Assessing the Clinical Benefits of Lipid-Disorder Drugs

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On October 16, 2013, the Endocrinologic and Metabolic Drugs Advisory Committee of the Food and Drug Administration (FDA) voted 9 to 2 against approval of Vascepa, a purified n–3 fatty acid formulation of ethyl eicosapentaenoic acid (EPA), for use as an adjunct to diet and in combination with a statin to reduce levels of triglycerides, non–high-density lipoprotein (non-HDL) cholesterol, apolipoprotein B, low-density lipoprotein (LDL) cholesterol, and very-low-density lipoprotein (VLDL) cholesterol in adult patients with mixed dyslipidemia and coronary heart disease or an equivalent risk of coronary heart disease. The sponsor and the FDA had previously agreed under a Special Protocol Assessment that triglyceride-lowering data from a 12-week study with lipid end points and 50% enrollment in a cardiovascular outcome trial would be sufficient for submission of a supplemental application seeking approval for the indication as an adjunct to a statin in patients with residually high triglyceride levels. After that agreement was reached, however, several clinical trials were published showing no cardiovascular benefit from drugs that lowered triglyceride levels or increased HDL cholesterol levels (see table).

This new information called into question the clinical benefit of the triglyceride target and the rationale for using triglyceride levels as a surrogate end point for regulatory approval. These issues affect clinical decisions, since several drugs are available for lowering triglyceride levels (e.g., fibrates, niacin, and n–3 fatty acids).

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From the Wakely Consulting Group, Boston.

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</table>

* ACCORD denotes Action to Control Cardiovascular Risk in Diabetes, AIM-HIGH Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes, CABG coronary-artery bypass grafting, CI confidence interval, EPA ethyl eicosapentaenoic acid, HDL-C high-density lipoprotein cholesterol, HPS2-THRIVE Heart Protection Study 2: Treatment of HDL to Reduce the Incidence of Vascular Events, ILLUMINATE Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events, JELIS Japan EPA Lipid Intervention Study, LDL-C low-density lipoprotein cholesterol, and NA not applicable.

† The hazard ratio or relative risk is for the comparison between the statin plus active drug and statin plus placebo or other comparator.

⁵ The results of the HPS2-THRIVE trial (ClinicalTrials.gov number, NCT00461630) have not been published but were reviewed at the October 16, 2013 meeting of the FDA’s Endocrinologic and Metabolic Drugs Advisory Committee. The listed change is for simvastatin with or without ezetimibe versus simvastatin plus niacin and laropiprant.

Other drugs in development also target previously untried mechanisms for modulating cholesterol levels, under the assumption that improving specific aspects of the lipid profile will translate into a reduced risk of major cardiovascular events.

The FDA approved Vascepa in 2012 for use in patients with severe hypertriglyceridemia (triglyceride level, ≥500 mg per deciliter (5.6 mmol per liter)), on the presumption that lowering very high triglyceride concentrations would reduce the risk of acute pancreatitis, despite a lack of outcome data on that end point. The October 2013 advisory committee meeting focused primarily on the results of the Effect of AMR101 (Ethyl Icosapentate) on Triglyceride Levels in Patients on Statins with High Triglyceride Levels (ANCHOR) trial, which involved 702 participants who were taking a statin drug aiming for an LDL cholesterol target of less than 115 mg per deciliter (2.97 mmol per liter) but still had triglyceride levels of 185 to 499 mg per deciliter (2.09 to 5.63 mmol per liter) and non-HDL cholesterol levels of at least 100 mg per deciliter (2.6 mmol per liter). These patients were thought to be at substantial cardiovascular risk despite control of LDL cholesterol levels. The results at 12 weeks showed a placebo-corrected 21% reduction in triglyceride levels with a Vascepa dose of 4 g per day and a 10% reduction with 2 g per day — both significant. There were significant reductions in lev-
els of non-HDL cholesterol, apo-
lipoprotein B, VLDL cholesterol, and markers of inflammation. The
safety of Vascepa was not a focus,
but a final determination of ben-
efit cannot be evaluated without
consideration of the potential
harms, and concerns were raised
regarding risks of bleeding and
worsening glycemic control. The
sponsor’s cardiovascular outcomes
trial (Reduction of Cardiovascular
Events with EPA–Intervention Trial,
or REDUCE-IT; NCT01492361) —
comparing Vascepa (4 g per day)
with placebo in a high-risk popu-
lation, with a composite end point
of fatal and nonfatal cardiovas-
cular events, coronary revascular-
ization, and hospitalization for
unstable angina — is not sched-
uled to be completed until 2017.

All existing and new drugs tar-
geting lipid disorders in the broad
population have the primary goal
of reducing the risk of cardiovas-
cular events. However, the FDA’s
Division of Metabolism and Endo-
crinology Products (DMEP) has a
long history of approving new lipid
drugs on the basis of favorable
changes in lipid metabolism alone.
Alterations in cholesterol metab-
olism are clearly associated with
a marked increase in cardiovas-
cular risk, as shown in numerous
observational and epidemiologic
studies. For statins, cardiovas-
cular outcomes trials performed af-
after approval definitively showed
that LDL cholesterol is an appro-
priate surrogate end point because
there is a direct relationship be-
tween lowering LDL cholesterol
levels with a statin and a reduced
relative risk of cardiovascular
events. Given this history, physi-
cians have focused treatment de-
cisions on obtaining target LDL
cholesterol goals.

This approach, however, is less
evidence-based when LDL chole-
terol levels are lowered with non-
statin drugs. In some situations,
the at-risk population is simply
too small to conduct a cardiovas-
cular outcomes trial. For exam-
ple, two new drugs (lomitapide
and mipomersen) were recently
approved by the FDA, solely on the
basis of changes in the LDL cho-
lesterol surrogate, for treating very
elevated levels of LDL cholesterol
in patients with homozygous fa-
miliar hypercholesterolemia. At an
October 2012 advisory committee
meeting reviewing lomitapide and
mipomersen, the FDA acknowl-
edged the difficulty of conduct-
ing a fully powered cardiovascular
outcomes trial in the very
small affected population (about
300 persons in the United States).
It is not known whether this
thinking will extend to larger but
still limited populations, such as
patients who cannot tolerate
statins or in whom a designated
LDL cholesterol goal cannot be
achieved even with a maximal
statin dose.

The DMEP has also approved
fibrates and niacin for lowering
triglyceride levels and raising
HDL cholesterol levels, without
substantial evidence that these
drugs and modulation of these
lipid targets have clinical benefit
in terms of reducing the risk of
fatal and nonfatal cardiovascular
events. Under consideration at
the October 2013 meeting were
several recent clinical trials that
did not show any clinical benefit
of fenofibrate or niacin when used
in combination with a statin,
thus calling into question the
wisdom of prior approvals of
these drugs based only on favor-
able changes in lipid fractions
(see table). At that meeting, the
FDA presented meta-analyses of
studies of n–3 fatty acids that re-
vealed mixed results for cardio-
vascular outcomes. The most fa-
vorable trial was the Japan EPA
Lipid Intervention Study (JELIS),
which showed a positive effect of
1800 mg per day of EPA on a
broad cardiovascular end point,
driven primarily by reductions in
nonfatal myocardial infarctions,
unstable angina, and cardiac re-
vascularization. This trial had
major design limitations, how-
ever, including the facts that it
was open-label and used low-
dose background statin therapy.
There are similar concerns regard-
ing HDL cholesterol, since trials
of torcetrapib and dalcetrapib did
not show clinical benefits.

The deliberations over Vascepa
highlight several challenging is-
ues in the development of new
treatments for lipid disorders.
There is now uncertainty regard-
ing the regulatory approach of
approving drugs on the basis of
favorable lipid effects and evalu-
ating clinical benefit after ap-
proval. If a new drug has a plau-
sible mechanism of action, the
intended patient population is
well defined, the benefit of a par-
ticular lipid surrogate end point
is clear, and there is no safety
concern, then is it reasonable to
bring the drug to market while
the definitive cardiovascular out-
come trial is ongoing? In judging
the risk–benefit ratio in the ab-
sence of clinical outcomes data,
the drug’s safety would need to
be well defined. This approach
would have the potentially posi-
tive effect of allowing patients to
use the drug while the outcome
trial was being completed — an
advantage if the drug were sub-
sequently shown to improve car-
diovascular outcomes. For exam-
ple, lovastatin was approved in

1987 on the basis of its effect in lowering LDL cholesterol levels, but the first outcomes data for pravastatin did not become available until 1995. But if a drug were put on the market and subsequently found to be ineffective or unsafe, patients would have been exposed to unnecessary and perhaps unforeseen risks. The FDA would then have to take action to remove the drug — a problem that is avoided if data showing convincing clinical benefit are required before approval.

Vascepa represents an important example of a drug whose clinical outcome benefits have not yet been established, and we do not yet fully understand its safety profile. The FDA’s decision about Vascepa may not set a firm precedent, however, since the estimated likelihood and magnitude of both benefits and risks are unique to each new candidate drug.

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

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HISTORY OF MEDICINE

Still Delirious after All These Years

David S. Jones, M.D., Ph.D.

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octors have recognized delirium for centuries. Transient alterations in consciousness, attention, orientation, perception, or behavior were well known with malaria and alcohol withdrawal or after surgery. Delirium became more prominent in the 1950s and 1960s with the emergence of intensive care. Intensive care units (ICUs) made it possible for patients to survive more severe illnesses and for doctors to attempt more aggressive interventions that required physiological monitoring, respiratory support, and intensive nursing. Delirium, “the ‘new madness of medical progress,’”1 became more prevalent and more visible. Doctors set out to understand and prevent it, but, as the Critical Care Medicine article by Reade and Finfer (pages 444–454) shows, this effort is a work in progress.

Delirium results from so many sources that decisive understanding remains elusive.

The first intensive research on delirium associated with intensive care focused on cardiac surgery. These studies demonstrate the strategies and struggles of doctors who worked to understand delirium. Open-heart surgery had developed rapidly in the 1950s and 1960s, in parallel with — and dependent on — intensive care. Patients who underwent such surgery often had frightening delirium. Consider one patient who underwent mitral-valve replacement.2 On postoperative day 5, she began to hear rock-and-roll music with laughter in the background, as if at a party. First she believed that her friends had hidden a record player under her mattress. As her paranoia deepened, she perceived insulting voices in the music and thought it was part of a plot to torture her. She suspected that one of her nurses was dating one of her married physicians (definitive proof of her delirium, at least for the authors). Whenever she closed her eyes, she felt as if her bed were moving and feared that she was being taken back to surgery. The delirium cleared 2 days after she was transferred out of the ICU.

In 1965, Donald Kornfeld and his colleagues at Columbia–Presbyterian Medical Center published one of the first major studies of the problem.3 Kornfeld’s team studied 99 adult patients after open-heart surgery. Chart review revealed evidence of perceptual distortions, disorientation, hallucinations, or paranoia in 38%. Interviews of 20 patients after open-heart surgery. This discrepancy is thought to be a result of the patients’ inability to recall their experiences while they were in the ICU.


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