence or absence of a history of MI, and duration of diabetes, Dr Filion and his associates said (*N Engl J Med* 2016 Mar 24. doi: 10.1056/NEJMoa1506115).

Similarly, incretin-based drugs were not associated with an increased rate of hospitalisation for HF when compared with other antidiabetic drugs among the approximately 80,000 patients who had a history of HF at baseline (HR, 0.86).

This study was supported by the Canadian Institutes of Health Research and the Quebec Foundation for Health Research. Dr Filion reported having no relevant financial disclosures; some of his associates reported ties to numerous industry sources.

DIABETES

Poor physical fitness upped diabetes risk regardless of weight

BY AMY KARON
Frontline Medical News
From Annals of Internal Medicine

Young, out-of-shape men were about three times more likely than physically fit men to develop type 2 diabetes later in life, even if their body weight was normal, reported the authors of a large registry study.

"These findings suggest that interventions to improve aerobic and muscle fitness levels early in life could help reduce risk for type 2 diabetes mellitus in adulthood," Dr Casey Crump, at the Icahn School of Medicine at Mount Sinai, New York, and his associates wrote in a study published online March 7 in *Annals of Internal Medicine*.

Future longitudinal studies of physical fitness could help identify "windows of susceptibility" and the best preventive measures, the researchers added.

A sedentary lifestyle is known to increase the risk of type 2 diabetes, but less is known about how physical fitness affects risk.

To explore the question, the researchers identified 1,534,425 men without baseline diabetes who underwent military conscription physical examinations between 1969 and 1997. They tracked the men until up to 62 years of age by analysing both the Swedish Hospital Registry and the Swedish Outpatient Registry (*Ann Intern Med* 2016 Mar 8; doi: 10.7326/M15-2002).

In all, 34,008 men developed type 2 diabetes over 39.4 million years of follow-up, the investigators said. Both low cardiorespiratory fitness and low muscle strength independently increased the risk for type 2 diabetes, regardless of whether the men had a high or normal body weight.

Moreover, the combination of low cardiorespiratory fitness and poor muscular fitness increased type 2 diabetes risk threefold (adjusted hazard ratio, 3.07; 95% confidence interval, 2.88 to 3.27; $P < 0.001$), with a positive additive interaction ($P < 0.001$).

Accounting for smoking lowered the associations between poor baseline fitness and type 2 diabetes by about 9%; but they remained significant ($P < 0.001$), suggesting that unmeasured confounding "had little influence on our main findings," the investigators said. If the associations are causal, then aerobic conditioning programs targeting men with low muscle strength might have the greatest public health impact, they added.

The US National Institutes of Health, the Swedish Research Council, and Region Skåne/Lund University funded the study. The researchers had no disclosures.

Endocrinology Conference 2016

MAY

13–15 May | Sunshine Coast, Australia
Endocrine Society of Australia (ESA) Seminar 2016
www.esaseminar.org.au

25–29 May | Orlando, Florida, USA
The American Association of AACE Annual Scientific Meeting
www.rheumatology.org/Education

28–31 May | Munich, Germany
2016 European Congress of Endocrinology
www.ece2016.org

JUNE

10–14 June | New Orleans, Louisiana, USA
76th Scientific Sessions of the American Diabetes Association
http://professional.diabetes.org/meeting

AUGUST

19–21 August | Surfers Paradise, Australia
The Endocrine Society of Australia: Clinical Weekend
www.esaclinicalweekend.org.au

21–24 August | Gold coast, Australia
The Endocrine Society of Australia & Society of Reproductive Biology Combined Annual Scientific Meeting
www.esa-srb.org.au

24–26 August | Gold coast, Australia
Australian Diabetes Society/Australian Diabetes Educators Association Annual Scientific Meeting
www.ads-adea.org.au

SEPTEMBER

3–6 September | Copenhagen, Denmark
Annual Meeting of the European Thyroid Association
www.eurothyroid.com/events

10–12 September | Paris, France
55th Annual ESPE Meeting 2016
www.espe2016.org

OCTOBER

31 October –4 November | New Orleans, Louisiana, USA
The Obesity Society: Annual Scientific Meeting
www.obesity.org/meetings/obesity-week

NOVEMBER

7–9 November | Brighton, UK
Society for Endocrinology BES 2016
www.endocrinology.org/meetings/2016

Ticagrelor cuts post-MI events in diabetes patients

BY MITCHEL L. ZOLER
Frontline Medical News
AT ACC16 in Chicago

The benefit from dual-antiplatelet therapy in high-risk patients following a myocardial infarction was especially apparent in post-MI patients with diabetes in a prespecified secondary analysis from a multicentre trial of ticagrelor with more than 21,000 patients.

Among post-MI patients with diabetes, treatment with ticagrelor plus aspirin led to an absolute 1.5% reduction in the rate of cardiovascular death, MI, or stroke during a median 33-month follow-up, compared with an absolute 1.1% cut in patients without diabetes, Dr Deepak L. Bhatt said at the annual meeting of the American College of Cardiology. The relative risk reduction, compared with placebo was 16% in both the diabetes and no diabetes subgroups, statistically significant differences in both subgroups.

"Long-term treatment with ticagrelor reduced the composite of cardiovascular death, MI, or stroke in patients with diabetes with a greater absolute risk reduction than in nondiabetic patients," said Dr Bhatt, professor of medicine at Harvard Medical School and executive director of Interventional Cardiovascular Programs at Brigham and Women's Hospital in Boston. Treatment with ticagrelor plus aspirin in post-MI patients with diabetes also led to an increased number of major bleeding episodes, compared with patients on aspirin alone, but no excess of intracerebral haemorrhages or fatal bleeds, he noted.

This finding of a significant benefit from ticagrelor in post-MI patients with diabetes confirms similar, prior findings with other antiplatelet drugs (including clopidogrel, prasugrel, and vorapaxar) and prior findings with ticagrelor, Dr Bhatt noted.

The new analysis used data collected in the Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial. The primary results from PEGASUS-TIMI 54 had shown that adding ticagrelor to aspirin treatment of high-risk post-MI patients, including those who both had or did not have diabetes, significantly cut the composite rate of cardiovascular death, MI, and stroke, compared with aspirin alone (*N Engl J Med* 2015 May 7;372[19]:1791-800). The study group included 6806 patients with diabetes (type 2 diabetes in 99% of these patients), and 14,355 without diabetes. All patients had their MI 1–3 years before entering the study.

Dr Bhatt and his associates examined the incidence of the various clinical endpoints measured in the study among only the patients with diabetes divided into those who received any dosage of ticagrelor (60 mg b.i.d. or 90 mg b.i.d.) or placebo, and also among the patients without diabetes. In addition to the primary endpoint, the new analysis showed that the rate of cardiovascular death during follow-up was 3.9% in the diabetes patients on dual therapy and 5.0% among the diabetes patients on aspirin only, a 22% relative risk reduction with ticagrelor added that was statistically significant. In contrast, among patients without diabetes the rates of cardiovascular death between those on and not on ticagrelor only differed by 0.2%, a 9% relative risk reduction that was not statistically significant. The same pattern occurred for the endpoint of death from coronary artery disease.

Concurrent with Dr Bhatt's report, the results appeared in an article published online (*J Am Coll Cardiol* 2016 Apr; doi: 10.1016/S0735-1097[16]30023-7).

A new study, THEMIS, is examining the safety and efficacy of combined ticagrelor and aspirin treatment in a lower-risk group of patients with diabetes, those with coronary artery disease who have not had a prior MI. Those results may be available in 2018.

PEGASUS-TIMI 54 was sponsored by AstraZeneca, the company that markets ticagrelor. Dr Bhatt has been an advisor to Cardax and Regado Biosciences and has received research support from AstraZeneca and several other companies.

Diabetes duration, depression linked in elderly men

BY LUCAS FRANKI
Frontline Medical News
From Maturitas

A longer duration of diabetes is associated with a greater risk of depression in men aged 70–89, according to Dr Osvaldo P. Almeida and associates.

In their sample of 5462 elderly men, 932 had diabetes, and 976 had current or past depression. Of those with diabetes, 215 had current or past depression. The odds ratio of diabetic men ever being depressed was 1.49, and the OR of current depression was 1.94.

The association between depression and diabetes duration was J shaped, with ORs of 1.92 for those with less than 10 years of diabetes history, 1.56 for those with 10–19.9 years of diabetes, 2.49 for those with 20–29.9 years of diabetes, and 3.13 for those with more than 30 years of diabetes.

Frailty was a very significant predictor of depression in diabetic men, but it accounted for about 15% of the association between diabetes and depression, the investigators noted.

"The severity of comorbidity may also play a role, and this could explain why the association between diabetes and depression becomes more obvious during the later stages of illness. Sufficiently powered prospective studies with prolonged follow-up, limited attrition, and robust measures of comorbidity should provide greater certainty about the true nature of these associations," the investigators concluded.

Find the study in *Maturitas* (doi: 10.1016/j.maturitas.2016.01.003).

Once-daily Levemir® in children and adolescents with type 1 diabetes[1,2]

A unique study examining the effect of basal insulin analogue choice on clinical outcomes in children and adolescents with newly diagnosed type 1 diabetes[2]

A retrospective chart review of 94 children and adolescents from a US diabetes clinic has shown that once-daily Levemir® achieves similar levels of glycaemic control as once-daily insulin glargine (100 U/mL) in the first year after diagnosis of type 1 diabetes.[2]

Standard practice in the clinic was to administer basal insulin once-daily; twice-daily dosing was used in only 3 subjects (2/38 with insulin glargine and 1/56 with Levemir®).† All subjects treated with Levemir® used NovoRapid® as their bolus insulin.[2]

Choice of basal insulin analogue not a predictor of glycaemic control at 1 year[2]

The study's primary outcome was the examination of factors associated with achieving goal HbA_{1c} (<7.5%) at 12 months after diagnosis. Variables analysed included type of basal insulin prescribed, gender, age, insurance coverage, type of rapid-acting insulin, ethnicity, BMI, set or flexible dosing, insulin dose, hypothyroidism or diabetic ketoacidosis (DKA) at diagnosis, diabetes education factors, frequency of monitoring, HbA_{1c} at diagnosis, and the person administering injections.[2]

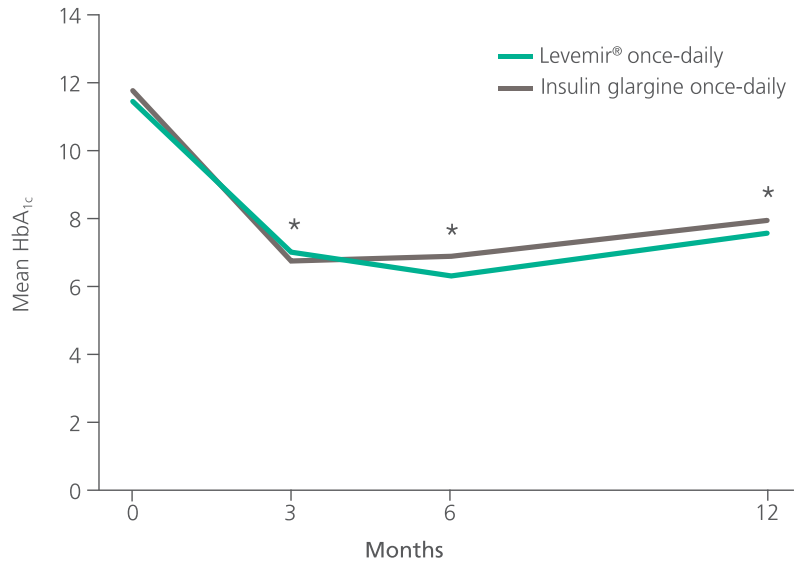
Mean age was 10.1 and 10.9 years in the Levemir® and insulin glargine groups, respectively.[2]

HbA_{1c} levels were collected at 0, 3, 6 and 12 months. HbA_{1c} at baseline was the only significant predictor of achievement of goal HbA_{1c}, and only at 3 months (p=0.002).[2]

Similar HbA_{1c} reductions with once-daily Levemir® *versus* once-daily insulin glargine[2]

At 12 months, there was no significant difference in the number of patients achieving HbA_{1c} goal with Levemir® versus insulin glargine (55% *vs* 42%, respectively; p=0.207).[2] Secondary endpoints included change in HbA_{1c} and number of cases of severe hypoglycaemia and DKA.

Once-daily Levemir® achieved similar HbA_{1c} reductions to once-daily insulin glargine (100 U/mL)[2]*



*NS=not significant, Levemir® *vs* insulin glargine.[2]

Adapted from Garrison *et al*, 2014.[2]

Too few episodes of severe hypoglycaemia or diabetic ketoacidosis occurred for statistical analysis in this study.[2]

Conclusions

Once-daily Levemir® provides similar levels of glycaemic control as once-daily insulin glargine in the first 12 months after diagnosis of type 1 diabetes in children and adolescents.[2]

When initiating Levemir® and NovoRapid® basal-bolus therapy in newly diagnosed patients, start with once-daily‡ Levemir® (at breakfast, evening meal or bedtime) and use NovoRapid® with each meal.[1,3]

†Insulin glargine is TGA-approved for once-daily use only.[4] Levemir® is TGA-approved for once-daily or twice-daily dosing.[1]

‡Some patients may benefit from twice-daily basal dosing depending on their needs.[1]

Levemir® and NovoRapid® basal-bolus insulin therapy is approved for patients at every life stage from age 2 years to adulthood, including pregnancy[1,3]

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My type of treatment[1,3]

For PBS information refer to the Primary advertisement. Please review the Product Information before prescribing. The Product Information is available on page 5 of this journal, or can be accessed at www.novonordisk.com.au.

References: 1. Levemir® Approved Product Information (Oct 2013). 2. Garrison RM, *et al.* Influence of the type of basal insulin and other variables on clinical outcomes in children with newly diagnosed type 1 diabetes. *Pediatr* 2014; 2014: 758343. 3. NovoRapid® Approved Product Information (Jul 2014). 4. Insulin glargine (100 U/mL) Approved Product Information (Aug 2015). 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. ® Registered trademark of Novo Nordisk A/S. AU/LM/1115/0289d. INK2552-02_CEN. March 2016.

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CONFERENCE COVERAGE

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With over 9000 attendees, nearly 3000 abstracts and over 200 other sessions, ENDO2016 is the leading global meeting on endocrinology research and clinical care. **Frontline Medical News** reporters share all the highlights of this meeting.

T2D patients on combination therapy benefit in switch from sitagliptin to liraglutide

BY BRIAN HOYLE

Switching from sitagliptin to liraglutide, in combination with metformin, improved control of hypoglycaemia and resulted in greater weight loss in patients with type 2 diabetes, reported Dr Maximo Maislos at the annual meeting of the Endocrine Society.

Results of a randomised, double-blind, double-dummy, active-controlled 26-week trial have indicated that liraglutide can be used as an add-on to metformin for patients with type 2 diabetes who have remained hyperglycaemic.

"Switching from sitagliptin to liraglutide resulted in superior [glycated haemoglobin] and body weight reductions, compared with continued sitagliptin treatment," said Dr Maximo Maislos of Ben-Gurion University, Beer-Sheva, Israel.

The LIRA-SWITCH trial (Efficacy and Safety of Switching From Sitagliptin to Liraglutide in Subjects With Type 2 Diabetes Not Achieving Adequate Glycaemic Control on Sitagliptin and Metformin) involved 407 patients. The majority (60%) were male; mean age was 56 years and mean body mass index was 32 kg/m^2. The subjects had all been treated with sitagliptin (100 mg/day) and metformin (greater than or equal to 1500 mg/day or a maximum tolerated dose greater than or equal to 1000 mg/day) for at least 90 days. Hyperglycaemia had not been well controlled, with a mean haemoglobin A_{1C} (HbA_{IC}) level of 0.08. The mean duration of type 2 diabetes was 8 years.

Subjects were randomised to continued sitagliptin along with metformin (n = 204) or liraglutide (1.8 mg daily) along with metformin (n = 203).

After 26 weeks of treatment, reduction in HbA_{IC} was significantly greater in the liraglutide arm than in the sitagliptin arm (0.014 vs 0.005%; estimated treatment difference [ETD], –0.006 95% confidence interval, –0.008 to –0.004; P < 0.0001). Those receiving liraglutide had statistically significantly greater weight loss, compared with those who continued on sitagliptin.

> Switching from sitagliptin to liraglutide resulted in superior [glycated haemoglobin] and body weight reductions, compared with continued sitagliptin treatment.

The less than 0.07 and less than or equal to 0.06 target levels of HbA_{IC} were achieved by 50.6% and 29.5%, respectively, of patients in the liraglutide arm. These percentages were significantly higher than the respective 26.9% and 9.9% of patients in the sitagliptin arm (P < 0.0001 for both). Fasting plasma glucose levels were significantly reduced with liraglutide treatment while decreases in systolic and diastolic blood pressure were similar in the two study arms.

Adverse events (AEs) occurred more often in the liraglutide group than in the sitagliptin group (68.8% vs 56.9%). Thirteen patients receiving liraglutide discontinued treatment, compared with five in the sitagliptin arm. The most common AEs in the liraglutide group were gastrointestinal disorders, principally nausea (21.8% with liraglutide vs 7.8% with sitagliptin) and diarrhoea (16.3% with liraglutide vs 9.3% with sitagliptin), followed by decreased appetite (8.9% vs 3.4%, respectively). These AEs tended to subside within the first few weeks of treatment.

Serious AEs occurred in eight patients in both arms. Rescue medication was needed for 30 patients receiving sitagliptin and 11 patients receiving liraglutide. No cases of pancreatitis were reported. In the sitagliptin group, one subject each developed bladder cancer and squamous cell carcinoma. Nocturnal hypoglycaemia did not develop in either trial arm.

Funding was provided by liraglutide maker Novo Nordisk. Dr Maislos had no disclosures.

Proactive endocrine screening urged for paediatric brain tumour survivors

BY M. ALEXANDER OTTO

More than a third of 419 children treated for brain tumours at Cincinnati Children's Hospital Medical Center later developed endocrine problems, according to a review presented at the Endocrine Society annual meeting.

Over 60% of the 96 suprasellar tumour patients developed endocrine dysfunction, which isn't surprising considering the location of the tumour, but wide-ranging endocrine problems were also common in the 145 posterior fossa, 158 supratentorial, and 20 spinal cord cases, ranging from 14% in the spinal cord group to 42% in the posterior fossa group, after some combination of radiation, chemotherapy, and surgery based on tumour location and other factors.

"Even with tumours that aren't supposed to be high risk, there was a high risk of endocrinopathies. We need yearly screening of these patients" for about 6 years, after which symptom-based screening may be sufficient. The clock should be restarted if there's a recurrence. "Not everyone does this" at Cincinnati Children's and probably most other institutions, said investigator and endocrinology fellow Dr Vincent Horne.

The findings are "changing how our oncology department is thinking about [screening]; there's a concentrated effort to increase proactive screening and follow these patients long term," he said.

"Even within our specialised, multidisciplinary centre," endocrinopathy screening referrals were low, about 61% overall and only 80% in the suprasellar group. "Patients at highest risk" – those with craniopharyngioma – "are being seen early by us," but others aren't being referred. It's possible that the extent of endocrine problems after paediatric brain tumour treatment is simply unrecognised, he said.

Endocrine abnormalities were found in 114 (45%) of the 254 patients evaluated, which translated to problems in more than a third of all patients.

More than half of the children had more than one problem, and most of the issues occurred within 6 years of treatment. Central hypothyroidism was found in 53% of the children, probably because Cincinnati Children's already has thyroid screening in place.

About 40% were growth hormone deficient, and almost a third had precocious puberty. About 30% were gonadotropin-releasing hormone deficient, over 20% had primary hypothyroidism, and about the same had diabetes insipidus. Just over 6% were hyperprolactinaemic.

Of the 151 patients who completed adrenocorticotropic hormone (ACTH) testing, 14.6% were deficient. ACTH deficient children were about evenly split between the suprasellar and supratentorial groups, with the remaining in the posterior fossa cohort.

"We are probably not thinking about" the risk of radiation "to locations like the posterior fossa. That group actually had the highest risk of primary hypothyroidism [20%] because of the spinal radiation. The supratentorial group is also receiving radiation; even though we think we are missing the hypothalamus, obviously that's not necessarily the case," Dr Horne said.

His team looked into endocrine screening because previous studies "were limited and done years ago." People are living longer now after treatment, "so we need to think about how to screen for endocrine disease. This is an attempt to clarify how we should do it," he said.

Children were a median of 8 years old at diagnosis, and the median radiation dose was 54 Gy.

There was no industry funding for the work, and the investigators had no disclosures.

VIEW VIDEO

Childhood obesity predicted by infant BMI

BY M. ALEXANDER OTTO

Infants above the 85th percentile for body mass index at 6 months are up to nine times more likely to be severely obese by the age of 6, according to a Cincinnati Children's Hospital investigation.

The finding means that paediatricians should routinely plot and follow body mass index (BMI) from an early age, just like height, weight, and head circumference, said investigator Dr Allison Smego, an endocrinology fellow.

She and her colleagues reviewed the charts from birth to age 6 of 783 lean children and 480 children above the 99th BMI percentile. BMI started differentiating when children were as young as 4 months old, about a year and half before the onset of clinical obesity. The predictive value of the 85th percentile threshold held at 6, 12, and 18 months. The finding was subsequently validated in over 2600 children.

In an interview at the annual meeting of the Endocrine Society, Dr Smego explained the findings.

Faster aspart speeds onset of activity in Type 1 diabetes

BY BRIAN HOYLE

A new formulation of faster-acting insulin aspart (faster aspart) provided more rapid and extensive glucose-lowering activity than did standard insulin aspart, based on results of a randomised, double-blind, crossover study presented at the annual meeting of the Endocrine Society.

Subcutaneous injections of faster aspart of 0.1 (low dose), 0.2 (moderate dose), and 0.4 (high dose) U/kg were associated with an onset of activity that was twice as fast as that of standard insulin aspart and with insulin exposure that was two-fold higher in the first 30 minutes, said Dr Tim Heise, CEO of finance and administration for Profil Institute for Metabolic Research, Neuss, "Faster aspart was well tolerated, and no safety issues were identified. No injection site infections were observed, and no serious adverse events were reported," said Dr Heise.

Faster aspart consists of insulin aspart along with niacinamide as an absorption modifier and L-arginine as a stabiliser. The aim of a faster-acting mealtime insulin is to mimic more closely the physiologic mealtime insulin response of the healthy pancreas.

What has not been clear is whether the benefits of faster aspart are concentration-dependent and whether the effective concentrations are clinically relevant.

The pharmacokinetic and pharmacodynamic properties of faster aspart were tested at three clinically relevant doses in 46 adults, aged 18 to 64 years, with type 1 diabetes. Study participants had been treated for a year or more with multiple daily injections of insulin or continuous subcutaneous insulin injection; their total insulin dose was less than 1.2 U/kg/day with less than 0.7 U/kg/day as a bolus dose. Body mass index ranged from about 19 to 28 kg/m2. Of the subjects, 76% were men, all were white, and they had diabetes for about 21 years.

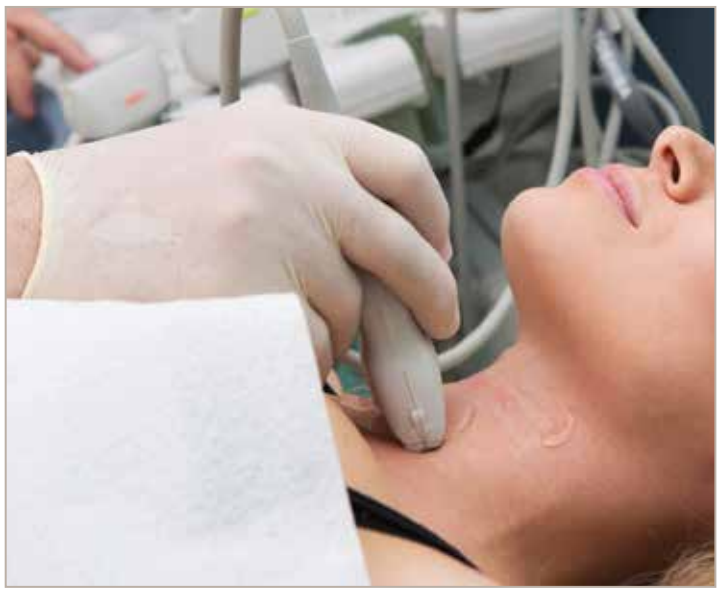
At all three doses, onset of activity was about twice as rapid with faster aspart as with standard insulin aspart; 50% of the maximum exposure to the dose was achieved in 8 to 12 minutes with faster aspart. This rapid appearance of activity was especially evident within 30 minutes of injection, with the kinetics becoming more similar to those of standard insulin aspart from 30 to 60 minutes.

Blood glucose was lowered by 0.3 mmol/L from baseline at a rate up to 26% faster with faster aspart. Similar to the exposure data, glucose reduction was especially evident in the first 30 minutes following injection of faster aspart, with the decline in glucose levels being about twice as great compared to insulin aspart.

Further information from a phase 3 study evaluating faster aspart will be reported at the American Diabetes Association meeting to be held this summer, according to Dr Heise.

Low thyroid function increases odds of type 2 diabetes

BY BRIAN HOYLE



Results of a population-based study involving more than 8000 adults from the Netherlands who were diabetes free at baseline has implicated low thyroid function with a 13% increased likelihood of developing type 2 diabetes, and up to 40% higher in individuals with prediabetes.

The heightened risk exists even for individuals with subclinical hypothyroidism, in whom thyroid-stimulating hormone (TSH) in the blood is still in the normal concentration range.

"These findings suggest we should consider screening people with prediabetes for low thyroid function," Dr Layal Chaker of Erasmus Medical Center, Rotterdam, the Netherlands, said at the annual meeting of the Endocrine Society.

Thyroid screening is recommended for patients with type 1 diabetes, since they are at increased risk of thyroid disease. An association between thyroid dysfunction in the form of hypothyroidism and type 2 diabetes has been surmised, since type 2 diabetes and hypothyroidism tend to be more prevalent in older adults, and since hypothyroidism has been linked with weight gain and reduced sensitivity to insulin.

To further study the link between thyroid function and diabetes, Dr Chaker and her colleagues studied data from 8452 participants aged 45 years and above (mean age 62 years, 58% female) from the Rotterdam Study, a prospective, longitudinal cohort study in the Ommoord district of Rotterdam that was undertaken to investigate the risk factors of cardiovascular, neurological, ophthalmologic, and endocrine diseases in the elderly. The cohort was considered representative of the general population in the Netherlands. All participants had blood tests to measure blood glucose, TSH, and free thyroxine (FT4). Normal blood glucose was considered to be under 5.9 mmol/L, prediabetes as over 5.9 to less than 7.0 mmol/L glucose, and diabetes as above 7.0 mmol/L.

Prediabetes and type 2 diabetes developed in 1100 and 798 subjects, respectively, during a mean follow-up of 7.9 years. Higher TSH levels increased the risk of development of type 2 diabetes risk (hazard ratio [HR] 1.13, 95% confidence interval [CI], 1.08-1.18, per logTSH). This risk held even for subjects whose TSH levels were at the lower end of the reference range of thyroid function (HR 1.24, CI, 1.06–1.45). The risk of diabetes was reduced in subjects with FT4 levels that were elevated (HR 0.96, CI, 0.93–0.99, per pmol/L) and for those whose FT4 levels were in the reference range (HR 0.96, CI, 0.92–0.99). Low thyroid function, even within the normal range, was associated with a 1.4 times risk of progression from prediabetes to type 2 diabetes (P = 0.002).

"Low and, surprisingly, low-normal thyroid function are risk factors for incident diabetes, especially in individuals with prediabetes," said Dr Chaker.

The data point to the need to clarify whether screening for and treatment of subclinical hypothyroidism can help curb the development of diabetes, she added.

Dr Chaker had no disclosures.

Early predictors of GDM identified in women with PCOS

BY BRIAN HOYLE

A prospective cohort study of women with polycystic ovarian syndrome who developed gestational diabetes mellitus during pregnancy has implicated fasting blood glucose, non-high density lipoprotein, and sex hormone-binding globulin as significant predictive factors for the development of GDM.

"Polycystic ovarian syndrome [PCOS] is the most common reproductive disorder in women of reproductive age and is commonly associated with metabolic disorders including diabetes and obesity. In women with GDM, a history of PCOS is associated with higher incidence of complications and postpregnancy glucose intolerance. Risk factors during early pregnancy in women with PCOS for development of GDM have not been well characterised," said Dr Wenyu Huang of Northwestern University, Chicago.

To provide some clarity, Dr Huang and his colleagues conducted a prospective cohort study. Inclusion criteria were age 18–45 years, diagnosis of PCOS prior to conception, singlet pregnancy, and enrolment during the first trimester. Preexisting chronic disease including diabetes, hypertension, and thyroid, kidney, or cardiovascular disease was grounds for exclusion. The findings were presented at the annual meeting of the Endocrine Society.

The 248 women with PCOS enrolled from 2011 to 2013 from a screened population of 25,000 pregnant women were followed from their first prenatal visit (before week 18) to delivery. Blood was collected at the first visit for analysis of metabolic hormones. A 75-g oral glucose tolerance test (OGTT) was carried out at week 24–28 and diagnosis of GDM was according to 2013 American Diabetes Association OGTT criteria.

Of the 248 women, 75 (30.2%) developed GDM, and 173 (69.8%) women had normal OGTT results. Examination over the same time period early in pregnancy revealed a higher incidence of GDM in women with PCOS.

In a univariate analysis, PCOS patients who developed GDM had higher fasting blood glucose (FBG), Homeostasis Model Assessment-Insulin resistance (HOMA-IR) score, total cholesterol, low-density lipoprotein cholesterol, non-HDL cholesterol, systolic and diastolic blood pressures, and free testosterone index. These patients also had lower levels of sex hormone–binding globulin (SHBG) and higher likelihood of family history of diabetes and earlier delivery.

Multiple logistic regression revealed associations between increased incidence of GDM and FBG greater than or equal to 4.86 mmol/L, non-HDL cholesterol greater than or equal to 2.84 mmol/L, and SHBG greater than or equal to 222 nmol/L. The predictive power of the three factors for the development of GDM in PCOS was relatively strong.

Future studies could aim to validate the prediction model and clarify the pathogenic basis of GDM in PCOS women, according to the researchers .

The study was funded by the Beijing Science Committee. Dr Huang had no disclosures.

More routine use of unilateral thyroidectomy advocated for papillary thyroid microcarcinoma

BY BRIAN HOYLE

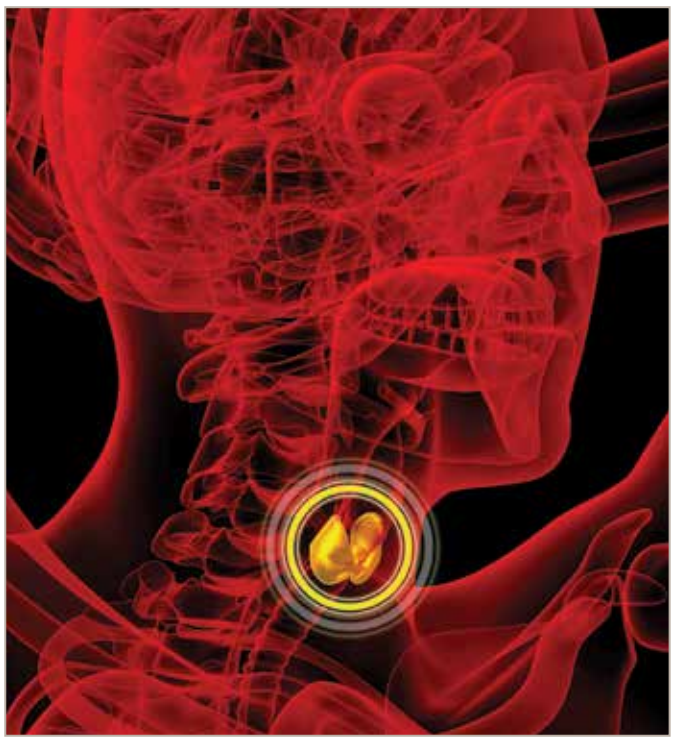
A study of over 60 years of patient data from the Mayo Clinic suggests a reconsideration of the routine use of unilateral thyroid lobectomy (UL) as the initial treatment for papillary thyroid microcarcinoma.

"Papillary thyroid microcarcinoma [PTM] patients have a normal life expectancy and typically are cured by adequate tumour resection. More than 99% of PTM patients are not at risk of either distant spread or mortality from cancer," said Dr Ian D. Hay of the Mayo Clinic, Rochester, Minnesota. Unilateral thyroid lobectomy is one treatment option for papillary thyroid microcarcinoma along with conventional bilateral nodal resection approaches of near-total thyroidectomy (NT) or total thyroidectomy (TT), or selective radioactive iodine remnant ablation (RRA).

Awareness of PTM is not new; examination of thyroid glands at autopsy going back decades has revealed their presence in 6%-36% of samples. A more recent development is the use of high-resolution ultrasound-guided biopsies of papillary thyroid carcinoma (PTC) lesions as small as 3 cm. For example, at the Mayo Clinic the diagnosis of PTM was about one annually from 1935 to 1944, while from 2005 to 2014 the average was close to one per day. "At Mayo, 34% of PTCs seen since 1995 are PTMs," Dr Hay said at the annual meeting of the Endocrine Society.

The best initial management of PTMs is disputed, with observation favoured by some, TT and RRA favoured by others, and ethanol ablation having been found to be effective by institutions including the Mayo Clinic. UL has been deemphasised, despite the 2015 American Thyroid Association Guidelines recommendation of UL as the usual surgical procedure for adults with PTM.

Dr Hay and his colleagues sought to provide some clarity to the issue by taking advantage of the institute's database of adult (18+ years) PTM patients who were consecutively treated from 1935 to 2014. The decades of data allowed a long-term look at patient outcomes. They examined data from 1345 patients, 954 women and 391 men with a median age at surgery of 48 years. The mean follow-up was 15.4 years, representing almost 21,000 patient years. Data on tumour recurrence and cause-specific mortality were derived from a data base of over 4300 PTC patients representing over 66,000 patient-years of observation.



Median tumour size was 7 mm (range, 0.08-1.0 cm). Extrathyroid invasion was evident in 18 (1.3%) cases and 298 tumours (26%) were multifocal. There were 399 (30%) node-positive tumours at diagnosis and 4 (0.3%) cases featuring initial distant metastases.

The mean MACIS (metastasis, age at presentation, completeness of surgical resection, invasion [extrathyroidal], size) score was 4.25 with little variation in score over time. Almost all (96%) patients had a MACIS score of under 6. Bilateral lobar resection was done in 1132 (95%) patients, with NT or TT comprising 80% of the cases. UL was done in only 202 (15%) cases. The use of TT skyrocketed from 3% of the cases done in the first 2 decades to 40% in the last 2 decades. Regional nodes were removed at surgery in 743 (55%) cases, either by "node picking" (23%) or compartmental dissection (32%).

Overall survival following surgery in PTM patients was similar to age- and gender-matched controls (397 deaths observed, 431 deaths expected; P = 0.16). Only four (0.3%) patients died of PTM. The rates of locoregional recurrence were similar for the unilateral and bilateral approaches (P = 0.90). In 1,148 patients with potentially curable PTM, defined as the absence of metastasis at diagnosis and no gross residual disease, the rates of tumour recurrence 10, 20, and 40 years after surgery were 6%, 7%, and 10%, respectively. In these 1148 patients, the 30-year locoregional recurrence rates after UL alone were similar to those seen after NT or TT followed by RRA (P = 0.99).

UL did not result in permanent unilateral vocal cord paresis or permanent hypoparathyroidism. These adversities were more likely to develop following bilateral lobectomy.

"Since [UL] produces comparable recurrence results when compared to bilateral surgery and is not associated with either cord paresis or hypoparathyroidism, then perhaps it is overdue for institutions like Mayo to individualise our treatment policies and more often employ UL when surgery, and not observation or ultrasound-guided percutaneous ethanol ablation, is chosen to treat PTM," said Dr Hay.

Dr Hay was adamant on the overuse of ultrasound in the detection of small-diameter carcinomas in the decision for bilateral surgery. "It's embarrassing how much we are wasting resources and doing too much ultrasound too often," he said in an interview.

Dr Hay had no disclosures.

Morning cortisol rules out adrenal insufficiency

BY M. ALEXANDER OTTO

A random morning serum cortisol above 306 nmol/L safely rules out adrenal insufficiency in both inpatients and outpatients, according to a review of 3300 adrenal insufficiency work-ups at the Edinburgh Centre for Endocrinology and Diabetes.

> **Basal serum cortisol as a screening test ... offers a convenient and accessible means of identifying patients who require further assessment.**

The finding could help eliminate the cost and hassle of unnecessary adrenocorticotropic hormone (ACTH) stimulation tests; the investigators estimated that the cut point would eliminate almost half of them without any ill effects. "You can be very confident that patients aren't insufficient if they are above that line," with more than 99% sensitivity. If they are below it, "they may be normal, and they may be abnormal." Below 49 nmol/L, adrenal insufficiency is almost certain, but between the cutoffs, ACTH stimulation is necessary, said lead investigator Dr Scott Mackenzie, a trainee at the centre.

In short, "basal serum cortisol as a screening test ... offers a convenient and accessible means of identifying patients who require further assessment," he said at the annual meeting of the Endocrine Society.

Similar cut points have been suggested by previous studies, but the Scottish investigation is the first to validate its findings both inside and outside of the hospital.

The team arrived at the 306 nmol/L morning cortisol cut point by comparing basal cortisol levels and synacthen results in 1628 outpatients. They predefined a sensitivity of more than 99% for adrenal sufficiency to avoid missing anyone with true disease. The cut point's predictive power was then validated in 875 outpatients and 797 inpatients. Morning basal cortisol levels proved superior to afternoon levels.

The investigators were thinking about cost-effectiveness, but they also wanted to increase screening. "We may be able to reduce the number of adrenal insufficiency cases we are missing because [primary care is] reluctant to send people to the clinic for synacthen tests" due to the cost and inconvenience. As with many locations in the United States, "our practice is to do [ACTH on] everyone." If there was "a quick and easy 9 am blood test" instead, it would help, Dr Mackenzie said.

Adrenal insufficiency was on the differential for a wide variety of reasons, including hypogonadism, pituitary issues, prolactinaemia, fatigue, hypoglycaemia, postural hypotension, and hyponatraemia. Most of the patients were middle aged, and they were about evenly split between men and women.

There was no outside funding for the work, and the investigators had no disclosures.

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Minimum Product Information. NovoMix® 30 (insulin aspart (rys)). Indication: Treatment of diabetes mellitus. **Contraindications:** Hypoglycaemia. Hypersensitivity to insulin aspart or excipients. **Precautions:** Inadequate dosing or discontinuation of treatment, especially in type 1 diabetes, 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. Do not use in insulin infusion pumps. No studies in children and adolescents under the age of 18. No clinical experience in pregnancy. 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. **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. NovoMix® 30 should be administered immediately before a meal, or when necessary after the start of a meal. Resuspend immediately before use. Discard the needle after each injection. Subcutaneous injection only. NovoMix® 30 must not be administered intravenously. (July 2014). **References: 1.** Liebl A *et al. Drugs* 2012; 72(11): 1495–520. **2.** Wu T *et al. Diabetes Ther* 2015; 6(3): 273–87. **3.** NovoMix® 30 Approved Product Information (Jul 2014). 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. ® Registered trademark of Novo Nordisk A/S. AU/NM/0316/0058. January 2016.

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Early oestrogen likely prevents bone fractures in Turner syndrome

BY M. ALEXANDER OTTO

The longer that oestrogen therapy is delayed in girls with Turner syndrome, the lower their bone density will be in subsequent years, based on results of a retrospective, cross-sectional study from Monash University, in Melbourne, Australia.

For every year after age 11 that Turner patients went without oestrogen – generally due to delayed initiation, but sometimes noncompliance – there was a significant reduction in bone mineral density in both the lumbar spine (Beta –0.582, $P < 0.001$) and femoral neck (Beta –0.383, $P = 0.008$).

Oestrogen deficiency and subsequent suboptimal bone mass accrual are known to contribute to the increased risk of osteoporosis in women with Turner syndrome, and about a doubling of the risk of fragility fractures, mostly of the forearm. About a third of the 76 women in the study had at least one fracture, explained investigator Dr Amanda Vincent, head of the Midlife Health and Menopause Program at Monash.

"Avoiding oestrogen deficiency is important to optimise bone health in Turner syndrome." It "depends on early diagnosis, age-appropriate pubertal induction, and optimisation of compliance," Dr Vincent said at the Endocrine Society annual meeting.

The median age of Turner syndrome diagnosis was 11 years, but oestrogen treatments didn't begin until a median age of 15. The women in the study were a median of about 30 years old, which means that they were adolescents at the time when oestrogen treatment was often delayed in the mistaken belief that growth hormone therapy would be more effective before puberty was induced.

It's now known that oestrogen replacement works synergistically with, and even potentiates, the effects of growth hormone. Current guidelines recommend pubertal induction by age 13 (*J Clin Endocrinol Metab* 2007 Jan;92(1):10–25).

> Avoiding oestrogen deficiency is important to optimise bone health in Turner syndrome.

The women had at least one dual-energy x-ray absorptiometry scan at Monash since 1998. Z-scores below –2, indicating low bone density, were found in the lumbar spines of about a quarter the subjects, and in the femoral necks of about 8%. Primary amenorrhoea and premature menopause, followed by vitamin D deficiency, were the most common risk factors for low bone mass. Almost 40% of the women reported non-continuous use of oestrogen. About half had undergone growth hormone therapy.

At a median height of 149 cm, the subjects were about 15 cm shorter than age-matched, healthy controls, and also had a slightly higher median body mass index of 25.6 kg/m^2. Lumbar spine bone area, bone mineral content, areal bone mineral density, and bone mineral apparent density were significantly lower in Turner syndrome patients. In the femoral neck, areal bone mineral density was significantly lower.

There was no relationship between bone markers and growth hormone use or Turner syndrome karyotype; the predominant karyotype was 45XO, but the study also included mosaic karyotypes.

The investigators had no disclosures.

Proposed revision of medullary thyroid cancer staging improves risk-stratification analysis

BY BRIAN HOYLE

An analysis of data from medullary thyroid cancer patients that partitioned the patients into groups with similar overall survival has spurred a rethink of the current American Joint Committee on Cancer (AJCC) staging system.

The results from researchers at Duke University, Durham, North Carolina, presented at the annual meeting of the Endocrine Society by Dr Mohamed Abdelgadir Adam, are timely, as the AJCC has embarked on a reconsideration of the staging of cancers, including medullary thyroid cancer (MTC), as part revisions for the eighth edition of the staging system.

"The existing AJCC staging system for MTC appears to be less than optimal in discriminating the risk of mortality among disease stage groups," said Dr Adam, who discussed the findings in a video interview.

MTC, a neuroendocrine tumour that affects C cells of the thyroid, comprises 3–5% of all cases of thyroid cancer and it can be a more aggressive disease than differentiated thyroid cancer. Yet the current AJCC MTC staging system has been extrapolated from differentiated thyroid cancer data.

"We sought to evaluate how well the current AJCC seventh edition stage groupings predict survival for patients with MTC, to suggest a possible staging revision to sharpen estimates of prognosis," said Dr Adam.

The researchers utilised the National Cancer Data Base, representing over 70% of incident cancer cases in the United States.

MTC patients who underwent thyroid surgery from 1998 to 2012 were identified. Patients with missing values for pathologic T, N, or M were excluded. The primary outcome in the 3315 patients was survival.

The researchers used a form of decision-tree analysis called recursive partitioning. In general, recursive partitioning is able to classify a population by splitting subjects into subgroups, each of which is homogeneous based on the particular outcome. In this study, the subgroup allocations were based on T, N, and M stages, with the outcome being overall survival. Kaplan-Meier and adjusted survival analyses enabled survival differences among the four subgroups (groups I, II, III and IV) to be explored.

The four groups were distinct in terms of survival time and allowed more accurate risk stratification. In particular, groups I and II were markedly better distinguished from one another than is the case with the current staging system. Survival differences across the stages were more distinct with the newly created T, N, and M groupings, compared with the current AJCC staging system.

After adjustment, survival differences across TNM groups were more distinct with the newly created TNM groupings (compared to subgroup I, hazard ratio of 3.06 for subgroup II; HR, 6.79 for III; and HR, 17.03 for IV), compared with the current AJCC staging (compared to stage I, HR, 1.45 for stage II; HR, 2.17 for III; and HR, 5.33 for IV).

"The AJCC is reevaluating all staging schemas, including MTC. The current AJCC staging system could be improved with the newly identified TNM groupings suggested here for more accurate patient risk stratification and possibly treatment selection," said Dr Adam.

Dr Adam had no disclosures.

Liraglutide acts on GLP-1 receptors to lessen desire for high-fat foods

BY BRIAN HOYLE

Two related studies of brain structure and the mechanism of the analog of glucagon-like peptide (GLP) hormone liraglutide indicate that the drug works to decrease reward-related activation of brain sites linked to desire for unhealthy foods in patients with type 2 diabetes.

"Our finding suggests that liraglutide may make people more attentive to what they are eating, particularly high-calories or high-fat foods," said study co-investigator Olivia Farr, PhD, of Beth Israel Deaconess Hospital and Harvard Medical School, Boston.

> This decreased activation means that individuals on liraglutide find highly desirable foods less attention-grabbing and less rewarding than they typically would without liraglutide.

Liraglutide, which has been approved for weight management for obese patients and those with type 2 diabetes, is known to promote weight loss, but the mechanism by which this occurs has not been fully understood. The investigators undertook two studies, one to examine human brains to identify GLP-1 receptors and the other to examine the impact liraglutide administration may have on neural responses to food cues in patients with type 2 diabetes.

Immunohistochemical examination of 22 human brain samples identified GLP-1 receptors in the hypothalamus, medulla oblongata, and parietal cortex. GLP-1 receptors have previously only been identified in animals. The findings support the role of the receptors in weight loss in patients on liraglutide.

The researchers then performed a second randomised, placebo-controlled, double-blind, cross-over study involving 18 adult patients with type 2 diabetes. The subjects received, in random order, injections of placebo or liraglutide. Liraglutide was titrated to 0.6 mg at visit 1, 1.2 mg at visit 2, and 1.8 mg at visit 3, which were a week apart, with the highest dose maintained in the 3 days between visits 3 and 4. The total period was 17 days. Visit 4 was an overnight stay followed by functional magnetic resonance imaging (fMRI). Then, after a 3-week washout period, the participants received the other treatment on the same schedule, with another fMRI scan.

During the fMRI, participants viewed images of different foods that had been determined in pre-trial testing to be generally perceived as desirable (typically cakes, pastries, fried food, and fast food) and undesirable (typically leafy greens, fruits, vegetables, and other low-calorie food). In addition, non-food images were shown to verify that the brain activation was driven by the food images. The regions of the brain that became active during inspection of the images were determined.

Liraglutide decreased activation of the parietal cortex in response to the highly desirable food images. Additionally, activation in the insula and putamen was reduced; these regions are involved in the brain's reward system. Increased perception of hunger and appetite by the participants when they viewed images of desirable foods correlated with increased activation of GLP-1 receptors in the parietal and visual cortices during liraglutide treatment. In participants experiencing nausea, decreased brain activation in the cingulate cortex was apparent. Hypothalamus-related activity was not evident.

"This decreased activation means that individuals on liraglutide find highly desirable foods less attention-grabbing and less rewarding than they typically would without liraglutide," said Dr Farr.

The researchers suggested that liraglutide could be suited for weight loss in those who opt for high-fat food as a means of pleasure. Further, the data point to a central mechanism contributing to or underlying effects of liraglutide on metabolism/weight loss.

The Harvard researchers are seeking to confirm the findings in a larger study using the 3-mg dose of liraglutide that has been approved for obesity. In addition, they will explore whether the brain response to liraglutide is a general phenomenon or whether individuals differ.

Dr Farr had no disclosures.

Weight cycling common following weight loss in obese individuals

BY BRIAN HOYLE

Examination of weight-loss patterns in over 177,000 people has revealed that, regardless of the initial 6-month weight loss, after 2 years the majority of patients become "cyclers," with periods of weight gain and loss rather than maintenance of the initial weight loss.

> Interventions that seek to maintain the weight conventionally are directed at dietary changes. But these modifications alone might not be enough to achieve and maintain weight loss.

"One-third of American adults are obese. In 2010, the cost of obesity and obesity-related comorbidities in the United States was estimated to be US$315.8 billion. Achieving and maintaining weight loss has proven to be difficult," said Joanna Huang, PharmD, senior manager of health economics and outcomes research at Novo Nordisk, Plainsboro, New Jersey, and lead investigator of the study presented at the annual meeting of the Endocrine Society.

The study examined the electronic records of about 178,000 obese patients whose weight loss had been by deliberate intent and not due to illness. The subjects were allocated into four groups based on the extent of weight loss in terms of body mass index (BMI) over 6 months: Those who remained stable and lost less than 5% (n = 151,902), those who lost 5–10% (modest loss; n = 16,637), those who lost 10–15% (moderate loss; n = 4035), and those who lost in excess of 15% (high loss; n = 5945).

The subjects who were at least 18 years of age at baseline (mean age 54–58 years), had at least one BMI measurement that was indicative of obesity (greater than or equal to 30 kg/m^2), with at least four BMI determinations done over at least 5 years. Subjects were mostly white (about 66% in all four groups) and mostly from the southern United States.

Regardless of the amount that the participants lost in the first 6 months, regain of 50% of more of body weight was common in the modest weight-loss group (40%) and moderate weight-loss group (36%), while only 19% of those in the high weight-loss group cycled back up in weight, reported study presenter Maral DerSarkissian, PhD, of the Analysis Group in Boston.

More than 73% and about 70% of those in the moderate and modest weight-loss group, respectively, experienced weight cycling within 2 years. In the stable and high weight-loss groups, the situation was somewhat more optimistic, with about 60% of participants cycling in weight within 2 years. Total regain of lost weight occurred in about 23%, 16%, and 7% of the modest, moderate, and high weight-loss group, respectively.

"Weight loss maintenance, even in the moderate and high weight-loss groups, is very difficult to achieve," said Dr Huang.

Interventions that seek to maintain the weight conventionally are directed at dietary changes. But, according to Dr DerSarkissian, "these modifications alone might not be enough to achieve and maintain weight loss."

Pharmacotherapy is another weight-loss option. The data indicated that only 2% of the participants were receiving weight-loss pharmacotherapy. Whether this figure is accurate is an open question, according to Dr Huang, since a lot of the data were compiled from physicians' notes. Since clinicians may not record weight-loss advice offered to their patients, the data base may well not reflect lifestyle interventions, including pharmacotherapy.

In addition, since the data captured only primary outpatient care, whether or not a patient ever had bariatric surgery was unknown. Other unrecorded factors that can influence weight over time included comorbidities, use of medications, diet changes, and changes in physical activity.

The data points to a multifactor approach to weight loss that includes counselling, positive reinforcement, dietary advice, pharmacotherapy where appropriate, and, in some cases, bariatric surgery.

"Successful and sustained clinically meaningful weight loss requires chronic and effective weight management strategies," said Dr Huang.

Dr Huang is an employee of Novo Nordisk and Dr DerSarkissian is a researcher for Novo Nordisk.

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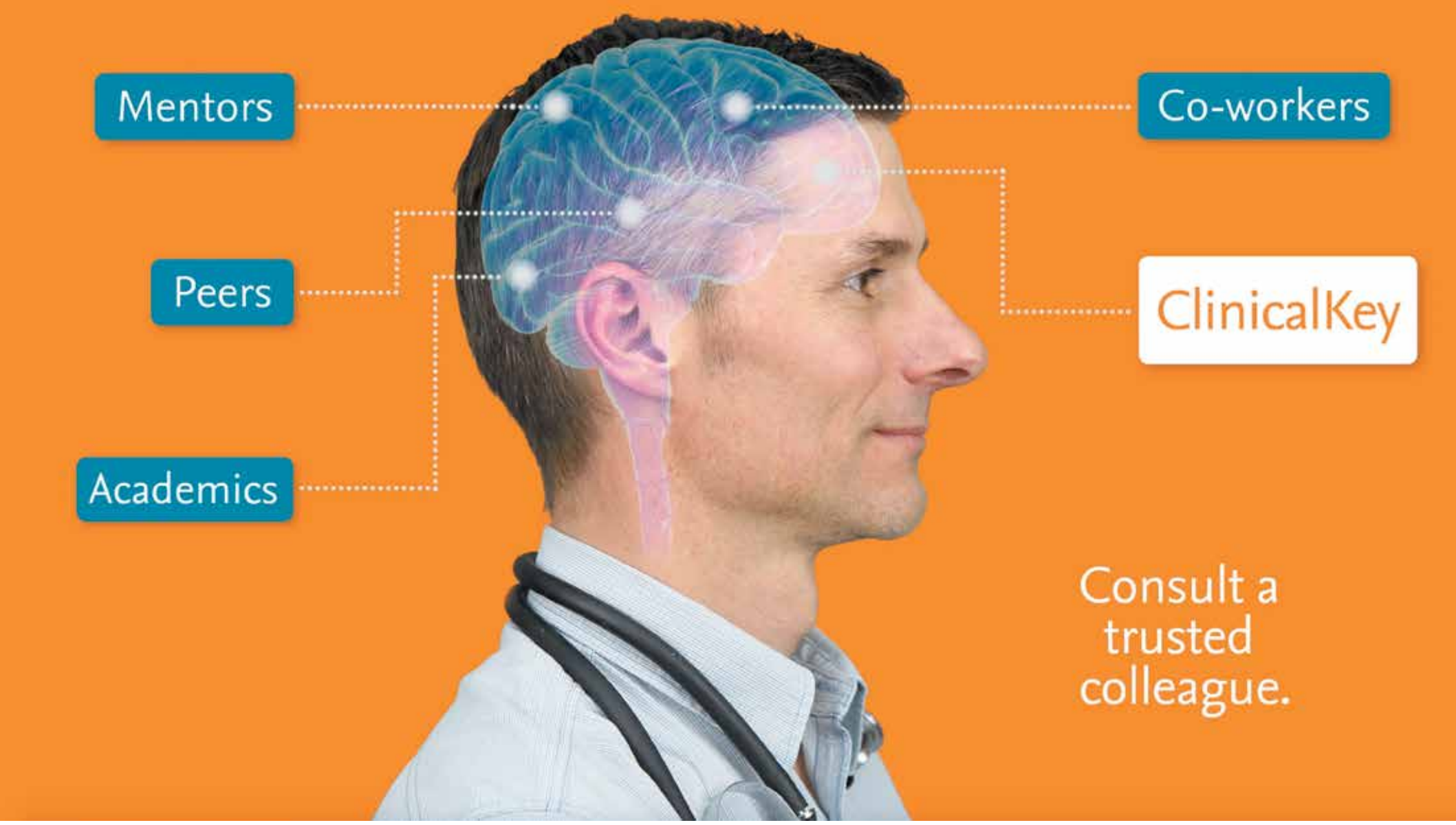

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