Among oral diabetes medications, only metformin appears possibly to be cardioprotective, and only rosiglitazone appears possibly to harm the cardiovascular system (CVS), according to a meta-analysis of 40 studies. Other oral diabetes agents appear to have no significant specific cardiovascular (CV) effects, positive or negative, according to the meta-analysis.

However, even these qualified findings on these drugs’ specific CV effects must be considered “inconclusive” because clinical studies of the issue have been too small, too short term, or too flawed to provide definitive answers, according to Elizabeth Selvin and her colleagues in the Arch. Intern. Med. 2008;168:2070-80).

Selvin et al performed the meta-analysis because the CV effects of oral diabetes medications are unclear and, in some cases, controversial. They identified only 40 randomised, controlled trials of these drugs that reported on CV events and CV mortality; most of these were not statistically powered to assess CV events and only two had follow-up for longer than 2 years. In general, there have been few trials of oral diabetes therapies that have lasted longer than 6 months, and reporting of CV events has been consistently “poor”.

Nevertheless, after pooling the results of the 40 studies, they found that metformin was associated with a statistically significant decrease in CV mortality, with an odds ratio of 0.74, compared with placebo or any other oral diabetes therapy.

In addition, when compared with any other diabetes agent or placebo, rosiglitazone was the only therapy associated with a possible increase in the risk of CV morbidity or mortality, but these results were not statistically significant.

“Larger, longer-term studies taken to hard end points and better reporting of CV events in short-term studies will be required to draw firm conclusions about major clinical benefits and risks related to oral diabetes agents.

In an editorial comment, David M. Nathan of Massachusetts General Hospital, Boston, said that this study adds to “the cottage industry of meta-analyses” and sheds some light on the issue. However, “in the end the conclusions drawn will be disappointing for health care practitioners who want a clear answer to the question, ‘Is it safe?’” (Arch. Intern. Med. 2008;168:2064-6).

Overall, the meta-analysis results are in accord with the current consensus algorithm, favouring the use of metformin and the sulphonylureas over thiazolidinediones and limiting the use of rosiglitazone because of its CV risks, commented Nathan.

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**Incretin Mimetics & Incretin Enhancers: In Brief**

The new incretin mimic exenatide and the incretin enhancer sitagliptin each have unique properties. Injections of exenatide were approved in 2005 in the USA as adjunctive therapy for patients who have type 2 diabetes. Orally administered sitagliptin was approved in 2006 for use as monotherapy or in combination with metformin or thiazolidinedione for patients with type 2 diabetes.

Incretin augments glucose-stimulated insulin secretion by intestinally-derived peptides. Exenatide and sitagliptin augment the incretin pathway, which appears to be attenuated in type 2 diabetes. The incretin effect is composed mainly of the peptides glucose-dependent insulinotropic polypeptide (GIP) and glucagon like peptide-1 (GLP-1), which normally get inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Exenatide is a GLP-1 receptor analogue that’s resistant to DPP-4 degradation and slows gastric emptying. Sitagliptin selectively inhibits DPP-4, giving the incretin enzymes a longer half-life to enhance their effects. We do not have long-term safety and efficacy data for these medications like we do with the other classes of medications for diabetes mellitus.
A meta-analysis has failed to clarify whether one drug is better than another when added to metformin in patients with type 2 diabetes.

Sulphonylureas and alpha-glucosidase inhibitors (and possibly glinides as well) appear to have about equal efficacy when used as add-ons to failed metformin monotherapy, Matteo Monami et al reported in their analysis of 27 clinical trials (Diabetes Res. Clin. Pract. 2008;79:196-203). On the other hand, thiazolidinediones appear to have a lesser effect on HbA1c at 6 months, although in the long term they may actually work better than insulin secretagogues.

Despite the fact that many patients with type 2 diabetes receiving metformin need additional treatments in order to reach an adequate metabolic control, the number of clinical trials assessing the effects of combined therapy with metformin and other agents in type 2 diabetes is surprisingly small, the investigators wrote. For this reason the result of the present meta-analysis should be considered with caution, as further evidence, if available, could affect the conclusions.

The investigators conducted their Medline search in January 2007, looking for randomised clinical trials in which metformin was associated with any one of a large number of add-on therapies. For their meta-analysis, they included only trials in which a hypoglycaemic agent was compared either with placebo or with another active drug in combination with metformin for at least 16 weeks. They excluded trials of ‘triple therapy’ that tested two or more drugs in combination with metformin.

The investigators identified 16 placebo-controlled trials and 11 trials in which two active treatments were compared. Among the placebo-controlled trials, five included sulphonylureas, five included alpha-glucosidase inhibitors, three included thiazolidinediones, two included glinides, and one included GLP-1 agonists. They were unable to identify trials involving pramlintide or DPP-IV inhibitors that met their inclusion criteria.

Combining trials for each class of drugs, sulphonylureas reduced HbA1c by an average of 0.85%, thiazolidinediones by 0.42%, and alpha-glucosidase inhibitors by 0.61%. After the researchers corrected for baseline HbA1c, the reduction obtained with sulphonylurea with respect to placebo was significantly greater than that of thiazolidinediones. On the other hand, there were no significant differences between sulphonylurea and alpha-glucosidase inhibitors or between alpha-glucosidase inhibitors and thiazolidinediones. Too few studies involving glinides and GLP-1 agonists prevented statistically valid comparisons with those agents.

Among the trials in which two active agents were compared, sulphonylureas were significantly superior to thiazolidinediones, with an overall difference between the two treatments of 0.17% in reducing HbA1c. There were no significant differences between sulphonylureas and insulin. Insulin regimens that were based on two administrations of biphasic insulin analogues were more effective than insulin glargine once a day, with an overall difference of 0.26% in reducing HbA1c. 

**INSULIN RESISTANCE THOUGHT TO PLAY ROLE IN BOTH LADA AND TYPE 2 DIABETES**

Insulin resistance may play a role in the pathogenesis of latent autoimmune diabetes in adults (LADA), reported Sofia Carlsson et al in Diabetologia 2007;50:55-8. In their population-based study, they found that increased age, BMI >30, and physical inactivity were equally significant risk factors for type 2 diabetes (T2DM) and for LADA. The association seen between these factors and LADA suggests a role for insulin resistance in the development of LADA. The researchers looked at incident cases of diabetes identified in two surveys conducted as part of the Nord-Trøndelag Health Study, a prospective, population-based study of all residents, aged 20+ years, of the Norwegian county. Similar surveys were conducted from 1984-1986 (baseline) and from 1995-1997 (follow-up). The surveys included a clinical exam and health and lifestyle questionnaires.

The first survey enrolled 76,885 subjects (90% of eligible population), and the second survey enrolled 65,258 subjects (71% of eligible population). Data were available for 38,800 men and women who participated in both surveys and were initially free of diabetes. Patients who reported diabetes only in the follow-up survey were referred to the clinic. They underwent measurements of FBG, C-peptide, and anti-GAD antibodies. Patients treated with insulin within 6 months of diagnosis and were either anti-GAD +ve or who had C-peptide levels < 150 pmol/L were classified as T1DM. Patients who were anti-GAD +ve and who had not been treated with insulin within 12 months of diagnosis were classified as having LADA. Patients who were anti-GAD –ve and had not been treated with insulin within 12 months of diagnosis were classified as having T2DM. During the 11-year period between the 1st and 2nd surveys, 18 patients developed T1DM, 81 developed LADA, and 738 developed T2DM. The risk of developing LADA or T2DM, but not T1DM, increased progressively with age. The relative risks of developing diabetes for subjects aged 65+, compared with 18-39-year age group, were 6.78 for type 2 diabetes and 5.62 for LADA. In addition, physical inactivity was associated with development of T2DM and LADA. A BMI > 30 was associated with significantly increased risks of LADA (RR 15.37) and T2DM (RR 15.0), but not of T1DM (RR 1.16). In this population, 70% of the cases of LADA could be attributed to overweight. If these results are confirmed in other populations, they imply that increasing rates of LADA can be expected to result from the current obesity epidemic and demographic transition.
"‘their relative as well as absolute effect on sexual activity is clinically favourable, with consistent statistical significance.’"

The analysis revealed that their effect may wane at low doses in patients with uncontrolled diabetes, and that higher doses may be required for this particular subgroup (Cochrane Database Syst. Rev. 2007 Jan. 24 [Epub doi:10.1002/14651858.CD002187.pub3]). Erectile dysfunction (ED) is a common complication of diabetes, with about half of men with diabetes experiencing ED at least once in the course of their disease. Different strategies have been tried to overcome this complication prior to PDE type 5 inhibitors, but none proved definitive.

The Cochrane reviewers analysed eight randomised controlled trials in which 976 men received a PDE-5 inhibitor and 741 received placebo for the treatment of ED. Overall, 80% of the participants had type 2 diabetes.

Six trials compared sildenafil with placebo at doses titrated between 25 mg and 100 mg. The other two trials compared tadalafl 10 mg and 20 mg with placebo, and vardenafl 10 mg and 20 mg with placebo. Patients used the medication no more than once daily for 10 days in one study, 16 weeks in one study, and 12 weeks in the remaining trials.

Five of eight trials included scores for Index of Erectile Function (IEF) questions 3 and 4 on frequency of penetration and maintaining an erection to complete intercourse. The weighted mean difference for the questions was 0.9 and 1.1 at the end of the study period, in favour of the intervention group.

In the seven trials that included scores for the IIEF erectile function domain, the weighted mean difference at the end of the study period was 6.6, in favour of the intervention group. The relative risk of answering "yes" to the question, ‘Did the treatment improve your erections?’ was 3.75 in the PDE-5 inhibitor arm, compared with the control arm. All eight trials asked the question. But the finding should be interpreted with caution because of significant heterogeneity between trials, wrote Moshe Vardi of the Lady Davis Carmel Medical Center, Haifa, Israel.

In four trials, men who took PDE-5 inhibitors had an average weighted mean difference of 26.7% more successful intercourse attempts than did control patients.

Headache was the most frequent adverse event, followed by flushing. In descending order of frequency, other symptoms reported were upper respiratory tract complaints and flu-like syndromes, dyspepsia, myalgia, abnormal vision, and back pain. The overall relative risk ratio for developing an adverse reaction was 4.8 in the treatment arm, compared with controls.

Mortality was not reported in any of the eight trials. Only one study reported treatment-related CV morbidity in the intervention arm. The 10 events recorded included 4 cases of chest pain, 2 of which were myocardial infarctions with documented ST elevation; 2 cases of congestive heart failure; and 2 cases of hypertension.

Further research is needed to assess the effects of PDE-5 inhibitors in women with diabetes and sexual dysfunction, in uncontrolled diabetic patients with ED, and on the CVS in patients with diabetes who are prone to coronary artery disease and may suffer silent ischaemia, the review noted.

The authors said it was unfortunate that no head-to-head comparisons among the three available PDE-5 inhibitors or between PDE-5 inhibitors and other treatment modalities were conducted, and they called for further research in these areas.

Simple Equation Links Haemoglobin A1c and Average Plasma Glucose

Data from an international trial have yielded a formula that accurately converts haemoglobin A1c values to estimated average blood glucose. The results of the A1c-Derived Average Glucose (ADAG) study, comprising glucose data from 643 diabetic and non-diabetic subjects from 10 centres around the world, provided this "simple, linear" equation to obtain glucose values in mmol/L: 1.583 × HbA1c - 2.52. Thus, an HbA1c of 6% is converted to approximately 7.0 mmol/l, 7% is converted to 8.6 mmol/l, and 8% is converted to 10.1 mmol/l. There's a linear correlation between the HbA1c and the calculated mean glucose over a wide range of A1c values. The results should apply to the majority of patients with diabetes, reported Robert Heine of Vrije University, Amsterdam, at the EASD. No need to pull out your calculator for every patient with diabetes, though. In August, a joint consensus statement from the EASD, the ADA, the IDF, and the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), advised that - pending the results from the ADAG study - clinical laboratories begin reporting both the HbA1c percentage and the ADAG, along with a third number, the "true" HbA1c value expressed in mmol/ml (Clin Chem. 2007; 53:1562-4 and Diabetes Care 2007;30:2399-400).

Clinically, this provides an opportunity to begin shifting discussions with patients away from HbA1c, and toward average glucose. The clinician can use one, two, or three values when communicating with the patient. The diabetes organisations would encourage physicians to use the estimated average glucose, said Richard Kahn. The reason, explained John Buse, is that ‘[The HbA1c] has always been confusing for patients. At home they measure their glucose, then every 3 months they get something that has the word ‘haemoglobin’ in it.’ In contrast, ‘The estimated average glucose is expressed in numbers that people are used to looking at all day every day,’ said Buse, director of the Diabetes Care Center at the University of North Carolina.
Physicians should offer bariatric surgery only to those adults who have a BMI of at least 40 kg/m² and are otherwise healthy, or 35 kg/m² if they have a complicating disease.

Weight loss below those thresholds as part of an intensified medical treatment before surgery is not a contraindication for surgery. In addition, surgery is indicated for those who've lost substantial amounts of weight in a conservative treatment program but later gained weight back, according to the guidelines, jointly issued by five medical societies and published online in the International Journal of Obesity.

Co-morbidities that qualify a patient with a BMI between 35-40 include metabolic disorders, cardio-respiratory disease, severe joint disease, or obesity-related psychological disorders. To qualify, patients should have failed to either lose weight or maintain weight loss without surgery, and must keep all medical appointments (Int. J. Obes. 2007 Feb. 27. [Epub doi:10.1038/sj.iijo.0803560]).

Contraindications for bariatric surgery include a life-threatening disease, no medical management of obesity, inability to participate in prolonged follow-up, substance abuse, lack of social support for the patient, or non-stabilised psychiatric disorders unless advised by a psychiatrist with expertise in treating obese patients.

The guidelines are supported by the International Federation for the Surgery of Obesity (IFSO), the IFSO European Chapter, the European Association for the Study of Obesity, and the International Obesity Task Force, which together formed the Bariatric Collaborative Scientific Group.

The document is based on a literature review of surgical studies published between 1980 and 2005, with evidence ranked using the Oxford Centre for Evidence-Based Medicine classification. For children and adolescents, bariatric surgery can be considered for children with BMI > 40 or at a percentile of 99.5 or greater for BMI for their age, according to the guidelines. It should be considered only if those patients have sought 6 months of specialised weight-reducing care, show skeletal and developmental maturity, will participate in comprehensive treatment before and after surgery, and have access to a surgical unit with specialised paediatric support.

For patients > 60 years, the objective of bariatric surgery is unlikely to extend life and should be performed to improve quality of life, according to the guidelines. For elderly patients, physicians should be able to demonstrate a favourable risk profile.

The document ranked specific procedures in decreasing order of average weight loss after surgery: biliopancreatic diversion with duodenal switch, nonadjustable gastric bypass, vertical banded gastropasty, and adjustable gastric banding. The complexity of the procedures, along with long-term metabolic risks, also decrease in that order.

After any bariatric surgery, patients should undergo follow-up care at interdisciplinary clinics for treatment of obesity, and should have access to 24-hour emergency service at the centre.

Physicians and other clinicians need to pay attention to nutritional deficiencies and adjust medical treatment for such co-morbidities as diabetes and hypertension during the period of rapid weight loss following a bariatric procedure, the document advised.

Metformin versus Insulin for the Treatment of Gestational Diabetes Mellitus (GDM)

**Background:** Metformin is a logical treatment for women with GDM, but randomised trials to assess the efficacy and safety of its use for this condition are lacking.

**Methods:** 751 women with GDM at 20 to 33 weeks of gestation were randomly assigned to open treatment with metformin (+ insulin if required) or insulin. The primary outcome was a composite of neonatal hypoglycaemia, respiratory distress, need for phototherapy, birth trauma, 5-minute APGAR score less than 7, or prematurity. The trial was designed to rule out a 33% increase (from 30-40%) in this composite outcome in infants of women treated with metformin as compared with those treated with insulin. Secondary outcomes included neonatal anthropometric measurements, maternal glycaemic control, maternal hypertensive complications, postpartum glucose tolerance, and acceptability of treatment.

**Results:** Of the 363 women assigned to metformin, 92.6% continued to receive metformin until delivery and 46.3% received supplemental insulin. The rate of the primary composite outcome was 32.0% in the group assigned to metformin and 32.2% in the insulin group (RR 1.00; 95% CI, 0.90 to 1.10). More women in the metformin group than in the insulin group stated that they would choose to receive their assigned treatment again (76.6% vs. 72.7%, P<0.001). There were no significant differences in rates of other secondary outcomes between the groups. There were no serious adverse events associated with the use of metformin.

**Conclusions:** In women with GDM, metformin (+ supplemental insulin) is not associated with increased perinatal complications as compared with insulin alone. The women preferred metformin to insulin treatment.

**Source:** NEJM 2008; 358:2003-20.15 May 8 2008 No.19