Comments and Response

Association of Dietary, Circulating, and Supplement Fatty Acids With Coronary Risk

TO THE EDITOR: We appreciate that Chowdhury and colleagues (1) have corrected some of the gross errors in their original paper. Of note, the inverse association of intake of long-chain ω-3 polyunsaturated fatty acids (PUFAs) with cardiovascular disease (CVD) risk is now significant. We also appreciate the sensitivity analysis showing that with exclusion of the outlying SDHS (Sydney Diet Heart Study), the included randomized, controlled trials (RCTs) show benefit of replacing saturated fatty acids (SFAs) with PUFAs. The extreme diet used in that study was never recommended or consumed in the United States. It included a trans fat–based margarine and probably very little ω-3 PUFAs, because sunflower oil was used to replace other fats as much as possible. However, other serious problems with Chowdhury and colleagues' analysis remain. They report that the nonsignificant findings for biomarkers of long-chain ω-3 fatty acid intake are based on total long-chain ω-3 PUFAs in only 4 studies. However, in the Supplement Tables, long-chain ω-3 PUFAs were actually examined in 13 studies, and findings for the specific long-chain PUFAs (eicosapentaenoic and docosahexaenoic acids) were robustly and significantly inverse. Thus, the results for both intake and biomarkers for long-chain ω-3 fatty acids support benefit. Although the findings for RCTs vary, these results would be expected because many of the populations studied had relatively high intake of ω-3 fatty acids and most individuals would likely experience little benefit.

The analysis for ω-6 PUFAs still includes only 8 studies and omits others included in Jakobsen and coauthors' (2) pooled analysis of original data and other published papers. The data on intake of ω-6 PUFAs from the Kuopio Heart Study (3), the study with the most positive association, are erroneous because the denominator is almost double the number of healthy participants. Contrary to what Chowdhury and colleagues state, they apparently included persons with prevalent CVD at baseline instead of limiting the analysis to healthy persons. The original study reported a relative risk (RR) of 0.38 (95% CI, 0.20 to 0.70) for fatal CVD among those with higher intake of PUFAs.

Chowdhury and colleagues still do not acknowledge the earlier pooled analysis of primary data based on a larger number of studies, which allowed direct comparisons among different types of fats. In that analysis, substitution of SFAs with PUFAs was associated with lower risks for coronary heart disease (CHD) (2). The large body of data showing that replacing SFAs with monosaturated fatty acids (MUFAs) or PUFAs reduces low-density lipoprotein (LDL) cholesterol is still not recognized.

Although Chowdhury and colleagues say that their conclusions did not change, a more inclusive and correct review of available evidence would support the replacement of SFAs with PUFAs.

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TO THE EDITOR: Chowdhury and colleagues (1) analyzed 8 studies to assess the association between circulating blood levels of SFAs and RR for coronary outcomes (1). From our point of view, the results of NSHDS (Northern Sweden Health and Disease Study) and VIP (Västerbotten Intervention Program) have been misinterpreted, and the studies should be excluded for the following reasons.

First, data from VIP (2, 3) have been included in the evaluation of NSHDS results (4). Second, VIP and NSHDS assessed the association between high intake of SFAs from dairy products (indicated by pentadecanoic acid [C15:0] and heptadecanoic acid [C17:0] or their sum in serum lipid esters) and CVD (3, 4). In both studies, negative associations between milk fat intake and first-ever myocardial infarction were found. Neither of the 2 studies described the impact of total circulating blood levels of SFA on coronary outcomes. Of note, C15:0 and C17:0 contribute only 0.5% to 1.0% of the fatty acids in total phospholipid levels (4). In contrast, the total SFA level in plasma phospholipids ranges between 40% and 45%, which is mainly composed of palmitic acid (C16:0) and stearic acid (C18:0) with approximately 50% to 60% and 30% to 40% of the total SFA level, respectively (5). Thus, C15:0 and C17:0 are markers for milk or ruminant fat intake (3, 4) but not for total SFA intake. However, there are several SFA sources, such as baking margarines, coconut oil, and palm oil, that do not contain C15:0 and C17:0. In agreement with this, we also found that proportions of C15:0 and C17:0 in human erythrocyte membranes are between 1.0% to 2.9% of total SFA levels and show no correlation with the concentration of total SFAs (ClinicalTrials.gov: NCT01437930 and NCT01742468). When we repeated the meta-analysis after excluding VIP and NSHDS results, we found a positive association of total SFA blood levels and coronary outcomes (RR, 1.21 [CI, 1.04 to 1.40]). This finding contradicts the overall conclusion drawn by Chowdhury and colleagues (1).

Proper communication of the health risks associated with dietary habits is essential to achieve appropriate lifestyle changes and improve cardiovascular health. The results of the meta-analysis gave rise to misleading headlines, like "Animal fat is not bad for the heart" (6), in the national lay press. Consumers may continue their unhealthy dietary habits in response to such simplified messages. Because of the impact of meta-analyses on the general public, thoroughly and reasonable selection of studies and careful evaluation of data are vital to reporting accurate results and protecting people from harm.

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TO THE EDITOR: The review by Chowdhury and colleagues (1) provides a sobering reappraisal of the widely presumed association between dietary fat and coronary disease. Unfortunately, their otherwise careful analysis uncritically accepts the assumption that the size of an intervention's effect in individual members (or subgroups) of a study population is the same as that of the entire study population; that is, the review fails to avoid the ecological fallacy.

Kent and coauthors (2) identify 2 potentially serious clinical consequences of ignoring the ecological fallacy. Both are due to the inherent risk-based heterogeneity of absolute treatment effects (3), which has been shown to vary as much as 20-fold between study population subgroups with the highest versus lowest baseline risk for adverse outcomes (2). The first problem is failure to recognize that some interventions whose efficacy is statistically confirmed in an entire study population provide no meaningful benefit to sizeable subgroups of that population. For example, warfarin prevents stroke more effectively than aspirin in the overall population of patients with nonvalvular atrial fibrillation, but the subgroup of patients without additional risk factors for stroke does not benefit incrementally from warfarin therapy (2). The second, and opposite, problem is failure to recognize that some interventions provide true benefit in subgroups of a study population even though the intervention is not shown statistically to "work" in the population as a whole. The inclusion of study populations at widely varying baseline risk for adverse coronary events in the review by Chowdhury and colleagues (1) greatly increases the likelihood that its broadly negative conclusion is, at least in part, falsely negative.

Interestingly, although risk-based targeting of clinical interventions is a neglected (and perhaps resisted) approach in many areas of clinical practice, including drug therapy (4), it is rapidly gaining acceptance as an appropriate, effective, and efficient clinical strategy in cancer screening (5). Kent and coauthors propose a multivariable technique for measuring the impact of clinical interventions in subgroups at different levels of baseline risk. The technique is relatively straightforward, has substantial statistical power, and avoids most of the usual methodological pitfalls of "one-variable-at-a-time" subgroup analyses (2).

In our view, truly evidence-based recommendations on dietary fat will be possible only when we have answered the crucial questions of which changes in dietary fat (if any) reduce the rate of coronary events, in whom, and under what conditions by careful risk-stratified examination of these causal relationships.

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TO THE EDITOR: Chowdhury and colleagues (1) concluded that evidence is insufficient to support guidelines that encourage high intake of PUFAs and low intake of SFAs by misrepresenting the strongest evidence for those guidelines.

An earlier meta-analysis (2) found a 19% reduction in CHD risk in RCTs that replaced saturated fat with ω-6 PUFAs. In their Supplement Figure 14, Chowdhury and colleagues found no signif-

icant risk reduction because they included 1 additional trial, the SDHS, which provided participants with margarine high in trans fatty acids. Without the SDHS, Chowdhury and colleagues found the same 19% risk reduction. Was that critical finding omitted from the printed study because it contradicted their main conclusion?

Furthermore, Chowdhury and colleagues incorrectly referred to the 8 trials examined as "supplementation" trials. In fact, those trials reduced saturated fats and replaced them with polyunsaturated fats, precisely what most guidelines recommend. The evidence from these trials trumps observational studies—plagued by imprecise dietary intake data and possible residual confounding—that have failed to find an association between fatty acids and risk for heart disease.

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TO THE EDITOR: Chowdhury and colleagues (1) concluded that their findings do not "yield clearly supportive evidence for current cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of saturated fats." Current guidelines recommend a PUFA intake (typically 5% to 11% of total energy intake) modestly higher than what is currently consumed in most Western countries and an SFA intake less than 10% of total energy intake. These recommendations are based on the totality of relevant evidence linking fatty acids and cardiovascular risk.

In this regard, there is an important body of epidemiologic evidence that Chowdhury and colleagues did not consider, presumably because their meta-analysis was based on aggregate data. A pooled analysis of participant data from 11 cohort studies, including 2155 coronary deaths among 344 696 persons (2), found a 26% reduction in coronary deaths when a 5% lower energy intake from SFAs was combined with a higher intake of PUFAs. This important evidence extends the knowledge about dietary fatty acids by showing the effects of SFA on coronary disease, not in isolation from other macronutrients but when replaced by other fatty acids or carbohydrates as would occur in persons following dietary guidelines.

Serum total cholesterol, a powerful causal risk factor for CVD, is reduced to a predictable extent when ω-6 PUFAs (or MUFAs) replace SFAs (3). The RCTs reporting clinical outcomes are more difficult to interpret; most were initiated many decades ago, involved various intervention diets, and had sparse information about participant compliance. Nevertheless, a meta-analysis of such trials by Mozaffarian and colleagues (4) showed that increasing intake of PUFA instead of SFA resulted in a 19% reduction in risk for coronary events, which closely matched predictions based on the effects of dietary fats on the total–high-density lipoprotein cholesterol ratio (3). The corresponding summary estimate reported by Chowdhury and colleagues includes 1 additional study, the reanalysis of the SDHS (5). Inclusion of this study, which involved the recommendation of a diet very high in PUFAs and reported relatively discrepant findings to the other studies, contributed to the slightly wider CI.

We submit that Chowdhury and colleagues' results do not contradict previous meta-analyses of aggregate data. Although nutritional guidelines should be regularly reviewed, we find no evidence here to suggest that current recommendations are inappropriate.

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TO THE EDITOR: We read the meta-analysis by Chowdhury and colleagues with great interest (1). The authors systematically reviewed prospective and observational studies as well as RCTs investigating the associations between fatty acid consumption and coronary disease using both dietary intake and circulating fatty acids as measures. The results reported a null association of total and individual MUFAs with coronary risk.

There has been a lot of debate regarding the potential role of MUFAs in the pathogenesis of atherosclerosis. We recently published a review on MUFAs and CVD (2) that summarized the results of 16 systematic reviews and meta-analyses of RCTs and cohort studies. We found that MUFA had a favorable influence on several cardiovascular risk factors and CVD end points. Some of the controversial findings might be explained by the origin of MUFAs in the respective studies, resulting in a confounder that should be taken into account when different dietary fats are being compared. Adopting a Western diet means that MUFA is predominantly supplied by foods of animal origin, whereas in Southern Europe extra-virgin olive oil is the dominant source of fat. Results of the recently published PREDIMED trial demonstrated major cardiovascular benefits of olive oil and nuts when compared with a low-fat diet (3). As a major outcome parameter, the risk for stroke was reduced, an event that had not been included in the meta-analysis by Chowdhury and colleagues.

A recent cohort study observed a significant association among dietary olive oil, higher plasma oleic acid, and reduced risk for stroke (4). Extra-virgin olive oil is regarded as the genuine driver of the Mediterranean diet and was found to be associated with a 26% reduced risk for all-cause mortality in the Spanish branch of the EPIC study (5). Furthermore, adherence to a Mediterranean diet was associated with a reduced risk for all-cause mortality, CVD, cancer, and neurodegenerative disease (6). Thus, the results of the present meta-analysis warrant further investigations with respect to the correlations between MUFA and cardiovascular risks. Future meta-analyses should focus on MUFAs and CVD (combining CHD and stroke) and should differentiate between the dietary sources of fatty acids (such as oleic acid and extra-virgin olive oil).

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TO THE EDITOR: The meta-analysis by Chowdhury and colleagues (1) regarding the association of various fatty acids with coronary risk piques my interest. Although the authors reported data regarding palmitoleic acid on coronary risk, they did not mention the potential impact of trans-palmitoleic acid on coronary risk. In their prospective cohort study, Mozaffarian and coauthors (2) assessed the effect of -palmitoleic acid on vascular risk factors, especially diabetes risk.

Trans-palmitoleic acid is generally acquired from exogenous sources and until recently has not been believed to be endogenously synthesizable. It is created by fermentation in the rumen of dairy cattle and is a marker for consumption of dairy fat, although a recent publication does suggest a pathway used for endogenous synthesis (3). Increasing levels of plasma trans-palmitoleic acid were associated with lower levels of insulin resistance, decreased C-reactive protein levels, higher HDL cholesterol levels, and a substantially reduced incidence of diabetes (multivariate hazard ratio, 0.41) (2). No data were reported on coronary risk. Given the salutary effect of trans-palmitoleic acid on multiple cardiovascular risk factors and the considerable contribution of dairy fat in the overall intake of saturated fat of most populations, perhaps dairy fat consumption could account for much of the mitigation of the heretofore expected, worsened cardiovascular risk with increased levels of trans-saturated fat.

I look forward to the inclusion of data on trans-palmitoleic acid levels and their impact on coronary risk in future studies of the association between nutrition and cardiovascular risk. I'd like butter on that slice of bread, please!

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TO THE EDITOR: Chowdhury and colleagues' (1) systematic review questions current dietary guidelines on fat quality in the diet. A close look at the authors' results reveals serious flaws in their data collection and analysis.

Guidelines for healthier fat intake must account for what replaces the restricted items. We now know that replacing SFA with sugar and refined carbohydrates does not reduce the risk for heart

disease, but replacement with PUFA does. This is the current scientific consensus and is the basis of recent recommendations to replace SFA with unsaturated fat in the diet (2).

Our primary concern is the public health implications of uncritical fanfare of a single publication. Data show that mixed messages, such as what Chowdhury and colleagues offer, increase the public's confusion and skepticism about effective dietary guidance. Ongoing scientific discussions about dietary factors, including SFA, and health are the foundation of scientific and public health progress. However, debunking the evidence about dietary fat and the risk for heart disease without constructive, science-based recommendations the public can actually use is at the very least unhelpful and contributes negatively to public health.

This analysis does not bring new scientific data or insights. The practical dietary recommendations on dietary fat therefore remain the same: Reduce intake of SFA ("hard" fat as found in fatty meat, whole-milk dairy products, butter, and pies) and eat products low in SFA and high in unsaturated fats, such as lean meats, reduced fat dairy foods, liquid vegetable oils, and related products.

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Disclosures: The authors form the steering committee of the International Expert Movement (IEM) on the health significance of fat quality in the diet. The IEM mission is "to disseminate sound scientific information about food and nutrition, especially fat quality in the diet, amongst professionals and the general public in actionable ways, in order to promote and advance nutritional improvement focusing on the quality of diets." International activities of the IEM are held under the auspices of the International Union of Nutritional Sciences and funded by an unrestricted grant from Unilever. Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=L14-0323.

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TO THE EDITOR: Chowdhury and colleagues (1) reported no association between SFA and coronary risk, thereby casting doubt on cardiovascular guidelines that advocate increased intake of PUFA at the former's expense. The review examined SFA, MUFA, and PUFA as separate entities. This method, however, is flawed because the health effect of a macronutrient that delivers a substantial amount of daily calories, such as SFA, cannot be studied in isolation but depends on whether other macronutrients are replaced.

Saturated fats are beneficial when they replace trans fatty acids (2). We also know that replacing them with carbohydrates (i.e., a low-fat diet vs. a diet high in SFA) does not confer heart health benefit because both LDL and HDL cholesterol will be reduced, with no change in the LDL:HDL ratio. When MUFAs are consumed instead of SFAs, there is a probable benefit. For PUFAs, the case is convincing based on prospective epidemiologic studies and RCTs (2). Replacing 5% of daily energy intake of SFA with PUFA would lower CHD risk by 13% on the basis of cohort studies and will reduce the risk by 10% on the basis of RCTs (3). Furthermore, it is a misconception that substantial replacement of SFA (such as 5% of total energy intake) could be achieved with ω-3 PUFA. In Western diets, α-linolenic acid combined with fish fatty acids can provide at most 2% to 3% of total energy intake. In these diets, most sources of ω-3 are also high in ω-6. Chowdhury and colleagues cite a meta-analysis (4) that showed a significantly reduced risk for CHD when replacing SFA with PUFA based on "mixed ω-3 plus ω-6 trials." It should be emphasized, however, that in these trials the level of ω-6 was much higher than that of ω-3 PUFA.

Estimates of associations and effects sizes for PUFA reported by Chowdhury and colleagues are fully compatible with earlier analyses of the same data that did take macronutrient replacement into account (2, 5, 6). Their conclusion that "Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats" is therefore misleading. Dietary guidelines should always be based on the totality of available evidence.

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TO THE EDITOR: We read Chowdhury and colleagues' review (1) with interest. The authors concluded that "Current evidence does not clearly support cardiovascular guidelines that encourage high consumption of polyunsaturated fatty acids and low consumption of total saturated fats." This review is timely, given conjecture around the association between dietary fats and CVD and the implications for clinical practice. From physiologic, nutritional, and clinical and public health perspectives, we would argue that CVD prevention and management guidelines should diverge from a narrow reductionist approach focusing on individual nutrients toward a whole-diet approach that considers the potential to influence underlying pathophysiologic mechanisms that are salient to CVD, particularly vascular inflammation.

From a physiologic perspective, current CVD guidelines are based on the putative cause of CVD being lipid accumulation, to which dietary intake is a significant contributor. However, powerful evidence identifies autoimmune inflammation and oxidative stress as key initiators of atherosclerosis. Although blood lipids are still considered to be important in CVD progression, their position in the causal chain may be as key mediators of the relationship between inflammation and CVD, rather than having a primary causal influence on the atherosclerotic process (2). Despite this framework being the "burgeoning area of cardiovascular medicine" (3), diet-related research in CVD prevention remains predominantly focused on cholesterol reduction (and by association, SFA consumption). As the modern Western diet is increasingly characterized by proinflammatory properties, including insufficient consumption of nutrient- and fiber-dense foods and overconsumption of ultra-processed food products that contain energy-dense sugars and hydrogenated plant-based oils, it is more pertinent to consider whole-diet as a key driver of this inflammatory process.

From a nutritional perspective, the sole-nutrient approach that underpins current CVD guidelines around SFAs is problematic. Although a reductionist approach is useful for scientific purposes, it neglects context (4), that is, the importance of sources of fatty acids and their effects when consumed with other foods. For example, fatty acids may be beneficial when consumed with vegetables rich in anti-inflammatory phytochemicals (5).

Finally, from a clinical and public health perspective, the focus on single nutrients results in a chasm between research and real-world pragmatism, where no nutrient is consumed in isolation and excess is as important as deficiency. Clinical CVD guidelines and public health strategies thus need to move beyond reductionism to promote a more practical, whole-diet approach that has the potential to ameliorate vascular inflammation.

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IN RESPONSE: Our systematic review and meta-analysis of the published literature aimed a priori to quantify 3 aspects of the evidence on fatty acids and CHD.

First, we considered results on self-reported dietary fatty acid intake from 32 prospective studies (512 420 participants, 15 945 cases of CHD), constituting more than 90% of the relevant data published before July 2013. We found essentially null associations of SFA, MUFA, and ω-6 PUFAs with CHD, whereas intake of long-chain ω-3 PUFAs was associated with lower risk for CHD and intake of trans fatty acids was associated with higher risk. In contrast with Dr. Willett and coworkers' claim, our review stated that prospective studies were eligible for inclusion if they involved either participants from general populations or patients with stable CVD at study entry, which explains the inclusion of both types of participants from the Kuopio Heart Study (the investigators of which provided us with updated data following correspondence). However, as alluded to by Dr. Willett and coworkers, we could not include 5 studies known to have information on dietary intake of ω-6 PUFAs and CHD because they had published insufficient numerical information and did not respond to our requests for further details (1). Nevertheless, as these studies comprised only about 15% of the relevant available data on ω-6 PUFAs, it is unlikely that their inclusion would have materially altered the RR we observed for CHD (0.98 [CI, 0.90 to 1.06]).

Second, we considered results on the relative concentrations of individual circulating fatty acids from 17 prospective studies (25 721 participants, 5519 cases of CHD). We found a possible inverse as-

sociation between margaric acid and CHD and possible positive associations between palmitic and stearic acids and CHD. We found some evidence that circulating levels of eicosapentaenoic and docosahexaenoic acid (the 2 main types of long-chain ω-3 fatty acids) and arachidonic acid were each associated with lower coronary risk. In contrast to Dr. Willett and coworkers' suggestion, the aforementioned results featured prominently in our review, particularly in Figure 2 and in the Results and Discussion sections. As Dr. Dawczynski and colleagues suggest, our review emphasized results based on individual fatty acids (rather than on the total composition in each class of fatty acid) because included studies typically measured different sets of individual fatty acids, thereby making it difficult to interpret results based on total compositions. However, as powerful prospective studies are now measuring large and uniform panels of individual fatty acids (2), they should enable reliable evaluation of hypotheses pertaining both to total and individual fatty acid compositions.

Third, we considered 27 RCTs of fatty acid supplementation or replacement (105 085 participants, 6229 cases of CHD). In aggregate, these trials have not suggested clear benefits after supplementation with α-linolenic acid (RR, 0.97 [CI, 0.69 to 1.36]) or with long-chain ω-3 fatty acid (RR 0.94 [CI, 0.86 to 1.03]), or replacement of SFA with ω-6 PUFA (RR 0.86 [CI, 0.69 to 1.07]). Although our finding for long-chain ω-3 fatty acid supplementation has been reinforced by a further null trial published since our meta-analysis (3) Dr. Willett and coworkers and Drs. Davidoff and Rosenberg correctly point out that future trials (and individual participant meta-analyses of these trials) could identify subgroups that benefit from such supplementation. In contrast with Dr. Liebman and colleagues' claim, our Results section described a subsidiary analysis that omitted the SDHS (a trial that used a margarine-based supplementation high in trans fat) (4), yielding an RR of 0.81 (CI, 0.68 to 0.98) for the remaining 7 trials of ω-6 PUFA interventions. However, as appreciated by Dr. Te Morenga and coworkers, this subanalysis is difficult to interpret because of borderline statistical significance and it is not clearly supported by other analyses, such as the RR of 0.92 (CI, 0.76 to 1.12) observed in the 3 available larger trials each reporting at least 100 CHD events (which are potentially less prone to selective publication bias and provide greater precision than the smaller trials).

We agree that nutritional guidelines should be based on the totality of evidence, including routes of evidence that were outside the scope of our meta-analysis of CHD studies. Drs. Schwingshackl and Hoffmann allude to evidence on stroke and additional cardiovascular outcomes. Dr. McCaulley alludes to a single prospective study that has reported inverse associations between circulating trans-palmitoleic acid and cardiovascular risk factors. Dr. Willett and coworkers and others allude to evidence from metabolic ward studies reporting that replacing dietary calories from saturated fat with those from polyunsaturated fat leads to small, but potentially important, reductions in LDL cholesterol concentration (5). Dr. Lartey and colleagues, Dr. Geleijnse and coworkers, and other correspondents allude to previous statistical modelling of individual-participant data from prospective studies, which has yielded a hazard ratio for CHD of 0.87 (CI, 0.77 to 0.97) per 5% lower energy intake from SFAs and a concomitant higher energy intake from PUFAs (1).

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