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Abstracts  
from

scientific  
sessions  
2004

Sessions: November 7–10  
Exhibits: November 7–9  
New Orleans, Louisiana  
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basic science



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## Named and Invited Lectures 2004

2004 Russell Ross Memorial Lectureship in Vascular Biology • 2004 George Lyman Duff Memorial Lecture • 2004 Sol Sherry Distinguished Lecture in Thrombosis • 2004 Thomas W. Smith Memorial Lecture • 2004 George E. Brown Memorial Lecture • 2004 Dickinson W. Richards Memorial Lecture • 2004 Katharine A. Lembricht Award • 2004 William W. L. Glenn Lecture • 2004 William J. Rashkind Memorial Lecture • 2004 T. Duckett Jones Memorial Lecture • 2004 Charles T. Dotter Memorial Lecture • 2004 Laennec Society Lecture • 2004 Ancel Keys Lecture • 2004 Lewis K. Dahl Memorial Lecture • 2004 Robert I. Levy Endowed Lecture in Lipid Metabolism

## New and Young Investigator Award/Prize Abstract Finalists

Lewis N. and Arnold M. Katz Basic Science Research Prize for Young Investigators • Melvin L. Marcus Young Investigator Awards in Cardiovascular Science • Cournand and Comroe Young Investigators Prizes in Cardiopulmonary and Critical Care • Outstanding Research Award in Pediatric Cardiology • Melvin Judkins Young Investigator Award in Cardiovascular Radiology • Vivian Thomas Young Investigator Award • Martha N. Hill New Investigator Awards • Elizabeth Barrett-Connor Research Award in Epidemiology and Prevention for Investigators in Training • Samuel A. Levine Young Clinical Investigator Awards • Laennec Society Young Clinician Award • NPAM New Investigator Award

## Abstracts From the Scientific Sessions 2004



# Diovan®

(valsartan)  
Tablets

Rx only

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

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

**INDICATIONS AND USAGE: Hypertension:** Diovan® (valsartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents.

**Heart Failure:** Diovan is indicated for the treatment of heart failure (NYHA class II-IV) in patients who are intolerant of angiotensin converting enzyme inhibitors. In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor. (See **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure in the full prescribing information for details.**)

**CONTRAINDICATIONS:** Diovan® (valsartan) is contraindicated in patients who are hypersensitive to any component of this product.

**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. When pregnancy is detected, Diovan® (valsartan) 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.

These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should advise the patient to discontinue the use of valsartan as soon as possible.

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 intra-amniotic environment.

If oligohydramnios is observed, valsartan 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.

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/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

**Hypertension:** Excessive hypertension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Diovan alone. 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, or the treatment should start under close medical supervision.

If excessive 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.

**Hypertension in Heart Failure Patients:** Caution should be observed when initiating therapy in patients with heart failure. Patients with heart failure given Diovan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients.

**PRECAUTIONS: General: Impaired Hepatic Function:** 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 Diovan® (valsartan) to these patients.

**Impaired Renal Function - Hypertension:** In studies of ACE inhibitors in hypertensive 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 hypertensive 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 Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

**Impaired Renal Function - Heart Failure:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, 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.

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). Evaluation of patients with heart failure should always include assessment of renal function.

**Concomitant Therapy in Patients with Heart Failure:** In patients with heart failure, concomitant use of Diovan, an ACE inhibitor, and a beta blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an increase in heart failure outcome (see **CLINICAL PHARMACOLOGY, Pharmacodynamics and Clinical Effects, Heart Failure in the full prescribing information.**)

**Information for Patients: Pregnancy:** Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

**Drug Interactions:** No clinically significant pharmacokinetic interactions were observed when valsartan was coadministered with amlodipine, atenolol, cimetidine, digoxin, 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.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

**Carcinogenesis, Mutagenesis, Impairment of Fertility:** 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/m<sup>2</sup> 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 *E. 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 6 times the maximum recommended human dose on a mg/m<sup>2</sup> basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

**Pregnancy: 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. 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 valsartan, 1,214 (36.2%) of hypertensive patients treated with valsartan were ≥ 65 years and 285 (7.9%) were ≥ 75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out. Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients.

**ADVERSE REACTIONS: Hypertension:** Diovan® (valsartan) has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. 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 was similar to placebo.

The overall frequency of adverse experiences was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse experiences that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%). Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

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 had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively (p < 0.001).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse experiences that occurred in controlled clinical trials of patients treated with Diovan (> 0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

**Body as a Whole:** Allergic reaction and asthenia; **Cardiovascular:** Palpitations; **Dermatologic:** Pruritus and rash; **Digestive:** Constipation, dry mouth, dyspepsia, and flatulence; **Musculoskeletal:** Back pain, muscle cramps, and myalgia; **Neurologic and Psychiatric:** Anxiety, insomnia, paresthesia, and somnolence; **Respiratory:** Dyspnea; **Special Senses:** Vertigo; **Urogenital:** Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

**Heart Failure:** The adverse experience profile of Diovan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse events vs. 7% of placebo patients.

The table shows adverse events in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

	Valsartan (n=3,282)		Placebo (n=2,740)	
Dizziness	17%	9%	Back Pain	3%
Hypotension	7%	2%	Dizziness, postural	2%
Diarrhea	5%	4%	Hyperkalemia	2%
Arthralgia	3%	2%	Hypotension, postural	2%
Fatigue	3%	2%		

Other adverse events with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

From the long term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse events not previously identified.

**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.

**Clinical Laboratory Test Findings:** In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

**Creatinine:** Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of Diovan-treated patients compared to 0.9% of placebo-treated patients.

**Hemoglobin and Hematocrit:** Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

**Liver Function Tests:** Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

**Neutropenia:** Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

**Serum Potassium:** In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of Diovan-treated patients compared to 5.1% of placebo-treated patients.

**Blood Urea Nitrogen (BUN):** In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of Diovan-treated patients compared to 6.3% of placebo-treated patients.

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).

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**Reference:** 1. Hermida RC, Calvo C, Ayala DE, et al. Administration time-dependent effects of valsartan on ambulatory blood pressure in hypertensive subjects. *Hypertension*. 2003;42:283-290.



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# DIOVAN DELIVERS

**USE IN PREGNANCY:** When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, DIOVAN should be discontinued as soon as possible. See **WARNINGS** in brief summary of complete Prescribing Information on next page.

DIOVAN is contraindicated in patients who are hypersensitive to any component of this product.

In hypertension, AEs more frequent with DIOVAN than placebo: viral infection (3% vs 2%), fatigue (2% vs 1%), abdominal pain (2% vs 1%); the most common AEs: headache and dizziness. An increase in dizziness was observed with 320 mg (8%) vs 10 mg to 160 mg (2% to 4%).

Because of the risk of hypotension, caution should be observed when initiating therapy in HF patients. Evaluation of HF patients should always include assessment of renal function. In patients with Heart Failure, concomitant use of DIOVAN, an ACE inhibitor, and a beta-blocker is not recommended. In the Valsartan Heart Failure Trial, this triple combination was associated with an unfavorable Heart Failure outcome.

In Val-HeFT, discontinuation due to adverse events was 10% for valsartan vs 7% for placebo; most common side effects were: dizziness (17% vs 9%), hypotension (7% vs 2%), and diarrhea (5% vs 4%).

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*In patients without CHD/CHD risk equivalents*

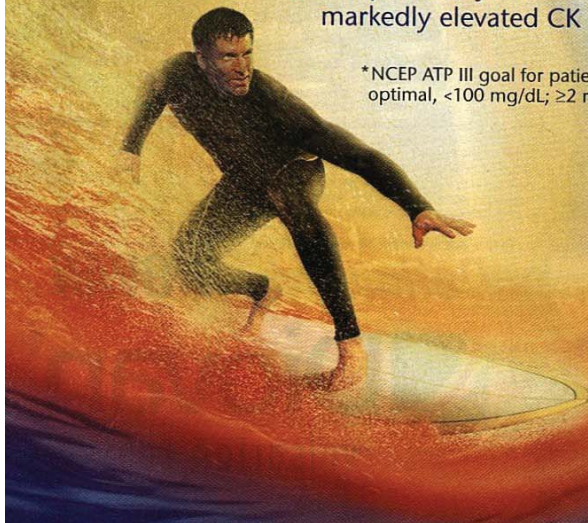
**94% of patients reached LDL-C goal at a low 10-mg dose\***<sup>2</sup>

CRESTOR is indicated as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, non-HDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia.

CRESTOR is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases, in women who are or may become pregnant, and in nursing mothers.

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with CRESTOR and with other drugs in this class. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Therapy with CRESTOR should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected.

\*NCEP ATP III goal for patients without CHD or CHD risk equivalents:  
optimal, <100 mg/dL; ≥2 risk factors, <130 mg/dL; 0-1 risk factor, <160 mg/dL.





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- Adverse reactions were **mild and transient**; incidence and discontinuation rates similar to placebo and other statins<sup>3,4</sup>
- The most frequent adverse events were myalgia (3.3%), constipation (1.4%), asthenia (1.3%), abdominal pain (1.3%), and nausea (1.3%)<sup>3,5</sup>

**CRESTOR was evaluated in over 10,000 patients in preapproval clinical trials**—more than any other statin prior to approval<sup>4,6-11</sup>

**Overall, more than 42,000 patients have taken CRESTOR in clinical trials, including ongoing trials in the GALAXY™ Program<sup>12</sup>**

- The GALAXY Program is a large, comprehensive, long-term evolving global research initiative evaluating the efficacy and safety of CRESTOR and demonstrating the AstraZeneca confidence in, and commitment to, this important therapeutic option

It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.

The effect of CRESTOR on cardiovascular morbidity and mortality has not been determined; long-term outcome studies are currently under way.

Please see brief summary of full Prescribing Information on reverse side of this advertisement.



**CRESTOR**<sup>®</sup>  
rosuvastatin calcium



**BRIEF SUMMARY:** For full Prescribing Information, see package insert.

**INDICATIONS AND USAGE** CRESTOR is indicated: 1. as an adjunct to diet to reduce elevated total-C, LDL-C, ApoB, nonHDL-C, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type IIa and IIb); 2. as an adjunct to diet for the treatment of patients with elevated serum TG (Fredrickson Type IV); 3. to reduce LDL-C, total-C, and ApoB in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. **CONTRAINDICATIONS** CRESTOR is contraindicated in patients with a known hypersensitivity to any component of this product. Rosuvastatin is contraindicated in patients with active liver disease or with unexplained persistent elevations of serum transaminases (see WARNINGS, Liver Enzymes). **Pregnancy and Lactation** Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. ROSUVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If the patient becomes pregnant while taking this drug, therapy should be discontinued immediately and the patient apprised of the potential hazard to the fetus. **WARNINGS** **Liver Enzymes** HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. The incidence of persistent elevations (>3 times the upper limit of normal [ULN]) occurring on 2 or more consecutive occasions) in serum transaminases in fixed dose studies was 0.4, 0.0, and 0.1% in patients who received rosuvastatin 5, 10, 20, and 40 mg, respectively. In most cases, the elevations were transient and resolved or improved on continued therapy or after a brief interruption in therapy. There were two cases of jaundice, for which a relationship to rosuvastatin therapy could not be determined, which resolved after discontinuation of therapy. There were no cases of liver failure or irreversible liver disease in these trials. It is recommended that liver function tests be performed before and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in the first 3 months of treatment with rosuvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities have resolved. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of rosuvastatin is recommended. Rosuvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease (see CLINICAL PHARMACOLOGY, Special Populations, Hepatic Insufficiency). Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of rosuvastatin (see CONTRAINDICATIONS). **Myopathy/Rhabdomyolysis** Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with rosuvastatin and with other drugs in this class. Uncomplicated myalgia has been reported in rosuvastatin-treated patients (see ADVERSE REACTIONS). Creatine kinase (CK) elevations (>10 times upper limit of normal) occurred in 0.2% to 0.4% of patients taking rosuvastatin at doses of up to 40 mg in clinical studies. Treatment-related myopathy, defined as muscle aches or muscle weakness in conjunction with increases in CK values >10 times upper limit of normal, was reported in up to 0.1% of patients taking rosuvastatin doses of up to 40 mg in clinical studies. Rare cases of rhabdomyolysis were seen with higher than recommended doses (80 mg) of rosuvastatin in clinical trials. Factors that may predispose patients to myopathy with HMG-CoA reductase inhibitors include advanced age (>65 years), hypothyroidism, and renal insufficiency. The incidence of myopathy increased at doses of rosuvastatin above the recommended dosage range. Consequently, 1. Rosuvastatin should be prescribed with caution in patients with predisposing factors for myopathy, such as, renal impairment (see DOSAGE AND ADMINISTRATION), advanced age, and hypothyroidism. 2. Patients should be advised to promptly report unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. Rosuvastatin therapy should be discontinued if markedly elevated CK levels occur or myopathy is diagnosed or suspected. 3. The risk of myopathy during treatment with rosuvastatin may be increased with concurrent administration of other lipid-lowering therapies or cyclosporine, (see CLINICAL PHARMACOLOGY, Drug Interactions, PRECAUTIONS, Drug Interactions, and DOSAGE AND ADMINISTRATION). The benefit of further alterations in lipid levels by the combined use of rosuvastatin with fibrates or niacin should be carefully weighed against the potential risks of this combination. Combination therapy with rosuvastatin and gemfibrozil should generally be avoided. (See DOSAGE AND ADMINISTRATION and PRECAUTIONS, Drug Interactions). 4. The risk of myopathy during treatment with rosuvastatin may be increased in circumstances which increase rosuvastatin drug levels (see CLINICAL PHARMACOLOGY, Special Populations, Race and Renal Insufficiency, and PRECAUTIONS, General). 5. Rosuvastatin therapy should also be temporarily withheld in any patient with an acute, serious condition suggestive of myopathy or predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., sepsis, hypotension, major surgery, trauma, severe metabolic, endocrine, and electrolyte disorders, or uncontrolled seizures). **PRECAUTIONS** **General** Before instituting therapy with rosuvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet and exercise, weight reduction in obese patients, and treatment of underlying medical problems (see INDICATIONS AND USAGE). Administration of rosuvastatin 20 mg to patients with severe renal impairment ( $CL_{CR} < 30 \text{ mL/min/1.73 m}^2$ ) resulted in a 3-fold increase in plasma concentrations of rosuvastatin compared with healthy volunteers (see WARNINGS, Myopathy/Rhabdomyolysis and DOSAGE AND ADMINISTRATION). Pharmacokinetic studies show an approximate 2-fold elevation in median exposure in Japanese subjects residing in Japan and in Chinese subjects residing in Singapore compared with Caucasians residing in North America and Europe. The contribution of environmental and genetic factors to the difference observed has not been determined. However, these increases should be considered when making rosuvastatin dosing decisions for patients of Japanese and Chinese ancestry. (See WARNINGS, Myopathy/Rhabdomyolysis; CLINICAL PHARMACOLOGY, Special Populations, Race.) **Information for Patients** Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug Interactions). **Laboratory Tests** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing. **Drug Interactions** **Cyclosporine:** When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac transplant patients, rosuvastatin mean  $C_{max}$  and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION). **Warfarin:** Coadministration of rosuvastatin to patients on stable

warfarin therapy resulted in clinically significant rises in INR (>4, baseline 2-3). In patients taking coumarin anticoagulants and rosuvastatin concomitantly, INR should be determined before starting rosuvastatin and frequently enough during early therapy to ensure that no significant alteration of INR occurs. Once a stable INR time has been documented, INR can be monitored at the intervals usually recommended for patients on coumarin anticoagulants. If the dose of rosuvastatin is changed, the same procedure should be repeated. Rosuvastatin therapy has not been associated with bleeding or with changes in INR in patients not taking anticoagulants. **Gemfibrozil:** Coadministration of a single rosuvastatin dose to healthy volunteers on gemfibrozil (600 mg twice daily) resulted in a 2.2- and 1.9-fold, respectively, increase in mean  $C_{max}$  and mean AUC of rosuvastatin (see DOSAGE AND ADMINISTRATION). **Endocrine Function** Although clinical studies have shown that rosuvastatin alone does not reduce basal plasma cortisol concentration or impair adrenal reserve, caution should be exercised if any HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones such as ketoconazole, spiroinolactone, and cimetidine. **CNS Toxicity** CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with several other members of this drug class. A chemically similar drug in this class produced dose-dependent optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in dogs, at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. Edema, hemorrhage, and partial necrosis in the interstitium of the choroid plexus was observed in a female dog sacrificed on day 24 at 90 mg/kg/day by oral gavage (systemic exposures 100 times the human exposure at 40 mg/kg/day based on AUC comparisons). Corneal opacity was seen in dogs treated for 52 weeks at 6 mg/kg/day by oral gavage (systemic exposures 20 times the human exposure at 40 mg/kg/day based on AUC comparisons). Cataracts were seen in dogs treated for 12 weeks by oral gavage at 30 mg/kg/day (systemic exposures 60 times the human exposure at 40 mg/kg/day based on AUC comparisons). Retinal dysplasia and retinal loss were seen in dogs treated for 4 weeks by oral gavage at 90 mg/kg/day (systemic exposures 100 times the human exposure at 40 mg/kg/day based on AUC). Doses  $\leq 30 \text{ mg/kg/day}$  (systemic exposures  $\leq 60$  times the

**Experiences** Adverse experiences, regardless of causality assessment, reported in  $\geq 2\%$  of patients in placebo-controlled clinical studies of rosuvastatin are shown in Table 1; discontinuations due to adverse events in these studies of up to 12 weeks duration occurred in 3% of patients on rosuvastatin and 5% on placebo.

**Table 1. Adverse Events in Placebo-Controlled Studies**

Adverse event	Rosuvastatin N=744	Placebo N=382
Pharyngitis	9.0	7.6
Headache	5.5	5.0
Diarrhea	3.4	2.9
Dyspepsia	3.4	3.1
Nausea	3.4	3.1
Myalgia	2.8	1.3
Asthenia	2.7	2.6
Back pain	2.6	2.4
Flu syndrome	2.3	1.8
Urinary tract infection	2.3	1.6
Rhinitis	2.2	2.1
Sinusitis	2.0	1.8

In addition, the following adverse events were reported, regardless of causality assessment, in  $\geq 1\%$  of 10,275 patients treated with rosuvastatin in clinical studies. The events in *italics* occurred in  $\geq 2\%$  of these patients. **Body as a Whole:** Abdominal pain, accidental injury, chest pain, infection, pain, pelvic pain, and neck pain. **Cardiovascular System:** Hypertension, angina pectoris, vasodilatation, and palpitation. **Digestive System:** Constipation, gastroenteritis, vomiting, flatulence, periodontal abscess, and gastritis. **Endocrine:** Diabetes mellitus. **Hemic and Lymphatic System:** Anemia and ecchymosis. **Metabolic and Nutritional Disorders:** Peripheral edema. **Musculoskeletal System:** Arthritis, arthralgia, and pathological fracture. **Nervous System:** Dizziness, insomnia, hypertension, paraesthesia, depression, anxiety, vertigo, and neuralgia. **Respiratory System:** Bronchitis, cough increased, dyspnea, pneumonia, and asthma. **Skin and Appendages:** Rash and pruritus. **Laboratory Abnormalities:** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. (See PRECAUTIONS, Laboratory Tests.) Other abnormal laboratory values reported were elevated creatine phosphokinase, transaminases, hyperglycemia, glutamyl transpeptidase, alkaline phosphatase, bilirubin, and thyroid function abnormalities. Other adverse events reported less frequently than 1% in the rosuvastatin clinical study program, regardless of causality assessment, included arrhythmia, hepatitis, hypersensitivity reactions (i.e., face edema, thrombocytopenia, leukopenia, vesiculobullous rash, urticaria, and angioedema), kidney failure, syncope, myasthenia, myositis, pancreatitis, photosensitivity reaction, myopathy, and rhabdomyolysis. **OVERDOSAGE** There is no specific treatment in the event of overdose. In the event of overdose, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin. **DOSAGE AND ADMINISTRATION** The patient should be placed on a standard cholesterol-lowering diet before receiving CRESTOR and should continue on this diet during treatment. CRESTOR can be administered as a single dose at any time of day, with or without food. **Hypercholesterolemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia (Fredrickson Type IIa and IIb)** The dose range for CRESTOR is 5 to 40 mg once daily. The therapy with CRESTOR should be individualized according to goal of therapy and response. The usual recommended starting dose of CRESTOR is 10 mg once daily. Initiation of therapy with 5 mg once daily may be considered for patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy (see WARNINGS, Myopathy/Rhabdomyolysis). For patients with marked hypercholesterolemia (LDL-C > 190 mg/dL) and aggressive lipid targets, a 20-mg starting dose may be considered. The 40-mg dose of CRESTOR should be reserved for those patients who have not achieved goal LDL-C at 20 mg (see WARNINGS, Myopathy/Rhabdomyolysis). After initiation and/or upon titration of CRESTOR, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. **Homozygous Familial Hypercholesterolemia** The recommended starting dose of CRESTOR is 20 mg once daily in patients with homozygous FH. The maximum recommended daily dose is 40 mg. CRESTOR should be used in these patients as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable. Response to therapy should be estimated from pre-apheresis LDL-C levels. **Dosage in Patients Taking Cyclosporine** In patients taking cyclosporine, therapy should be limited to CRESTOR 5 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions). **Concomitant Lipid-Lowering Therapy** The effect of CRESTOR on LDL-C and total-C may be enhanced when used in combination with a bile acid binding resin. If CRESTOR is used in combination with gemfibrozil, the dose of CRESTOR should be limited to 10 mg once daily (see WARNINGS, Myopathy/Rhabdomyolysis, and PRECAUTIONS, Drug Interactions). **Dosage in Patients With Renal Insufficiency** No modification of dosage is necessary for patients with mild to moderate renal insufficiency. For patients with severe renal impairment ( $CL_{CR} < 30 \text{ mL/min/1.73 m}^2$ ) not on hemodialysis, dosing of CRESTOR should be started at 5 mg once daily and not to exceed 10 mg once daily (see PRECAUTIONS, General, and CLINICAL PHARMACOLOGY, Special Populations, Renal Insufficiency).

Rx only

**References:** 1. Data on file, DA-CRS-02. 2. Shepherd J, Hunninghake DB, Barter P, et al. Guidelines for lowering lipids to reduce coronary artery disease risk: a comparison of rosuvastatin with atorvastatin, pravastatin, and simvastatin for achieving lipid-lowering goals. *Am J Cardiol*. 2003;91(suppl):11C-19C. 3. Shepherd J, Hunninghake DB, Stein EA, et al. The safety of rosuvastatin. *Am J Cardiol*. In press. 4. Prescribing Information for CRESTOR. AstraZeneca, Wilmington, DE. 5. Data on file, DA-CRS-01. 6. New Drug Application for atorvastatin (four-month safety update). 7. New Drug Application for simvastatin (simvastatin safety update II). 8. New Drug Application for pravastatin (medical officer's review and evaluation of NDA report). 9. New Drug Application for cerivastatin (conclusion with regard to the safety of cerivastatin). 10. New Drug Application for fluvastatin (analysis). 11. New Drug Application for lovastatin (integrated safety results and exposure). 12. Data on file, DA-CRS-11.

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human exposure at 40 mg/kg/day based on AUC comparisons) following treatment up to one year, did not reveal renal findings. **Carcinogenesis, Mutagenesis, Impairment of Fertility** In a 104-week carcinogenicity study in rats at dose levels of 2, 20, 60, or 80 mg/kg/day by oral gavage, the incidence of uterine stromal polyps was significantly increased in females at 80 mg/kg/day at systemic exposure 20 times the human exposure at 40 mg/kg/day based on AUC. Increased incidence of polyps was not seen at lower doses. In a 107-week carcinogenicity study in mice given 10, 60, 200 mg/kg/day by oral gavage, an increased incidence of hepatocellular adenoma/carcinoma was observed at 200 mg/kg/day at systemic exposures 20 times human exposure at 40 mg/kg/day based on AUC. An increased incidence of hepatocellular tumors was not seen at lower doses. Rosuvastatin was not mutagenic or clastogenic with or without metabolic activation in the Ames test with *Salmonella typhimurium* and *Escherichia coli*, the mouse lymphoma assay, and the chromosomal aberration assay in Chinese hamster lung cells. Rosuvastatin was negative in the *in vivo* mouse micronucleus test. In rat fertility studies with oral gavage doses of 5, 15, 50 mg/kg/day, males were treated for 9 weeks prior to and throughout mating and females were treated 2 weeks prior to mating and throughout mating until gestation day 7. No adverse effect on fertility was observed at 50 mg/kg/day (systemic exposures up to 10 times human exposure at 40 mg/kg/day based on AUC comparisons). In testicles of dogs treated with rosuvastatin at 30 mg/kg/day for one month, spermatid giant cells were seen. Spermatid giant cells were observed in monkeys after 6-month treatment at 30 mg/kg/day in addition to vacuolation of seminiferous tubular epithelium. Exposures in the dog were 20 times and in the monkey 10 times human exposure at 40 mg/kg/day based on body surface area comparisons. Similar findings have been seen with other drugs in this class. **Pregnancy** **Pregnancy Category X** See CONTRAINDICATIONS. Rosuvastatin may cause fetal harm when administered to a pregnant woman. Rosuvastatin is contraindicated in women who are or may become pregnant. Safety in pregnant women has not been established. There are no adequate and well-controlled studies of rosuvastatin in pregnant women. Rosuvastatin crosses the placenta and is found in fetal tissue and amniotic fluid at 3% and 20%, respectively, of the maternal plasma concentration following a single 20 mg/kg oral gavage dose on gestation day 16 in rats. A higher fetal tissue distribution (25% maternal plasma concentration) was observed in rabbits after a single oral gavage dose of 1 mg/kg on gestation day 18. If this drug is administered to a woman with reproductive potential, the patient should be apprised of the potential hazard to a fetus. In female rats given oral gavage doses of 5, 15, 50 mg/kg/day rosuvastatin before mating and continuing through day 7 postcoitus results in decreased fetal body weight (female pups) and delayed ossification at the high dose (systemic exposures 10 times human exposure at 40 mg/kg/day based on AUC comparisons). In pregnant rats given oral gavage doses of 2, 20, 50 mg/kg/day from gestation day 7 through lactation day 21 (weaning), decreased pup survival occurred in groups given 50 mg/kg/day, systemic exposures  $\geq 12$  times human exposure at 40 mg/kg/day based on body surface area comparisons. In pregnant rabbits given oral gavage doses of 0.3, 1, 3 mg/kg/day from gestation day 6 to lactation day 18 (weaning), exposures equivalent to human exposure at 40 mg/kg/day based on body surface area comparisons, decreased fetal viability and maternal mortality was observed. Rosuvastatin was not teratogenic in rats at  $\leq 25 \text{ mg/kg/day}$  or in rabbits  $\leq 3 \text{ mg/kg/day}$  (systemic exposures equivalent to human exposure at 40 mg/kg/day based on AUC or body surface comparison, respectively). **Nursing Mothers** It is not known whether rosuvastatin is excreted in human milk. Studies in lactating rats have demonstrated that rosuvastatin is secreted into breast milk at levels 3 times higher than that obtained in the plasma following oral gavage dosing. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from rosuvastatin, a decision should be made whether to discontinue nursing or administration of rosuvastatin taking into account the importance of the drug to the lactating woman. **Pediatric Use** The safety and effectiveness in pediatric patients have not been established. Treatment experience with rosuvastatin in a pediatric population is limited to 8 patients with homozygous FH. None of these patients was below 8 years of age. **Geriatric Use** Of the 10,275 patients in clinical studies with rosuvastatin, 3,159 (31%) were 65 years and older, and 698 (6.8%) were 75 years and older. The overall frequency of adverse events and types of adverse events were similar in patients above and below 65 years of age. (See WARNINGS, Myopathy/Rhabdomyolysis.) The efficacy of rosuvastatin in the geriatric population ( $\geq 65$  years of age) was comparable to the efficacy observed in the non-elderly. **ADVERSE REACTIONS** Rosuvastatin is generally well tolerated. Adverse reactions have usually been mild and transient. In clinical studies of 10,275 patients, 3.7% were discontinued due to adverse experiences attributable to rosuvastatin. The most frequent adverse events thought to be related to rosuvastatin were myalgia, constipation, asthenia, abdominal pain, and nausea. **Clinical Adverse**

Information for Patients Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. When taking rosuvastatin with an aluminum and magnesium hydroxide combination antacid, the antacid should be taken at least 2 hours after rosuvastatin administration (see CLINICAL PHARMACOLOGY, Drug Interactions). **Laboratory Tests** In the rosuvastatin clinical trial program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., 80 mg). However, this finding was more frequent in patients taking rosuvastatin 40 mg, when compared to lower doses of rosuvastatin or comparator statins, though it was generally transient and was not associated with worsening renal function. Although the clinical significance of this finding is unknown, a dose reduction should be considered for patients on rosuvastatin 40 mg therapy with unexplained persistent proteinuria during routine urinalysis testing. **Drug Interactions** **Cyclosporine:** When rosuvastatin 10 mg was coadministered with cyclosporine in cardiac transplant patients, rosuvastatin mean  $C_{max}$  and mean AUC were increased 11-fold and 7-fold, respectively, compared with healthy volunteers. These increases are considered to be clinically significant and require special consideration in the dosing of rosuvastatin to patients taking concomitant cyclosporine (see WARNINGS, Myopathy/Rhabdomyolysis, and DOSAGE AND ADMINISTRATION). **Warfarin:** Coadministration of rosuvastatin to patients on stable



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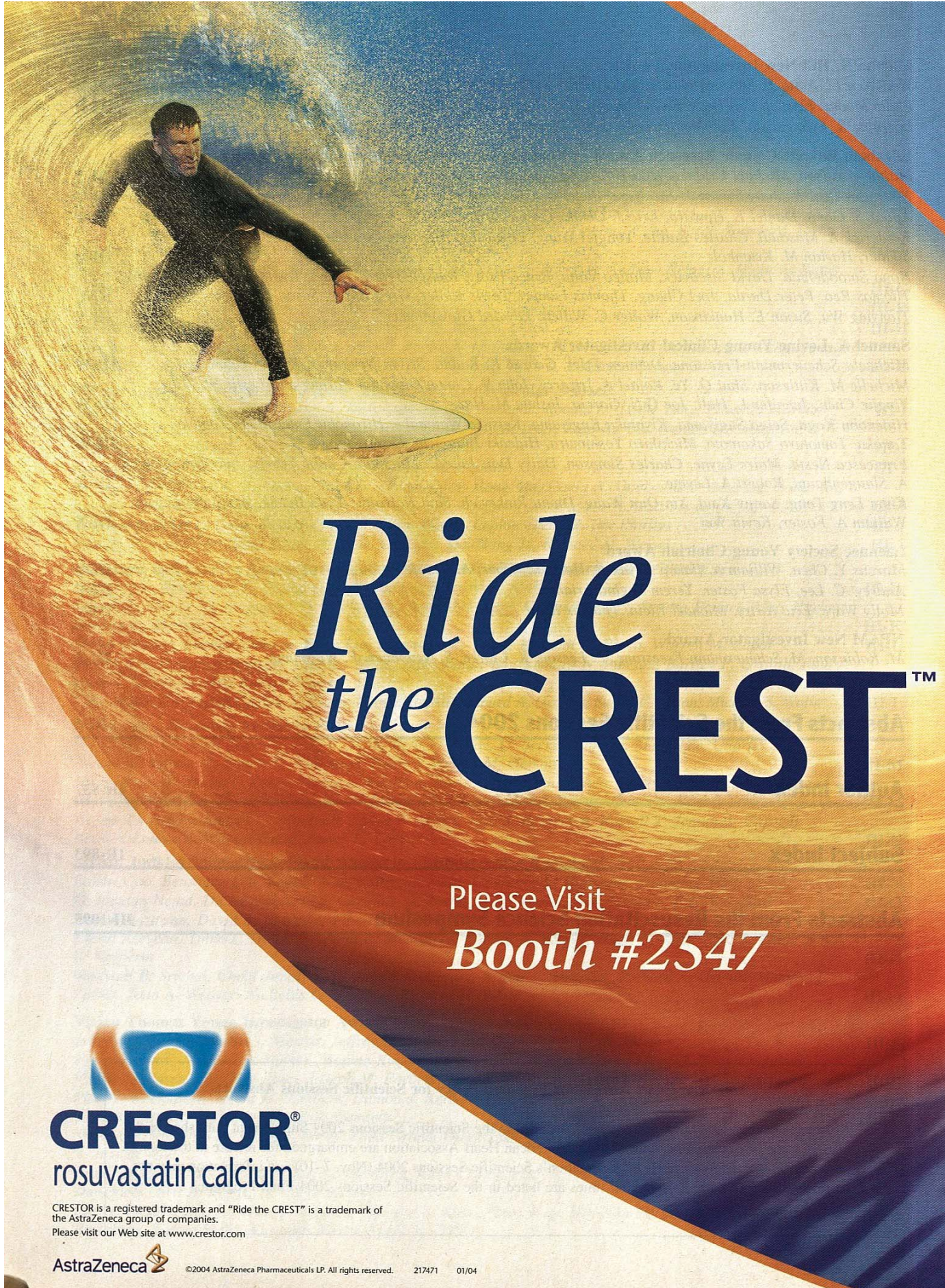
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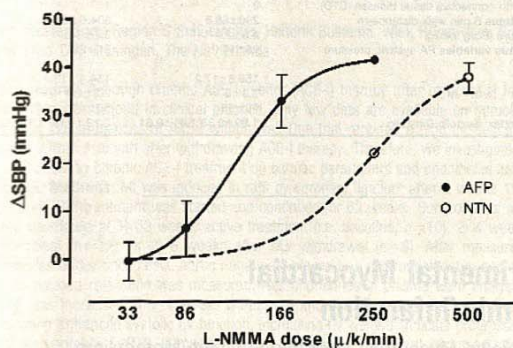
of membranous RhoA and phosphorylated ERM in brainstem were greater both in angiotensin II-treated rats and SHR than in WKY. Valsartan reduced the expression levels of membranous RhoA in angiotensin II-treated rats and SHR. In addition, Y-27632 or valsartan reduced the expression levels of phosphorylated ERM in both groups. Subcutaneous infusion of phenylephrine increased SBP to the same level of angiotensin II infusion in WKY. However, it did not alter the expression levels of membranous RhoA and phosphorylated ERM. Conclusions: These results suggest that 1) the pressor response induced by central infusion of angiotensin II is substantially mediated by activation of Rho/Rho-kinase pathway in brainstem via AT1 receptors, 2) this pathway may also be involved in hypertensive mechanism in SHR.

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### Endothelial Nitric Oxide and Hypertension in Autonomic Failure

Alfredo Gamboa, Cyndya Shiao, Andre Diedrich, Bonnie K Black, Ginnie Farley, Satish R Raj, David Robertson, Italo Biaggioni; Vanderbilt Univ, Nashville, TN

More than half of patients with autonomic failure (AF) have severe supine hypertension despite low or unresponsive norepinephrine levels and often undetectable plasma renin activity. Supine hypertension is related to increased vascular resistance but the mechanism is not known. To test the hypothesis that nitric oxide deficiency contributes to supine hypertension we blocked endogenous nitric oxide synthase with L-NMMA in 5 AF patients and 7 normal controls (supine SBP 173±6 and 107±5 mmHg, respectively). Systolic blood pressure (SBP) was normalized to 110 mmHg in AF with graded head-up tilt, and baroreflexes were eliminated with trimethaphan in normal controls to mimic autonomic failure. The pressor response to graded doses of L-NMMA was shifted to the left in AF (Figure); The dose necessary to increase SBP by 30 mmHg was 3.4-fold lower in AF compared to controls (136±24 and 465±103 µg/k/min respectively,  $p < 0.02$ ). In conclusion, contrary to our original hypothesis, our results suggest an increased tonic release of nitric oxide in AF. Thus, NO deficiency does not contribute to supine hypertension in autonomic failure. On the contrary, this enhanced tonic NO may contribute to orthostatic hypotension in these patients.



1413

### Oral Administration of a Mineralocorticoid Receptor Antagonist Reduces Brain, Heart, and Blood-borne Proinflammatory Cytokines in Heart Failure

Yu-Ming Kang, Carver College of Med, Univ of Iowa, Iowa City, IA; Ralph F Johnson, Univ of Iowa, Iowa City, IA; Zhi-Hua Zhang, Carver College of Med, Univ of Iowa, Iowa City, IA; Robert M Weiss, Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA; Alan K Johnson, Univ of Iowa, Iowa City, IA; Robert B Felder, Carver College of Med, Univ of Iowa and VA Med Ctr, Iowa City, IA

**Introduction:** Brain and blood-borne cytokines may contribute to neurohumoral excitation in heart failure (HF). We previously reported that blockade of mineralocorticoid receptors (MR) in the central nervous system with spironolactone (SL) reduces circulating tumor necrosis factor (TNF)- $\alpha$  in HF rats. The effect of SL on proinflammatory cytokines (PIC) in the brain and on other important circulating PIC - interleukin (IL)-1 $\beta$  and IL-6 - was not determined. **Hypothesis:** Chronic treatment with oral SL will reduce brain and blood-borne PIC in rats with HF following MI. **Methods and Results:** Rats underwent coronary artery ligation to induce MI (48.2±2.0% of left ventricle, with ejection fraction of 35.5±4.1% by echocardiography), or sham surgery (SHAM). Six weeks later, immunohistochemistry of the paraventricular nucleus (PVN) of hypothalamus, a region critical to cardiovascular regulation, revealed more PVN neurons (MI vs SHAM, \*\* $P < 0.01$ ) positive for TNF- $\alpha$  (59.5±3.3% vs 10.8±0.9%) and IL-1 $\beta$  (70.7±3.9% vs 13.8±1.2%) in MI (n=6) than in SHAM (n=6) rats. Double staining demonstrated that these neurons were distributed among PVN neurons expressing Fra-like immunoreactivity, indicating chronic neuronal activation. MI rats (n=6) treated with SL (1 mg/kg/day orally for 6 weeks) had fewer (MI+SL vs MI, # $P < 0.01$ ) Fra-like positive PVN neurons (85.5±5.4% vs 183.8±5.0), and fewer PVN neurons positive for TNF- $\alpha$  (22.4±1.8% vs 32.4±1.7%) and IL-1 $\beta$  (19.1±1.3% vs 38.4±2.1%). Levels of TNF- $\alpha$ , IL-1 $\beta$  and IL-6 in brain and heart tissues and in plasma were also lower in MI rats treated with SL (see table). **Conclusion:** In rats with ischemia-induced heart failure, orally administered SL has a global inhibitory influence on the appearance of proinflammatory cytokines in brain, heart and plasma. The beneficial influence of MR antagonism in patients with HF may result at least in part from blocking aldosterone-induced cytokine synthesis. (Table: \* $P < 0.05$  MI+SL vs MI+VEH)

Group	plasma IL-1 $\beta$ (pg/ml)	plasma IL-6 (pg/ml)	heart IL-1 $\beta$ (pg/mg protein)	hypothalamus IL-1 $\beta$ (pg/mg protein)	hypothalamus TNF- $\alpha$ (pg/mg protein)	brain-stem TNF- $\alpha$ (pg/mg protein)	brain-stem IL-6 (pg/mg protein)	cortex IL-1 $\beta$ (pg/mg protein)	heart/BW Ratio (mg/g)	lung/BW (mg/g)
MI+VEH (n=7)	131.1±10.9	119.5±9.7	53.4±6.5	47.1±7.9	6.8±0.7	6.1±0.9	67.1±10.1	26.4±4.1	7.2±0.2	13.5±0.6
MI+SL (n=7)	57.5±3.1*	53.3±8.6*	32.6±5.9*	29.4±5.1*	3.8±0.6*	2.8±0.5*	39.4±5.5*	25.8±5.2	6.4±0.3*	12.1±0.6*
SHAM+SL (n=7)	48.2±3.6	33.7±2.8	23.7±6.5	17.4±4.8	2.8±0.7	2.1±0.6	25.3±4.8	24.3±4.9	3.3±0.1	5.2±0.3
SHAM+VEH (n=6)	53.9±2.4	36.1±2.6	27.6±5.4	18.8±4.0	3.2±0.9	2.4±0.8	28.0±8.7	23.6±6.5	3.4±0.1	5.1±0.3

## Pulmonary Arterial Hypertension: New Therapies

Subspecialty: Integrative Biology

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Abstracts 1414-1418

1414

### Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension

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**Objective:** To evaluate the effects of inhaled TRE on pulmonary hemodynamics and gas exchange in severe pulmonary hypertension (PH) and to assess safety, tolerability and clinical efficacy in patients with severe PH. **Background:** TRE is a stable prostacyclin analogue that has been approved for treatment of pulmonary arterial hypertension as a continuous subcutaneous infusion. Iloprost, another prostacyclin analogue, has been shown to be efficacious in a randomised controlled study as repetitive inhalation. **Methods:** In an open-label study a preservative free solution of inhaled TRE was applied to 17 patients with severe pulmonary hypertension during Swan-Ganz catheter investigation. Patients received a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 µg/ml). Hemodynamics were observed for 2 hours. Two patients with idiopathic PAH received compassionate treatment with 4 inhalations of TRE per day after the acute test. **Results:** Patients (male/female = 4/13) suffered from iPAH (n=5), PAH other (n=8) and CTEPH (n=4); PVR 948 ± 112 dyn\*s\*cm<sup>-5</sup>, PAP 48.3 ± 2.7 mmHg, PAWP 8.9 ± 0.5 mmHg, CVP 10.8 ± 1.6 mmHg, CO 3.8 ± 0.3 l/min, SvO<sub>2</sub> 61.8 ± 1.8 %. TRE inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes. Maximum PVR decrease was -31.2 ± 4.5 % after 30 min. PVR and SVR at 120 minutes after inhalation were 89.2 ± 4.2 % and 101.0 ± 4.0 % of the baseline values, respectively. The AUC for the observation period (120min) was -22.9 ± 3.8 % for PVR and -4.9 ± 3.2% for SVR. The compassionate use patients have been treated for more than 3 months. In both patients NYHA class improved (from IV to III and from III to II), and six minute walk increased (from 0 m (bedridden) to 143 m, and from 310 m to 486 m, respectively). No side effects have been observed by the patients during long-term treatment. **Conclusion:** Inhaled TRE shows strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing. Tolerability is excellent even at high drug concentrations and short inhalation times (3 breaths). Long-term treatment effects are very promising. The current results warrant controlled studies investigating this approach in a larger series of patients. Supported by Lung RX

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### Rho-kinase in Pulmonary Hypertension

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**Objectives:** Pulmonary hypertension (PH) is a poor prognostic disease with limited treatment. Rho-kinase is involved in the pathophysiology of several diseases underlying smooth muscle hypercontraction. But the role of is unknown. The purpose of this preliminary report was to indicate the efficacy of fasudil, a Rho-kinase inhibitor in patients with pulmonary hypertension using interventional hemodynamic assessment. **Methods:** Fasudil was intravenously injected in 10 patients (9 female, mean ± SD, 46 ± 15 years, NYHA II n=2, III n=7, IV n=1) with primary (n=5) and secondary (n=5) PH who were not received any vasodilator. Fasudil was administered 30mg with 1mg/min. Hemodynamic data were measured using Swan-Ganz catheter until 60 minutes after starting administration of fasudil. Hemodynamic and arterial blood gas data of baseline and the lowest total pulmonary resistance (TPR) time were compared. **Results:** The lowest TPR time was within 30 to 60 minutes after administration. Administration of fasudil significantly decreased TPR from 13.6 ± 6.8 U to 10.3 ± 4.9 U (-23.2 ± 9.2 %,  $p < 0.001$ ) and mean pulmonary arterial pressure (mPAP) from 43.6 ± 14.5 mmHg to 38.8 ± 13.9 mmHg (-11.6 ± 10.4 %,  $p < 0.02$ ). Cardiac index (CI) was significantly increased from 2.39 ± 0.66 L/min/m<sup>2</sup> to 2.74 ± 0.73 L/min/m<sup>2</sup> (+16.5 ± 15.1 %,  $p < 0.01$ ). Although TPR was equally decreased in both primary and secondary PH, the changes in the parameters that prescribed TPR, namely CI and mPAP, were different between the two groups subjects. Increased CI was a major factor into reducing TPR in primary PH, while reduced mPAP



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