who were taking NSAIDs in which half the patients were randomly assigned to celecoxib, similarly showed a risk of heart disease that was no higher among patients taking celecoxib than among those taking other NSAIDs.[5] Also, in a meta-analysis of observational studies[2] celecoxib was not found to be associated with an increased risk of cardiovascular events at doses lower than 400 mg per day. Naproxen is the only extensively studied NSAID for which the risk of heart disease has not been reported to be higher than that associated with nonuse of NSAIDs.[1,2] That low-dose celecoxib was equivalent in risk to naproxen in the PRECISION trial is reassuring. In other studies, ibuprofen has been found to be associated with a risk of heart disease that is slightly higher than that associated with either naproxen or no NSAIDs.[1]

The finding in the PRECISION trial that gastrointestinal adverse events were less common with celecoxib than with conventional NSAIDs is consistent with early results from the Celecoxib Long-Term Arthritis Safety Study (CLASS).[6] Given the attrition of treatment adherence in the PRECISION trial, the long-term relative gastrointestinal safety of celecoxib is still not clear.

The mean dose of celecoxib used in the PRECISION trial was just over 200 mg per day. Doses higher than 200 mg per day were prohibited for patients with osteoarthritis, who made up 90% of the study population.

Although celecoxib may be safer than anticipated, two recent meta-analyses[7,8] of treatment for knee or hip osteoarthritis have reported that celecoxib is among the weakest of NSAIDs in terms of pain control. Only 40% of patients treated with celecoxib at a dose of 200 mg per day, as compared with 78% of those treated with 1 g of naproxen daily, had at least minimal clinically important improvement. In the PRECISION trial, there were significantly greater improvements in pain scores among patients taking naproxen than among those taking celecoxib, although the differences were small. One of the limitations of the PRECISION trial was the failure to evaluate other NSAIDs. One conventional NSAID, diclofenac, clearly poses a higher risk of cardiovascular events[2] than other NSAIDs, and, for this reason, its oral use should be discouraged.

Ultimately, the PRECISION trial provides information that can help guide treatment decisions. Celecoxib, especially at a dose lower than 400 mg per day, may deserve a more central place in the antiinflammatory armamentarium.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Breathing Easier with Fish Oil — A New Approach to Preventing Asthma?

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Asthma and lower respiratory infections are leading causes of morbidity and mortality in pediatric populations. Thus, having low-cost, effective, safe options for prevention could have important implications for both clinical practice and public health.

In this issue of the *Journal*, Bisgaard and et al.[1] report that high-dose supplementation of the

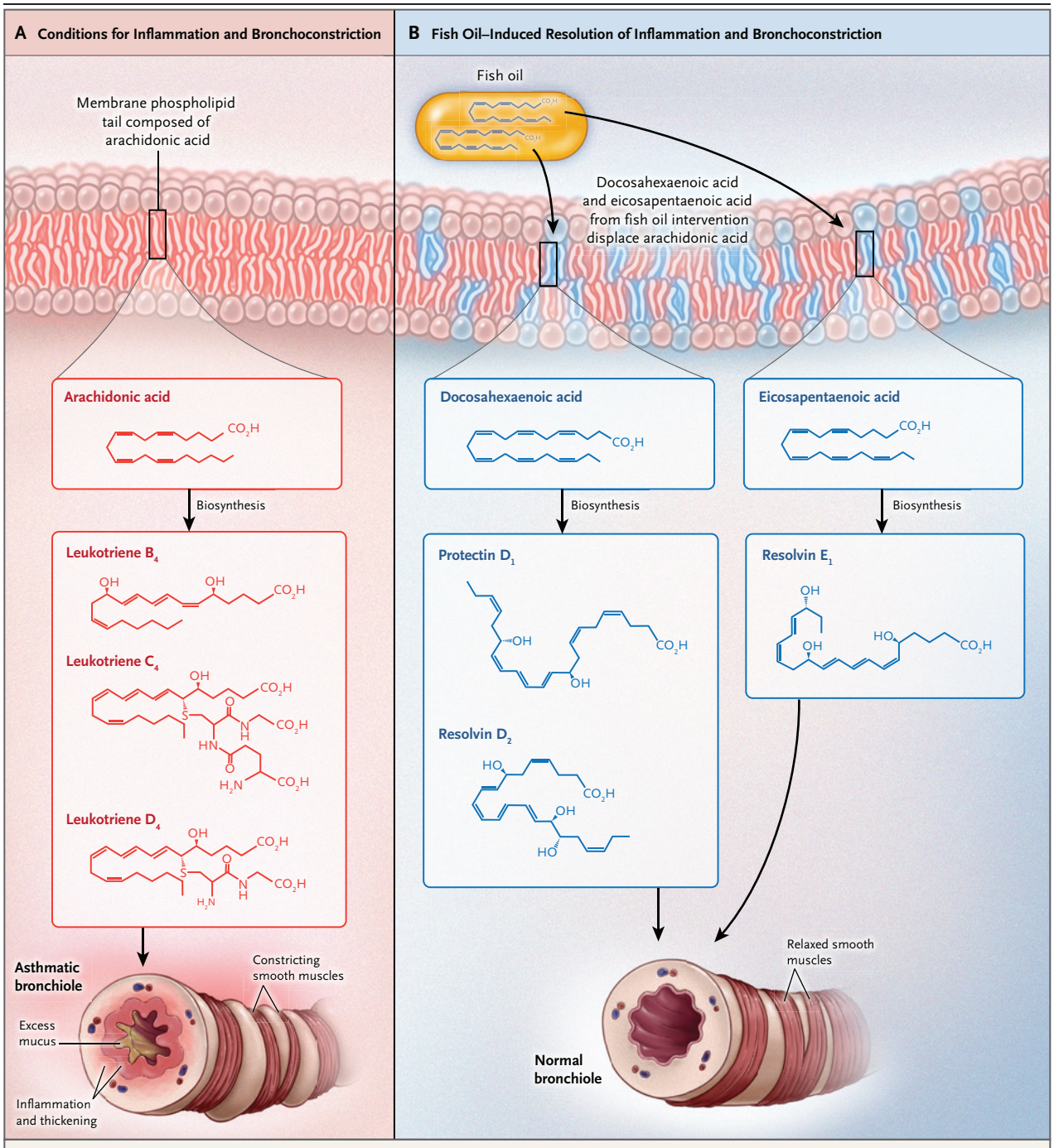

Figure 1. Model Depicting Fish Oil–Induced Alterations in Lipid Mediators of Inflammation and Bronchoconstriction.

Leukotrienes synthesized from arachidonic acid mediate bronchoconstriction and airway inflammation (Panel A). The docosahexaenoic acid and eicosapentaenoic acid in fish oil displace arachidonic acid in membrane phospholipids, which serve as precursors for biosynthesis of lipid mediators. This effect shifts the balance away from mediators of inflammation and bronchoconstriction and toward the resolution of inflammation and host defense (Panel B).

n–3 polyunsaturated fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) derived from fish oil in the third trimester of pregnancy significantly decreased the risk of persistent wheeze and asthma (the primary outcome) during the first 5 years of a child's life. The intervention also decreased the rate of lower respiratory infections (a secondary outcome) but had no

significant effect on allergic rhinitis or eczema. No major side effects were reported. Major strengths of the trial include its double-blind, randomized, placebo-controlled design, moderate-to-large sample size, low dropout rate, and extensive use of clinical phenotyping.

A particularly salient finding was that the preventive effect of fish oil was driven almost exclusively by children of the prespecified subgroup of mothers with low baseline blood levels of EPA and DHA (relative reduction in risk of persistent wheeze and asthma, 54%; P=0.011). Effects were most evident in children of mothers with a variant of the gene encoding fatty acid desaturase that is associated with low ability to produce EPA and DHA from their dietary precursor, alpha-linolenic acid. Together, these observations support the plausibility of the findings and point toward a precision-medicine approach in which factors such as blood levels of fatty acids, genotype, and parental history of asthma could potentially be used to tailor interventions to those most likely to benefit. These results also highlight the importance of measuring baseline EPA and DHA levels in future trials involving fish oil.

The findings of Bisgaard et al. build off an extensive body of preclinical work linking lipid mediators to inflammation and could provide clues to the fundamental mechanisms underlying the development of asthma. It is well known that the EPA and DHA present in foods and fish oil increase blood levels of EPA and DHA and displace arachidonic acid in membrane phospholipids that serve as precursors for the biosynthesis of lipid mediators.[2] Leukotrienes made from arachidonic acid[3] — including leukotrienes B_4, C_4, and D_4 — are potent mediators of bronchoconstriction and airway inflammation[4]; this knowledge spurred the development of antileukotriene medications, whose use is well established in the treatment of asthma in adults.[5] In preclinical studies, lipid mediators derived from EPA and DHA dampen airway hyperresponsiveness,[6,7] promote the resolution of inflammation,[8] and protect against viral infection.[9] When these observations are taken together, it is tempting to speculate that the preventive effects of fish oil on asthma and respiratory infections are due to shifts in the balance of lipid mediators away from inflammation and bronchoconstriction and toward the resolution of inflammation and host defense (Fig. 1).

Although these results are highly promising, a note of caution is warranted. The dose of EPA plus DHA provided in this trial (2.4 g per day) was approximately 15 to 20 times as high as the average U.S. intake from foods. Before these findings can be applied to clinical practice, it is therefore imperative to ensure that this dose had no adverse effects on behavior, cognition, or other long-term outcomes. Future work is also needed to determine whether lower doses are effective and whether these results can be replicated in other populations.

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