New Data Challenge Medicare Criteria for ICDs

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Denver Bureau

NEW ORLEANS — Medicare's policy of covering implantable cardioverter defibrillator therapy in patients with nonischemic dilated cardiomyopathy with a disease duration of 9 months or more was undercut by two studies presented at the annual meeting of the Heart Rhythm So-

The studies by two separate teams of in-

vestigators independently showed that the risk of sudden cardiac death-and the benefit from implantable cardioverter defibrillator (ICD) therapy—was the same whether patients met the 9-month criteri-

The patients with nonischemic dilated cardiomyopathy who met Centers for Medicare and Medicaid Services (CMS) criteria for ICD implantation, except that their disease had been diagnosed less than 9 months earlier, had benefits similar to

those seen in patients whose condition had been diagnosed at least 9 months earlier and who therefore were eligible for ICD coverage. The benefit was also seen in patients whose nonischemic dilated cardiomyopathy (NIDCM) was diagnosed less than 3 months earlier.

"These results suggest that any delay in ICD implantation will reduce survival benefit. Therefore, if ICD therapy is selected for a patient with nonischemic cardiomyopathy ... then the ICD should be implanted without delay," said Kelley P. Anderson, M.D., of the Marshfield (Wis.) Clinic.

In January, CMS expanded coverage for ICD therapy beyond patients with ischemic cardiomyopathy for the first time, to include selected individuals with NIDCM.

But to be eligible, patients had to have New York Heart Association class III or worse heart failure, a left ventricular ejection fraction of 35% or less, and—the focus of controversy—they had to have nonischemic dilated cardiomyopathy of more than 9 months' duration. Patients who had been diagnosed 3-9 months earlier would be eligible for reimbursement but only if they were entered in a special registry, the details of which the Heart Rhythm Society and CMS are still hammering out.

Patients with nonischemic dilated cardiomyopathy of less than 3 months' duration are ineligible for ICD coverage be-

This study shows a clear benefit, irrespective of when patients were diagnosed. CMS may want to revisit the coverage criteria in light of these findings.

cause CMS has deemed there is a lack of clinical evidence benefit.

Dr. Anderson presented new retrospective post hoc analysis of data from the prospective Defibrillators in Nonischemic Cardiomyopathy Treatment

Evaluation (DEFINITE) trial, in which 458 patients with NIDCM were randomized to optimal medical therapy for heart failure with or without an ICD, regardless of the duration of NIDCM.

At 2.5 years of follow-up, survival in the 150 patients with nonischemic dilated cardiomyopathy of not more than 3 months' duration at randomization was 89.9%, after the investigators controlled for treatment assignment. This wasn't significantly different from the 84.0% rate in patients with NIDCM of greater than 3 months' duration. Similarly, survival in the 216 patients with NIDCM of 9 months' duration or less was comparable to that of patients with greater than 9 months' duration.

Moreover, among the subgroup of patients with nonischemic dilated cardiomyopathy of 3 months' duration or less at the time of randomization, those assigned to receive an ICD were 63% more likely to be alive at 2.5 years than were those randomized to optimal medical management. Similarly, those whose NIDCM had been diagnosed 9 months or less prior to ICD implantation were 52% more likely to survive to 2.5 years than were comparable patients randomized to medical therapy, he continued.

Late-breaker session cochair David S. Cannom, M.D., called the new DEFINITE data "very provocative," adding, however, that he found troubling what he termed the "startlingly high" early arrhythmic event rate in the study population.

"The argument might be that you've picked a particularly vulnerable population that's suffering from an acute syndrome of Continued on following page

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BRIEF SUMMARY

INDICATIONS AND USAGE

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mbien (zolpidem tartrate) is indicated for the short-term treatment of insomnia.

mbien has been shown to decrease sleep latency and increase the duration of
eep for up to 35 days in controlled clinical studies.

Hypnotics should generally be limited to 7 to 10 days of use, and reevaluation
the patient is recommended if they are to be taken for more than 2 to 3 weeks.

mbien should not be prescribed in quantities exceeding a 1-month supply (see
farmings).

with withdrawal from other CNS-depressant drugs (see *Drug Abuse and modence*).

nbien, like other sedative/hypnotic drugs, has CNS-depressant effects. Due rapid onset of action, Ambien should only be ingested immediately prior ing to bed. Patients should be cautioned against engaging in hazardous pations requiring complete mental alertness or motor coordination such as triting machinery or driving a motor vehicle after ingesting the drug, includatential impairment of the performance of such activities that may occur the ollowing ingestion of Ambien. Ambien showed additive effects when commod with alcohol and should not be taken with alcohol. Patients should also be oned about possible combined effects with other CNS-depressant drugs, ge adjustments may be necessary when Ambien is administered with such s because of the potentially additive effects.

PERCALITIONS

Dosage and Administration to decrease the possibility of side effects. These patients should be closely monitored.

We in patients with concomitant illness: Clinical experience with Ambien in patients with concomitant systemic illness is Imited. Caution is advisable in patients with concomitant systemic illness is Imited. Caution is advisable in using Ambien in patients with diseases or conditions that could affect metabolism or hemodynamic responses. Although studies did not reveal respiratory depressant effects at hypnotic doses of Ambien in normals or in patients with mild to moderate chronic obstructive pulmonary disease (COPD), a reduction in the Total Arousal Index together with a reduction in lowest oxygen saturation and increase in the times of oxygen desaturation below 80% and 90% was observed in patients with mild-to-moderate sepanea when treated with Ambien 10 mgl when compared to placebo. However, precautions should be observed if Ambien is prescribed to patients with compromised respiratory function, since sedative/hypnotics have the capacity to depress respiratory drive. Post-marketing reports of respiratory insufficiency, most of which involved patients with pre-existing respiratory insufficiency, most of which involved patients with pre-existing respiratory insufficiency, most of which involved patients with pre-existing respiratory insufficiency, and the patient of the patients with a patient separated by the patient of the patients with the patient of the patients with the patient of the patients with the patient of the patients of the patients of the patients with patients with patients with the patients with the patients and the closely monitored (see Pharmacokinetics). A study in subjects with hepatic impairment did reveal prolonged elimination in this group; therefore, treatment should be initiated with 5 mg in patients with hepatic compromise, and they should be dosely monitored.

**Use in depression:*A swith other sedative/hypnotic drugs, Ambien should be administered with aution to pat

Laboratory tests: There are no specific laboratory tests recommended.

Drug interactions CNS-active drugs: Ambien was evaluated in healthy volunteers in single-dose interaction studies for several CNS drugs. A study involving haloperidol and zolpidem revealed no effect of haloperidol on the pharmacokinetics or pharmacokyments of zolpidem. Impiramine in combination with zolpidem produced no pharmacokinetic interaction other than a 20% decrease in peak levels of mipramine, but there was an additive effect of decreased alertness. Similarly, chlorpromazine in combination with zolpidem produced no pharmacokinetic interaction, but there was an additive effect of decreased alertness and psychomotor performance. The lack of a drug interaction following single-dose administration does not predict a lack following chronic administration. An additive effect on psychomotor performance between alcohol and zolpidem was demonstrated.

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A single-dose interaction study with zolpidem 10 mg and fluoxetine 20 mg afteady-state levels in male volunteers did not demonstrate any clinically significant pharmacokinetic or pharmacokinamic interactions. When multiple doses of oppidem and fluoxetine at steady-state concentrations were evaluated in healthy emales, the only significant change was a 17% increase in the zolpidem half-life. There was no evidence of an additive effect in psychomotor performance. Following five consecutive nightly doses of zolpidem 10 mg in the presence of entraline 50 mg (17 consecutive daily doses, at 7:00 am, in healthy female of interest, zolpidem C__ was significantly lecreased (53%). Pharmacokinetics of sertraline and N-desmethylsertraline were inaffected by zolpidem.

ed by zolpidem.

The systematic evaluations of Ambien in combination with other CNS-ruge have been limited, careful consideration should be given to the bology of any CNS-active drug to be used with zolpidem. Any drug with pressant effects could potentially enhance the CNS-depressant effects of

Inficant alterations in zolpidem pharmacokinetics were found.

Drug/Laboratory test interactions: Zolpidem is not known to interfere with commonly employed clinical laboratory tests. In addition, clinical data indicate that zolpidem does not cross-react with benzodiazepines, opiates, barbiturates, occaine, cannabinoids, or amphetamines in two standard urine drug screens.

Carcinogenesis, mutagenesis, impairment of fertility
Carcinogenesis: Zolpidem was administered to rats and mice for 2 years at dietary dosages of 4, 18, and 80 mg/kg/day, In mice, these doses are 26 to 520 times or 2 to 35 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. In rats these doses are 45 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. In rats these doses are 45 to 876 times or 6 to 115 times the maximum 10-mg human dose on a mg/kg or mg/m² basis, respectively. No evidence of carcinogenic potential was observed in mice. Renal liposarcomas verseen in 4/100 rats (3 males, 1 female) receiving 80 mg/kg/day and a renal liposar was observed in one male rat at the 18 mg/kg/day dose. Incidence rates of lipoma and liposarcoma for zolpidem were comparable to those seen in historical controls and the tumor findings are thought to be a spontaneous occurrence.

Mutagenesis: Zolpidem did not have mutagenic activity in several tests includ-

mg/m². No effects on any other retruity parameters were noted.

Pregnancy
Teratogenic effects: Category B. Studies to assess the effects of zolpidem on human reproduction and development have not been conducted.

Teratology studies were conducted in rats and rabbits.

In rats, adverse maternal and fetal effects occurred at 20 and 100 mg base/kg and included dose-related maternal lethargy and ataxia and a dose-related trend to incomplete ossification of fetal skull bones.

In rabbits, dose-related maternal sedation and decreased weight gain occurred at all doses tested. At the high dose, 16 mg base/kg, there was an increase in postimplantation fetal loss and underossification of sternebrae in viable fetuses.

This drug should be used during pregnancy only if clearly needed.

**Materatogenic effects: Studies to assess the effects on children whose mothers

This drug should be used during pregnancy only if dearly needed.

Nontrartogenic effects: Studies to assess the effects on children whose mothers took zolpidem during pregnancy have not been conducted. However, children born of mothers taking sedative/hynotic drugs may be at some risk for whit-drawal symptoms from the drug during the postnatal period. In addition, neonatal flaccidity has been reported in infants born of mothers who received sedative/hynotic drugs during pregnancy.

Labor and delivery: Ambien has no established use in labor and delivery.

Nursing mothers: Studies in lactating mothers indicate that between 0.004 and 0.019% of the total administered dose is excreted into milk, but the effect of zolpidem on the infant is unknown.

The use of Ambien in nursing mothers is not recommended.

have not been established.

Geriatric use: A total of 154 patients in U.S. controlled dinical trials and 897 patients in non-U.S. clinical trials who received zolpidem were ≥60 years of age. For a pool of U.S. patients receiving zolpidem at doess of ≈10 mg or placeb, there were three adverse events occurring at an incidence of at least 3% for zolpidem and for which the zolpidem incidence was at least twice the placebo incidence (ie, they could be considered drug related).

Adverse Event	Zolpidem	Placebo
Dizziness	3%	0%
Drowsiness	5%	2%
Diarrhea	3%	1%

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events.

Adverse events are further classified and enumerated in order of decreasing frequency using the following definitions: frequent adverse events are defined as those occurring in greater than 1/100 subjects; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in less than 1/1,000 patients.

psepitation, steep disorder, vertigo, vision abnormal, vomiting, infrequent: abnormal hepatic function, agitation, arbritis, bronchitis, cerebrovascular disorder, coughing, cystitis, decreased cognition, detached, difficulty concentrating, dysarthria, dyspheaia, dyspnea, adema, emotional lability, eye riritation, eye pain, falling, lever, flatulence, gastroenteritis, halucination, hyperglycemia, hypertension, hypoesthesia, illusion, increased SGPT, increased sweating, leg cramps, malaise, menstrual disorder, migraine, pallor, paresthesia, postural hypotension, pruntus, scleritis, sleeping (after daytime dosing), speech disorder, stupine, synope, techyoradia, taste perversion, thirst, tinnitus, trauma, tremor, urinary incontinence, vaginitis.

symptomatology, including tatal outcomes.

Recommended treatment: General symptomatic and supportive measures should be used along with immediate gastric lavage where appropriate. Intravenous fluids should be administered as needed. Flumazenil may be useful. Respiration, pulse, blood pressure, and other appropriate signs should be monitored and general supportive measures employed. Sedating drugs should be withheld following zolpidem overdosage. Zolpidem is not dialyzable.

The possibility of multiple drug ingestion should be considered.

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some type—say, a viral etiology—that would get better over a short period of time anyway without an ICD," said Dr. Cannom, director of cardiology at Good Samaritan Hospital, Los Angeles, and a past president of the Heart Rhythm Society.

His cochair, Sanjeev Saksena, M.D., commented that he'd be very interested to see serial ejection fraction data for the DEFINITE participants.

A significant improvement over time would suggest Dr. Cannom's hunch is correct

"We are often pressured to intervene to

put in an ICD in these patients with nonischemic cardiomyopathy [of short duration], and then 3 or 4 weeks later the ejection fraction has improved," said Dr. Saksena, professor of medicine at Robert Wood Johnson Medical School in New Brunswick, N.J.

Dr. Anderson replied that the investigators attempted to exclude from DEFINITE any patients with myocarditis or other reversible causes of NIDCM, although that can be difficult. He added that the ejection fraction data are still being processed.

But even if it turns out many of these patients have a self-limited, reversible car-

diomyopathy, the challenge will be to protect them from arrhythmic death during those initial months of high vulnerability.

"Maybe one should use a home external defibrillator, or a life vest, or maybe after a period of time explant an ICD," he said.

In a separate presentation, Kevin J. Makati, M.D., presented a retrospective study involving 131 patients with NIDCM treated at Tufts-New England Medical Center, Boston.

Of the 131 patients, 79 had been diagnosed with the disorder at least 9 months and a mean of 66 months prior to ICD implantation. The remaining 52 had carried the diagnosis of NIDCM for less than 9

and a mean of 1.4 months at the time of implantation.

During 27 months of follow-up, there were no differences between the two patient groups in terms of the occurrence of ventricular arrhythmias or life-threatening ventricular arrhythmias.

"This study shows a clear benefit of ICDs for patients with cardiomyopathy, irrespective of when they were diagnosed," commented Stephen C. Hammill, M.D., immediate past president of the Heart Rhythm Society.

"CMS may want to revisit the coverage criteria for these patients in light of these findings," he said.





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