Does diet-beverage intake affect dietary consumption patterns? Results from the Choose Healthy Options Consciously Everyday (CHOICE) randomized clinical trial.

Carmen Piernas et al, From Chapel Hill, NC.

Background: Little is understood about the effect of increased consumption of low-calorie sweeteners in diet beverages on dietary patterns and energy intake.

Objective: We investigated whether energy intakes and dietary patterns were different in subjects who were randomly assigned to substitute caloric beverages with either water or diet beverages (DBs).

Design: Participants from the Choose Healthy Options Consciously Everyday randomized clinical trial (a 6-mo, 3-arm study) were included in the analysis [water groups: $n = 106$ (94% women); DB group: $n = 104$ (82% women)]. For energy, macronutrient, and food and beverage intakes, we investigated the main effects of time, treatment, and the treatment-by-time interaction by using mixed models.

Results: Overall, the macronutrient composition changed in both groups without significant differences between groups over
time. Both groups reduced absolute intakes of total daily energy, carbohydrates, fat, protein, saturated fat, total sugar, added sugar, and other carbohydrates. The DB group decreased energy from all beverages more than the water group did only at month 3 ($P$-group-by-time < 0.05). Although the water group had a greater reduction in grain intake at month 3 and a greater increase in fruit and vegetable intake at month 6 ($P$-group-by-time < 0.05), the DB group had a greater reduction in dessert intake than the water group did at month 6 ($P$-group-by-time < 0.05).

**Conclusions:** Participants in both intervention groups showed positive changes in energy intakes and dietary patterns. The DB group showed decreases in most caloric beverages and specifically reduced more desserts than the water group did. **Our study does not provide evidence to suggest that a short-term consumption of DBs, compared with water, increases preferences for sweet foods and beverages.**

**Ref**

Why are the results in HPS2-THRIVE disappointing?

From the heart.org

The combination of niacin and laropiprant did not significantly reduce the risk of the combination of coronary deaths, nonfatal MI, strokes, or coronary revascularizations compared with statin therapy.

The failure of niacin in the 26 673-patient HPS2-THRIVE study was announced in late December by Merck, with the company stating that it no longer had any plans to take the drug before the US Food and Drug Administration (FDA) to gain approval.

Full results of the HPS2-THRIVE study will be presented by lead investigator Dr Jane Armitage (Oxford University, UK) on March 9, 2013 at American College of Cardiology 2013 Scientific Sessions in San Francisco, CA.

New data shed some light on the adverse events associated with extended-release niacin and the antiflushing agent laropiprant with investigators reporting the HDL-raising therapy when added to statins was associated with a significantly increased risk of definite myopathy [1].

Regarding muscle side effects, 75 patients treated with niacin/laropiprant developed definite myopathy (0.16%/year) compared with 17 patients in the placebo arm (0.04%/per year). This translated into a risk ratio of 4.4 (95% CI 2.6-7.5). The absolute risk of any myopathy was also significantly higher among Chinese patients, with an excess risk ratio of 5.2 for the Chinese population (95% CI 3.4-7.8).
The mechanism for this myopathy-related interaction between niacin and simvastatin is not clear. Nor is it clear why the rate of myopathy on simvastatin alone is higher among Chinese individuals.

After 3.9 years of follow-up in HPS2-THRIVE, 25% of patients randomized to niacin/laropiprant had stopped taking the medication compared with 17% in the placebo arm. The reasons for stopping therapy were primarily for skin and gastrointestinal side effects. Skin-related reasons for stopping niacin/laropiprant were approximately four times higher than in the placebo arm (5.4% vs 1.2%, respectively; p<0.001). Gastrointestinal side effects were twice as common in the active-treatment arm (3.9% vs 1.7%, respectively, p<0.001) with most of the reasons cited being indigestion and diarrhea. Diabetic complications, mainly hyperglycemia, were observed in 0.9% of those treated with niacin/laropiprant vs 0.4% in the placebo arm. There was no excess risk of hepatobiliary side effects.

In the absence of the full study data it has been speculated that these findings might relate to the effects of laropiprant, although it is not possible to definitively discern this, with the lack of niacin and laropiprant monotherapy comparator arms.

Based on the adverse-event outcomes published online in the European Heart Journal, Dr Ulf Landmesser (University Hospital, Zurich, Switzerland), who wrote an accompanying editorial [2], notes that, data from the HPS2-THRIVE study raise the question as to whether or not laropiprant is really biologically inert with respect to atherosclerosis and thrombosis. He points out that a recent study showed aneurysm formation
and accelerated atherogenesis were evident in mice with deleted prostaglandin D2 receptors. The effects of inhibition of the prostaglandin D2 receptor-1 by laropiprant on thrombosis and atherosclerosis in humans in vivo are probably difficult to predict and complex, since it has been observed that on the one hand laropiprant at low concentrations prevented the inhibitory effects of prostaglandin D2 on platelet function, including effects on platelet aggregation and thrombus formation, but on the other hand laropiprant at higher concentrations attenuated platelet activation induced by thromboxane and inhibited thrombus formation.

**Two messages:**

1/ **Niacin is known to have a broad spectrum of lipid-modifying activity, including LDL cholesterol, triglycerides and lipoprotein(a). On the plus side, it is acknowledged that niacin has been in clinical use for over 50 years and has a well characterised adverse effect profile. In contrast, there is limited experience with laropiprant.**

2/ **HDL cholesterol concentration is considered a surrogate for the efficiency of cholesterol efflux from tissues. Moreover, HDL cholesterol concentration is a static measurement, and does not take into account the dynamics of HDL particle population and its functionality. Thus, HDL function may be a preferable measure.**

**However, which is the best index of HDL functionality? And how do we translate this measure to the clinical setting? Currently, measurement of HDL functionality is a research tool and much remains to be done to validate it.**

A new demonstration of the favorable role of HDL with potential future therapy for stroke is proposed by P.Amarenco’s team.

High-density Lipoprotein–based Therapy Reduces the Hemorrhagic Complications Associated With Tissue Plasminogen Activator Treatment in Experimental Stroke

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Abstract

Background and Purpose—We have previously reported that intravenous injection of high-density lipoproteins (HDLs) was neuroprotective in an embolic stroke model. We hypothesized that HDL vasculoprotective actions on the blood–brain barrier (BBB) may decrease hemorrhagic transformation-associated with tissue plasminogen activator (tPA) administration in acute stroke.

Methods—We used tPA alone or in combination with HDLs in vivo in 2 models of focal middle cerebral artery occlusion (MCAO) (embolic and 4-hour monofilament MCAO) and in vitro in a model of BBB. Sprague–Dawley rats were submitted to MCAO, n=12 per group. The rats were then randomly injected
with tPA (10 mg/kg) or saline with or without human plasma purified-HDL (10 mg/kg). The therapeutic effects of HDL and BBB integrity were assessed blindly 24 hours later. The integrity of the BBB was also tested using an in vitro model of human cerebral endothelial cells under oxygen–glucose deprivation.

**Results**—tPA-treated groups had significantly higher mortality and rate of hemorrhagic transformation at 24 hours in both MCAO models. Cotreatment with HDL significantly reduced stroke-induced mortality versus tPA alone (by 42% in filament MCAO, \( P=0.009 \); by 73% in embolic MCAO, \( P=0.05 \)) and tPA-induced intracerebral parenchymal hematoma (by 92% in filament MCAO, by 100% in embolic MCAO; \( P<0.0001 \)). This was consistent with an improved BBB integrity. In vitro, HDLs decreased oxygen–glucose deprivation–induced BBB permeability (\( P<0.05 \)) and vascular endothelial cadherin disorganization.

**Conclusions**—**HDL injection decreased tPA-induced hemorrhagic transformation in rat models of MCAO. Both in vivo and in vitro results support the vasculoprotective action of HDLs on BBB under ischemic conditions.**

**Ref**

Olive oil and nuts are better than fat restriction

Unrestricted Mediterranean diets beat low-fat advice for primary CVD prevention: PREDIMED

R. Estruch

A Mediterranean diet supplemented with either extra virgin olive oil or mixed nuts may cut the risk of cardiovascular events by as much as 30% in subjects at high risk of developing heart disease, as compared with people advised to eat a reduced-fat diet [1].

The Mediterranean diet already reigns supreme in secondary prevention of CV events. PREDIMED, which looked at diet effects on hard clinical end points, carves out an important role for this dietary eating pattern in primary prevention.

These results support the benefits of the Mediterranean diet for CV risk reduction and are particularly relevant given the challenges of achieving and maintaining weight loss.

PREDIMED enrolled 7447 men and women ranging in age from 55 to 80 years, none of whom had established cardiovascular disease but who were at high CV risk. Subjects were randomized to one of two Mediterranean diet groups (one supplemented with olive oil, the other with nuts) or to a control diet wherein subjects were advised to try to reduce dietary fat.

Patients in the Mediterranean-diet groups were invited to regular dietary training sessions; by contrast, those in the control group were, for the first three years, sent leaflets explaining a low-fat diet. After a protocol amendment at the three-year mark, low-fat-diet patients were also invited to
regular group sessions and offered personalized advice at the same level of intensity as the Mediterranean groups.

The study was stopped when an interim analysis at 4.8 years revealed a clear signal of benefit among subjects eating the Mediterranean diets. In the olive-oil and mixed-nut Mediterranean diet groups, the primary end point (MI, stroke, or CV death) was reduced by 30% and 28% respectively, as compared with the control group.

Study dropouts, meanwhile, were twice as common in the control diet group as in the Mediterranean diet group (11.3% vs 4.9%). "Favorable trends" were seen for both stroke and MI rates among subjects eating the Mediterranean diet, but numbers were too low to be relevant statistically. A total of 288 subjects experienced an event in the study: 96 events in the olive-oil group, 83 in the nut group, and 109 in the control group.
Of special note, subjects randomized to the Mediterranean diets were not told to reduce calories, a major barrier to success in many dietary interventions, particularly the long-supported "low-fat" approach.

There are very few studies of any diets that are rigorously designed and that address hard clinical outcomes. This randomized controlled trial is by far the best in class when it comes to dietary studies.

Take home message

"Animal fat should be avoided,", whereas "vegetal fats—extra virgin olive oil and nuts—should be recommended [within] a healthy food pattern such as the Mediterranean diet."

"People should know that the Mediterranean diet is a diet healthier than others and should know the key
components of this food pattern. The plan should be to increase the intake of the key foods (vegetables, fruit, nuts, fish, legumes, extra virgin olive oil, and red wine in moderation), also increase the intake of white meat, and decrease the intake of red and processed meat, soda drinks, whole dairy products, commercial bakery goods, and sweets and pastries."

Dr Steven Nissen, of the Cleveland Clinic calls PREDIMED "a spectacular study that was extremely difficult to perform."

"The findings are compelling and should alter the dietary advice we give patients. The currently popular ultralow-fat diets . . . are clearly not best for patients," "The standard AHA-recommended diet should be modified to reflect these findings: fat is not the problem with the American diet, we just eat the wrong types of fats."

Ref

It’s a very old story…

Atherosclerosis evident in four ancient populations, including hunter-gatherers

R.C. Thompson

Whole-body computed tomography (CT) scans of mummies from four geographical regions across a period of 4000 years suggest that atherosclerosis was more common in ancient populations than previously believed.

The study is published March 10, 2013 in the Lancet[1] to coincide with a presentation here at the American College of Cardiology 2013 Scientific Sessions.

The research is unique in that it assesses atherosclerosis across four different preindustrial populations from different geographical regions. The ancient Egyptians and Peruvians were farmers, the ancestral Puebloans were forager-farmers, and the Unangans of the Aleutian Islands were hunter-gatherers without agriculture. None of the cultures was known to be vegetarian, and all were believed to be quite physically active.

The diets of these peoples were quite disparate, as were the climates. Indigenous food plants varied greatly over the wide geographical distance between these regions of the world. Fish and game were present in all of the cultures, but protein sources varied from domesticated cattle among the Egyptians to an almost entirely marine diet among the Unangans.

In total, whole-body CT scans were performed on 137 mummies, including 76 ancient Egyptians, 51 ancient
Peruvians, five ancestral Puebloans, and five Unangan hunter-gatherers. Probable or definite atherosclerosis was evident in 34% of the mummies—29 ancient Egyptians, 13 ancient Peruvians, two ancestral Puebloans, and three Unangan mummies had documented evidence of atherosclerosis as defined by calcified plaque in the wall of the artery (or probable atherosclerosis if calcifications were observed along the course of the artery).

The following figures come from a precedent paper In JACC

Atherosclerosis was observed in the aorta of 28 mummies and in the iliac or femoral arteries of 25 mummies. Another 25 mummies had atherosclerosis in the popliteal or tibial arteries, while 17 had carotid-artery disease and six had atherosclerosis observed in the coronary arteries. One in four
of the mummies had atherosclerosis in at least two vascular beds.

**Figure Legend:**
Atherosclerosis in the Superficial Femoral Arteries
Computed tomography maximum intensity projection of the upper legs showing extensive calcifications along the course of the superficial femoral arteries in the mummy of a man who lived during the 18th Dynasty (Hatiay, Mummy #23).

Based on calculations using architectural changes in the bone structures, the mean age at the time of death was 43 years old, and age was positively correlated with atherosclerosis.

Thompson and colleagues note that all four populations lived at a time when infections would have been a common cause of death. The high level of chronic infection and inflammation might have promoted the inflammatory aspects of atherosclerosis, they write, which would be consistent with the accelerated course of disease observed in patients with rheumatoid arthritis and lupus.

**In conclusion, atherosclerosis was common in four preindustrial populations, including a preagricultural**
hunter-gather population, and across a wide span of human history. It remains prevalent in contemporary human beings. The presence of atherosclerosis in premodern human beings suggests that the disease is an inherent component of human aging and not associated with any specific diet or lifestyle."

Ref