Diovan® (valsartan) Safety

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Studies and Randomized Patients by Dataset

Dataset	Study number	Patients, n	
		Valsartan	All treatments
Primary dataset (double-blind, controlled, short-term trials)			
Placebo controlled	103, 104, 106, Val-HeFT§	3,219	5,979
Positive controlled	110	70	141
Total		3,289	6,120
Long-term trial dataset	Val-HeFT	2,511	5,010
Open-label trial dataset	102, 105, ANG 102	90	94
Total completed trials		3,379	6,214

§First 4 months.

Valsartan Heart Failure Program Completed Double-blind Trials

Study	Primary variable	Exposure	Treatment group	N	Design/Population
103	Hemodynamics	4 wk	Valsartan 40, 80, 160 mg BID, placebo, lisinopril 5/10 mg OD	116	Parallel design, NYHA class II – IV, PCWP ≥ 15 mm Hg
104	Hemodynamics	4 wk	Valsartan 80, 160 mg BID, placebo	83	Parallel design, NYHA class II – IV, PCWP ≥ 15 mm Hg
106	ETT/QOL	16 wk	Valsartan 40, 80, 160 mg BID, placebo	770	Parallel design, NYHA class II – IV, ejection fraction < 40%
Val-HeFT	Morbidity/ mortality	up to 185 wk	Valsartan 40→80→160 mg BID, placebo	5,010	Parallel design, forced titration, NYHA class II – IV, ejection fraction < 40%, LVIDD > 2.9 cm/m^2
110	Walk Test	12 wk	Valsartan 80→160 mg OD Enalapril 5→10 mg BID	141	Parallel design, forced titration, NYHA class II – III, ejection fraction ≤ 45%
Total randomized to valsartan				3,289	
Total randomized to placebo				2,745	

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Valsartan Exposure (Primary Dataset)

	Patients, n					
	Valsartan total daily dose, mg					
Days	0§	80	160	320	All	Placebo
≥ 1	473	2,787	2,840	2,302	3,285	2,743
≥ 30	121	534	614	2,047	3,041	2,649
≥ 60	60	355	477	1,953	2,886	2,536
≥ 90	18	288	296	1,346	2,727	2,478

§Valsartan treatment interruptions during the double-blind period in one trial (Val-HeFT) were captured in the 0 mg group and excluded from the "all" column.

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Valsartan Exposure (Val-HeFT)

	Patients, n					
	Valsartan total daily dose, mg					
Days	0§	80	160	320	All	Placebo
≥ 1	1,191	2,508	2,342	2,118	2,508	2,497
≥ 60	361	310	396	1,900	2,323	2,371
≥ 180	67	224	268	1,693	2,155	2,235
≥ 360	9	162	199	1,543	1,968	2,063
≥ 720	0	69	77	722	1,061	1,108

§Valsartan treatment interruptions during the double-blind period were captured in the 0 mg group and excluded from the "all" column.

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Baseline Demographic Characteristics (Primary Dataset)

	Valsartan N = 3,289	Placebo N = 2,745
Age, mean yr	62.5	63.0
Age group, n (%)		
< 65 yr	1,773 (54)	1,431 (52)
≥ 65 yr	1,516 (46)	1,314 (48)
≥ 75 yr	451 (14)	416 (15)
Race, n (%)		
White	2,918 (89)	2,475 (90)
Black	271 (8)	190 (7)
Oriental/other	100 (3)	80 (3)
Sex, n (%)		
Male	2,639 (80)	2,205 (80)
Female	650 (20)	540 (20)

Baseline Disease Characteristics (Primary Dataset) (1)

	Valsartan N = 3,289	Placebo N = 2,743
Duration of HF, mean mo	50.5	51.2
LVEF§, mean %	26.6	26.9
Mean sitting DBP, mm Hg	75.2	75.6
Mean sitting SBP, mm Hg	123.4	124.1
NYHA classification, n (%)		
I	4 (< 1)	5 (< 1)
II	2,006 (61)	1,660 (61)
III	1,221 (37)	1,021 (37)
IV	58 (2)	59 (2)

§Not available for studies 103, 104, and 110.

Baseline Disease Characteristics (Primary Dataset) (2)

HF etiology§	Patients, n (%) Valsartan N = 3,214	Patients, n (%) Placebo N = 2,719
Coronary heart disease	1,842 (57)	1,546 (57)
Idiopathic cardiomyopathy	985 (31)	825 (30)
Hypertension	212 (7)	210 (8)
Other	175 (5)	138 (5)

§Does not include study 103, which allowed multiple etiology selections.

Baseline Cardiovascular Therapy (Primary Dataset)

	Patients, n (%)	
	Valsartan N = 3,289	Placebo N = 2,745
ACE inhibitors	2,887 (88)	2,511 (92)
Diuretics	2,807 (85)	2,326 (85)
Digoxin	2,195 (67)	1,853 (68)
Nitrates (long and short acting)	1,174 (36)	1,015 (37)
Beta-blockers	1,074 (33)	930 (34)
Amiodarone	401 (12)	359 (13)
Calcium channel blockers	347 (11)	337 (12)

Patient Disposition (103, 104, 106, 110)

	Patients, n (%)	
	Valsartan N = 778	Placebo N = 246
Completed	658 (84.6)	220 (89.4)
Discontinued prematurely	120 (15.4)	26 (10.6)
AE	67 (8.6)	9 (3.7)
Protocol violation or noncompliance	24 (3.1)	5 (2.0)
Death	10 (1.3)	4 (1.6)
Withdrew consent	7 (0.9)	4 (1.6)
Lost to follow-up	5 (0.6)	1 (0.4)
Administrative	4 (0.5)	2 (0.8)
Abnormal laboratory value(s)	2 (0.3)	0
Lack of efficacy	1 (0.1)	1 (0.4)

Ten Most Frequent AEs (Primary Dataset)

	Patients, n (%)	
	Valsartan N = 3,282	Placebo N = 2,740
Total patients with AEs	2,380 (72.5)*	1,876 (68.5)
Dizziness (exc vertigo)	568 (17.3)*	255 (9.3)
Hypotension NOS	218 (6.6)*	65 (2.4)
Chest pain NEC	168 (5.1)	153 (5.6)
Cough	157 (4.8)	135 (4.9)
Diarrhea NOS	148 (4.5)	100 (3.6)
Nasopharyngitis	146 (4.4)	107 (3.9)
Upper respiratory tract infection NOS	144 (4.4)	116 (4.2)
Nausea	137 (4.2)	106 (3.9)
Headache NOS	132 (4.0)	116 (4.2)
Arthralgia	90 (2.7)	58 (2.1)

*$P < .05$.

NOS = Not otherwise specified; NEC = Not elsewhere classified.

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Ten Most Frequent AEs (Val-HeFT)

Adverse events	Patients, n (%) Valsartan N = 2,506	Patients, n (%) Placebo N = 2,494
Total patients with AEs	2,295 (91.6)*	2,235 (89.6)
Dizziness (exc vertigo)	627 (25.0)*	451 (18.1)
Hypotension NOS	347 (13.8)*	201 (8.1)
Chest pain NEC	337 (13.4)	352 (14.1)
Congestive cardiac failure aggravated	276 (11.0)	387 (15.5)*
Cough	257 (10.3)	267 (10.7)
Nasopharyngitis	250 (10.0)	229 (9.2)
Upper respiratory tract infection NOS	244 (9.7)	260 (10.4)
Diarrhea NOS	238 (9.5)*	193 (7.7)
Nausea	218 (8.7)	236 (9.5)
Bronchitis NOS	196 (7.8)	210 (8.4)

*$P < .05$.
NOS = Not otherwise specified; NEC = Not elsewhere classified.

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AEs by Age, Gender, and Race (Primary Dataset)

	Valsartan		Placebo	
	N	Patients with AE, %	N	Patients with AE, %
Age				
< 65 yr	1,770	71.9	1,428	66.0
≥ 65 yr	1,512	73.3	1,312	71.2
Gender				
Male	2,632	71.2	2,200	67.1
Female	650	77.7	540	74.1
Race				
White	2,911	72.1	2,472	67.5
Black	271	75.3	190	75.8
Other	100	76.0	78	80.8

Dose Response AE Data (106)

Adverse events	Valsartan, mg 80 N = 185	160 N = 194	320 N = 197	All N = 576	Placebo N = 192
Total patients with AEs, %	72.4	75.8	77.7	75.3	77.6
Dizziness (exc vertigo)	20.5	16.0	13.7	16.7	11.5
Chest pain NEC	7.0	7.7	8.6	7.8	7.8
Hypotension NOS	7.6	6.2	4.1	5.9	1.0
Upper respiratory tract infection NOS	4.9	5.2	5.6	5.2	7.8
Diarrhea NOS	4.9	4.1	6.1	5.0	5.2
Nasopharyngitis	3.2	6.2	5.1	4.9	5.2
Cough	4.3	6.7	3.6	4.9	6.8
Nausea	7.0	4.6	2.5	4.7	4.7
Back pain	5.4	4.6	3.6	4.5	4.2
Headache NOS	7.0	3.6	3.0	4.5	4.7
⋮					
Hyperkalemia	1.1	2.6	3.6	2.4	1.0

NEC = Not elsewhere classified; NOS = Not otherwise specified.

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Ten Most Frequent AEs Causing Permanent Treatment Discontinuation (Val-HeFT)

Adverse events	Patients, n (%) Valsartan N = 2,506	Patients, n (%) Placebo N = 2,494
Discontinuation for any AE	249 (9.9)*	181 (7.3)
Dizziness (exc vertigo)	41 (1.6)*	11 (0.4)
Hypotension NOS	32 (1.3)	20 (0.8)
Renal impairment NOS	27 (1.1)*	6 (0.2)
Blood creatinine increased	13 (0.5)*	3 (0.1)
Diarrhea NOS	13 (0.5)*	3 (0.1)
Hyperkalemia	13 (0.5)*	2 (0.1)
Fatigue	11 (0.4)	5 (0.2)
Cardiac failure aggravated	10 (0.4)	3 (0.1)
Nausea	10 (0.4)	7 (0.3)
Congestive cardiac failure aggravated	9 (0.4)	18 (0.7)

NOS = Not otherwise specified.
*$P < .05$.

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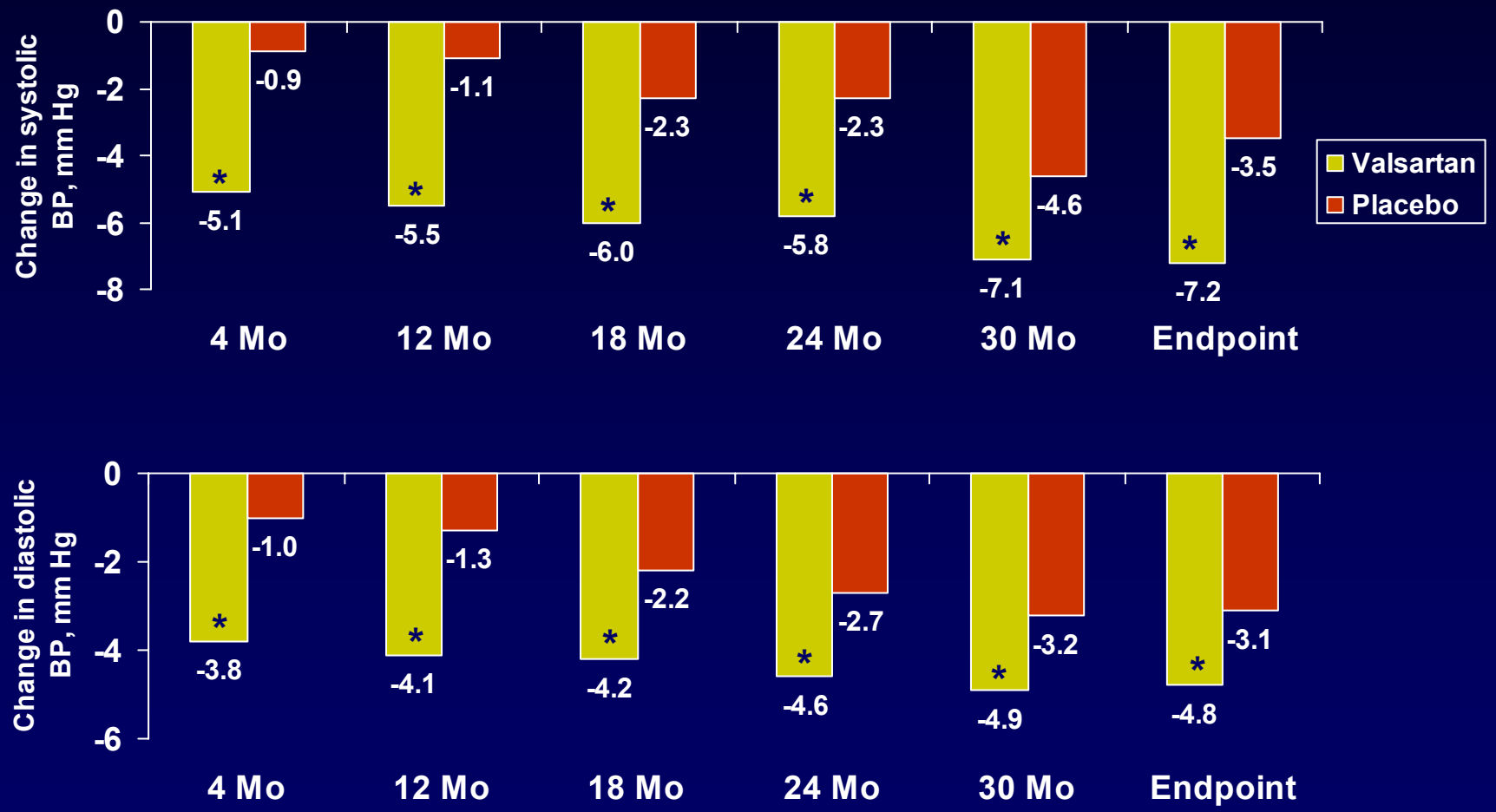
Change From Baseline Sitting Systolic and Diastolic Blood Pressure§ (Val-HeFT)



§Least square mean change.
*$P < .01$.

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Ten Most Frequent SAEs (Val-HeFT)

	Patients, n (%)	
	Valsartan N = 2,506	Placebo N = 2,494
Total patients with SAEs	1,282 (51.2)	1,342 (53.8)
Congestive cardiac failure aggravated	231 (9.2)	331 (13.3)*
Sudden death unexplained	135 (5.4)	152 (6.1)
Chest pain NEC	120 (4.8)	120 (4.8)
Ventricular tachycardia	84 (3.4)	77 (3.1)
Myocardial infarction	83 (3.3)	72 (2.9)
Pneumonia NOS	63 (2.5)	79 (3.2)
Syncope	62 (2.5)	60 (2.4)
Angina pectoris	63 (2.5)	49 (2.0)
Atrial fibrillation	59 (2.4)	98 (3.9)*
Cardiac arrest	58 (2.3)	63 (2.5)

NEC = Not elsewhere classified; NOS = Not otherwise specified.
*$P < .05$.

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Ten Most Frequent SAEs (Primary Dataset)

	Patients, n (%)	
	Valsartan N = 3,282	Placebo N = 2,740
Total patients with SAEs	548 (16.7)	490 (17.9)
Congestive cardiac failure aggravated	66 (2.0)	79 (2.9)*
Hypotension NOS	32 (1.0)	15 (0.5)
Chest pain NEC	31 (0.9)	36 (1.3)
Ventricular tachycardia	26 (0.8)	20 (0.7)
Syncope	26 (0.8)	17 (0.6)
Cardiac failure congestive	25 (0.8)	16 (0.6)
Myocardial infarction	25 (0.8)	15 (0.5)
Sudden death unexplained	24 (0.7)	30 (1.1)
Cardiac arrest	22 (0.7)	18 (0.7)
Angina pectoris§	21 (0.6)	16 (0.6)
Atrial fibrillation	21 (0.6)	24 (0.9)
Pneumonia NOS	21 (0.6)	24 (0.9)

NEC = Not elsewhere classified; NOS = Not otherwise specified.
*$P < .05$.

Deaths by Principal Cause Investigator Assessment (Val-HeFT)

Principal cause of death	Patients, n (%) Valsartan N = 2,511	Patients, n (%) Placebo N = 2,499
Total deaths§	505 (20.1)	499 (20.0)
Sudden death‖	228 (9.1)	227 (9.1)
Pump failure, progressive HF even if terminal event was arrhythmia or vascular event	143 (5.7)	130 (5.2)
Other noncardiovascular event	43 (1.7)	34 (1.4)
Vascular event¶	30 (1.2)	33 (1.3)
Noncardiovascular event—cancer	20 (0.8)	24 (1.0)
Unknown	15 (0.6)	22 (0.9)
Acute myocardial infarction—documented	14 (0.6)	11 (0.4)
Acute myocardial infarction—presumed	12 (0.5)	18 (0.7)

§ Until last patient, last visit.
‖ Unexpected or with premonitory worsening HF, arrhythmia, or ischemia.
¶Stroke, cardiac procedure, or other.

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Mean Change From Baseline to Final Visit for Selected Chemistry Parameters (Primary Dataset)

	Valsartan			Placebo		
Parameter	N	Mean Baseline	Mean change	N	Mean Baseline	Mean change
Creatinine, mg/dL	3,178	1.3	0.1*	2,699	1.3	0
Potassium§, mEq/L	2,989	4.4	0.1*	2,509	4.4	0
BUN, mg/dL	3,047	22.0	3.9*	2,666	21.7	0.5
Uric acid, mg/dL	2,937	7.4	0.3*	2,506	7.4	0

*$P < .05$.
§Excluding values ≥ 7 mEq/L.

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Incidence of Patients With Prespecified Percent Change From Baseline to Final Visit for Selected Chemistry Parameters (Primary Dataset)

	Patients, n (%)	
	Valsartan	Placebo
Creatinine		
≥ 50% increase	123 (3.9)*	24 (0.9)
Potassium§		
≥ 20% decrease	81 (2.7)	104 (4.2)*
≥ 20% increase	298 (10.0)*	128 (5.1)
BUN		
≥ 50% increase	506 (16.6)*	169 (6.3)
Uric acid		
≥ 50% increase	93 (3.2)*	48 (1.9)

*$P < .05$.

§Excluding values ≥ 7 mEq/L.

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Safety Summary

- Valsartan (80 to 320 mg/day) is well tolerated in patients with NYHA Class II – IV HF
- AEs included dizziness, hypotension, and postural dizziness
- AEs resulting in discontinuation included dizziness and hypotension
- Increases in BUN, Cr, K^+, and uric acid were more frequent with valsartan
- Safety profile consistent with pharmacology of agents affecting the RAS and background therapies