

Endovascular Beats Open Surgical Repair for AAA

BY ROBERT FINN
San Francisco Bureau

SCOTTSDALE, ARIZ. Endovascular repair of abdominal aortic aneurysms was associated with fewer perioperative complications than was open repair in a large study based on Medicare data.

At an international congress on endovascular interventions sponsored by the Arizona Heart Institute, Dr. James F. McKinsey reported on 174,974 patients who

had open repair and 38,629 patients who underwent endovascular repair. In the open surgery group, 30-day mortality was over 2.5 times greater than in the endovascular group, a significant difference. (See box.)

Also, endovascular repair was associated with fewer peripheral vascular complications (1.6% vs. 3.3%), a lower incidence of postoperative shock (0.1% vs. 0.4%), and fewer infections (0.7% vs. 2.9%).

Endovascular repair was associated with

significantly fewer gastrointestinal, pulmonary, renal, neurologic, cardiac, and surgical complications.

The mean length of hospital stay (3 days vs. 9 days) also strongly favored the endovascular group.

Device malfunction was the only complication that was significantly greater in the endovascular group, compared with the open surgery group (3.0% vs. 1.1%).

“The people undergoing endovascular repair were a sicker group to start with,”

said Dr. McKinsey, of Columbia University Medical Center, New York. They tended to have elevated lipid levels as well as a higher incidence of diabetes, hypertension, coronary artery disease, and cerebrovascular disease.

In recent years, several controlled clinical trials arrived at the same conclusion: that endovascular repair of abdominal aortic aneurysms (AAA) is superior to open repair. “The difficulty with these trials is that they were generally done in centers of excellence that are really geared toward endovascular repair, and may not reflect the average common-day experience in the United States,” Dr. McKinsey said.

Using the full Medicare database has several advantages. Information from 41 million patients is included, and this allows detailed subgroup analysis to be conducted while retaining statistical power. Furthermore, the use of unique patient identifiers makes longitudinal studies possible, even when patients are seen at more than one hospital.

On the other hand, patients in this database are not randomly assigned to a treatment, diagnostic codes are not uniformly consistent, and some desirable data—such as test results—are absent.

The study included patients with diagnostic codes indicating primary or secondary diagnoses of AAA with or without rupture.

There were several exclusion criteria, including ruptured thoracic aneurysm, ruptured thoracoabdominal abdominal aneurysm, and complications resulting from other vascular devices, implants, or grafts.

References: 1. Data on file, Novartis Pharmaceuticals Corp. 2. Chobanian AV, Bakris GL, Black HR, et al, and the National High Blood Pressure Education Program Coordinating Committee. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure—the JNC 7 Report. *JAMA*. 2003;289:2560-2572.

Diovan HCT®

(valsartan and hydrochlorothiazide, USP) Combination Tablets
80 mg/12.5 mg; 160 mg/12.5 mg; 160 mg/25 mg; 320 mg/12.5 mg; 320 mg/25 mg

Rx only

BRIEF SUMMARY: Please see package insert for full prescribing information.

USE IN PREGNANCY

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan HCT should be discontinued as soon as possible. See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

INDICATIONS AND USAGE

Diovan HCT® (valsartan and hydrochlorothiazide, USP) is indicated for the treatment of hypertension. This fixed dose combination is not indicated for initial therapy (see **DOSEAGE AND ADMINISTRATION** in the full prescribing information).

CONTRAINDICATIONS

Diovan HCT® (valsartan and hydrochlorothiazide, USP) is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria or hypersensitivity to other sulfonamide-derived drugs.

WARNINGS

Fetal/Neonatal Morbidity and Mortality: Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting enzyme inhibitors. There have been reports of spontaneous abortion, oligohydramnios and newborn renal dysfunction when pregnant women have taken valsartan. When pregnancy is detected, Diovan HCT (valsartan and hydrochlorothiazide, USP) should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. In addition, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin-angiotensin system, has been associated with a potential risk of birth defects in retrospective data. Healthcare professionals that prescribe drugs acting directly on the renin-angiotensin system should counsel women of childbearing potential about the potential risks of these agents during pregnancy. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment. If oligohydramnios is observed, Diovan HCT should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a nonstress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Valsartan - Hydrochlorothiazide in Animals: There was no evidence of teratogenicity in mice, rats, or rabbits treated orally with valsartan at doses up to 600, 100 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide at doses up to 180, 31 and 3 mg/kg/day. There was no evidence of teratogenicity in mice, rats and rabbits, respectively, representing 9, 3.5 and 0.5 times the maximum recommended human dose (MRHD) of valsartan and 38, 13 and 2 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.) Fetotoxicity was observed in association with maternal toxicity in rats and rabbits at valsartan doses of ≥200 and 10 mg/kg/day, respectively, in combination with hydrochlorothiazide doses of ≥60 and 3 mg/kg/day. Fetotoxicity in rats was considered to be related to decreased fetal weights and included fetal variations of sternbrae, vertebrae, ribs and/or renal papillae. Fetotoxicity in rabbits included increased numbers of late resorptions with resultant increases in total resorptions, postimplantation losses and decreased number of live fetuses. The no observed adverse effect doses in mice, rats and rabbits for valsartan were 600, 100 and 3 mg/kg/day, respectively. In combination with hydrochlorothiazide doses of 180, 31 and 1 mg/kg/day. These no adverse effect doses in mice, rats and rabbits, respectively, represent 9, 3 and 0.18 times the MRHD of valsartan and 38, 13 and 0.5 times the MRHD of hydrochlorothiazide on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day valsartan in combination with 25 mg/day hydrochlorothiazide and a 60-kg patient.)

Valsartan in Animals: No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6 and 0.1 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Hydrochlorothiazide in Animals: Under the auspices of the National Toxicology Program, pregnant mice and rats that received hydrochlorothiazide via gavage at doses up to 3000 and 1000 mg/kg/day, respectively, on gestation days 6 through 15 showed no evidence of teratogenicity. These doses of hydrochlorothiazide in mice and rats represent 608 and 405 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.) Intrauterine exposure to thiazide diuretics is associated with fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults.

Hypotension in Volume- and/or Salt-Depleted Patients: Excessive reduction of blood pressure was rarely seen (0.7% in patients with uncomplicated hypertension treated with Diovan HCT in controlled trials. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan HCT, or the treatment should start under close medical supervision. If hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

Hydrochlorothiazide: Impaired Hepatic Function: Thiazide diuretics should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations of fluid and electrolyte balance may precipitate hepatic coma. **Hypersensitivity Reaction:** Hypersensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma, but are more likely in patients with such a history. **Systemic Lupus Erythematosus:** Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus. **Lithium:** Lithium generally should not be given with thiazides (see **PRECAUTIONS, Drug Interactions, Hydrochlorothiazide, Lithium**).

PRECAUTIONS

Serum Electrolytes: Valsartan - Hydrochlorothiazide: In the controlled trials of various doses of the combination of valsartan and hydrochlorothiazide the incidence of hypotensive patients who developed hypokalemia (serum potassium <3.5 mEq/L) was 3.0%, the incidence of hyperkalemia (serum potassium >5.7 mEq/L) was 0.4%. In controlled clinical trials of Diovan HCT® (valsartan and hydrochlorothiazide, USP), the average change in serum potassium was near zero in subjects who received Diovan HCT 160/12.5 mg, 320/12.5 mg, or 320/25 mg but the average subject who received Diovan HCT 80/12.5 mg, 80/25 mg or 160/25 mg experienced a mild reduction in serum potassium. In clinical trials, the opposite effects of valsartan (80, 160 or 320 mg) and hydrochlorothiazide (12.5 mg) on serum potassium approximately balanced each other in many patients. In other patients, one or the other effect may be dominant. Periodic determinations of serum electrolytes to detect possible electrolyte imbalance should be performed at appropriate intervals.

Hydrochlorothiazide: All patients receiving thiazide therapy should be observed for clinical signs of fluid or electrolyte imbalance: hyponatremia, hypochloremic alkalosis, and hypokalemia. Serum and urine electrolyte determinations are particularly important when the patient is vomiting excessively or receiving parenteral fluids. Warning signs or symptoms of fluid and electrolyte imbalance, irrespective of cause, include dryness of mouth, thirst, weakness, lethargy, drowsiness, restlessness, confusion, seizures, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, and gastrointestinal disturbances such as nausea and vomiting. Hypokalemia may develop, especially with brisk diuresis, when severe cirrhosis is present, or after prolonged therapy. Interference with adequate oral electrolyte intake will also contribute to hypokalemia. Hypokalemia may cause cardiac arrhythmia and may also sensitize or exaggerate the response of the heart to the toxic effects of digitalis (e.g., increased ventricular irritability). Although any chloride deficit is generally mild and usually does not require specific treatment except under extraordinary circumstances (as in liver disease or renal disease), chloride replacement may be required in the treatment of metabolic alkalosis. Dilutional hyponatremia may occur in edematous patients in hot weather; appropriate therapy is water restriction, rather than administration of salt except in rare instances when the hyponatremia is life-threatening. In actual salt depletion, appropriate replacement is the therapy of choice. Hyperuricemia may occur or frank gout may be precipitated in certain patients receiving thiazide therapy. In diabetic patients dosage adjustments of insulin or oral hypoglycemic agents may be required. Hyperglycemia may occur with thiazide diuretics. Thus latent diabetes mellitus may become manifest during thiazide therapy. The antihypertensive effects of the drug may be enhanced in the postmyocardectomy patient. If progressive renal impairment becomes evident, consider withholding or discontinuing diuretic therapy. Thiazides have been shown to increase the urinary excretion of magnesium; this may result in hypomagnesemia. Thiazides may decrease urinary calcium excretion. Thiazides may cause intermittent and slight elevation of serum calcium in the absence of known disorders of calcium metabolism. Marked hypercalcemia may be evidence of hidden hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy.

Impaired Hepatic Function: Valsartan: As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering valsartan to these patients.

Impaired Renal Function: Valsartan: As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be observed in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of valsartan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. **Hydrochlorothiazide:** Thiazides should be used with caution in severe renal disease. In patients with renal disease, thiazides may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

Information for Patients: Pregnancy: Female patients of childbearing age should be told about the consequences of exposure to drugs that act on the renin-angiotensin system. Discuss other treatment options with female patients planning to become pregnant. Patients should be asked to report pregnancies to their physicians as soon as possible. **Symptomatic Hypotension:** A patient receiving Diovan HCT should be cautioned that lightheadedness can occur, especially during the first days of therapy, and that it should be reported to the prescribing physician. The patients should be told that if syncope occurs, Diovan HCT should be discontinued until the physician has been consulted. All patients should be cautioned that inadequate fluid intake, excessive perspiration, diarrhea, or vomiting can lead to an excessive fall in blood pressure, with the same consequences of lightheadedness and possible syncope. **Potassium Supplements:** A patient receiving Diovan HCT should be told not to use potassium supplements or salt substitutes containing potassium without consulting the prescribing physician.

Drug Interactions: Valsartan: No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amiodipine, atenolol, cimetidine, dipoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone. Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin. **CYP 450 Interactions:** The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown. **Hydrochlorothiazide:** When administered concurrently the following drugs may interact with thiazide diuretics: **Alcohol, barbiturates, or narcotics** - Potential of orthostatic hypotension may occur. **Antidiabetic drugs** (oral agents and insulin) - Dose adjustment of the antidiabetic drug may be required. **Other antihypertensive drugs** - Additive effect or potentiation. **Cholestyramine and colestipol resins** - Absorption of hydrochlorothiazide is impaired in the presence of anionic exchange resins. Single doses of either cholestyramine or colestipol resins bind the hydrochlorothiazide and reduce its absorption from the gastrointestinal tract by up to 85% and 43% respectively. **Corticosteroids, ACTH** - Intensified electrolyte depletion, particularly hypokalemia. **Pressor amines** (e.g., norepinephrine) - Possible decreased response to pressor amines but not sufficient to preclude their use. **Skeletal muscle relaxants, nondepolarizing** (e.g., tubocurarine) - Possible increased responsiveness to the muscle relaxant. **Lithium** - Should not generally be given with diuretics. Diuretic agents reduce the renal clearance of lithium and add a high risk of lithium toxicity. Refer to the package insert for lithium preparations before use of such preparations with Diovan HCT. **Non-steroidal anti-inflammatory Drugs** - In some patients, the administration of a non-steroidal anti-inflammatory agent and hydrochlorothiazide may result in an additive antihypertensive effect. **Loop and thiazide diuretics:** Therefore, when Diovan HCT and non-steroidal anti-inflammatory agents are used concomitantly, the patient should be observed closely to determine if the desired effect of the diuretic is obtained.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Valsartan - Hydrochlorothiazide: No carcinogenicity, mutagenicity or fertility studies have been conducted with the combination of valsartan and hydrochlorothiazide. However, these studies have been conducted for valsartan as well as hydrochlorothiazide alone. Based on the preclinical safety and human pharmacokinetic data, there is no indication of any adverse interaction between valsartan and hydrochlorothiazide. **Valsartan:** There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.) Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *Escherichia coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test. Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is about 6 times the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.) **Hydrochlorothiazide:** Two-year feeding studies in mice and rats conducted under the auspices of the National Toxicology Program (NTP) uncovered no evidence of a carcinogenic potential of hydrochlorothiazide in female mice (at doses of up to approximately 600 mg/kg/day) or in male and female rats (at doses of up to approximately 100 mg/kg/day). The NTP, however, found equivocal evidence for hepatocarcinogenicity in male mice. Hydrochlorothiazide was not genotoxic *In Vitro* in the Ames mutagenicity assay of *Salmonella* Typhimurium strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and in the Chinese Hamster Ovary (CHO) test for chromosomal aberrations in *Human lymphocytes*, Chinese hamster cell chromosomes, Chinese hamster bone marrow chromosomes, and the *Drosophila* sex-linked recessive lethal trait gene. Positive test results were obtained only in the *In Vitro* CHO Sister Chromatid Exchange (clastogenicity) and in the Mouse Lymphoma Cell (mutagenicity) assays, using concentrations of hydrochlorothiazide from 43 to 1300 mcg/mL, and in the *Aspergillus nidulans* non-disjunction assay at an unspecified concentration. Hydrochlorothiazide had no adverse effects on the fertility of mice and rats of either sex in studies wherein males and females were mated prior to mating, to doses of up to 100 and 4 mg/kg, respectively, prior to mating and during gestation. These doses of hydrochlorothiazide in mice and rats represent 19 and 1.5 times, respectively, the maximum recommended human dose on a mg/m² basis. (Calculations assume an oral dose of 25 mg/day and a 60-kg patient.)

Pregnancy Categories C (first trimester) and D (second and third trimesters): See **WARNINGS: Fetal/Neonatal Morbidity and Mortality.**

Nursing Mothers: It is not known whether valsartan is excreted in human milk, but valsartan was excreted in the milk of lactating rats. Thiazides appear in human milk. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Geriatric Use: In the controlled clinical trials of Diovan HCT, 764 (17.5%) of patients treated with valsartan-hydrochlorothiazide were ≥65 years and 118 (2.7%) were ≥75 years. No overall difference in the efficacy or safety of valsartan-hydrochlorothiazide was observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS

Diovan HCT® (valsartan and hydrochlorothiazide, USP) has been evaluated for safety in more than 5700 patients, including over 900 patients treated for over 6 months (see **CLINICAL TRIALS**). Adverse experiences have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse experiences with Diovan HCT was comparable to placebo. The overall frequency of adverse experiences was neither dose-related nor related to gender, age or race. In controlled clinical trials, discontinuation of therapy due to side effects was required in 2.3% of valsartan-hydrochlorothiazide patients and 3.1% of placebo patients. The most common reasons for discontinuation of therapy with Diovan HCT were dizziness, headache, and cough. The most serious adverse experience that occurred in controlled clinical trials was at least 2% of patients treated with Diovan HCT and at a higher incidence in valsartan-hydrochlorothiazide (n=4372) than placebo (n=262) patients was nasopharyngitis (2.4% vs 1.9%). Dose-related orthostatic effects were seen in fewer than 1% of patients. In individual trials, a dose-related increase in the incidence of dizziness was observed in patients treated with Diovan HCT. Other adverse experiences that have been reported with valsartan-hydrochlorothiazide (>0.2% of valsartan-hydrochlorothiazide patients in controlled clinical trials) without regard to causality, are listed below:

Cardiovascular: Palpitations and tachycardia. **Ear and Labyrinth:** Tinnitus and vertigo. **Gastrointestinal:** Dyspepsia, diarrhea, flatulence, dry mouth, nausea, abdominal pain, abdominal pain upper, and vomiting. **General and Administration Site Conditions:** Asthenia, chest pain, fatigue, peripheral edema and pyrexia. **Infections and Infestations:** Bronchitis, bronchitis acute, influenza, gastroenteritis, sinusitis, upper respiratory tract infection and urinary tract infection. **Investigations:** Blood urea increased. **Musculoskeletal:** Arthralgia, back pain, muscle cramps, myalgia, and pain in extremity. **Nervous System:** Dizziness postural, paresthesia, and somnolence. **Psychiatric:** Anxiety and insomnia. **Renal and Urinary:** Polyuria. **Reproductive System:** Erectile dysfunction. **Respiratory, Thoracic and Mediastinal:** Dyspnea, cough, nasal congestion, pharyngolaryngeal pain and sinus congestion. **Skin and Subcutaneous Tissue:** Hyperhidrosis and rash. **Vascular:** Hypotension. Other reported events seen less frequently in clinical trials included abnormal vision, anaphylaxis, bronchospasm, constipation, depression, dehydration, decreased libido, dysuria, epistaxis, flushing, gout, increased appetite, muscle weakness, pharyngitis, pruritus, sunburn, syncope, and viral infection.

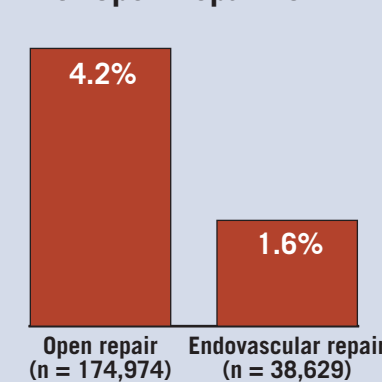
Valsartan: In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, hydrochlorothiazide, or lisinopril were 20%, 19%, 69% respectively (p < 0.001). Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Post-Marketing Experience: The following additional adverse reactions have been reported in post-marketing experience: **Hypersensitivity:** There are rare reports of angioedema. **Digestive:** Elevated liver enzymes and very rare reports of hepatitis. **Renal:** Impaired Renal Function. **Clinical Laboratory Tests:** Hyperkalemia; **Dermatologic:** Alopecia. Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Hydrochlorothiazide: Other adverse experiences that have been reported with hydrochlorothiazide, without regard to causality, are listed below: **Body As A Whole:** weakness; **Digestive:** pancreatitis, jaundice (intrahepatic cholestatic jaundice), sialadenitis, cramping, gastric irritation; **Hematologic:** aplastic anemia, agranulocytosis, leukopenia, hemolytic anemia, thrombocytopenia; **Hypersensitivity:** purpura, photosensitivity, urticaria, necrotizing angitis (vasculitis and cutaneous vasculitis), fever, respiratory distress including pneumonitis and pulmonary edema, anaphylactic reactions; **Metabolic:** hypoglycemia, glycosuria, hyperuricemia; **Musculoskeletal:** muscle spasm; **Nervous System/Psychiatric:** restlessness; **Renal:** renal failure, renal dysfunction, interstitial nephritis; **Skin:** erythema multiforme including Stevens-Johnson syndrome, exfoliative dermatitis including toxic epidermal necrolysis, **Special Senses:** transient blurred vision, xanthopsia.

Clinical Laboratory Test Findings: In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan HCT. **Creatinine/Blood Urea Nitrogen (BUN):** Minor elevations in creatinine and BUN occurred in 2% and 15%, respectively, of patients taking Diovan HCT and 0.4% and 0.6%, respectively, given placebo in controlled clinical trials. **Hemoglobin and Hematocrit:** Greater than 20% decreases in hemoglobin and hematocrit were observed in less than 0.1% of Diovan HCT patients, compared with 0.0% in placebo-treated patients. **Liver Function Tests:** Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan HCT-treated patients. **Neutropenia:** Neutropenia was observed in 0.1% of patients treated with Diovan HCT and 0.4% of patients treated with placebo. **Serum Electrolytes:** See **PRECAUTIONS**. Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from moisture. Dispense in tight container (USP).

30-Day Mortality Higher With Open Repair for AAA



Source: Dr. McKinsey

VERBATIM

“I have to say things are going to get worse here before they get better.”

Dr. Ian Gould, on the rising prevalence of MRSA-associated community-acquired pneumonia, p. 43

ELSEVIER GLOBAL MEDICAL NEWS