HEART OF THE MATTER

Black Boxes

The Food and Drug Administration is abdicating some of its responsibility to you and me by placing boxed warnings on its approvals for potent drugs in the face of difficult decisions regarding their risks and benefits. In the past, the approval process has been straightforward, but as we develop stronger drugs with significant risks, it has become much more complex.

Two recent approvals serve as examples. Dronedarone is a recently approved antiarrhythmic drug developed to replace amiodarone for the maintenance of normal sinus rhythm in patients with paroxysmal atrial fibrillation. Because of the long-term effects of amiodarone on thyroid function and lung toxicity, dronedarone was developed by making structural changes in the amiodarone molecule to prevent that toxicity. Amiodarone has been effective in maintaining normal sinus rhythm, but with a trend toward increased mortality in New York Heart Association class III heart failure patients. The initial clinical trial with dronedarone, ANDROMEDA, carried out in NYHA class III-IV patients, was stopped prematurely because of the increased heart failure mortality.

BY SIDNEY GOLDSTEIN, M.D.

ATHENA, a later short-term trial in patients with at least one episode of paroxysmal AF in the previous 3 months with dronedarone, reported a significant decrease in atrial fibrillation compared with placebo. It excluded NYHA class IV patients and those with chronic AF (N. Engl. J. Med. 2009;360:668-78). Dronedarone had a significant improvement in mortality and recurrent hospitalization (36.9% vs. 29.3%), compared with placebo. It also decreased the rehospitalization for AF from 21.8% to 14.6%. There was no ascertainment of amiodarone-like side effects because of ATHENA's short duration. Since it did not compare dronedarone with amiodarone, it is not clear which drug has a better anti-arrhythmic effect.

The FDA approval of dronedarone for the prevention of AF came with a black box warning that it " is contraindicated in patients with NYHA Class IV heart failure, or NYHA Class II-III heart failure with a recent decompensation requiring hospitalization or referral to a specialized heart failure clinic." The FDA left it up to us to decide when to use this drug in heart failure, a moving target at best.

Shortly after this decision, the FDA approved the use of the antiplatelet agent prasugrel, for use in patients with acute coronary syndromes who were likely to undergo percutaneous coronary intervention. In the TRITON trial, comparing clopidogrel with prasugrel in ACS, prasugrel was shown to have a greater benefit for recurrent MI, cardiovascular mortality, or nonfatal stroke (12.1% vs. 9.9%), a result largely driven by "troponin-defined" non-fatal MIs. However, prasugrel was associated with an increased incidence of bleeding and thrombotic strokes about five times that of clopidogrel (6.5% vs. 1.2%), particularly in thin and elderly patients. With this information, the FDA approved prasugrel for the reduction of thrombotic cardiovascular events in ACS patients who are managed with PCI. The approval came with a black box warning that cautioned against its use in patients with a propensity to bleed and in patients aged older than 75 years, or with body weight less than 60 kg.

The current discussion of the approval process of these two drugs, whose therapeutic and safety benefits are narrow, indicates an awareness of the cautions. Over time, the black box warnings lose some of their impact and may become less important in our therapeutic decisions. It has been suggested that with the more liberal use of these warnings, they have lost some of their meaning.

There is nothing wrong with the FDA's passing on the drug-use decision process to the doctors on the front line, but it should be emphasized that many of these drugs come with a significant risk if used in the wrong patient. Doctors beware! ■

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Francis S. Collins Takes NIH Helm

Dr. Francis S. Collins, former director of the National Human Genome Research Institute, became director of the National Institutes of Health on Aug. 17 after being approved unanimously by the Senate.

"The National Institutes of Health stands as a model when it comes to science and research," President Obama said when he nominated Dr. Collins for the post in July. "My administration is committed to promoting scientific integrity and pioneering scientific research, and I am confident that Dr. Francis Collins will lead the NIH to achieve these goals."

Dr. Collins oversaw the federal Human Genome Project, which resulted in the complete mapping of the human genome in April 2003, finishing at about the same time as a parallel private effort. Dr. Collins' research also has resulted in the discovery of several genes, including those responsible for cystic fibrosis, neurofibromatosis, Huntington's disease, and type 2 diabetes. Dr. Collins is interested in the intersection of science and faith and has written two books on the subject.

—Joyce Frieden

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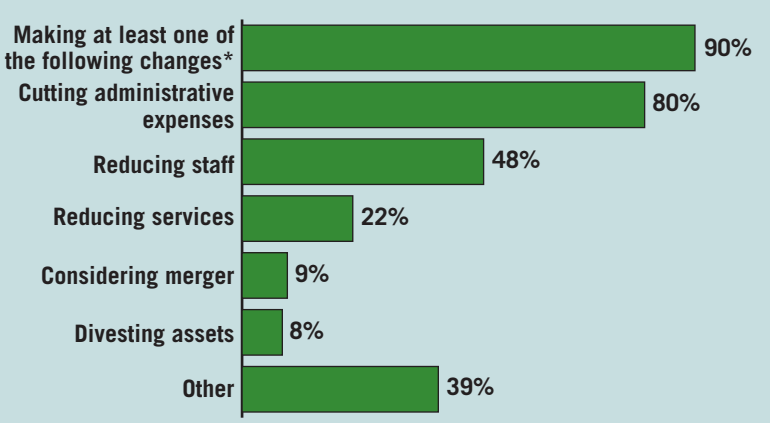
VITAL SIGNS

Most Hospitals Addressing Economic Downturn



* Percentage of hospitals making changes since September 2008.
Note: Based on 1,078 survey responses from community hospitals in March 2009.
Source: American Hospital Association

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