

others must develop high-performing health systems, and some of the ACA's Medicare and Medicaid reforms directly stimulate the development of accountable care organizations and patient-centered medical homes. Exchanges can help nurture these systems by organizing a receptive market — one in which each family can select the health care system it prefers, at a price reflecting the competitive value of that system, and can switch systems annually if dissatisfied.

One important constraint on the influence of consumer choice, however, is the relatively small number of people who will be covered through public exchanges. Two movements may increase the effect of consumer choice on the demand for integrated delivery systems. First, employers are beginning to use private exchanges, and if this trend accelerates, millions of employees may also be shopping among competing delivery systems. Second, several states have begun envisioning co-

ordinated state purchasing strategies for Medicaid, government employees, and public exchanges that would drive payment and delivery-system reform.

If such purchasing initiatives are implemented as part of a series of coordinated initiatives to nourish innovative delivery systems, they could eventually garner enough market power to help reshape medical care. To succeed, purchasing coalitions would have to work closely with private insurance carriers and physicians to drive long-term change. This vision assumes that the politics of health care reform can accommodate the sustained effort necessary for systemic, evolutionary change executed through public-private collaborations. That is a tall order.

To achieve these ambitious objectives, exchanges must perform a balancing act familiar to any retailer. As essentially commercial enterprises, exchanges can lead “disruptive” change only so long as they are willing to follow

customer preferences. This requirement is both an advantage and a disadvantage for a fundamentally conservative, market-oriented vehicle for health care reform.

Disclosure forms provided by the author are available with the full text of this article at [NEJM.org](http://NEJM.org).

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This article was published on January 15, 2014, at [NEJM.org](http://NEJM.org).

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DOI: 10.1056/NEJMp1315956

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## 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

Results of Cardiovascular Outcome Trials of Drugs That Modulate Triglyceride and Cholesterol Levels.*					
Trial	Drug	Primary End Point	Change in Triglyceride and Cholesterol Levels		Cardiovascular Outcome†
			Statin plus Placebo or Other Comparator	Statin plus Active Drug	
ACCORD Lipid <sup>1</sup>	Simvastatin plus fenofibrate vs. simvastatin	Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke	Triglycerides, -9%; HDL-C, +6%; LDL-C, -21%	Triglycerides, -22%; HDL-C, +8%; LDL-C, -19%	Hazard ratio, 0.92; 95% CI, 0.79–1.08; P=0.32
AIM-HIGH <sup>2</sup>	Simvastatin plus niacin vs. simvastatin	Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, acute coronary syndrome, or revascularization	Triglycerides, -8%; HDL-C, +10%; LDL-C, -6%	Triglycerides, -29%; HDL-C, +25%; LDL-C, -12%	Hazard ratio, 1.02; 95% CI, 0.87–1.21; P=0.80
HPS2-THRIVE‡	Simvastatin with or without ezetimibe vs. simvastatin plus niacin and laropiprant	Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or revascularization	NA	Triglycerides, -33 mg/dl (-0.37 mmol/liter); HDL-C, +6 mg/dl (+0.16 mmol/liter); LDL-C, -10 mg/dl (-0.28 mmol/liter)	Relative risk, 0.96; 95% CI, 0.90–1.03; P=0.29
JELIS <sup>3</sup>	EPA plus statin vs. EPA	Death from cardiovascular causes, fatal or nonfatal myocardial infarction, unstable angina, angioplasty, stenting, or CABG	Triglycerides, -4%; HDL-C, +4%; LDL-C, -25%	Triglycerides, -9%; HDL-C, +3%; LDL-C, -25%	Hazard ratio, 0.81; 95% CI, 0.69–0.95; P=0.01
ILLUMINATE <sup>4</sup>	Torcetrapib plus atorvastatin vs. atorvastatin	Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or acute coronary syndrome	Triglycerides, +1%; HDL-C, +2%; LDL-C, +3%	Triglycerides, -9%; HDL-C, +72%; LDL-C, -25%	Hazard ratio, 1.25; 95% CI, 1.14–2.19; P=0.006
Dal-OUTCOMES <sup>5</sup>	Dalcetrapib plus statin vs. statin	Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, unstable angina, or cardiac arrest	Triglycerides, +17%; HDL-C, +11%	Triglycerides, +10%; HDL-C, +40%	Hazard ratio, 1.04; 95% CI, 0.93–1.16; P=0.52

\* 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.

‡ 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.

acids). 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,  $\geq 500$  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, apolipoprotein B, VLDL cholesterol, and markers of inflammation. The safety of Vascepa was not a focus, but a final determination of benefit 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 population, with a composite end point of fatal and nonfatal cardiovascular events, coronary revascularization, and hospitalization for unstable angina — is not scheduled to be completed until 2017.

All existing and new drugs targeting lipid disorders in the broad population have the primary goal of reducing the risk of cardiovascular events. However, the FDA's Division of Metabolism and Endocrinology Products (DMEP) has a long history of approving new lipid drugs on the basis of favorable changes in lipid metabolism alone. Alterations in cholesterol metabolism are clearly associated with a marked increase in cardiovascular risk, as shown in numerous observational and epidemiologic studies. For statins, cardiovascular outcomes trials performed after approval definitively showed that LDL cholesterol is an appropriate surrogate end point because there is a direct relationship between lowering LDL cholesterol levels with a statin and a reduced relative risk of cardiovascular events. Given this history, physicians have focused treatment decisions on obtaining target LDL cholesterol goals.

This approach, however, is less

evidence-based when LDL cholesterol levels are lowered with non-statin drugs. In some situations, the at-risk population is simply too small to conduct a cardiovascular outcomes trial. For example, two new drugs (lomitapide and mipomersen) were recently approved by the FDA, solely on the basis of changes in the LDL cholesterol surrogate, for treating very elevated levels of LDL cholesterol in patients with homozygous familial hypercholesterolemia. At an October 2012 advisory committee meeting reviewing lomitapide and mipomersen, the FDA acknowledged the difficulty of conducting 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 favorable changes in lipid fractions (see table). At that meeting, the FDA presented meta-analyses of

studies of n-3 fatty acids that revealed mixed results for cardiovascular outcomes. The most favorable 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 revascularization. This trial had major design limitations, however, including the facts that it was open-label and used low-dose background statin therapy. There are similar concerns regarding HDL cholesterol, since trials of torcetrapib and dalcetrapib did not show clinical benefits.

The deliberations over Vascepa highlight several challenging issues in the development of new treatments for lipid disorders. There is now uncertainty regarding the regulatory approach of approving drugs on the basis of favorable lipid effects and evaluating clinical benefit after approval. If a new drug has a plausible mechanism of action, the intended patient population is well defined, the benefit of a particular 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 outcome trial is ongoing? In judging the risk-benefit ratio in the absence of clinical outcomes data, the drug's safety would need to be well defined. This approach would have the potentially positive effect of allowing patients to use the drug while the outcome trial was being completed — an advantage if the drug were subsequently shown to improve cardiovascular outcomes. For example, 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](http://NEJM.org).

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DOI: 10.1056/NEJMp1313866

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## HISTORY OF MEDICINE

# Still Delirious after All These Years

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Related article, p. 444-54

Doctors 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,’”<sup>1</sup> 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.<sup>2</sup> 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 insult-

ing 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.<sup>2</sup> 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 found delirium in more — 70%.