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Shah B, Newman JD, Woolf K, et al. Anti-Inflammatory Effects of a Vegan Diet Versus the American Heart Association-Recommended Diet in Coronary Artery Disease Trial. J Am Heart Assoc. 2018;7(23):e011367.

What We Know, Think We Know, or Are Starting to Know

While the effect of low-density lipoprotein cholesterol [LDL-C] on coronary heart disease [CHD] risk is well-established, and considered a causal factor, the separate effects of inflammation on CHD have only more recently come under direct scrutiny. Observational cohorts in the late 1990' s and early 2000' s were the first to identify that high-sensitivity C-reactive protein [hsCRP] was independently associated with an increased future risk of heart attacks [myocardial infarction: MI], stroke, and cardiovascular death [1,2]. These associations were observed in participants with otherwise normal cholesterol levels.

A 2002 analysis comparing hsCRP to LDL-C for predicting major CHD events over a mean of 8-years follow-up found a near identical rate of CHD events in each quintile of both hsCRP and LDL-C, indicating that an independence of both risk factors for CHD risk [1]. A number of statin intervention studies around the same period found, as secondary outcomes, that statins have an anti-inflammatory effect in addition to their LDL-lowering effect [3,4]. The reduction in risk from statin therapy was shown to be greater in participants with higher baseline hsCRP levels [3,4].

Up until recently no trial had examined the effects of targeting reductions in hsCRP independent of LDL-C levels. The recent CANTOS study did just that; the study investigated the effects of an anti-inflammatory drug on CHD events in patients who had suffered a prior MI, who were on intensive statin therapy with an average LDL-C 80mg/dL range*, but with elevated hsCRP >2mg/L [5]. There was a significant reduction in risk in participants achieving a hsCRP level of <2mg/L, with no change in LDL-C [5].

The role of dietary interventions in inflammation at this point remains relatively broad, and emphasises dietary patterns; Mediterranean and Nordic dietary patterns are all associated with reduced inflammatory markers [6,7]. The unifying characteristics appear to be an emphasis on vegetables, fruits wholegrains, and unsaturated fats from plant and marine sources [6,7]. This study tested a vegan diet against the American Heart Association recommended diet for effects on hsCRP.

*Geek Box: Blood Lipid Levels

Context will be helpful in any study you read with blood cholesterol levels as an outcome, so let's expand on this here. We now have overwhelming proof that LDL-C causes atherosclerosis. Now, this doesn't mean that other lipoproteins are not a risk factor, it just means they have not yet satisfied the scientific criteria for causality. But they are close; for example, lipoprotein(a), or Lp(a), has an intervention trial beginning which is directly targeting Lp(a) reductions, and if that is successful, Lp(a) will also be deemed causal. However, LDL-C remains the prime focus for now, and is the main focus of treatment guidelines. Current guidelines indicate that normal LDL-C is <116mg/dL or <3.0mmol/L, but in people with no other health issues, an LDL-C of up to 130mg/dL or 3.3mmol/L is not currently considered a major concern. This is, however, an ongoing conversation as the evidence for 'lower is better and earlier is better' continues to get stronger. For people at moderate cardiovascular risk, the goal is LDL-C <100mg/dL or <2.6mmol/L. For high risk, the goal is a reduction of >50% from baseline, aiming for LDL-C <70mg/dL or <1.8mmol/L. Very high-risk in primary prevention [i.e., have not suffered a cardiovascular event yet], the goal is LDL-C <55mg/dL or <1.4mmol/L. The goals for secondary prevention the goals are the same as very-high risk primary prevention, however, if a second event occurs, the goal is LDL-C <40mg/dL or <1.0mmol/L. It is helpful reading papers to have these latest treatment guidelines from the European Atherosclerosis Society in mind. And, if a paper ever reports in either mg/dL or mmol/L, and you understand one or the other better, then to convert mg into mmol, divide by 38.6; to convert mmol into mg, multiple by 38.6.

The Study

The study was designed as a prospective, randomised, open-label, blinded endpoint trial.* 100 participants with a history of diagnosed coronary artery disease [CAD] attending New York University Langone Medical Center underwent 1:1 computerised randomization to either a vegan diet [VD] or the AHA-recommended diet [AHAD].

The participants were in secondary prevention, meaning that they had suffered a prior coronary event. Key study foods were provided on a weekly basis, and cookbooks to comply with the vegan and low-fat, low-cholesterol AHA diet, respectively. Both diets were kept relatively similar in terms of foods, with the main aim being the substitution of animal protein sources for plant protein sources in the VD.

Adherence with the diets was based on scoring systems. The VD was scored 1 point each for abstinence from: 1) meat, poultry, eggs; 2) dairy; 3) seafood; a maximum of 6 points was available from both 24hr recalls each week, and 5-6 points was deemed adherent for that week. For the AHAD, 1 point was scored for: 1) <5oz animal protein per day; 2) only low-fat/non-fat dairy; 3) fish >2 times per week. A score of 4-5 deemed adherent for the AHA diet. Overall adherence was deemed to be adherence for 2/3 weeks before the follow-up visits at week 4 and week 8.

Both study groups had access to the study dietitian by email or phone. Participants completed two 24-hour recalls each week, which were used to assess dietary adherence and diet composition. The intervention lasted 8-weeks, with participants attending for in-clinic visits at baseline, week 4, and week 8; a 4-day food record was completed prior to the week 4 and 8 visits, respectively.

The primary endpoint of the study was hsCRP. Secondary endpoints were inflammatory markers, anthropometric data, glcyaemic markers, and blood lipids.

*Geek Box: PROBE Trials

A prospective, randomised, open-label, blinded endpoint [PROBE] trial is an alternative to the traditional double-blind, placebo controlled trials which are the 'gold standard' in biomedical sciences. PROBE studies are designed to be cost effective alternative to placebo-controlled, double-blind RCTs. Randomisation in a PROBE trial is still conducted appropriately, but the aim of a PROBE trial is to conduct the study in similar conditions as regular clinical practice. Because the treatment of patients is conducted openly, it may be a way of achieving better compliance from patients with the intervention, which is important for dietary intervention studies. In a PROBE study, an endpoint committee is established to select endpoint and set guidelines for the evaluation of the data, for example, the analysis will be conducted by people blinded to the treatment groups. Such study designs are incredibly useful when the goal is not necessarily to compare an intervention to a placebo, but to compare two interventions in a side-by-side manner. This is important for nutrition, given that there is no true placebo for food. The prospective nature of the study allows for the effect of the interventions to be evaluated over time. PROBE designs are of real utility in nutrition science, given the interventions always involve behaviour change, require a degree of investigator input, and absent a placebo for food, are more informative where two specific diets are compared to each other.

Results: Participants in the vegan diet group were older than those in the AHA diet group (63.0 vs. 59.5). 78% had dyslipidemia in both groups, 62 and 64% had hypertension in the VD and AHA groups, respectively. T2DM and history of prior MI present in around 30%. Nearly all participants on statins (94% in the VD and 96% in the AHA); 58% in the VD on intensive statin therapy [40-80mg atorvastatin or 20-40mg rosuvastatin); 56% in the AHA.

- ***Diet*:** Both diets resulted in similar decreased in total energy, protein, total fat, and saturated fat. However, energy intake overall was higher in the VD group, while protein intake was significantly lower: 96g to 50g vs. 86g to 80g from baseline to week 8 in the VD and AHA, respectively. .

  Dietary fibre intake increased significantly in the VD group: 21g to 36g vs. 22g to 25g from baseline to week 8 in the VD and AHA, respectively. The VD significantly increased grain intake, while the AHAD resulted in a decrease.

  The VD resulted in significantly lower intake of vitamin B12, zinc, and omega-3 fatty acids.

- ***Primary Endpoint*:** VD resulted in 32% lower hsCRP compared to AHA, after adjusting for baseline hsCRP levels. After adjusting for additional factors which could influence inflammatory status, the significance remained and the VD displayed a 33% lower concentration of hsCRP vs. the AHA.

  Secondary Endpoints: The VD resulted in a non-significant 13% reduction in LDL-C vs. AHAD, after adjustement for age, race, waist circumference, present diabetes, and prior MI. There was no change in other lipid parameters.

  There was no significant differences in weight loss, fasting glucose, hemoglobin A1c [HbA1c], or insulin levels, or other secondary endpoints, between diets.

The Critical Breakdown

Pros: The study aimed to treat both dietary groups similarly, with the only significant dietary difference being from plant vs. animal protein in the respective diets. Both groups had the same level of access to the study dietitian, were provided with key study foods for both diets, and corresponding cookbooks. Participants were on stable medication regimens, and had low baseline LDL-C levels, allowing for a more direct test of the effects of diet on hsCRP.

Cons: Baseline hsCRP levels were not particularly high at baseline [more under Key Characteristic, below]. Dietary adherence and nutritional analysis was largely based on 24-hour recalls, which are prone to significant within-person variability. Despite the similar treatment afforded both diet groups, adherence in the AHAD was quite poor [more under Interesting Finding, below]. Diets were consumed under free-living conditions, and deviation from protocol cannot be ruled out, and appears evident in the AHAD group. An 8-week intervention is a very short-duration intervention, and may be a factor in the lack of any significant effect overall on most parameters measured.

Key Characteristic

Baseline levels of hsCRP were not that high, having regard to the large drug intervention studies which have examined hsCRP and LDL-C and heart disease. hsCRP has the following ranges:

- <1mg/L: low CHD risk
- 1-3mg/L: moderate CHD risk
- >3mg/L: high CHD ris

However, substantial differences are observed between hsCRP >2mg/L and <2mg/L; in the CANTOS trial, participants with hsCRP concentrations >2mg/L did not have any significant reduction in clinical events after 3 months; those who achieved hsCRP <2mg/L at 3 months had 25% reduction in risk [(5)].

Secondly, the most significant effect of the VD occurred between baseline and 4-weeks, dropping from 1.25mg/L to 1.00mg/L; from week 4 to the end of the 8-week intervention, hsCRP increased from 1.00mg/L to 1.10mg/L. In contrast the AHA diet decreased from 1.15mg/L to 1.10mg/L at week 4 and remained at the level to the end of the intervention.

These changes beg the question of whether 'statistical significance' in fact corresponds to 'clinically meaningful'. Given this background knowledge, why the study did not deliberately stipulate an inclusion criteria of >2mg/L hsCRP, is a bit of a head scratch. Arguably, this would have been a much more robust test of the effects of the diets.

Interesting Finding

The investigators made substantial efforts to ensure that both dietary groups received equal support, as a noted limitation of too many dietary interventions is a bias toward the intervention group. In fact, often the 'control' group is just a continuation of habitual diet, rather than a direct head-to-head comparison of two diets that might both be beneficial. This study sought to achieve that, by providing email and phone access to the study dietitian for both groups. Both groups were provided with key foods to achieve their respective dietary recommendations, and corresponding cookbooks. And if a participant in the AHA diet consumed no animal protein or dairy, they were still deemed to have been compliant with the protocol.

Despite this relative equilibrium between the two dietary arms of he study, adherence between diet groups was significantly different. In the vegan and AHA groups, respectively: 96% vs. 84% at 4-weeks; 94% vs. 70% at 8-weeks.

Two things were evident in the data:

a) linear decreases in dietary adherence over time in the AHAD group, and;

b) very substantial differences between the groups over the course of the 8-week intervention.

The implication is that the effects of the vegan diet may be statistically overexaggerated compared to the AHA diet, and/or that participants in the vegan diet group may have been more motivated, or received more emphasis in the contacts with study personnel, introducing the potential for investigator bias.

Relevance

Management of residual risk may have a role for diet, but it is relatively underwhelming compared to the available evidence for pharmacotherapy. It is difficult to say that this study adds much, and in fact it is arguable given the participant characteristics and inclusion criteria that the study focused on the wrong primary endpoint.

In the treatment of heart disease, it has emerged that despite achieving what guidelines say are target treatment levels, there remains what is known as "residual risk", i.e., patients may still have a secondary coronary event despite having achieved low cholesterol and/or inflammation levels.

Two phenotypes have been shown in this respect: “Residual Inflammatory Risk” and “Residual Cholesterol Risk” [8]:

- Residual Cholesterol Risk: LDL-C >70mg/dL and hsCRP <2mg/L
- Residual Inflammatory Risk: LDL-C <70mg/dL and hsCRP >2mg/L

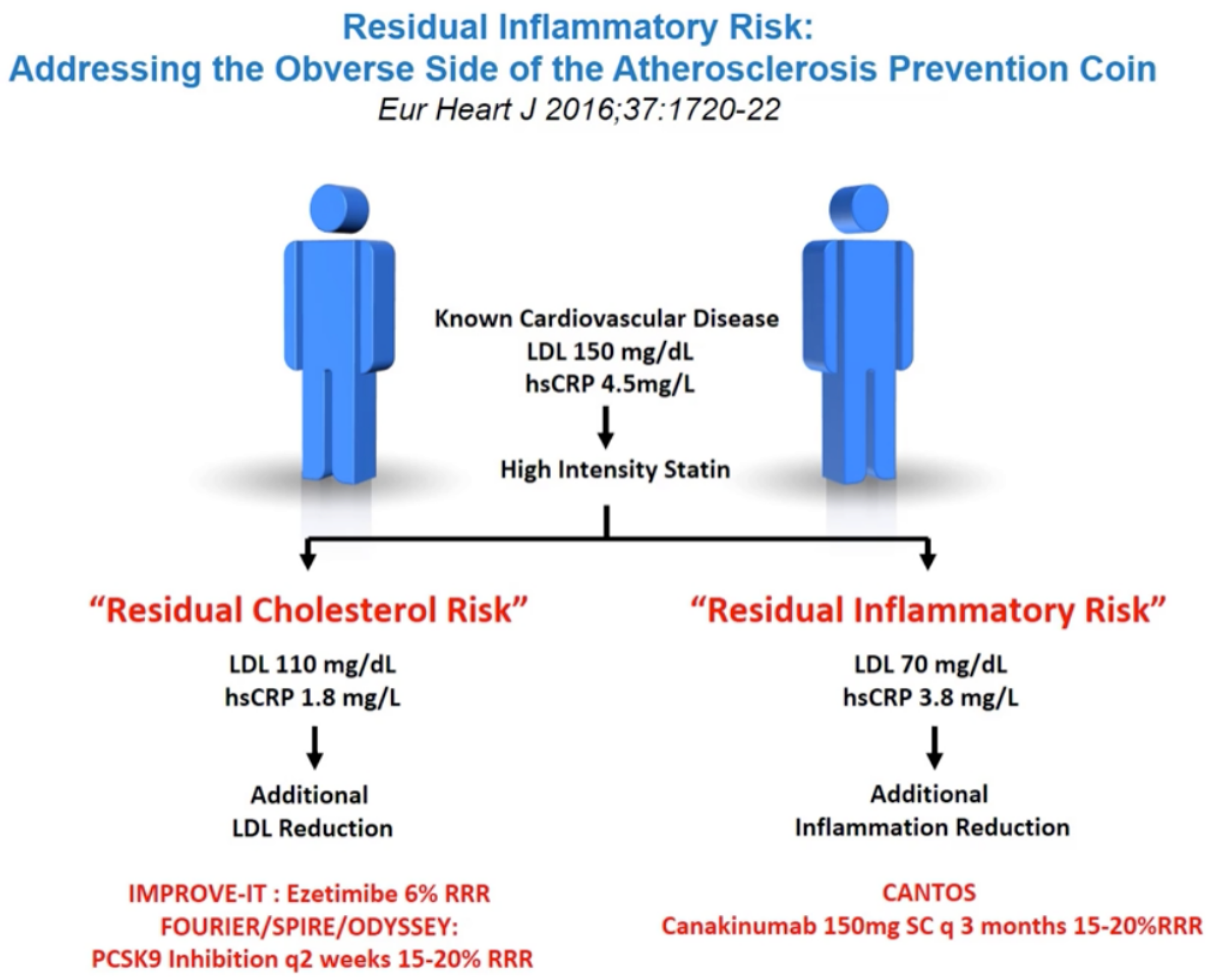

***Figure** from [8] illustrating the respective concepts of residual cardiovascular risk, either “residual cholesterol risk” (**left**) or “residual inflammatory risk” (**right**).*

These thresholds are set in the context of primary prevention. In secondary prevention, the LDL-C treatment goal is <55mg/dL [9]. Based on their baseline characteristics, the present study participants fall into a category of hsCRP that would not meet the criteria for residual inflammatory risk; the residual risk in this group in secondary prevention would remain at levels of LDL-C observed in this study.

More particularly, despite the reduction in hsCRP the VD still did not achieve hsCRP levels of <1mg/L. Therefore, while statistically the findings are certainly not a false positive, it is arguable that they are somewhat of a clinical 'false positive'.

In relation to LDL-C, all participants had LDL-C of <75mg/dL at baseline, thus at a level which is desired for primary prevention of 'at risk' levels. In the AHAD, LDL-C levels did not change, but in the VD group LDL-C decreased from 73mg/dL to 63mg/dL, which was not statistically significant. Could the VD have helped achieved an LDL-C level of <55mg/dL? An 8-week intervention is likely too short in duration to tell us.

Application to Practice

It remains difficult to separate the dietary characteristics - higher fibre, increasing plant protein sources, low saturated fat - from the binary construct of 'animal exclusive vs. animal inclusive'.

Objectively, the data remains unconvincing that there is any enormous advantage to vegan diets over other healthful dietary patterns for cardiovascular disease risk management. The vast majority of endpoints in this study were not different between diets.

Labels on diets continue to be problematic; let's keep focus on characteristics, and the most likely explanation for the results in this study is the significant difference in fibre intake between diets. Thankfully for the practitioner, advice to increase fibre in the diet transcends the label one puts on a diet.

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