Very low LDL-C with statins safe regarding major known side effects, but caution urged

In a post-hoc analysis of data from the JUPITER trial of statin therapy, achieving LDL-C levels <30 mg/dL appeared safe as concerns the major side effects known to be associated with the drugs. Brendan Everett et al at Brigham and Women's Hospital and Harvard Medical School, Boston, noted that of study participants with baseline LDL-C <130 mg/dL who were administered the study drug at 20 mg, 767 achieved at least one on-treatment LDL-C of <30 mg/dL during a median follow-up of two years; 7,387 did not.

The rates of any adverse event, myalgia, nervous system disorders, creatinine kinase elevations, liver function test abnormalities, or cancer were not significantly different between participants achieving LDL-C <30 mg/dL or ≥30 mg/dL (all \( P >0.05 \)). According to Everett and colleagues, exploratory analyses evaluating a broad spectrum of potential adverse effects showed an increase in total renal or urinary disorders (adjusted relative risk [RR] 1.49; 95% confidence interval [CI], 1.19 to 1.86), which appeared to primarily reflect an increase in haematuria (RR 2.20; CI 1.47 to 3.28). The researchers also noted that "other hypotheses generating findings of uncertain pathobiology" include possible increases in psychiatric (RR 1.43; CI 1.09 to 1.88) and hepatobiliary disorders (RR 1.68; CI 1.09 to 2.60).

Considering the potential adverse effects on less-well described pathways, close monitoring in future trials of very low LDL-C reduction is warranted, the researchers concluded.


American study confirms clinical impression that statins increase muscle symptoms

Researchers from Hartford Hospital, Connecticut, reported on their blinded, controlled trial that confirmed the impression that statins increase muscle symptoms in previously untreated subjects. Beth A. Parker, et al administered either statin 80 mg daily to patients (n=202, 103 women, age 43 ±16) or placebo (n=217, 113 women, age 45 ±16) to healthy, statin-naive subjects for six months or until they met the study definition of myalgia (new and unexplained muscle pain on study drug that abated with de-challenge and reoccurred upon re-challenge). The researchers measured serum lipids, CK), ALT, and muscle strength (handgrip, elbow and knee isometric and isokinetic strength, knee endurance) at baseline and treatment completion.

Following data analysis, CK and ALT increased in the statin subjects by 20.8 and 15.7 U/L resp., with no change in PL subjects. There were no significant changes in muscle strength or aerobic performance in the active drug vs. placebo. However, 19 statin subjects and 10 placebo subjects met the study definition for myalgia (X2 3.74; \( P=0.05 \)). The myalgic statin subjects exhibited muscle strength declines in 10 of 16 measured variables, whereas the myalgic placebo subjects exhibited strength declines in four of 16 variables (X2 4.6; \( P=0.03 \)).

The researchers noted that statin-associated myalgia induced skeletal muscle strength declines that could exacerbate existing disease pathologies and compromise quality of life.”


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BACKGROUND

Despite the increasing prevalence of type 2 diabetes in youth, there are few data to guide treatment. We compared the efficacy of three treatment regimens to achieve durable glycaemic control in children and adolescents with recent-onset type 2 diabetes.

METHODS

Eligible patients 10 to 17 years of age were treated with metformin (dose of 1000 mg twice daily) to attain a glycated haemoglobin level of less than 8 % and were randomly assigned to continued treatment with metformin alone or to metformin combined with rosiglitazone (4 mg bd) or a lifestyle-intervention programme focusing on weight loss through eating and activity behaviours. The primary outcome was loss of glycaemic control, defined as a glycated haemoglobin level of at least 8 % for 6 months or sustained metabolic decompensation requiring insulin.

RESULTS

Of the 699 randomly assigned participants (mean duration of type 2 diabetes, 7.8 months), 319 (45.6%) reached the primary outcome over an average follow-up of 3.86 years. Rates of failure were 51.7% (120 of 232 participants), 38.6% (90 of 233), and 46.6% (109 of 234) for metformin alone, metformin plus rosiglitazone, and metformin plus lifestyle intervention, respectively. Metformin plus rosiglitazone was superior to metformin alone (P=0.006); metformin plus lifestyle intervention was intermediate but not significantly different from metformin alone or metformin plus rosiglitazone. Prespecified analyses according to sex and race or ethnic group showed differences in sustained effectiveness, with metformin alone least effective in non-Hispanic black participants and metformin plus rosiglitazone most effective in girls. Serious adverse events were reported in 19.2 % of participants.

CONCLUSIONS

1. Monotherapy with metformin was associated with durable glycaemic control in approximately half of children and adolescents with type 2 diabetes.

2. The addition of rosiglitazone, but not an intensive lifestyle intervention, was superior to metformin alone.

(Funded by the National Institute of Diabetes and Digestive and Kidney Diseases and others; TODAY ClinicalTrials.gov number, NCT00081328.)
Temporal increases in the consumption of sugar-sweetened beverages have paralleled the rise in obesity prevalence, but whether the intake of such beverages interacts with the genetic predisposition to adiposity is unknown.

METHODS
We analyzed the interaction between genetic predisposition and the intake of sugar-sweetened beverages in relation to body-mass index (BMI) and obesity risk in 6934 women from the Nurses’ Health Study (NHS) and in 4423 men from the Health Professionals Follow-up Study (HPFS) and also in a replication cohort of 21,740 women from the Women’s Genome Health Study (WGHS). The genetic-predisposition score was calculated on the basis of 32 BMI-associated loci. The intake of sugar-sweetened beverages was examined prospectively in relation to BMI.

RESULTS
In the NHS and HPFS cohorts, the genetic association with BMI was stronger among participants with higher intake of sugar-sweetened beverages than among those with lower intake. In the combined cohorts, the increases in BMI per increment of 10 risk alleles were 1.00 for an intake of less than one serving per month, 1.12 for one to four servings per month, 1.38 for two to six servings per week, and 1.78 for one or more servings per day (P<0.001 for interaction). For the same categories of intake, the relative risks of incident obesity per increment of 10 risk alleles were 1.19 (95 % confidence interval [CI], 0.90 to 1.59), 1.67 (95 % CI, 1.28 to 2.16), 1.58 (95 % CI, 1.01 to 2.47), and 5.06 (95 % CI, 1.66 to 15.5) (P=0.02 for interaction). In the WGHS cohort, the increases in BMI per increment of 10 risk alleles were 1.39, 1.64, 1.90, and 2.53 across the four categories of intake (P=0.001 for interaction); the relative risks for incident obesity were 1.40 (95 % CI, 1.19 to 1.64), 1.50 (95 % CI, 1.16 to 1.93), 1.54 (95 % CI, 1.21 to 1.94), and 3.16 (95 % CI, 2.03 to 4.92), respectively (P=0.007 for interaction).

CONCLUSIONS
The genetic association with adiposity appeared to be more pronounced with greater intake of sugar-sweetened beverages.

(Funded by the National Institutes of Health and others.)
Hypoglycaemia and Risk of Death in Critically ill Patients

BACKGROUND
Whether hypoglycaemia leads to death in critically ill patients is unclear.

METHODS
We examined the associations between moderate and severe hypoglycaemia (blood glucose 2.3 to 3.9 mmol/l and ≤2.2 mmol/l, respectively) and death among 6026 critically ill patients in intensive care units (ICUs). Patients were randomly assigned to intensive or conventional glucose control. We used Cox regression analysis with adjustment for treatment assignment and for baseline and post-randomization covariates.

RESULTS
Follow-up data were available for 6026 patients: 2714 (45.0 %) had moderate hypoglycaemia, 2237 of whom (82.4 %) were in the intensive-control group (i.e., 74.2 % of the 3013 patients in the group), and 223 patients (3.7 %) had severe hypoglycaemia, 208 of whom (93.3 %) were in the intensive-control group (i.e., 6.9 % of the patients in this group). Of the 3089 patients who did not have hypoglycaemia, 726 (23.5 %) died, as compared with 774 of the 2714 with moderate hypoglycaemia (28.5 %) and 79 of the 223 with severe hypoglycaemia (35.4 %). The adjusted hazard ratios for death among patients with moderate or severe hypoglycaemia, as compared with those without hypoglycaemia, were 1.41 (95 % confidence interval [CI], 1.21 to 1.62; P<0.001) and 2.10 (95 % CI, 1.59 to 2.77; P<0.001), respectively. The association with death was increased among patients who had moderate hypoglycaemia on more than 1 day (>1 day vs. 1 day, P=0.01), those who died from distributive (vasodilated) shock (P<0.001), and those who had severe hypoglycaemia in the absence of insulin treatment (hazard ratio, 3.84; 95 % CI, 2.37 to 6.23; P<0.001).

CONCLUSIONS
In critically ill patients, intensive glucose control leads to moderate and severe hypoglycaemia, both of which are associated with an increased risk of death. The association exhibits a dose-response relationship and is strongest for death from distributive shock. However, these data cannot prove a causal relationship.

The NICE-SUGAR Study Investigators
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