High Prevalence of Valvular Disease Found in the Elderly

BY MITCHEL L. ZOLER Philadelphia Bureau

NEW ORLEANS — Almost 12% of Americans aged 75 years or older have valvular heart disease, according to echocardiographic findings from an unselected population of 1,745 people.

The prevalence of valvular heart disease was also high (7.8%) in an unselected group of 3,879 Americans aged 65-74 years, Vuyisile T. Nkomo, M.D., reported in a poster at the annual scientific sessions of the American Heart Association.

This high prevalence of valvular heart disease in the elderly subjects, many of whom were probably asymptomatic, suggests that physicians need to assess elderly patients carefully for valvular disease by their history and physical examination, said Dr. Nkomo, a cardiologist at the Mayo Clinic in Rochester, Minn. An echocardiogram, the definitive way to identify valvular heart disease, should be obtained for people who are suspected to have clinically significant valvular dis-

"Routine screening by echocardiography of all asymptomatic elderly people may be prohibitively expensive," he told this newspaper. "This may be where handheld echocardiography devices may be useful, if they come to be used as an extension of the physical examination.

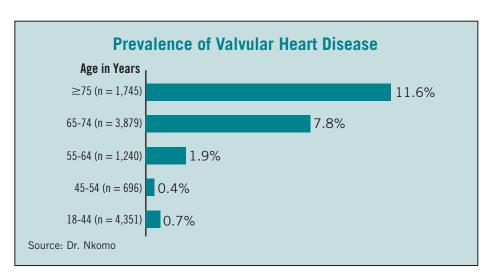
"Waiting for symptoms to appear before making a diagnosis of valvular heart disease—or suspecting valvular disease but waiting for symptoms before getting an echocardiogram—may be waiting too long," Dr. Nkomo added. That's because of the excess risk for people who become symptomatic, compared with those who are still asymptomatic when their valvular disease is first diagnosed.

If an asymptomatic person is found to have, for example, moderately severe mitral regurgitation, then an annual echocardiogram should be done to monitor whether the severity is progressing and intervention is needed, he said.

To examine the prevalence of valvular heart disease in the general population, Dr. Nkomo and his associates sorted through echocardiographic data collected on 11,911 people in three large, population-based studies that were sponsored by the National Heart, Lung, and Blood Institute. Data came from the Coronary Artery Risk Development in Young Adults (CARDIA) study, the Atherosclerosis Risk in Communities (ARIC) study, and the Cardiovascular Health Study (CHS). The echocardiograms were done between 1989 and 1996 in men and women who were at least 18 years old.

A total of 555 people had valvular heart disease that was of at least moderate severity, representing an overall, age- and gender-adjusted rate of 2.3%. But there was a striking link between age and the prevalence of valve disease: The rate was lowest in people under 45 years old, with a prevalence of 0.7%, and in those aged 45-54 years old, with a prevalence of 0.4%. The rate rose sharply upward among the next three age strata. The prevalence of valvular disease among people aged 55-64 years was 1.9%.

Mitral regurgitation was the most common type of valvular disease, in 6.5% of those aged 65-74 and in 9.4% of those aged 75 or older. Next most common was aortic valve regurgitation, found in 1% of people aged 65-74and 2% of those aged 75 or older. The prevalence of these and any other valvular diseases seen was roughly the same between men and women.



ZOMIG® (zolmitriptan) Tablets

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BRIEF SUMMARY of PRESCRIBING INFORMATION

INDICATIONS AND USAGE: 2001/IRG is indicated for the acute treatment of migraine with or without aura in adults. 20MIG is not intended for the prophylactic therapy of migraine of for use in the management of hemiplegic or basilar migraine (see CONTRAINDICATIONS) saled effectiveness of ZOMIG have not been established for cluster headache, which is present in an older, predominantly male

ZOMIG should not be administered to patients with hemiplegic or basilar migraine. Concurrent administration of MAO-A inhibitors or use of zolimitriptan within 2 weeks of discontinuation of MAO-A inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY: Drug Interactions and PRECAUTIONS: Drug Interactions). ZOMIG is contraindicated in patients who are hypersensitive to zolimitriptan or any of its inactive ingredients.

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WARNINGS: ZOMIG should only be used where a clear diagnosis of migraine has been established. Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events: ZOMIG should not be given to patients with documented ischemic or vasospastic coronary artery diseases (EUI) by predicted by the presence of risk factors (e.g., hypothesiston, hypocrinobesterolemian immercagnized coronary artery diseases (EUI) by predicted by the presence of risk factors (e.g., hypothesiston, hypocrinobesterolemian immercagnized coronary artery diseases (EUI) by predicted by the presence of risk factors (e.g., hypothesiston, hypocrinobesterolemian immercagnized coronary artery and the predicted produced by the predicted produced in the patient is reasonably free of coronary artery and schemic myocardial disease or or deris significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular valuation, the patient's medical procedures to detect cardiovascular valuation in the sensitivity of cardiac diagnostic procedures detect to the patient's development of the detect of the patient's development of the detect of the patient's development of the detect of the patient's development of the develop

ognized cardiovascular disease will be inadvertently exposed to zolmitriplan.

Cardiac Events and Falatilities: Serious adverse cardiac events, including acute myocardial infarction, have been reported within a few hours following administration of zolmitriplan. Lift-interesting disturbances of cardiac rightim, and death have been reported within a few hours following daministration of other 5+TH agonists. Considering the extent of use of 5+TH agonists in patients with migraine, the incident of these events is externely low. Zolfid can cause coronary vascispasin; at least one of these events occurred in a patient with no cardiac ordinacy accounts of the patient with migraine, the incident in the cardiac patients with a cardiac accounted in a patient with no cardiac relationship cannot be excluded. In the cases where there has been known underlying coronary artery disease, the relationship is uncertain. Patients with symptomatic Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disprendents are exposed.

orders should not receive ZOMIG.

Premarketing experience with zolmitriptan: Among the more than 2,500 patients with migraine who participated in premarketing controlled clinical trials of ZOMIG Tablets, no deaths or serious cardiac events were reported.

Postmarketing experience with zolmitriptan: Serious cardiovascular events have been reported in association with the use of ZOMIG Tablets, and in very rare cases, these events have occurred in the absence of known cardiovascular disease. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by zolmitriptian or to reliably assess causation in individual cases.

Cerebrovascular Events and Falalities with 5-HT1 agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with 5-HT2 agonists; and some have resulted in falalities. In a number of cases, it appears possible that the cerebrovascular events were primary, the agonist having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine, when they were not. It should be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, transient ischemic attack).

Other Vasospasm-Related Events: 5-HT1 agonists may cause vasospastic reactions other than coronary artery vasospasm such as peripheral and gastrointestinal schemic events including schemic collists and gastrointestinal infarction or necrosis have been reported with ZOMIG Tablets, these may present as bloody diarrhea or addorninal pain.

schemic boths and user animation of necross have been reported wint zowns tables, ness may bresen as broody during a biddominal paid.

Increase in Blood Pressure: As with other 5-HT, agonists, significant elevations in systemic blood pressure have been reported on rare occa-sions with ZoMidS Tablet use, in patients with and without a history of hypertension; very rarely these increases in blood pressure have been accounted with significant clinical events. Zomintriplan is contrandicated in patients with uncontrolled hypertension. In volunteers, were measured only in the small inpatient study and no effect on blood pressure was seen. In a study of patients with uncontrolled were measured only in the small inpatient study and no effect on blood pressure was seen. In a study of patients with underate to severe liver disease, 7 of 27 experienced 20 to 80 mm Hg elevations in systolic and/or disatolic blood pressure after a dose of 10 mg of zolinitriplan (see CONTRAINDICATIONS). An 48% increase in mean pulmonary artery pressure was seen following dosing with another 5-HT₁ agonist in a study evaluating subjects undergoing cardiac catheterization.

PRECAUTIONS

General: As with other 5-HT_{1B/1D} agonists, sensations of tightness, pain, pressure, and heaviness have been reported after treatment with 20/MIG Tablets in the precordium, throat, neck and jaw. Because zolimitriptan may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following dosing should be evaluated for the presence of CAD or a predisposition to Prizomatel's variat angina before needwing additional doses of medication, and should be monitored electrocardicing phickup/if dosing is recorded and similar symptoms recur. Similarly, patients who experience their symptoms or signs suggestive of decreased arterial flow, such as schemical symptoms or flowpasts symptoms produced by the such as the symptoms of the sy

to treatment with zonimitypian were noted in any of the toxicity studies. Authority in oxystematic monitoring of optimal mologic functions with an oxystematic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long-term ophthalmologic monitoring are offered, prescribers should be aware of the possibility of sintegrating tablet contains 5.62 mg phenylatamine. Each 5 mg orally disintegrating tablet contains 5.62 mg phenylatamine. Information for Patients: See Patients 1.82 mg phenylatamine. Information for the tot of the separate leafter provided for patients. 20MIG-2MT Orally Disinfegrating Tablet placed on the tongue, where it will dissolve and be swallowed with the saliva. Laboratory 18:81: No monitoring of specific laboratory tests is recommended.

Drug interactions: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis that these effects may be additive, use of repotamine-containing or ergot-type medications (like dihydroergotamine or methysergide) and zointriptam within 24 hours of each other should be avoided (see CONTRANDICATIONS). Ocnomitant use of other 5-HT gapp agonists within 24 hours of 20MIG treatment is not recovered to the control of the patients of the p

shown no impairment of fertility at doses up to 400 mg/kg/day. Exposure at this dose was approximately 3000 times exposure at the maximum recommended human dose of 10 mg/day.

Pregnancy: Pregnancy: Category C: There are no adequate and well controlled studies in pregnant women; therefore, zolmitriptan should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In reproductive boxicity statis in rats and rabbits, oral administration of zolmitriptan to pregnant animals was associated with embryolethality and fetal abnormalities. When pregnant rais were administered oral zolmitriptan during the period of organogenesis at doses of 100, 400 and 1200 mg/kg/kg/ where was a dose-related increase in embryolethality which became statistically significant at the high dose. The maternal plasame exposures at these doses were approximately 280, 1100 and 5000 times the exposure in humans receiving the maximum recommended aduly dose of 10 mg/kg/day (maternal plasma exposures equivalent to 11 and 42 times exposure in humans receiving the maximum recommended total daily dose of 10 mg), and increased incidences of fetal mail-formations (fued stemebrae, not anomalies) and variations (migro) blood vessel variations, irregular cossification pattern of risk) were observed at 30 mg/kg/day. Three mg/kg/day was an oeffect dose (equivalent to human exposure) at a dose of 10 mg). When female rats were given zolmitriptand uring gestation, pattern of risk) were observed at 30 mg/kg/day. Three mg/kg/day was an oeffect dose (equivalent to human exposure).

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Nursing Mothers: It is not known whether zolmitripitan is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when zolmitriptan is administered to a nursing woman. Lactating rats dosed with zolmitriptan had milk levels equivalent to maternal plasma levels at 1 hours. Pediatric Use: Sately and effectiveness of ZOMIG in pediatric plasma take not been established therefore, ZOMIG is not recommended for use in patients under 18 years of age. Postmarketing experience with other triptans includes a limited number of reports that describe pediatric patients who have experienced clinically serious adverse events that are similar in nature to those reported rary nadius. Geriatric Use: Although the pharmacokinetic disposition of the drug in the elderly is similar to that seen in younger adults, there is no information about the sately and effectiveness of zolmitripal in this population because patients over age 65 were excluded from the controlled clinical trials. (see CLINICAL PHARMACOLOGY: Special Populations)

ADVERSE REACTIONS: Serious cardiac events, including myocardial infarction, have occurred following the use of ZOMIG Tablets. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported, in association with drugs of this class, have included coronary artery sexopasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular librillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

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Incidence in Controlled Clinical Trials: Among 2,633 patients retracted with ZOMIG Tablets in the active and placebo controlled trials, no patients withdrew for reasons related to adverse events, but as patients treated a single headache in these trials, the opportunity for discontinuation was limited. In a long-term, open label study where patients were allowed to trad multiple migrate attacks for up to 1 year, 8% (167 out of 2,058) withdrew from the trial because of adverse experience. The most common events were paresthiesia, asthenia, nausea, dizziness, pain, releast or neck tightness or heaviness, somnolence and warm sensation. Table 1 lists the adverse events that occurred in 2.2% of the 2,074 patients in any one of the 2,004 fill mg. 2,004 fill 5.3 mg or 200MIG. 5 mg Tablets dose groups of the rotrolled clinical rails. Only events that were more frequent in a 2,004 fill fablets group compared to the placebo groups are included. The events of effect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In advail clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Several of the adverse events appear dose related, notably paresthesia, sensation of heaviness or tightness in chest, neck, jaw, and throat, dizziness, somnolence, and possibly asthenia and nausea.

Table 1: Adverse Experience Incidence in Five Placebo-Controlled Migraine Clinical Trials: Events Reported By ≥ 2% Patients Treated With ZOMIG Tablets

Adverse Event Type	Placebo (n=401)	ZOMIG 1 mg (n=163)	ZOMIG 2.5 mg (n=498)	ZOMIG 5 mg (n=1012)
	(11-401)	(11-100)	(11-430)	(11-1012)
ATYPICAL SENSATIONS	6%	12%	12%	18%
Hypesthesia	1%	1%	1%	2%
Paresthesia (all types)	2%	5%	7%	9%
Sensation warm/cold	4%	6%	5%	7%
PAIN AND PRESSURE SENSATIONS	7%	13%	14%	22%
Chest-pain/tightness/pressure and/or heaviness	1%	2%	3%	4%
Neck/throat/jaw-pain/tightness/pressure	3%	4%	7%	10%
Heaviness other than chest or neck	1%	1%	2%	5%
Pain-location specified	1%	2%	2%	3%
Other-pressure/tightness/heaviness	0%	2%	2%	2%
DIGESTIVE	8%	11%	16%	14%
Dry mouth	2%	5%	3%	3%
Dyspepsia	1%	3%	2%	1%
Dysphagia	0%	0%	0%	2%
Nausea	4%	4%	9%	6%
NEUROLOGICAL	10%	11%	17%	21%
Dizziness	4%	6%	8%	10%
Somnolence	3%	5%	6%	8%
Vertigo	0%	0%	0%	2%
OTHER				
Asthenia	3%	5%	3%	9%
Palpitations	1%	0%	<1%	2%
Myalgia	<1%	1%	1%	2%
Myasthenia	<1%	0%	1%	2%
Sweating	1%	0%	2%	3%

ZOMIG is generally well tolerated. Across all doses, most adverse reactions were mild and transient and did not lead to long-tasting effects. The incidence of adverse events in controlled clinical trials was not affected by gender, weight, or age of the patients; use of prophylactic medications; or presence of aura. There were insufficient data to assess the impact of race on the incidence of adverse events.

Other Events: In the paragraphs that follow, the frequencies of less commonly reported adverse clinical events are presented. Because the reports include events observed in open and uncontrolled studies, the role of ZOMIG in their causation cannot be reliably determined. Furthermore, variability associated with adverse event reporting, the terminology used to describe adverse events, etc., limit the value frequency estimates provided. Event frequencies are calculated as the number of patients who used ZOMIG Tablets (n=4,027) and reported an event divided by the total number of patients exposed to ZOMIG Tablets. All reported events are included except hose already isself in the previous table, those to openeral to be informative, and those not reasonably associated with this Dody system categories and enumerated in order of decreasing frequency using the following definitions: infrequent adverse events are those occurring in 1/100 to 1/1,000 patients.

Infoquent was evenis are mose occurring in Info 10 to 17,000 patients and rare adverse events are those occurring in fewer than 17,000 patients. Infrequent was hyperesthesia. General: Infrequent were allergy reaction, chills, facial edema, fever, malaise and horsensitivity. Cardiovascular: Infrequent were arrhythmias, hypertension and syncope. Bare were bradycardia, extasystoles, postural hypotension, QT prolongation, tachycardia and thrombophiebits. Digestive: Infrequent were increased appetite, tongue edema, esophagists, gastroenteritsis, liver function abnormality and thirst. Bare were anorexia, constipation, gastrinis, hematemesis, panettis, melena, and ulcer. Hemic: Infrequent was ecchymosis. Bare were cyanosis, thrombocytopenia, eosinophilia and leukopenia. Metabolic: Infrequent was edema. Rare were hypertyperional and lakliane phosphatase increased. Musculoskelteal: Infrequent weak pain, leg cramps and tenosynovitis. Rare were arrhifitis, asthenia, tetany and twitching. Neurological: Infrequent were aglitation, anxiety, depression, emotional ability and insomnia. Pare were astabilisia, amnesis, apathy, ataxia, dystonia, euphoria, hallucinations, cerebral schemia, hyperkinesia, hypotonia, hypertonia and irritability. Respiratory: Infrequent were bronchitis, bronchospasm, epistaxis, hiccup, laryngitis, and yawn. Rare were apina and voice atteration. Sixti: infrequent were pruntius, rash and urforaris. Special Senses: infrequent were dry eye, eye pain, hyperacussis, ear pain, parosmia, and tinnitus. Rare were diplopia and lacrimation. Urogenital: Infrequent were hematuria, cystitis, polyuruq, urinary frequency, urinary uringency. Pare were missacriage and dysmenorrhea.

The adverse experiences profile seen with 20MIG-2MIT Tablets was similar to that seen with 20MIG Tablets.

Postamaketing Experience with 20MIG Tablets. The following section enumerates potentially important adverse events that have occurred in clinical practice and which have been reported spontaneously to various surveillance systems. The e

cardiovascular: Coronary artery vasospasm; transient myocardial ischemia, angina pectoris, and myocardial infarctio Digestive: Very are gastrointestinal ischemic very transpoporni, aminorita intryucturular ischemic very are gastrointestinal ischemic very transis including spletic infarction, ischemic colitis, and gastrointestinal infarction or necrosis have been reported; these may present as bloody diarrhea or abdominal pain (see WARNINGS).

**Neurological: As with other acute migraine treatments including other 5-HT₁ agonists, there have been rare reports of headache.

**General: As with other 5-HT₁ grap agonists, there have been very rare reports of anaphylaxis or anaphylactoid reactions in patients receiving ZOMIG. There have been rare reports of hypersensitivity reactions, including angioedema.

DRUG ABUSE AND DEPENDENCE: The abuse potential of ZOMIG has not been assessed in clinical trials.

OVERDOSAGE: There is no experience with clinical overdose. Volunteers receiving single 50 mg oral doses of zolmitriptan commonly experienced sedation. The elimination half-life of ZDMIG is 3 hours (see CLINICAL PHARMACOLOGY), and therefore monitoring of paids after overdose with ZDMIG should continue for at least 15 hours or while symptoms or signs persist. There is no specific antioties to zolmitriptan. In cases of severe intoxication, intensive care procedures are recommended, including establishing and maintaining a patent airway, ensuring adequate oxygenation and ventilation, and monitoring and support of the cardiovascular system. It is unknown what effect hemodialysis or peritoneal dialysis has on the plasma concentrations of zolmitriptan.

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