Chronic kidney disease is major risk factor for future coronary events

**Background:** Diabetes is regarded as a coronary heart disease risk equivalent - i.e., people with the disorder have a risk of coronary events similar to those with previous myocardial infarction (MI). This study aimed to assess whether chronic kidney disease should be regarded as a coronary heart disease risk equivalent.

**Methods:** A population-based cohort with measures of eGFR and proteinuria was studied. Validated algorithms based on hospital admission and medical-claim data to classify participants with baseline history of MI or diabetes were used and to ascertain which patients were admitted to hospital for MI during follow-up (the primary outcome). For primary analysis, a baseline chronic kidney disease as eGFR 15-59.9 ml/min per 1.73 m² (stage 3 or 4 disease) was defined. Poisson regression was used to calculate unadjusted rates and relative rates of MI during follow-up for five risk groups: people with previous MI (with or without diabetes or CKD), and (of those without previous MI), four mutually exclusive groups defined by the presence or absence of diabetes and CKD.

**Findings:** During a median follow-up of 48 months (IQR 25-65), 11 340 of 1 268 029 participants (1 %) were admitted to hospital with MI. The unadjusted rate of MI was highest in people with previous MI (18.5 per 1000 person-years, 95% CI 17.4-19.8). In people without previous MI, the rate of MI was lower in those with diabetes (without CKD) than in those with CKD (without diabetes; 5.4 per 1000 person-years, 5.2-5.7, vs. 6.9 per 1000 person-years, 6.6-7.2; p<0.0001). The rate of incident myocardial infarction in people with diabetes was substantially lower than for those with CKD when defined by eGFR of less than 45 and severely increased proteinuria (6.6 per 1000 person-years, 6.4-6.9 vs. 12.4 per 1000 person-years, 9.7-15.9).

**Interpretation:** Our findings suggest that CKD could be added to the list of criteria defining people at highest risk of future coronary events.


Does normoglycaemia reversion hold secret to preventing diabetes?

Those with prediabetes have a significantly reduced risk for progressing to full diabetes if they have a history of reverting to normal glucose regulation. This reduction in risk applies irrespective of how the reversion was achieved or however transiently, say Leigh Perreault (University of Colorado, Denver) and colleagues.

"This analysis draws attention to the significant long-term reduction in diabetes risk when someone with prediabetes returns to normoglycaemia, supporting a shift in the standard of care to early and aggressive glucose-lowering treatment in patients at highest risk." (The Lancet)

During a mean 5.4-year follow-up of participants from the Diabetes Prevention Program (DPP), the investigators found that prediabetic individuals were 56 % less likely to progress to diabetes if they had reverted to normal glucose regulation at least once.

"The magnitude of this risk reduction approximates that seen with intensive lifestyle intervention - the most potent intervention - but with a greater enduring effect on long-term diabetes prevention." Cox proportional hazard modelling showed that diabetes risk was reduced by 47 % if the prediabetic individuals had achieved normoglycaemia once, 61 % if they had achieved it twice, and 67 % if they had achieved it three times during DPP. Furthermore, the risk-reduction benefit with normoglycaemia status was seen irrespective of which DPP treatment group the participants had been allocated to (lifestyle intervention n=736; metformin n=647; placebo, n=607).

This suggests that achievement of normal glucose regulation is more important than the method used to achieve it, says the team.

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Insulin seems to be a more effective add-on regimen than sitagliptin in patients with diabetes inadequately controlled by metformin monotherapy, show study findings.

Insulin glargine lowered patients' glycated haemoglobin (HbA₁c) levels 0.59 % more than sitagliptin during the 24-week study, report Pablo Aschner (Hospital Universitario San Ignacio, Bogotà, Colombia) and colleagues in The Lancet.

In addition, patients who received the insulin regimen were 1.6 times more likely than those given sitagliptin to achieve an HbA₁c of less than 7 %, and 2.5 times more likely to achieve an HbA₁c of less than 6.5 %.

Aschner and team say that, until now, no studies have compared the use of dipeptidyl peptidase-4 (DPP-4) inhibitors with that of basal insulin in people with diabetes who have not responded to metformin.

The Evaluation of Insulin Glargine versus Sitagliptin in Insulin-naïve Patients (EASIE) trial was a multicenter, randomized, open-label study conducted across 17 countries and including 513 patients with type 2 diabetes who had an HbA₁c of 7 % or more despite having taken metformin for at least 6 months.

Throughout the study, patients in the insulin group self-monitored their blood glucose and injected insulin doses that were titrated to attain a fasting plasma glucose between 4.0 and 5.5 mmol/L. Those taking sitagliptin took their medication (100 mg) orally once a day.

After 24 weeks, the mean HbA₁c level among the insulin glargine patients was reduced significantly further than in the sitagliptin patients, by 1.72 % compared with 1.13 %.

In addition, more insulin patients achieved an HbA₁c of less than 7 % than sitagliptin patients, at 68 % versus 42 %. The corresponding rates for attainment of an HbA₁c value lower than 6.5 % were 40% versus 17 %.

Furthermore, significantly more of the insulin versus sitagliptin patients reached the HbA₁c goal of less than 7 % by week 12, only halfway through the treatment period.

However, symptomatic hypoglycaemic events were more frequent with insulin versus sitagliptin use, at 4.21 versus 0.50 events per patient-year, although severe hypoglycaemia was seen in only three (1 %) patients on insulin and one (<1 %) on sitagliptin. And, 6 % of patients in the insulin group had at least one serious treatment-emergent adverse event, compared with 3 % of those in the sitagliptin group.

The authors say that, given the potential long-term benefits and improved efficacy of insulin, "strong arguments could be made" to use insulin early in the course of disease, when a fairly low dose can be used and the risk for hypos reduced.

"The results of this comparative effectiveness trial might help physicians to choose between two drugs for patients whose diabetes is uncontrolled on metformin and provide clinical experience to guide the design of future studies needed to assess the long-term efficacy of these two therapeutic strategies," write Ascher et al.
Aspirin linked to high bleeding rate in diabetes

Diabetes may be associated with an increased risk for major bleeding irrespective of aspirin use, researchers say. In the latest analysis of aspirin use for primary prevention, the drug was significantly associated with an increased risk for gastrointestinal or cerebral bleeding episodes. However, in patients with diabetes, the high rate of bleeding was not independently associated with aspirin use.

The population-based cohort study, published in JAMA, was conducted by Antonio Nicolucci (Consorzio Mario Negri Sud, Italy) and team. It included 186,425 patients who were treated with low-dose aspirin (≤300 mg) and 186,425 controls who did not use aspirin between January 2003 and December 2008.

During a median follow-up period of 5.7 years, the incidence of hemorrhagic events was 5.58 per 1000 person-years for aspirin users versus 3.60 per 1000 person-years for non-aspirin users, corresponding to an incidence rate ratio (IRR) of 1.55.

Aspirin use was associated with a significantly greater risk for major bleeding in most of the subgroups investigated, including gender, age, and hypertension. However, it was not associated with a significantly increased risk for bleeding in patients with diabetes.

Moreover, the baseline risk for bleeding in the absence of aspirin therapy was higher among individuals with diabetes than those without diabetes, at 5.35 versus 3.32 events per 1000 person-years, whereas aspirin use was associated with a significantly higher bleeding risk in diabetes patients only (IRR for gastrointestinal bleeding 1.08; intracranial bleeding 1.01).

The authors say that the lack of an excess bleeding risk in patients with diabetes "deserved additional consideration."

"Weighing the benefits of aspirin therapy against the potential harms is of particular relevance in the primary prevention setting, in which benefits seem to be lower than expected based on results in high-risk populations," they remark.

"Diabetes might represent a different population in terms of both expected benefits and risks associated with antiplatelet therapy," Nicolucci et al conclude.

In a related editorial, Jolanta Siller-Matula (Medical University of Vienna, Austria) states that Nicolucci and team's study reinforces European guidelines for aspirin use. She adds: "Future studies investigating the risks and benefits for individual patients appear to be mandatory to help physicians appropriately make recommendations about aspirin use for primary prevention."

Statins may slow prostate enlargement

Taking statins may slow prostate growth in men with raised prostate-specific antigen (PSA) levels, report researchers. The findings, presented at the American Urological Association 2012 Annual Meeting, showed that statin use was associated with a reduction in prostate volume in a study of over 6000 men.

"We don't yet understand the mechanisms that might be causing this," said lead researcher Robert Muller from Duke University in Durham. "Some have suggested that statins may have anti-inflammatory properties, and inflammation has been linked to prostate growth."

Muller and team had previously found that starting a statin was associated with a 4.1% reduction in PSA levels within 1 year, and given that PSA correlates with prostate volume, the researchers hypothesized that statins may affect prostate volume.

To investigate, they analyzed data available for 6093 men who participated in the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial, a 4-year randomized study of dutasteride versus placebo in the prevention of prostate cancer. Prostate volume was measured by transrectal ultrasound at 2 and 4 years, and compared with baseline measures.

The researchers report that 1032 (16.9%) men were using statins at baseline. The team found that 2 years into the trial, prostate growth was significantly reduced among the statin users in both the placebo and the dutasteride groups. After adjustment for multiple confounders, the respective decreases in prostate volume growth were 3.9% and 5.0%. There were no further reductions, however, over the next 2 years, report Muller et al.

The authors say these reductions in prostate volume are consistent with their previous findings. "The declines in PSA in our prior study may be due to reductions in PV," they suggest.

"Prostate enlargement was once considered an inexorable consequence of aging and genetics but there is growing awareness that prostate growth can be influenced by modifiable risk factors," said Muller. "In this context, the role of blood cholesterol levels and cholesterol-lowering drugs such as statins warrants further study," he concludes.
Although type 2 diabetes (T2D) is increasingly common in young patients, few studies have addressed its complications. Therefore, the Australian authors have sought to assess the risk of microvascular complications in T2D and hypertension in comparison with type 1 diabetes (T1D) by performing a meta-analysis.

This meta-analysis included 25 studies involving 3,321 patients who were aged 28 or less. The median age of the patients with T2D was 14.5 years, the median duration of the diabetes was 1.7 years, and the median rate of glycated haemoglobin 7.7 %. The pooled analysis revealed prevalence rates for micro- and macroalbuminuria respectively of 18 % (17-20 %) and 5 % (3-7 %), the prevalence of hypertension was 28 % (26-29 %), that of diabetic retinopathy 2 % (1-3 %), that of peripheral neuropathy 2 % (1-4 %), and that of autonomic neuropathy 43 % (25-63 %).

In comparison with T1D, the analysis shows an increased risk of microalbuminuria (odds ratio = 3.5, confidence interval at 95 % from 1.6 to 7.8) and of hypertension (3.4, 2.4-4.8) in young subjects with T2D.

This meta-analysis shows more than a tripling of the risk of microalbuminuria and hypertension in children and adolescents with T2D for a lesser duration of diabetes than that of T1D. The authors, who were critical of the methodological shortcomings in the studies listed, insist on the need for implementing large-scale prospective studies so as to understand the specific risk factors of complications of T2D in young patients better in order to guide the detection, prevention, and treatment.

JIM.fr McLennan C et al.: Prevalence of microvascular complications in youth with type 2 diabetes: Systematic review and meta-analysis. 15th International Congress of Endocrinology & the 14th European Congress of Endocrinology (Florence, Italy): 5-9 May 2012

This is a Swedish randomised controlled trial, which included 2,010 obese subjects treated with bariatric surgery and 2,037 obese control subjects.

A decrease of 5 units of BMI reduces the incidence of diabetes regardless of the degree of obesity

At 2 years, in patients whose BMI was 35-40, 40-45, or ≥ 45 at the start, and who reduced their initial BMI by 5 units, the incidence rates of type 2 diabetes are respectively 2.4, 2.0 and 3.4 % vs. 6.5, 7.7, and 9.3 % in those subjects whose weight remained stable.

Also independently of the initial degree of obesity, the results were similar at 10 years of follow-up.

JIM.fr Peltonen M et al. Diabetes risk in relation to weight loss, weight stability and degree of obesity - The Swedish Obese Subjects (SOS) study. 15th International Congress of Endocrinology & the 14th European Congress of Endocrinology (Florence, Italy): 5-9 May 2012