Association of Nut Consumption with Total and Cause-Specific Mortality

BACKGROUND:
Increased nut consumption has been associated with a reduced risk of major chronic diseases, including cardiovascular disease and type 2 diabetes mellitus. However, the association between nut consumption and mortality remains unclear.

METHODS:
The association between nut consumption and subsequent total and cause-specific mortality among 76,464 women in the Nurses' Health Study (1980–2010) and 42,498 men in the Health Professionals Follow-up Study (1986–2010) was examined. Participants with a history of cancer, heart disease, or stroke were excluded. Nut consumption was assessed at baseline and updated every 2 to 4 years.

RESULTS:
During 3,038,853 person-years of follow-up, 16,200 women and 11,229 men died. Nut consumption was inversely associated with total mortality among both women and men, after adjustment for other known or suspected risk factors. The pooled multivariate hazard ratios for death among participants who ate nuts, as compared with those who did not, were 0.93 (95% confidence interval [CI], 0.90 to 0.96) for the consumption of nuts less than once per week, 0.89 (95% CI, 0.86 to 0.93) for once per week, 0.87 (95% CI, 0.83 to 0.90) for two to four times per week, 0.85 (95% CI, 0.79 to 0.91) for five or six times per week, and 0.80 (95% CI, 0.73 to 0.86) for seven or more times per week (P<0.001 for trend). Significant inverse associations were also observed between nut consumption and deaths due to cancer, heart disease, and respiratory disease.

CONCLUSIONS:
In two large, independent cohorts of nurses and other health professionals, the frequency of nut consumption was inversely associated with total and cause-specific mortality, independently of other predictors of death.

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Severe hypoglycaemia and risks of vascular events and death

BACKGROUND:
Severe hypoglycaemia may increase the risk of a poor outcome in patients with type 2 diabetes assigned to an intensive glucose-lowering intervention. We analyzed data from a large study of intensive glucose lowering to explore the relationship between severe hypoglycaemia and adverse clinical outcomes.

METHODS:
We examined the associations between severe hypoglycaemia and the risks of macrovascular or microvascular events and death among 11,140 patients with type 2 diabetes, using Cox proportional-hazards models with adjustment for covariates measured at baseline and after randomization.

RESULTS:
During a median follow-up period of 5 years, 231 patients (2.1%) had at least one severe hypoglycaemic episode; 150 had been assigned to intensive glucose control (2.7% of the 5571 patients in that group), and 81 had been assigned to standard glucose control (1.5% of the 5569 patients in that group).

The median times from the onset of severe hypoglycaemia to the first major macrovascular event, the first major microvascular event, and death were 1.56 years (interquartile range, 0.84 to 2.41), 0.99 years (interquartile range, 0.40 to 2.17), and 1.05 years (interquartile range, 0.34 to 2.41), respectively.

During follow-up, severe hypoglycaemia was associated with a significant increase in the adjusted risks of major macrovascular events (hazard ratio, 2.88; 95% confidence interval [CI], 2.01 to 4.12), major microvascular events (hazard ratio, 1.81; 95% CI, 1.19 to 2.74), death from a cardiovascular cause (hazard ratio, 2.68; 95% CI, 1.72 to 4.19), and death from any cause (hazard ratio, 2.69; 95% CI, 1.97 to 3.67) (P<0.001 for all comparisons).

Similar associations were apparent for a range of nonvascular outcomes, including respiratory, digestive, and skin conditions (P<0.01 for all comparisons). No relationship was found between repeated episodes of severe hypoglycaemia and vascular outcomes or death.

CONCLUSIONS:
Severe hypoglycaemia was strongly associated with increased risks of a range of adverse clinical outcomes. It is possible that severe hypoglycaemia contributes to adverse outcomes, but these analyses indicate that hypoglycaemia is just as likely to be a marker of vulnerability to such events.

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What can we do for patients with diabetes and persistent proteinuria despite blockade of the renin-angiotensin system?


Baseline albuminuria, but also treatment-induced changes in albuminuria and residual albuminuria after single RAS blockade and appropriate antihypertensive therapy, are of prognostic value for risk of severe renal outcomes, like end-stage renal disease (ESRD), as well as for CV risk. In a post-hoc analysis of the RENAAL study, a 50 % reduction in proteinuria translated into a 50 % reduction of risk for ESRD, suggesting that those with reduced proteinuria after 6 months of RAS blockade are less prone to renal and CV events than are non-responders.

However, many patients remain at very high risk of ESRD despite adequate renoprotective therapy, especially if they retain a high rate of proteinuria. For example, in RENAAL, 20 % of the patients on the full dose of an angiotensin II receptor antagonist, (ARA) developed ESRD within only a 3-year follow-up. So, how can we improve the prognosis of these patients?

The ONTARGET study compared ramipril, telmisartan, and their combination in high CV risk patients; many of them had diabetes. No CV benefit of the combination was shown on the primary CV composite outcome, and severe renal side effects occurred more frequently with the double blockade. However, the trial was not designed to test the renal and CV effects of the combination of both drugs in patients with type 2 diabetes and persistent proteinuria despite single RAS blockade. Thus the issue of a favourable risk: benefit ratio of the double blockade in this special setting remained. This was the purpose of the VA NEPHRON-D trial (NCT00555217), but a premature termination of the study was recently announced, for safety reasons. Finally, The ALTITUDE trial evaluated the combination of a new drug, aliskiren, a direct renin inhibitor, with conventional single RAS blockers. The trial was also terminated early because of an increased risk of adverse outcomes (stroke, hypotension, and hyperkalaemia).

What next? Many factors associated with a rapid decline of GFR in patients with type 2 diabetes and persistent proteinuria have been reported in recent decades, and offer potential therapeutic targets. One of these is restriction in dietary protein (recommended daily dose 0.8-1.0 g/kg body weight), but recent trials have produced conflicting results.

Uncontrolled diabetes is also associated with a worsening prognosis. Until recently, very few data supported a benefit of strict glycaemic control in the progression of established DKD, with most of these studies being observational in nature. Interestingly, a post-hoc analysis of the randomized controlled ADVANCE trial suggested that patients in the intensive glucose arm actually had a lower risk of ESRD, with an impressive 65 % reduction. With low absolute numbers of such events in both arms, this secondary outcome may be considered exploratory and needs further confirmation.

Plasma vitamin D concentrations are associated with progression of DKD. Paricalcitol, a vitamin D receptor agonist, showed a significant, albeit modest, effect on residual albuminuria in patients with DKD. However, this randomized controlled trial was designed as a proof of concept, and data on clinical outcomes are awaited in a larger study.

A fascinating approach is to target the inflammation and fibrosis that are the hallmarks of the advanced stages of DKD. Many clinical trials are ongoing, evaluating the effects of drugs inhibiting inflammatory factors and fibrotic processes, such as monoclonal antibodies against Connective Tissue Growth Factor and against Tumour Growth Factor b, or chemokine receptor antagonists (CCR2/5), among others. However, a recent disappointment came from the early termination for safety reasons of BEACON (NCT01351675). This clinical trial assessed the effect of bardoxolone, an oral antioxidant and inflammation modulator used initially in oncology that induces Nrf2, a major regulator of inflammation and antioxidant genes.

Unfortunately for patients with DKD and persistent albuminuria, there is no equivalent of laser treatment for proliferative retinopathy. Many therapeutic avenues are still open, however, and clinical research in that field is of prominent importance. As CV protection is the first issue in these patients, we need to maintain the fight against kidney disease progression.
Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

**BACKGROUND**

The cardiovascular safety and efficacy of many current antihyperglycaemic agents, including saxagliptin, a dipeptidyl peptidase 4 inhibitor, are unclear.

**METHODS**

We randomly assigned 16,492 patients with type 2 diabetes who had a history of, or were at risk for, cardiovascular events to receive saxagliptin or placebo and followed them for a median of 2.1 years. Physicians were permitted to adjust other medications, including antihyperglycaemic agents. The primary end point was a composite of cardiovascular death, myocardial infarction, or ischaemic stroke.

**RESULTS**

A primary end-point event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3 % and 7.2 %, respectively, according to 2-year Kaplan–Meier estimates; hazard ratio with saxagliptin, 1.00; 95 % confidence interval [CI], 0.89 to 1.12; P=0.99 for superiority; P<0.001 for non-inferiority); the results were similar in the “on-treatment” analysis (hazard ratio, 1.03; 95 % CI, 0.91 to 1.17).

The major secondary end point of a composite of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, coronary revascularization, or heart failure occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8 % and 12.4 %, respectively, according to 2-year Kaplan-Meier estimates; hazard ratio, 1.02; 95 % CI, 0.94 to 1.11; P=0.66). More patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5 % vs. 2.8 %; hazard ratio, 1.27; 95 % CI, 1.07 to 1.51; P=0.007).

Rates of adjudicated cases of acute and chronic pancreatitis were similar in the two groups (acute pancreatitis, 0.3 % in the saxagliptin group and 0.2 % in the placebo group; chronic pancreatitis, <0.1 % and 0.1 % in the two groups, respectively).

**CONCLUSIONS**

DPP-4 inhibition with saxagliptin did not increase or decrease the rate of ischaemic events, though the rate of heart failure rates increased. Although saxagliptin improves glycaemic control, other approaches are necessary to reduce cardiovascular risk in patients with diabetes.

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