RESEARCH LETTER

Clinical Trial Evidence and Use of Fish Oil Supplements

Randomized clinical trials (RCTs) with “hard” end points and meta-analyses of these trials should influence clinical practice because they represent the highest level of evidence. Health care behaviors based on less robust evidence are often established before such RCTs are conducted. If the results of high-quality RCTs contradict established practice, numerous barriers exist to their acceptance and implementation.1 ω-3 Fatty acid (FA) supplements are commonly used for the management of cardiovascular, neurocognitive, ophthalmic, and inflammatory disorders. In 2002, their use in the secondary prevention of heart disease was endorsed by the American Heart Association.2 Recently, their health effects have been studied in several RCTs and meta-analyses, many of which were reported in high-impact journals. Here, we report the relationship between these publications in influential journals and the use of ω-3 FAs.

Methods | Data on annual sales of fish oils and ω-3 FAs from 2007 through 2012 were obtained from Euromonitor International (http://www.euromonitor.com/). Using MEDLINE and Factiva, we identified RCTs or meta-analyses of RCTs of ω-3 FAs and accompanying editorials, published in the top-ranking internal medicine journals (New England Journal of Medicine, The Lancet, JAMA, PLoS Medicine, JAMA Internal Medicine, British Medical Journal, and Annals of Internal Medicine),3-26 between January 1, 2005, and December 31, 2012, and news reports generated within 2 weeks of each publication. We independently assessed editorial disposition toward the use of ω-3 FAs using a scale from 1 (clearly unfavorable) to 5 (clearly favorable).

Results | Between January 1, 2005, and December 31, 2012, a total of 18 RCTs (primary end points: 10 cardiovascular, 4 neurocognitive, 1 cancer, 1 immune, 1 gastrointestinal, and 1 respiratory) and 6 meta-analyses of RCTs (all cardiovascular primary end points) of ω-3 FAs were published in the high-impact journals3-26 (Table). Only 2 publications reported benefit of the intervention on the primary end point.3,7 The median (range) editorial score was 4 (1.5-5), indicating overall enthusiasm for the use of ω-3 FAs (Table). The median (range) number of news reports per publication was 11 (0-27). Between 2007 and 2012, sales of fish oils and ω-3 FA supplements in the United States increased steadily, from $425 to $1043 million (Figure). The median (range) year-on-year increase was $124 (104-150) million. Similar patterns of sales were observed in the United Kingdom and Australasia (data not shown).

Discussion | This analysis suggests that publications in prominent medical journals of RCTs and meta-analyses of RCTs of ω-3 FAs are well received by editors and journalists, resulting in widespread coverage that drives the market for these products.

Table. RCTs and Meta-Analyses of RCTs Published in High-Impact Internal Medicine Journals From 2005 Through 2012

<table>
<thead>
<tr>
<th>Source</th>
<th>Design</th>
<th>Intervention</th>
<th>No.</th>
<th>Primary Outcome</th>
<th>Result</th>
<th>Editorial Score</th>
<th>News Stories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Studer et al, 20053</td>
<td>Meta-analysis RCT</td>
<td>ω-3 FA</td>
<td>20 260</td>
<td>Mortality&lt;br&gt;Cardiac mortality&lt;br&gt;No cardiac mortality</td>
<td>Benefit&lt;br&gt;Benefit&lt;br&gt;No benefit</td>
<td>...</td>
<td>0</td>
</tr>
<tr>
<td>Raitt et al, 20054</td>
<td>Double-blind RCT</td>
<td>Fish oil</td>
<td>200</td>
<td>Ventricular arrhythmia</td>
<td>No benefit</td>
<td>...</td>
<td>12</td>
</tr>
<tr>
<td>Hooper et al, 20065</td>
<td>Meta-analysis RCT</td>
<td>ω-3 FA</td>
<td>33 625&lt;br&gt;33 193&lt;br&gt;31 255&lt;br&gt;17 433</td>
<td>Cardiovascular events&lt;br&gt;Mortality&lt;br&gt;Stroke&lt;br&gt;Cancer</td>
<td>No benefit&lt;br&gt;No benefit&lt;br&gt;No benefit&lt;br&gt;No benefit</td>
<td>3</td>
<td>24</td>
</tr>
<tr>
<td>Brouwer et al, 20065</td>
<td>Double-blind RCT</td>
<td>Fish oil</td>
<td>546</td>
<td>Ventricular arrhythmia or mortality</td>
<td>No benefit</td>
<td>...</td>
<td>1</td>
</tr>
<tr>
<td>Yokoyama et al, 20077</td>
<td>Open-label RCT</td>
<td>EPA</td>
<td>18 645</td>
<td>Major coronary events</td>
<td>Benefit</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Feagan et al, 20088</td>
<td>Double-blind RCT</td>
<td>ω-3 FA</td>
<td>738</td>
<td>Relapse of Crohn disease</td>
<td>No benefit</td>
<td>...</td>
<td>9</td>
</tr>
<tr>
<td>Tavazzi et al, 20088</td>
<td>Double-blind RCT</td>
<td>ω-3 FA</td>
<td>6975</td>
<td>Mortality&lt;br&gt;Mortality or cardiovascular hospitalization</td>
<td>No benefit&lt;br&gt;No benefit</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>Leon et al, 20089-10</td>
<td>Meta-analysis RCT</td>
<td>ω-3 FA</td>
<td>1148&lt;br&gt;31 111&lt;br&gt;32 159&lt;br&gt;32 439</td>
<td>Ventricular arrhythmia&lt;br&gt;Bedness or sudden cardiac death&lt;br&gt;Cardiac death&lt;br&gt;Mortality</td>
<td>No benefit&lt;br&gt;No benefit&lt;br&gt;No benefit&lt;br&gt;No benefit</td>
<td>4.5</td>
<td>2</td>
</tr>
<tr>
<td>Makrides et al, 200911</td>
<td>Double-blind RCT</td>
<td>DHA</td>
<td>657</td>
<td>Neurodevelopment</td>
<td>No benefit</td>
<td>5</td>
<td>13</td>
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<tr>
<td>Carney et al, 200912</td>
<td>Double-blind RCT</td>
<td>DHA + EPA</td>
<td>122</td>
<td>Depression score</td>
<td>No benefit</td>
<td>...</td>
<td>8</td>
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<tr>
<td>Galan et al, 201013</td>
<td>Double-blind RCT</td>
<td>ω-3 FA</td>
<td>2501</td>
<td>Cardiovascular events</td>
<td>No benefit</td>
<td>...</td>
<td>0</td>
</tr>
<tr>
<td>Makrides et al, 201014</td>
<td>Double-blind RCT</td>
<td>DHA</td>
<td>2399&lt;br&gt;726</td>
<td>Postpartum depression&lt;br&gt;Neurodevelopment</td>
<td>No benefit&lt;br&gt;No benefit</td>
<td>...</td>
<td>27</td>
</tr>
<tr>
<td>Kromhout et al, 201015</td>
<td>Double-blind RCT</td>
<td>ω-3 FA</td>
<td>4837</td>
<td>Cardiovascular events</td>
<td>No benefit</td>
<td>...</td>
<td>13</td>
</tr>
</tbody>
</table>

(continued)
ω-3 FAs have had little effect on the use of these supplements. Sales of ω-3 FAs steadily increased despite contemporaneous accrual of high-level evidence that the supplements lack efficacy across a range of health outcomes for which their use is advocated. Since 10% of adults in the United States take an ω-3 FA or fish oil supplement, most commonly for heart health or to lower cholesterol, the null results of 9 of the 10 RCTs and 5 of the 6 meta-analyses studying cardiovascular disease might have been expected to influence use. It remains to be seen whether a recently published trial sequential analysis, which reports proof of no efficacy of ω-3 FAs in the secondary prevention of cardiovascular disease, alters use of the supplements.

For prescribed interventions, numerous factors, including academic and/or medical specialists’ biases, contribute to resistance to the translation into clinical practice of robust evidence that contradicts established behaviors. The editorialists’ positive views on ω-3 FAs may have influenced the responses of health practitioners to the results of the source trials. However, only 10% of those who take ω-3 FAs do so on the advice of a health care professional. Additional factors that may contribute to increasing use of a nonprescribed intervention despite accumulating evidence of its ineffectiveness include anecdotal evidence, low cost, ready availability, assumptions of safety, supportive news reports, and selective presentation of evidence by the supplements industry.

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**Published Online:** December 16, 2013. doi:10.1001/jamainternmed.2013.12765.
Author Contributions: Dr Grey had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Both authors.

Acquisition of data: Grey.

Analysis and interpretation of data: Both authors.

Drafting of the manuscript: Grey.

Critical revision of the manuscript for important intellectual content: Bolland.

Conflict of Interest Disclosures: None reported.

Funding/Support: The Health Research Council of New Zealand.

Role of the Sponsor: The Health Research Council of New Zealand had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.


Use and Yield of Endoscopy in Patients With Uncomplicated Gastroesophageal Reflux Disorder

Practice guidelines recommend esophagogastroduodenoscopy (EGD) screening for Barrett esophagus (BE) or esophageal cancer for patients with uncomplicated gastroesophageal reflux disease (GERD), especially in high-risk patients (symptoms for >5 years, white race, male sex, age >50 years, and family history of BE or esophageal cancer). However, the extent of using screening EGD, its predictors, and diagnostic yield are unclear. We aimed to determine prevalence, predictors, and yield of

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