Variability in glycosylated haemoglobin (A1C) predicts the development of complications in patients with type 1 diabetes. "Consider not only the level of A1C, but also the A1C variability profile of a patient as a risk indicator of diabetic complications," stated Johan Waden from Helsinki University. "In our study, cardiovascular events were related to A1C variability but not to the actual A1C level."

Waden et al used data from the observational, longitudinal Finnish Diabetic Nephropathy (FinnDiane) Study to analyse the effect of both the mean A1C and the variability of A1C on the prediction of type 1 diabetes complications.

Complete data on renal status and serial measurements were available for 2107 patients, and data on cardiovascular disease events were available for 1845 patients.

The intrapersonal mean of serially measured A1C values was 8.5% with a variability (standard deviation) of 0.78, the authors report.

The variability in A1C increased according to baseline renal status, from 0.75 in patients with normoalbuminuria to 0.82 with microalbuminuria, 0.89 with macroalbuminuria, and 0.79 with end-stage renal disease.

A1C variability was significantly higher in patients who progressed to cardiovascular disease events (0.87) than in those who did not (0.79), the researchers note.

A1C variability was greater in all subgroups of patients who worsened in renal status, the investigators say, and the results were similar when coefficient of variation was used as the measure of A1C variability.

Higher A1C variability was associated with younger age, lower age at onset of diabetes, shorter duration of diabetes, lower insulin sensitivity, dyslipidaemia, higher baseline A1C, both current and ever smoking, lower socio-economic class, and lower leisure-time physical activity.

In multivariate models, the standard deviation of serial A1C measurements predicted progression in renal status and cardiovascular disease events independently of mean serial A1C.

"Our data include only patients with type 1 diabetes, and our findings are not necessarily applicable to type 2 diabetes," Waden cautioned. "Our data are purely observational, and the causal relationships have to be further studied."

"If A1C variability plays a role in the development of diabetic nephropathy, we would expect an association also with other microvascular diabetic complications (retinopathy and neuropathy) since the risk factor profile, especially the glycaemic control, is to a large extent similar to that of nephropathy," Waden said.

"We showed that patients with signs of a disadvantageous lifestyle (low socio-economic status, smoking, and low physical activity) had higher A1C variability," Waden added. "Other additional factors such as diet and psychosocial aspects would also be interesting to study. Infections may be implicated and this could also be further studied."

The American College of Physicians (ACP) has issued recommendations for the treatment of erectile dysfunction (ED), defined as the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance.

Evaluation and consideration of treatment are indicated when ED persists for at least 3 months.

The new clinical practice guidelines, which are published in Annals of Internal Medicine, advise therapy with an oral phosphodiesterase type 5 (PDE-5) inhibitor in the treatment of ED, unless they are receiving nitrate therapy or have another contraindication to use of PDE-5 inhibitors.

"The evidence is insufficient to compare the effectiveness or adverse effects of different PDE-5 inhibitors for the treatment of ED because of only a few head-to-head trials," Amir Qaseem said.

The guideline recommend that you prescribe a specific PDE-5 inhibitor, taking into account convenience and ease of use, medication costs, and safety effects profile. Available PDE-5 inhibitors include sildenafil, vardenafil, tadalafl, mirodenafil, and udenafil.

Because available evidence is inconclusive about the efficacy of hormonal therapy for ED in patients with low testosterone levels, the ACP does not recommend routine hormonal blood tests with ED. Measurement of hormone levels may be appropriate in specific patients. Clinicians should consider the presence of symptoms such as decreased libido, premature ejaculation, or fatigue, and of physical findings such as testicular or muscle atrophy, when considering whether to measure hormone levels in individual patients. Risk factors for ED include advanced age, diabetes, vascular diseases, psychiatric disorders, and possibly hypogonadism. World-wide prevalence of ED is high.

The review of evidence included information from 130 RCT’s of oral PDE-5 inhibitors used for ED as monotherapy or in combination. The authors identified these trials published between May 2007 and April 2009.

Regardless of the cause of ED, treatment with a PDE-5 inhibitor was associated with statistically significant and clinically meaningful improvements in sexual intercourse and in ED.

For sildenafil and vardenafil, improvement related to higher doses, but this was not true for tadalafl. Higher doses were also linked to a higher risk for adverse effects. Adverse effects included headaches, flushing, dyspepsia, rhinorrhoea, visual disturbances, myalgia, nausea, diarrhoea, vomiting, dizziness, and chest pain. Priapism was reported infrequently. PDE-5 inhibitors did not differ significantly in the incidence of adverse events. The incidence for serious adverse events was less than 2%, and did not differ between PDE-5 inhibitors and placebo.

Evidence regarding efficacy of hormonal therapy for ED was inconclusive because trials comparing testosterone vs. placebo in hypogonadal men with ED were small.

Specific recommendations in this clinical practice guideline, and their accompanying level of evidence rating, are as follows:

1. The ACP recommends that clinicians begin treatment with a PDE-5 inhibitor in men who seek treatment of ED and who have no contraindication to use of PDE-5 inhibitors (grade: strong recommendation; high-quality evidence).

2. The ACP recommends that clinicians choose a specific PDE-5 inhibitor based on the individual preferences of men with ED, considering ease of use, cost of medication, and adverse effects profile (grade: weak recommendation; low-quality evidence).

3. The ACP does not recommend for or against routine use of hormonal blood tests or hormonal therapy for patients with ED (grade: insufficient evidence to determine net benefits and harms).

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Metformin, gliclazide, and repaglinide appear superior to other single-drug treatments."

Four widely prescribed oral sulphonylurea drugs are associated with significantly increased risk of all-cause mortality, compared with metformin in type 2 diabetic patients having a history of MI, according to a Danish national cohort study.

The study included all Danish adults with a prior MI who started on oral glucose-lowering monotherapy during 1997-2006. The conclusion: Glimepiride, glyburide, Glipizide, and tolbutamide were associated with 33%-43% higher mortality risk than was metformin, Tina Ken Schramm said at the annual congress of the European Society of Cardiology.

In contrast, single-agent gliclazide and repaglinide had all-cause mortality risks similar to metformin.

“The clinical implication of this is that metformin, gliclazide, and repaglinide appear superior to other single-drug treatments received. We believe that metformin in general should be part of the treatment of type 2 diabetes to reduce mortality, but gliclazide and repaglinide may be good alternatives,” said Schramm of the Heart Center at Copenhagen University.

Metformin deserves the nod as the first-line agent on the basis of the results of the landmark United Kingdom Prospective Diabetes Study, which convincingly established the drug as the safest glucose-lowering agent available, she added.

Out of the total Danish population of roughly 4.1 million, 107,870 individuals with type 2 diabetes initiated monotherapy with a glucose-lowering agent during the 9-year study period. Among them were 9,135 with a prior MI, who formed the population for this study.

Glimepiride was the most widely prescribed of the glucose-lowering medications in Denmark, being used by 43% of subjects. Next came metformin (32%), glyburide (13%), Glipizide and gliclazide (7% each), tolbutamide (6%), and repaglinide (2%). Acarbose was prescribed as monotherapy in only 44 patients nation-wide – far too small a number to allow meaningful results. Similarly, the thiazolidinediones, which in Denmark are not recommended therapy in this clinical setting, were used too seldom to draw any conclusions, Schramm explained.

Metformin served as the comparator in determining all-cause mortality risks for the other oral glucose-lowering agents in a multivariate analysis adjusted for age, gender, years of diabetes, cardiovascular medications, and socio-economic status.

Audience members asked if confounding was a potential issue in the study – that is, perhaps patients on drugs other than metformin were sicker, or had previously been on metformin but proved intolerant or unresponsive to it. Schramm replied that it’s unlikely, since when she performed a sub-analysis restricted to those patients starting their first-ever glucose-lowering agent the results were unchanged.

She undertook the study because most prior studies of oral glucose-lowering medications did not look beyond glucose-lowering efficacy in terms of outcomes.

EASD The Netherlands, 17-21 September 2007, presentation P0383

Aspirin Prophylaxis for CVD in Diabetes

Most professional guidelines recommend aspirin for primary prevention of CV events in diabetes. These are mostly based on indirect evidence inferred from large trials in those at high risk for CV events, and there are few trials of the preventive efficacy of aspirin therapy in diabetic populations.

Aspirin's efficacy in the primary prevention of CV events is therefore somewhat controversial. Clinical experts are of varying opinions on this issue, with some stating that aspirin is proven ineffective for this indication and others suggesting that evidence is still inconclusive, warranting more trials.

A meta-analysis of randomised controlled trials showed no proof of a clear benefit of aspirin in the primary prevention of major CV events, cardiovascular mortality, or all-cause mortality in people with diabetes. Subgroup analysis by sex showed that aspirin significantly reduced the risk for MI in men by 43%, but no benefit was found in women.
All statins may not be equal as far as diabetes patients are concerned. Among patients with diabetes initiating statin therapy for the first time, those who took atorvastatin experienced 12% fewer cardiovascular events than did those who took simvastatin, said Joshua Benner, IMS Health Care, Virginia. Benner spoke at the annual scientific sessions of the American Diabetes Association.

The observational, comparative-effectiveness study made use of a large managed-care database including patient information from 92 health care plans in the United States. In all, the investigators identified 12,304 patients with diabetes initiating statin therapy with simvastatin and 33,772 initiating statin therapy with atorvastatin.

The investigators included only adult patients who were continuously enrolled in their health plan for 1 year prior to their first statin prescription and for at least 30 days after. Patients had to be taking either 20 mg or 40 mg of simvastatin or 10 mg or 20 mg of atorvastatin. The simvastatin group was followed for a mean of 591 days, and the atorvastatin group was followed for a mean of 556 days.

Among patients taking atorvastatin, the unadjusted rate of cardiovascular events requiring hospitalisation was 3.35 per 100 person-years, significantly lower than the rate for simvastatin, which was 4.45 per 100 person-years.

After adjustment for age, gender, type of health plan, payer type, geographic region, calendar year of statin initiation, physician speciality, co-morbidities, concomitant therapies, and prior health care cost, the hazard ratio for atorvastatin was 0.88 relative to simvastatin, indicating a 12% reduction in cardiovascular risk.

Atorvastatin and simvastatin were the two most commonly prescribed statins in the United States during the study period, which ran from January 2003 to September 2005, Benner said. “The comparison between these two statins is especially important given the recent trends in their utilisation, where simvastatin recently became generic and is now preferred by many payers in the United States.”

Patients taking atorvastatin persisted with that prescription for a mean of 219 days, significantly longer than the 153 days for the patients taking simvastatin. Although the investigators did not compile data on adverse events, Benner said that this difference in persistence times suggests that there were fewer dose-limiting or treatment-limiting side effects among those taking atorvastatin.

“Future studies are going to be required in order for us to determine whether differences in persistence, achieved LDL levels, or other factors may have contributed to the improved outcomes in diabetes patients taking atorvastatin,” Benner said.

He also said that the investigators have not yet concluded that atorvastatin’s greater efficacy justifies its higher cost. “I’m sure you can assume that that’s where a number of analyses are headed in the future, because this raises the important policy question of what is the clinical and economic value of a marginal increase in effectiveness,” he said.

Benner disclosed that the IMS Health Group conducts research and consulting projects were supported by manufacturers of numerous lipid-lowering medications.

No differences in mortality between users of pancreatic-specific and non-pancreatic-specific sulphonylureas: a cohort analysis

J.M. Evans et al, Diabetes Obesity and Metabolism, 10, 2008, 350-352

The study aimed to examine whether there was differences in mortality between users of different sulphonylureas (SU's) in type 2 diabetes. The authors conclude that "the observed mortality difference between SU and metformin users could be explained by improved insulin sensitivity in those taking metformin, rather than a direct toxic effect of sulphonylureas. We consider that these findings do not support the concept that sulphonylureas increase mortality by direct cardiovascular toxicity and provide no evidence that a pancreatic-specific sulphonylurea should be chosen over a non-specific type.

This rehabilitates glibenclamide, a non pancreatic-specific SU accused of cardio toxicity for the last 2 years.