Fish Oil for Heart Disease—Happy to Be in Second Place

From 1970-1977, the Minnesota Vikings played in the National Football League’s championship game—the Super Bowl—four times. They lost every time. The Denver Broncos repeated the feat until finally winning in their fifth attempt. Both teams were mocked and pitted for their futility; however, there were worse fates than second place. The rest of their conference teams had spent millions of dollars and countless hours of work for the same opportunity and fell short. Obviously, first place was the goal, but coming in second was still better than 26 other competitors.

In the highly competitive field of lipid treatment, many groups strive to stand out from their peers. Niacin, fibrates, and resins were the early favorites but were overtaken by statins. Statins are the usual first-line recommended medical treatment by multiple expert panels for high-risk primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD). The large volume of morbidity and mortality data makes them the undisputed champions for treating dyslipidemia.

Ezetimibe has been touted as add-on therapy for additional low-density lipoprotein cholesterol (LDL-C) lowering; however, we are still waiting for data to show that the LDL-C effect of this agent results in any benefit for myocardial infarction, stroke, cardiovascular mortality, or overall mortality. Hormone replacement therapy also showed value for LDL-C lowering in observational studies; however, we now know that stroke and myocardial infarction risk actually increase despite the improvement in lipid values. Obviously, other known factors are at work, such as antiinflammatory and antiplatelet effects to explain why some agents that lower LDL-C help morbidity and mortality, while others are neutral or actually harmful.

Into the fray, a new challenger is now gaining notoriety—omega fatty acids, also known as fish oil supplements. (Terminology is complex regarding marine versus plant sources and subcomponents of omega fatty acids. An extensive description is beyond the scope of this editorial, and excellent reviews are available.) Many clinicians have rightfully been leery of unproven claims from the herbal sector. As food supplements, they carry the classic label: “(T)his product is not intended to diagnose, treat, cure, or prevent any disease.” A few notable exceptions exist, such as the Rotta preparation of glucosamine for joint pain, but the majority of agents lack substantive support of effectiveness.

Evidence has been building lately for omega fatty acids, especially for secondary ASCVD prevention. In a randomized controlled trial of patients with recent myocardial infarction, 2,836 individuals were given omega fatty acids (dose 850-882 mg) while 2,828 were given placebo. After 3.5 years, the treatment group had a lower rate for the combined end point of overall mortality, nonfatal stroke, and recurrent infarction relative to placebo (12.3% vs. 14.6%, number needed to treat = 44, P=0.048). A meta-analysis in 2002 pooled 11 trials involving almost 16,000 patients for primary and secondary prevention, performed over the previous 30 years. With an average follow-up of 20 months and dosing ranging from 0.3-6.0 g/day, results showed omega fatty acids significantly decreased the risk of fatal myocardial infarction (risk ratio = 0.7; 95% confidence interval [CI], 0.6-0.80), sudden death (risk ratio=0.6; 95% CI, 0.6-0.9), and overall mortality (risk ratio=0.8; 95% CI, 0.7-0.9).

Pulling the evidence into tighter focus was a meta-analysis in 2005 that compared true end points, such as overall mortality, among the various classes of lipid-lowering agents. In more than 100,000 patients enrolled in 35 statin trials, the risk ratio for overall mortality was 0.87 for statins compared with placebo (95% CI, 0.81-0.94), with a 20% average reduction in total cholesterol. Surprisingly, for overall mortality in 15 studies involving 20,000+ patients with preexisting heart disease treated with omega fatty acids, the risk ratio was 0.77 (95% CI, 0.63-0.94), despite a negligible 2% average reduction in total cholesterol. Statins lowered cholesterol 10-fold more than omega fatty acids yet did not outperform on mortality measures in patients with ASCVD. Fibrates, niacin, resins, and diet therapy all failed to show significance in lowering overall mortality. For primary prevention with statins, it is necessary to treat 228 persons (95% CI, 123-2,958) for 3.3 years. In patients with known heart disease, 50 patients (95% CI, 38-78) would have to be treated with a statin to prevent one additional death, and 44 patients (95% CI, 31-84) would need to be treated with fish oil to prevent one additional death, each over an average 4.4 years of therapy (excluding one low-quality study).

Not all reviews of omega fatty acids have been positive. An earlier Cochrane meta-analysis that was last reviewed in 2004 failed to find a reduction in overall mortality for omega fatty acids. No safety concerns were found, but the authors recommended additional research. An evidence report from the Agency for Healthcare Research and Quality evaluated 123 trials for the effect of omega fatty acids on intermediate markers for ASCVD. Consistent with prior studies, they found a reduction of triglycerides ranging from 10% to 33%, but negligible effects on LDL-C or high-density lipoprotein cholesterol. The report did not assess the effect on overall mortality.

Despite the differences among reviews, the U.S. Food and Drug Administration determined in November 2004 that sufficient data existed to approve the first prescription omega fatty acid agent in the United States; the agent was first launched in Austria in July 2002. Containing 1 g per capsule, the agent is indicated for adjunct therapy to diet at 4 g daily to reduce very high (≥500 mg/dL) triglyceride levels in adult patients. Of note, the prescription agent will vary markedly from over-the-counter preparations. For example, a 1 g capsule of the prescription agent will have roughly triple the amount of fish oil as a popular 1 g capsule available commercially at present (eicosapentaenoic acid 465 mg vs. 180 mg; docosahexaenoic acid 375 mg vs. 120 mg). It is expected that the
manufacturer will push for approval of 1 g daily dosing in post-myocardial infarction patients for secondary prevention of ASCVD.

Although more studies are needed, omega fatty acids are now standing out from the crowd. They will likely never replace statins as first-line therapy for dyslipidemia, but they have more data to support a benefit for reducing mortality in patients with preexisting heart disease than do the other antilipid agents. Central to their success in population management of coronary heart disease and mortality risk will be low discontinuation rates. As discussed previously in JMCP, 18-month discontinuation rates greater than 50% are common for all antilipid drug classes. Despite various hurdles, omega fatty acids are now ready to take over second place in the lineup for treatment of hypertriglyceridemia and secondary prevention of ASCVD.

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DISCLOSURE

The author is a board-certified family physician assigned to Eglin AFB Florida, where he serves as residency program director. The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of any organization, including the U.S. Air Force medical department or the U.S. Air Force. He discloses no potential bias or conflict of interest relating to this editorial.

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As required by the Medicare Modernization Act, organizations offering Medicare Part D prescription drug plans (PDPs) are obligated to provide medication therapy management programs (MTMPs) as part of the benefit. While medication therapy management (MTM) has been performed by pharmacists in a variety of settings for years, a consensus definition of MTM was not developed until last year. As defined in the Act, MTMPs are “furnished by a pharmacist [and] designed to assure . . . that covered part D drugs are appropriately used to optimize therapeutic outcomes through improved medication use, and to reduce the risk of adverse events, including adverse drug interactions.”

While the Act defines the beneficiaries who are targeted for MTM (those with multiple chronic conditions, taking multiple medications, and likely to have high drug expenses) and basic elements of the program (promotion of enhanced enrollee understanding of the appropriate use of medications, adverse event risk reduction, increased medication adherence, and detection of adverse drug events and patterns of prescription drug overuse or underuse), the government has taken a decidedly hands-off approach to regulating MTMPs. Citing insufficient standards and performance measures to evaluate MTMPs and the inability to determine what requirements would enhance MTMPs and improve patient outcomes, the Centers for Medicare and Medicaid Services (CMS) has given what it considers maximum flexibility to plans so they may develop MTMs that can achieve the goal of improving therapeutic outcomes.

Organizations that bid on the Part D drug plans have remained silent about their MTMP plans, but some guidance is available as to what can be expected for MTM services at certain pharmacy settings. In April 2005, the American Pharmacists Association and the National Association of Chain Drug Stores Foundation released a model framework for implementing MTM services in a community pharmacy setting. The framework (a) provides 9 factors that community pharmacists can consider when targeting patients for MTM services, (b) identifies 5 core components of MTM programs in community pharmacy (medication therapy review, a personal medication record, a medication action plan, intervention and referral, and documentation and follow-up) and describes pharmacist responsibilities for each, and (c) provides sample personal medication records and medication action plans for community pharmacists to use in their programs. Regarding senior care, the American Society of Consultant Pharmacists (ASCP) released an issue paper on MTM services for ambulatory Medicare beneficiaries in April 2004, reviewing the goals of MTM services in the elderly and the types of MTM services that a pharmacist could provide to ambulatory seniors. An MTM for low-income ambulatory seniors was described by Stebbins et al. in a recent issue of JMCP.

However, there is little guidance for developing MTM services for those residing in long-term care (LTC) facilities. At this time, the only point that is clear is that MTM services need to be distinct from the monthly drug regimen review (DRR) process mandated for all LTC residents. While the DRR process may save as much as $3.6 billion per year in medication-related problems, these problems still generate an estimated $4 billion in annual costs in the LTC setting. Inappropriate prescribing remains a problem for the nation’s 1.8 million LTC and assisted-living residents and is a significant factor contributing to the risks for morbidity and mortality.

While the deadline has passed for submitting bids for Part D PDPs for 2006, organizations preparing bids for PDPs for 2007 and beyond should look for evidence of success in MTM services in the LTC arena when formulating their bids. In this issue, Trygstad et al. describe results of the North Carolina Polypharmacy Initiative, a targeted drug therapy management consultation where a pharmacist reviews medical records and Medicaid pharmacy claim drug profiles to determine if a potential drug therapy problem alert requires action and, if so, to make interventions and determine if a therapy change was enacted. As measured by the study objectives, the program was successful because it was associated with a reduction in potential drug therapy problem alerts and median per-patient-per-month prescription drug costs. The program further demonstrated the utility of consultant pharmacists in the LTC setting since physicians implemented nearly 60% of pharmacist recommendations.

However, the study by Trygstad et al. did not look at health outcomes and therefore did not determine if the drug therapy changes would maintain or improve the quality of care that residents received. It is unlikely that a consultant pharmacist would make a recommendation that would result in lower quality of care for an LTC resident, but the study by Trygstad et al. measured only intermediate (process of care) and drug cost outcomes. Research is still necessary to demonstrate that a pharmacy intervention program designed for multiple disease states in LTC leads to improvements in resident health outcomes. Such research would provide powerful evidence of an intervention’s utility. It is easy to sympathize with the researchers; by intervening in many different disease states, it is very difficult to quantify the impact of the program on LTC resident health outcomes. Limiting the study to retrospective pharmacy claims data makes even more remote the possibility of determining health outcomes.

In the MTMP described in the study, the pharmacist had the ability to recommend that drug therapy be withdrawn, modified, or added, as each case required. Changes to drug therapy impact more than prescription drug expenses; these changes can have an effect on immediate and longer-term medical expenses as well. However, the study only presented prescription drug costs and did not report the impact of the intervention on medical costs or overall health care costs. The true cost for a
health system of an intervention or series of interventions is best assessed by examining overall costs.

How Part D providers choose to examine the costs of MTMPs may very well depend upon the type of program they are offering. Medicare Advantage prescription drug (MA-PD) plans are at risk for overall health costs, so their level of interest in the impact of a MTMP on overall costs is likely to be greater than a PDP, which is not at risk for overall health costs. One must wonder if the Part D program will suffer from the silo approach to health care finance that managed care plans have struggled to overcome. CMS’s proposal for linking deidentified Part D prescription claim data to hospital, physician, and other medical utilization data in a public database may allow health policy analysts to compare prescription drug expenses and overall health care expenses for PDPs and MA-PDs.

More questions than answers presently remain pertaining to MTM services in LTC facilities. While the forthcoming report from the Department of Health and Human Services on standards of practice for pharmacy services (including clinical services) provided to patients in LTC settings will be a useful tool for PDP developers to consider when designing or refining MTMPs, the experiences that the LTC industry encounter starting on January 1, 2006 (“Part D-Day”), will be even more valuable. The sharing of MTM best practices by PDPs and LTC facilities can reduce the trial-and-error approach to MTM services and can improve the quality of services delivered to LTC residents.

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Evaluating the Relationship Between Diabetes Treatment and Health Care Costs—Measuring the Atom With a Yardstick?

In this issue of JMCP, Shetty et al. evaluated the relationship between poor glycemic control, defined as a glycated hemoglobin (HbA1c, now commonly abbreviated as simply A1c) >7%, and diabetes-related medical and pharmacy costs. They used 18-months of data from medical and pharmacy administrative claims as well as laboratory data. Other studies have been conducted with similar data sources that also characterized the relationship of poor glycemic control to health care costs, hospitalizations, and resources used. A principal limitation of each of these analyses was the inability of the investigators to determine disease duration. In their analysis, Shetty et al. attempted to adjust for a number of potential confounders, including age, gender, physician specialty, comorbid conditions, and total baseline costs. However, they looked at patients for only a 6-month preindex and a 12-month follow-up period, so they could not estimate whether patients were newly diagnosed diabetics or whether they had disease of long-standing duration. The average diabetic many years after diagnosis is very different from a patient with new-onset diabetes; they are more dependent on insulin, more difficult to control, and have more insulin resistance. Thus, if investigators had been able to control for the length of time each patient had the disease, the relationship between A1c level and costs would have been better elucidated.

Of course, the duration of disease is difficult to determine in these types of analyses. To measure resource utilization directly, investigators require health plan data for patients who are continuously enrolled over the entire study period in order to ensure that all resources used by the patient are captured. Because patients frequently change health plans over the course of their lifetimes, the follow-up period required to determine disease duration would be prohibitive for this type of analysis. The ideal database for this type of analysis would include patient data for an entire lifetime, but such an administrative claims database does not exist anywhere in the United States. Alternatively, small-scale analyses could be conducted using medical and pharmacy data from small, rural communities where populations are relatively stable and receive health care from a closed set of hospitals and clinics. However, even then, a large proportion of patients would likely have to be excluded because of moving into or out of the geographic area. In addition, patients would not be representative of the larger population as a whole, and sample sizes might be too small to ensure adequate power.

Another limitation to these types of analyses is that International Classification of Diseases, Ninth Revision (ICD-9) coding is replete with errors. Shetty et al. used a range of ICD-9 codes indicative of type 2 diabetes and excluded patients with two or more claims for type 1, presumably because investigators realized that disease misclassification was likely present in the database. Interestingly, the investigators reported that 35.5% of the patients with two or more ICD-9 codes for type 2 diabetes also had two or more ICD-9 codes for type 1. As a result, more than one third of the source population had to be excluded because of an inability to determine which disease the patient actually had. This illustrates the error inherent in using a database such as this, and one has to ask whether excluding the patients with conflicting diagnoses really eliminated all of the misclassification bias. Any residual non-differential misclassification of disease in this database would bias the results of the analysis to the null hypothesis. Thus, we might expect an even stronger association between a lack of glycemic control and increased medical and pharmacy costs.

The accuracy of administrative databases has been questioned previously. Peabody et al. attempted to characterize the extent of error in administrative data sources by sending scripted actors to simulate the symptoms of 4 diseases, including diabetes. Although a study designed to measure how accurately patients who are feigning illness are diagnosed with that illness has its own inherent problems, investigators reported that administrative data sets contained the correct primary diagnosis only about 57% of the time. They broke down the places in the chain of events following the patient encounters where errors were made and found that the clinicians made incorrect diagnoses 13% of the time, encounter forms were missing or incomplete 8% of the time, and the data were incorrectly entered from encounter forms 22% of the time. Even if the clinicians in this study made incorrect diagnoses because the patients did not really have the disease, the administrative database was still wrong 30% of the time.

Interestingly, Peabody et al. found that the accuracy of the database for comorbid or secondary diagnoses among diabetes patients, such as hypertension and hypercholesterolemia, was even lower. They reported finding accurate secondary diagnoses only 36% of the time, and most of the error (42%) occurred when the data were incorrectly or incompletely entered from the encounter forms. The investigators attributed the poor quality of recording of comorbid condition to specific variations in administrative systems at each site; not all of the sites required the entry clerks to document secondary diagnoses. In light of the questionable quality of these data sources with respect to comorbidities, one has to wonder about the true impact of these conditions on the outcomes reported by Shetty et al. The investigators adjusted for 11 comorbidities in their analysis, but only 6 of them were significantly correlated with cost (hypertension, dyslipidemia, retinopathy, nephropathy, neuropathy, and diseases of the lower extremities). If comorbidity tracking was as inaccurate in their dataset as it was in that evaluated by Peabody et al., the impact on the study outcomes could have been substantial.

An additional problem with these data sources is the degree of resolution. Encounter forms used in the clinic setting usually have a list of the top 20 to 30 potential diagnoses clinicians are
likely to see. These diagnoses tend to correspond to the most
general classification of a disease, including the NEC (not else-
where classified) or NOS (not otherwise specified) categories. A
report by a Canadian investigator into the accuracy of ICD-9
reporting of complications in gall-bladder surgery found that
when non-specific codes were interpreted as indicating clinically
important complications, the rate of these complications
appeared much higher. The interpretation of nonspecific diagnosis
codes must be tempered with the understanding that these
categories may be used excessively, despite the existence of
more-specific codes that are more accurate. This results in poor
resolution for investigators using these data to answer outcomes
research questions, and yet, they are often asked pointed,
specific questions that require telescopic resolution in order to
answer adequately. Outcomes research is often an attempt to
measure minute details with somewhat inaccurate instruments—
analogous to measuring atomic particles with a yardstick.
Frequently, investigators attempt to answer these questions
anyway, and it is left up to the reader to determine the
magnitude of the limitations of the reported results.

Data sources for outcomes researchers are very crude tools.
Understanding the inaccuracies and limitations of administrative
datasets is critical. To discount all outcomes research because of
these limitations is to be overcautious and is unwarranted.
These databases are valuable, particularly because they allow us
to readily and inexpensively evaluate large numbers of patients
across geographically diverse areas and because they are often
closed systems, capturing all patient encounters over the enroll-
ment period. Few other data sources have such characteristics.
However, readers should bear in mind the limitations when
interpreting and evaluating these studies and when basing
patient care decisions on them. Perhaps a utopian future exists
where national health tracking databases include patient data
for a lifetime and administrative systems document patient data
with high resolution. Until then, our only choice is to keep
sharpening our instruments and learning what we can from the
available sources.

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