Device Approvals Often Based on Scant Data

BY MARY ANN MOON

Premarketing approval of cardiovascular devices by the Food and Drug Administration often rests on a very shaky foundation, according to a review of 123 studies.

Most of the clinical studies the FDA has relied on to approve CV devices are neither blinded nor randomized. About half are not controlled or use only historical controls, which produces biased results favoring the devices, the study investigators reported. In addition, most of the studies exclude data on patients who have unfavorable outcomes and are performed in subjects who are not representative of the patient populations that will be using the devices.

Moreover, the majority of such FDA approvals have rested on the results of a single study, reported Dr. Sanket S. Dhruva and associates at the University of California, San Francisco (JAMA 2009;302:2679-85).

The public assumes that the FDA's premarketing approval "is the most rigorous device approval process, and strict standards for cardiovascular devices are expected given their far-reaching effects, permanent nature, and use in critically ill patients." Yet the type and quality of the evidence on which the FDA bases its approval have never been systematically examined until now, the investigators noted.

They reviewed the 123 clinical studies underlying FDA approval of 78 cardiovascular devices between 2000 and 2007.

The mean number of studies supporting each approval was only 1.6; fully 65% of the device approvals were supported by only a single study.

Most approvals did not cite even one blinded or one randomized study. Overall, only 27% of the supporting studies were randomized and only 14% were blinded.

Nearly half of the studies supporting FDA approval failed to include a control group for comparison. Of those that did include a control group, retrospectively selected controls were commonly used, which biases the results in favor of the device, the authors wrote.

Many studies excluded data from lead-in periods, which effectively excludes subjects who have immediate unfavorable outcomes. Most also showed large discrepancies between the number of subjects enrolled and the number included in final analyses, with no explanation of the missing data.

In all, data on 10,352 study subjects were excluded, which constitutes nearly a third of the total study population. Twenty percent of the studies did not even report the number of subjects participating.

In more than one-third of the device approvals, "we were not able to ascertain that even 1 study had been conducted in the United States. This results in uncertain generalizability of approved medical devices to the US population," Dr. Dhruva and associates said.

In addition, many devices were approved "using a post hoc analysis of data," which can bias the results in favor of the device, they said.

"The importance of the 'seal of FDA approval' cannot be overstated. Many manufacturers immediately encourage widespread use of their devices based on FDA approval through direct-to-consumer advertising, detailing to physicians, and continuing medical education venues," the investigators noted.

The findings of this study are particularly disturbing given that FDA device approval effectively preempts consumers from bringing lawsuits because of problems with device safety or effectiveness. Moreover, manufacturers are not required to seek out and report device malfunctions, "so device-related adverse events are substantially underreported," they said.

The investigators noted that a limitation of the study may be that the data source is primarily publicly available summaries of safety and effectiveness data. ■

Disclosures: *Dr. Dhruva's associate in this study, Dr. Rita Redberg, reported being a member of the FDA Circulatory System Devices Panel and a member of the California Technology Assessment Forum. No other potential conflicts were reported.*

Sudden Cardiac Death in the Young Not Tied to Exertion

BY BRUCE JANCIN

ORLANDO — Sudden cardiac death accounted for 8% of all mortality in individuals aged up to 35 years in Denmark, in a first-of-its-kind comprehensive national study.

The 7-year study provides a unique picture of sudden cardiac death (SCD) in the young. The extensive Danish national health record system permitted systematic investigation of all 6,629 Danish deaths in subjects aged 35 years and younger during 2000-2006, with review of all death certificates and the autopsy reports in most presumed cases, Dr. Bo G. Winkel said at the annual scientific sessions of the American Heart Association.

Of the fatal events, 31% happened during sleep as did 58% while individuals were awake and relaxed.

DR. WINKEL

Two-thirds of the SCDs occurred at home, 14% in a hospital, and 17% in public places. Of the fatal events, 31% happened during sleep, 58% while individuals were awake and relaxed, and 10% during moderate- to high-intensity physical activities ranging from snow shoveling to sports, reported Dr. Winkel of the Danish Arrhythmia Research Centre at the University of Copenhagen.

There was a spike in cases during the first year of life unequaled until age 15. The mean age at the time of SCD was 26 years, with a median of 29 years.

Autopsies were conducted in 454 of the 619 patients with presumed SCDs. The autopsies revealed definite evidence of SCD in 224 cases and negative findings strongly suggestive of sudden arrhythmic death syndrome in another 136. This syndrome comprises underlying primary arrhythmogenic diseases including long QT syndrome, catecholaminergic polymorphic ventricular tachycardia, and Brugada syndrome.

The autopsies showed pulmonary embolism to be the cause of death in 49 cases, ischemic heart disease in 39, myocarditis and aortic dissection in 23 each, and hypertrophic cardiomyopathy in 18, Dr. Winkel said.

Based on this 7-year Danish experience, he estimated the annual incidence of SCD in the 0-35 age group to be a maximum of 3.1 cases per 100,000 population.

Dr. Michael Ackerman commented that although youthful SCD accounts for only 1%-3% of the 300,000 SCDs per year occurring in the United States, these early events have a particularly devastating emotional impact for the families involved.

"The math changes quite a bit when you talk about preventing the sudden death of a 5-year-old versus extending the life of an 80-year-old," said Dr. Ackerman, professor of medicine, pediatrics, and pharmacology and director of the Windland Smith Rice Sudden Death Genomics Laboratory at the Mayo Clinic, Rochester, Minn.

The study was funded by the Danish Heart Foundation. ■

Anticonvulsant Use Elevated In Sudden Death Cases

BY MITCHEL L. ZOLER

ORLANDO — Patients who experienced sudden cardiac death had a significantly higher rate of treatment with a sodium-channel blocking, anticonvulsant drug, compared with people who did not have sudden death, in a case-control study of more than 10,000 people.

"This finding may explain a proportion of the sudden deaths seen in epilepsy patients," Dr. Abdennasser Bardai said at the annual scientific sessions of the American Heart Association.

About 10% of epilepsy patients have an unexpected death that is not seizure related—a phenomenon so common that it's been named "sudden unexplained death in epilepsy." Dr. Bardai and his associates hypothesized that many of these deaths might be triggered by anticonvulsant drugs, especially those that block sodium channels such as carbamazepine, lamotrigine, and phenytoin. Although the sodium-channel blockade these drugs cause is aimed at neurons, the same property can also affect cardiac cells and may potentially cause arrhythmia.

To explore a possible link between anticonvulsant use and sudden death, the researchers used data collected in the Netherlands' Integrated Primary Care Information database. They focused on medical records for people aged 18 or older during 1995-2007 in cases for which at least 1 year's record existed.

Among the more than 478,000 people who met these criteria, 926 experienced sudden death, defined as a natural death heralded by a sudden loss of consciousness within 1 hour after the onset of acute symptoms, or an unwitnessed, unexpected death of someone seen in stable medical condition less than 24 hours before with no evidence of a noncardiac cause. The researchers matched each case with about 20 other people from the database with a similar age and identical gender, reaching a total of 9,832 controls. The average age of the cases and controls was 72 years, and 26% were men.

In a multivariate analysis that controlled for age, gender, smoking, alcohol abuse, concomitant medications, cardiovascular disease, arrhythmia, hypertension, diabetes, heart failure, and hypercholesterolemia, people who died from sudden death were 2.5-fold more likely to be on treatment with an anticonvulsant drug than were controls, a statistically significant difference, reported Dr. Bardai, a cardiovascular diseases researcher at the Academic Medical Center in Amsterdam.

In a second adjusted analysis that divided anticonvulsant drug use into agents that block sodium channels and those that don't, the sudden death cases were 2.9-fold more likely to be on a sodium-channel blocking anticonvulsant, compared with controls, a statistically significant difference.

In contrast, the fraction of sudden death cases on treatment with an anticonvulsant that doesn't block sodium channels was not significantly different from the rate at which these drugs were used by the controls.

Dr. Bardai said that he and his associates had no financial disclosures. ■

Pages 12a—12b◊