

Letters to the Editor

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Drug Combo Adds No Benefit in Patients with Type 2 Diabetes

Article: Management of Blood Glucose with Noninsulin Therapies in Type 2 Diabetes

Issue Date: July 1, 2015

See additional reader comments at: <http://www.aafp.org/afp/2015/0701/p27.html>

TO THE EDITOR: I applaud the authors for focusing their review on clinically relevant and useful guidance for managing blood glucose levels with noninsulin therapies. The streamlined algorithm in *Figure 1*, however, is misleading in two regards.

First, the algorithm suggests that a dipeptidyl-peptidase-4 (DPP-4) inhibitor and a glucagon-like peptide-1 (GLP-1) receptor agonist are a recommended combination. Combining medications from these two classes has been investigated in one animal study and one randomized controlled trial in humans.¹ In the animal study, adding sitagliptin (Januvia) to liraglutide (Victoza) did not increase the blood concentration of liraglutide, change its pharmacokinetics, or reduce its breakdown. In the human trial, patients taking metformin plus sitagliptin were randomized to either add exenatide (Byetta, Bydureon) or substitute sitagliptin with exenatide. Although the triple-therapy group had an additional 0.3% decrease in A1C level, this change is smaller than what would be expected after adding other recommended agents. Also, it is much lower than the average A1C decrease with GLP-1 receptor agonists (0.8% to 2%) that would be expected in the absence of coadministered DPP-4 inhibitors.

The best available evidence suggests that coadministration of DPP-4 inhibitors and GLP-1 receptor agonists is clinically inferior to other options for enhancing glycemic control. As this review points out, this combination is not approved by the U.S. Food and Drug Administration, nor recommended in the algorithm from the American Diabetes

Association (ADA), which is a source for the simplified algorithm in *Figure 1*.²

Second, *Figure 1* suggests that adding a sulfonylurea to a basal insulin is a recommended combination. However, the ADA algorithm does not recommend this combination. In the algorithm's initial publication, the authors noted, "Insulin secretagogues do not seem to provide for additional HbA_{1c} reduction or prevention of hypoglycemia or weight gain after insulin is started, especially after the dose is titrated and stabilized."³ The American Association of Clinical Endocrinologists/American College of Endocrinology comprehensive diabetes management algorithm from 2015 similarly states, "Consider discontinuing or reducing sulfonylurea after basal insulin started."⁴

Given the variety of recommended combinations to help patients with type 2 diabetes mellitus achieve their personalized goals, we should not be using nonrecommended combinations that add little or no clinical benefit.

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IN REPLY: We thank Dr. Geurin for bringing up two issues that may have caused confusion. The intent of the algorithm was to simplify the available medication choices, rather than recommend specific medications or combinations as preferred add-on therapy. We recommended that a comprehensive, ►

patient-centered approach be used to select drug therapy, while considering A1C levels, fasting or postprandial glucose control, weight loss, and adverse effects. We thought the similar mechanisms of action for drug classes listed in *eTable B* would lead readers to conclude that concomitant therapy would not be acceptable, but we should have been more explicit.

Dr. Geurin's second concern was that *Figure 1* also suggested that the addition of a sulfonylurea to established basal insulin therapy was a recommended combination. Although we concur that this drug combination is not ideal, we also recognize that some patients may have limited medication choices because of cost, adverse effects, contraindications, or personal preference. An exhaustive review of the evidence for and against various combination therapies was beyond the scope of our article.

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Foods Containing Saturated Fat: Dietary Limits Are Still Essential

Article: Nutrition Myths and Healthy Dietary Advice in Clinical Practice

Issue Date: May 1, 2015

See additional reader comments at: <http://www.aafp.org/afp/2015/0501/p634.html>

TO THE EDITOR: Lesser and colleagues should be commended for addressing nutrition, an often neglected subject in family medicine. However, I question the assertion that consuming whole foods containing saturated fat is inversely associated with incident cardiovascular disease and type 2 diabetes mellitus. Although they suggest that consuming more dietary fiber in the form of whole foods *may* help prevent cardiovascular disease and diabetes, they do not advise an upper limit for saturated fatty acid (SFA) intake. These recommendations may cause patients to replace high-fiber whole plant foods with foods containing SFAs and protein, resulting in meat-based "low-carb" diets, which are associated with greater all-cause mortality (*Table 1*).¹

Although the authors highlight the association between processed meat and cardiovascular and all-cause mortality, two of their

references show a similar association for *unprocessed* meat. One study observed dose-response relationships for unprocessed and processed meat across mortality categories,² and the other reported a 31% increase in risk of cardiovascular disease for each 5 g per day of total energy from meat SFA.³ Although the authors' proposed alternatives to processed foods (pastured meat or eggs, wild game) contain a more favorable fatty acid profile, no evidence shows any patient-oriented benefit over unprocessed meat.

Although pointing out that simply substituting SFAs with refined carbohydrates does not improve outcomes, the authors dispute the value of substituting SFAs with polyunsaturated fatty acids. The cited Cochrane review concluded the exact opposite: "Lifestyle advice to all those at risk of cardiovascular disease ... should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturates."⁴ The ▶

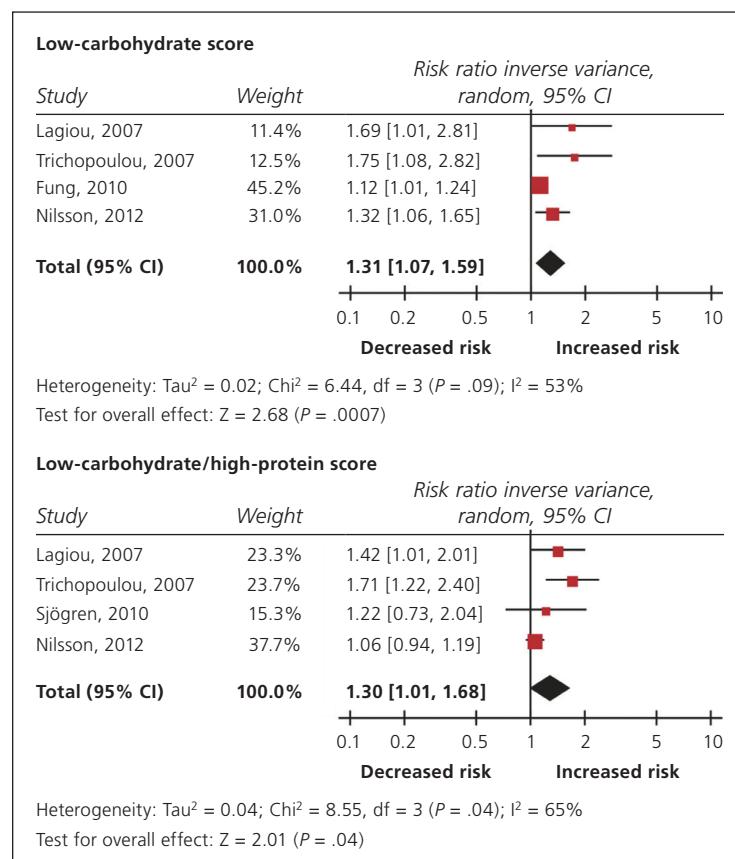


Table 1. Adjusted risk ratios for all-cause mortality associated with low-carbohydrate diets. Analysis was based on low-carbohydrate and low-carbohydrate/high-protein scores. Boxes = estimated risk ratios; bars = 95% CIs; diamonds = random-effects model risk ratios; width of diamonds; pooled CIs. The size of each box is proportional to the weight of each study in the meta-analysis. (CI = confidence interval.)

Adapted from Noto H, et al. Low-carbohydrate diets and all-cause mortality: a systematic review and meta-analysis of observational studies. *PLoS One*. 2013;8(1):e55030.

review found a 14% reduction in cardiovascular events at six months after reducing SFA by reducing and/or modifying dietary fat, along with other lifestyle changes, and this increased to 22% after two years. This relative risk reduction is comparable to that achieved by pharmacologic treatment of mild to moderate hypertension.

Finally, the authors state that consuming dairy foods may lower the risk of type 2 diabetes, obesity, and cardiovascular disease. However, two of the provided meta-analyses supporting this assertion have coauthors funded by the National Dairy Council, and more recent studies about dairy have been mixed.^{5,6} Such a body of evidence is not sufficient to disregard American College of Cardiology and American Heart Association recommendations to not exceed 6% of total calories from SFAs, or the American Diabetes Association's recommended upper limit of 10%.

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IN REPLY: We thank Dr. Sherwood for the letter and hope he and other readers take away from our article that humans should eat mostly plants in minimally processed form. That said, individuals can include foods from animals if they choose and still have a healthy diet. Dr. Sherwood worries that we do not set a limit for SFA intake. One reason we do not is that SFAs are a heterogeneous group of compounds with nonuniform effects.¹ It makes little sense to lump different SFAs in a group (just as it would make little sense to lump SFAs in a group with unsaturated fatty acids). Nonetheless, many studies consider SFAs collectively. Perhaps the most rigorous review of such studies found no effects on cardiovascular or all-cause mortality with reduction of SFAs or with substituting saturated fat with other fats.² The abstract of this review makes the recommendation Dr. Sherwood notes, but the only direct association with SFAs in the text is to

cardiovascular events, and this association was statistically insignificant when authors removed biased studies (i.e., those having differences between intervention and control arms other than related to dietary fats).² Another issue with an SFA limit is that people eat foods, not isolated SFAs. Dr. Sherwood conflates SFAs with meat and dairy, but plenty of other foods contain SFAs (e.g., nuts, which are associated with decided health benefits).³

Regarding meat, our two cited meta-analyses do indeed show direct associations between unprocessed meat consumption and cardiovascular risk or mortality. However, effects may depend on patient characteristics (e.g., as per the meta-analysis by O'Sullivan and colleagues, some populations show *decreased* mortality with meat consumption) and on meat quality (nutritional composition varies considerably with how animals are raised⁴; existing studies on adverse effects do not consider this nuance). As for dairy, we agree that the funding source may bias conclusions.⁵ However, consistent evidence suggests that dairy is not harmful (e.g., the meta-analysis by O'Sullivan and colleagues) and may even be beneficial (with potential benefits possibly mediated by the SFAs themselves⁶).

Dr. Sherwood also raises concern about low-carbohydrate diets and mortality. We do not recommend focusing on carbohydrates, just like we do not recommend focusing on SFAs (or any other food constituent). We believe the focus should be on foods and food combinations. We advise eating real foods, mostly from plants, but allow for inclusion of well-raised meats and other animal products per individual preferences.

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