ACTUALITÉS NÉPHROLOGIQUES
JEAN HAMBURGER
HÔPITAL NECKER

NECKER SEMINARS IN NEPHROLOGY

Endothelin Receptor Antagonists in Kidney Disease

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Vascular and renal effects of endothelin 1 are closely related to ET-A and ET-B receptors

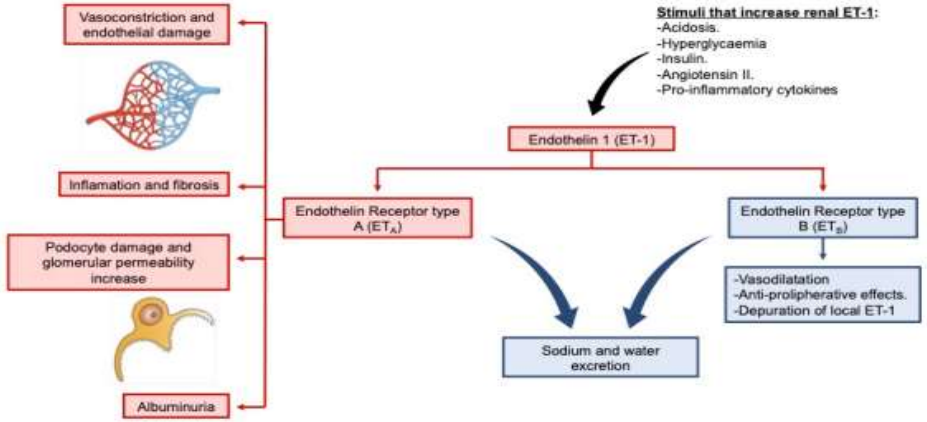
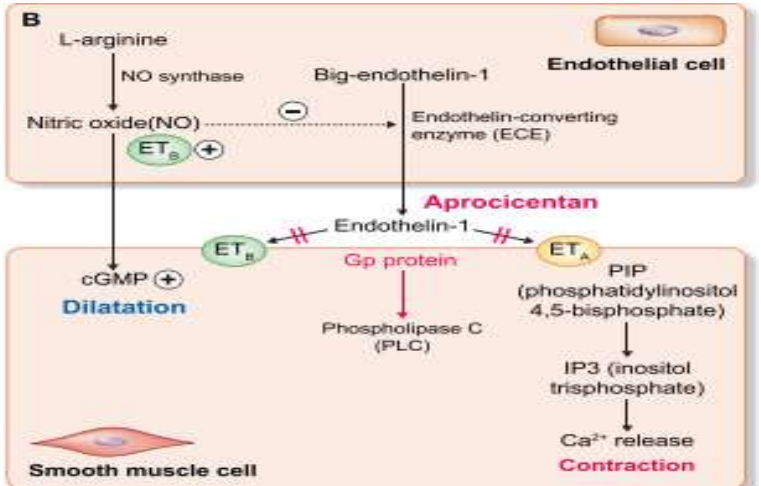


Figure 1. Scheme of the endothelin system. ET-1 acts thought its binding to ET_A and ET_B producing opposite effects in the kidney. The effects caused by the activation of ET_A are shown in red and the effects of ET_B activation are shown in blue. In pathological conditions, the hyperglycaemia, acidosis and the presence of insulin, angiotensin II and proinflammatory cytokines causes the increase of ET-1 concentration, which produces deleterious effects on renal function, such as vasoconstriction and endothelial damage, inflammation, fibrosis, podocyte damage or albuminuria.



Opposite effects of ETA /ETB R

ETA

- ***High blood pressure***
- ***Vasconstrictor effect***
- ***Inflammation***
- ***Fibrosis***

ETB

- ***Renal NA excretion***

Zoccali C CKJ 2023
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Main endothelin receptor antagonists and selectivity for the ET receptors

ERA	Affinity	Year of Development ¥	Status ¥
BQ-123	ET_A	1995	–
Darusentan	ET_A ~1000-fold	1996	Investigational
Atrasentan	ET_A ~1800-fold	1996	Investigational
Sitaxentan	ET_A ~6500-fold	1997	–
Ambrisentan	ET_A >4000-fold	2004	Approved in 2007
Macitentan	ET_A ~1000-fold	–	Approved in 2013
Avosentan	ET_A ~500-fold	2006	Investigational
Zibotentan	ET_A	2010	Investigational
BQ-788	ET_B	1994	–

Table 2. *Cont.*

ERA	Affinity	Year of Development ¥	Status ¥
Bosentan	ET_A/ET_B	1999	Approved in 2001
Tezosentan	ET_A/ET_B	2001	–
Aprocitentan	ET_A/ET_B	2015	Investigational
Sparsentan	ET_A * ~1000-fold	2005	Investigational

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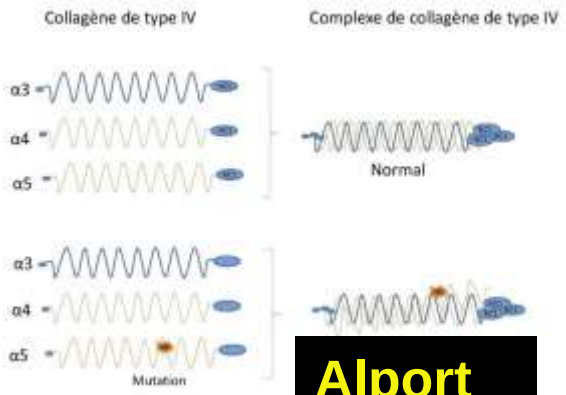
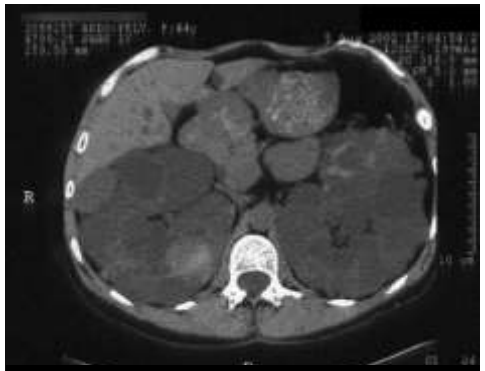
A wide range of potential uses

Preclinical studies :



Alport

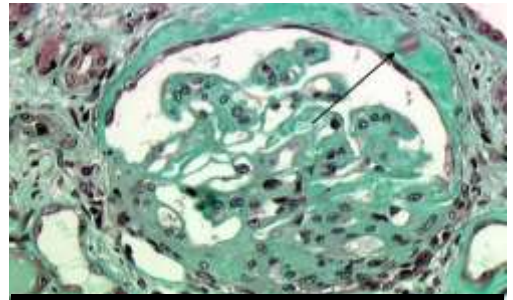


ADPKD

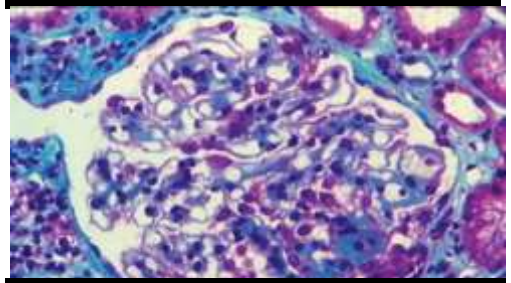
Sickle cell nephropathy

Clinical studies :

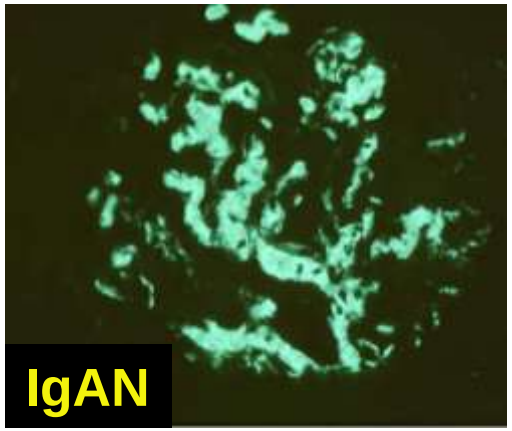
Resistant hypertension



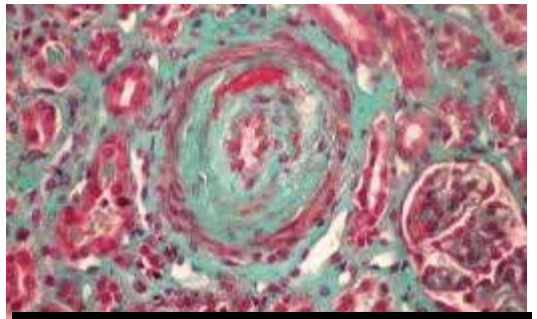
DB kidney disease



FSGS



IgAN



Systemic sclerosis

Essential/ Resistant Hypertension

Tableau I. Essais randomisés contrôlés démontrant l'efficacité thérapeutique des antagonistes des récepteurs de l'endothéline (ARE) dans l'hypertension artérielle

ARE: antagonistes des récepteurs de l'endothéline; ETA: récepteur A de l'endothéline; ETB: récepteur B de l'endothéline; HTA: hypertension artérielle; TAS: tension artérielle systolique; TAD: tension artérielle diastolique; ns: non significatif; na: non applicable; *placebo-substracted.

Auteur Publication	Population HTA	Durée (mois)	Antagonisme	ARE testé (dose max)	TA (mmHg) TAS/TAD	Valeur p	Autres effets
Krum, 1998[11]	Stade I-II (n=267)	1	ETA-ETB	Bosentan 2000 Enalapril 20 Placebo	-10,3/-5,7 -9/-5,8 -0,9/-1,8	<0,05 <0,05	
Nakow, 2002[18]	Stade II (n=387)	1½	Sélectif ETA	Darusentan 100 Placebo	-11,3/-8,3* na	0,0001	
Raichlin 2008[19]	HTA et risque CV élevé (n=72)	6	Sélectif ETA	Atrasentan 10 Placebo	-14/7 -4/-1	<0,001	Métabolisme glycémique, lipidique et de l'acide urique
Black, 2007[20]	HTA résistante (n=115)	2½	Sélectif ETA	Darusentan 300 Placebo	-11,5/-6,3* na	0,015/0,002	
Weber, 2009[12] DORADO	HTA résistante, Risque CV élevé (n=379)	2	Sélectif ETA	Darusentan 300 Placebo	-18/-11 -9/-5	<0,0001	Antiprotéinurique
Bakris, 2010[13] DORADO-AC	HTA résistante (n=849)	2½	Sélectif ETA	Darusentan Guanfacine Placebo	-15/-10 -12/-6 -14/-8	ns	

An estimated 1·3 billion people have Hypertension of which approximately 10% have resistant hypertension

Global public health concern

(Forni Revu Med Suisse 2011)

Essential Hypertension

Bosentan/Placebo/Enalapril

267 patients with mild-to moderate essential hypertension (stage I –II PAD entre 95 et 115 mmHg PAM >85 /24H)

TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.*

CHARACTERISTIC	PLACEBO (N=49)	BOSENTAN 100 mg (N=50)	BOSENTAN 500 mg (N=49)	BOSENTAN 1000 mg (N=45)	BOSENTAN 2000 mg (N=50)	ENALAPRIL (N=50)
			mean ±SD			
Male sex (%)	55	70	76	64	74	66
Age (yr)	56±9	56±9	55±10	54±10	55±11	59±10
Weight (kg)	76±13	82±11	83±11	83±13	85±14	79±13
Height (cm)	168±11	171±9	173±8	171±8	173±8	171±8
Heart rate (bpm)	71.8±7.8	73.7±7.5	73.5±8.1	74.8±7.5	73.4±7.7	76.2±8.4
Office blood-pressure measurements (mm Hg)						
Diastolic pressure	101.7±4.5	103.9±4.1	101.1±5.0	107.4±4.7	102.9±4.8	102.2±5.0
Systolic pressure	158.3±14.1	168.6±16.3	161.2±14.3	161.5±14.7	161.3±13.2	161.9±14.3
Ambulatory blood-pressure monitoring (mm Hg)						
24-Hr diastolic pressure	94.4±7.2	97.6±6.7	94.1±6.7	96.4±6.5	96.2±7.5	94.1±5.3
Daytime diastolic pressure	99.2±7.1	102.6±7.3	98.5±7.6	100.8±6.1	101.0±7.4	99.2±5.7
Nighttime diastolic pressure	85.2±8.9	87.9±7.6	85.5±8.1	87.7±8.4	86.6±9.4	83.5±7.0
24-Hr systolic pressure	149.5±13.4	160.4±16.9	153.7±12.3	152.6±14.0	153.6±11.6	152.3±12.0
Daytime systolic pressure	155.2±13.7	166.8±18.0	158.9±12.8	155.4±14.0	158.2±11.9	158.6±12.3
Nighttime systolic pressure	138.4±15.2	147.8±17.2	143.3±14.2	142.0±15.6	142.0±13.5	138.6±14.6
Serum creatinine (μmol/liter)†	90±14	93±15	94±17	94±11	92±13	91±15
Neurohormonal factors‡						
Plasma norepinephrine (nmol/liter)	1.8±0.9	1.4±1.1	1.5±1.0	1.7±0.9	1.8±1.3	1.9±1.0
Plasma renin activity (mIU/liter)	18.4±10.4	17.8±11.0	25.4±30.9	27.0±25.0	15.2±8.9	16.3±12.6
Plasma angiotensin II (ng/liter)	8.2±10.0	11.7±21.8	12.1±23.7	8.0±9.3	5.6±6.0	9.9±17.4
Plasma endothelin-1 (ng/liter)	4.1±0.5	4.0±0.8	4.2±1.1	4.0±0.7	4.0±1.0	4.0±0.9
Plasma big endothelin-1 (ng/liter)	13.3±2.1	13.1±3.3	14.4±4.4	13.4±2.6	13.3±2.5	13.7±3.3

The mean duration of active treatment was similar in all six groups, ranging from 25.9 to 27.6 days.

A total of 267 patients had completed the week 4 assessment at the time the study

Primary end point of the study (the change from baseline in the office measurement of diastolic pressure in the sitting position) at 4 W

(Krum H NEJM 1998)

Essential Hypertension

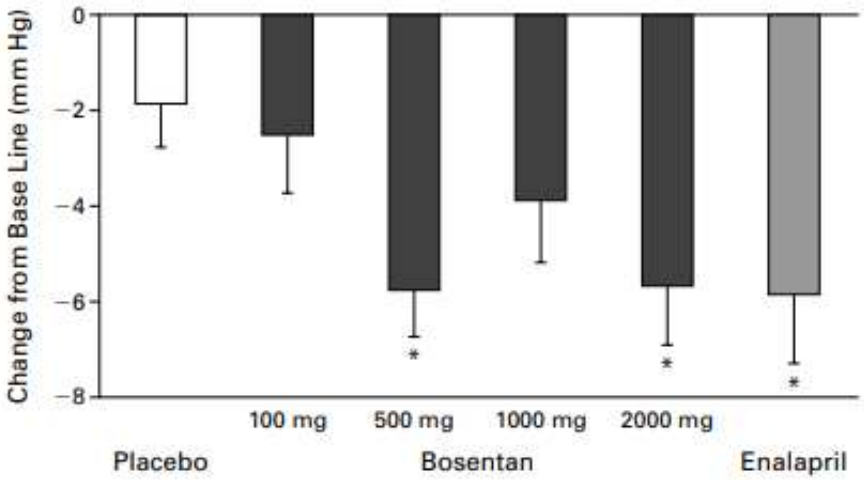


Figure 1. Mean (±SE) Change from Base Line in Diastolic Pressure in Patients with Mild-to-Moderate Hypertension Assigned to Receive Placebo, Bosentan (100, 500, 1000, or 2000 mg Daily), or Enalapril (20 mg Daily).

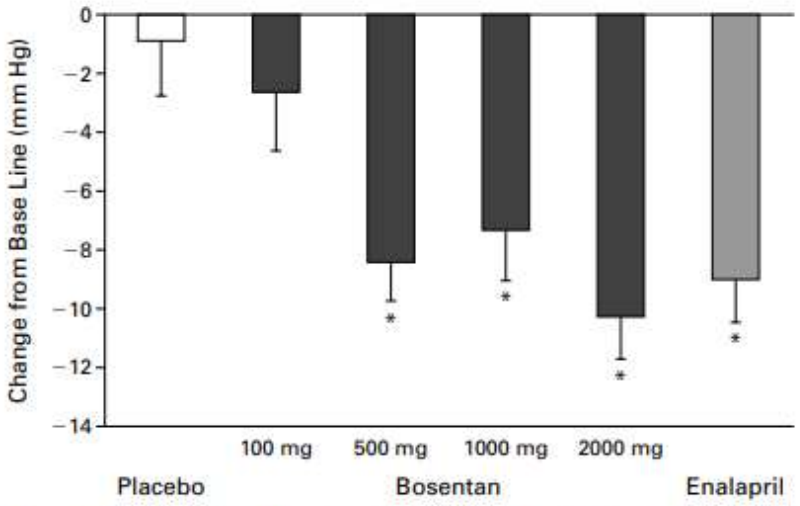


Figure 2. Mean (±SE) Change from Base Line in Systolic Pressure in Patients with Mild-to-Moderate

As compared with placebo, bosentan resulted in a significant reduction in diastolic pressure with a daily dose of 500 or 2000 mg (an absolute reduction of 5.7 mm Hg at each dose), which was similar to the reduction with enalapril (5.8 mm Hg)

(Krum H NEJM 1998)

Essential Hypertension

TABLE 3. CHANGES FROM BASE LINE IN NEUROHORMONAL FACTORS.*

NEUROHORMONAL FACTOR	PLACEBO (N=19)	BOSENTAN 100 mg (N=17)	BOSENTAN 500 mg (N=22)	BOSENTAN 1000 mg (N=17)	BOSENTAN 2000 mg (N=21)	ENALAPRIL (N=20)
	mean ±SE					
Plasma renin activity (mIU/liter)	−2.5±6.6	1.4±7.0	−4.9±6.2	−2.7±7.0	0.7±6.3	44.1±6.5†
Angiotensin II (ng/liter)	0.3±6.3	−6.8±5.8	−2.5±5.0	−0.4±5.8	2.4±5.1	−2.8±5.3
Endothelin-1 (ng/liter)	−0.1±0.3	0.6±0.3	0.7±0.2†	0.7±0.3†	1.2±0.2†	−0.1±0.2
Big endothelin-1 (ng/liter)	−0.3±0.8	2.2±0.9†	0.9±0.8	2.0±0.9†	1.2±0.8	2.3±0.8†
Norepinephrine (nmol/liter)‡	0.3±0.3	0.4±0.3	0.5±0.3	0.6±0.3	0.2±0.3	0.3±0.3

*One value, excluded from the table but included in the nonparametric analysis, was more than 5 SD from the mean: angiotensin II, 208.0 ng per liter, in a patient receiving 500 mg of bosentan daily.

†$P<0.05$ for the comparison with placebo.

The incidence of reported adverse events (including those considered to be unrelated to the study drug) was similar among the six treatment groups

The most common adverse events reported with bosentan were headache

Conclusion Long term treatment with the endothelin-receptor antagonist bosentan in patients with mild-to-moderate hypertension results in significant reductions in blood pressure as compared with placebo

(Krum H NEJM 1998)

Resistant Hypertension

Darusentan/Placebo

379 patients treatment of resistant HTA

Primary endpoints were the change from baseline to week 14 in sitting systolic and diastolic blood pressures.

= with systolic blood pressure of 140 mm Hg or more
(≥130 mm Hg if patient had diabetes or chronic kidney disease)
who were receiving at least three blood-pressure-lowering drugs including a diuretic

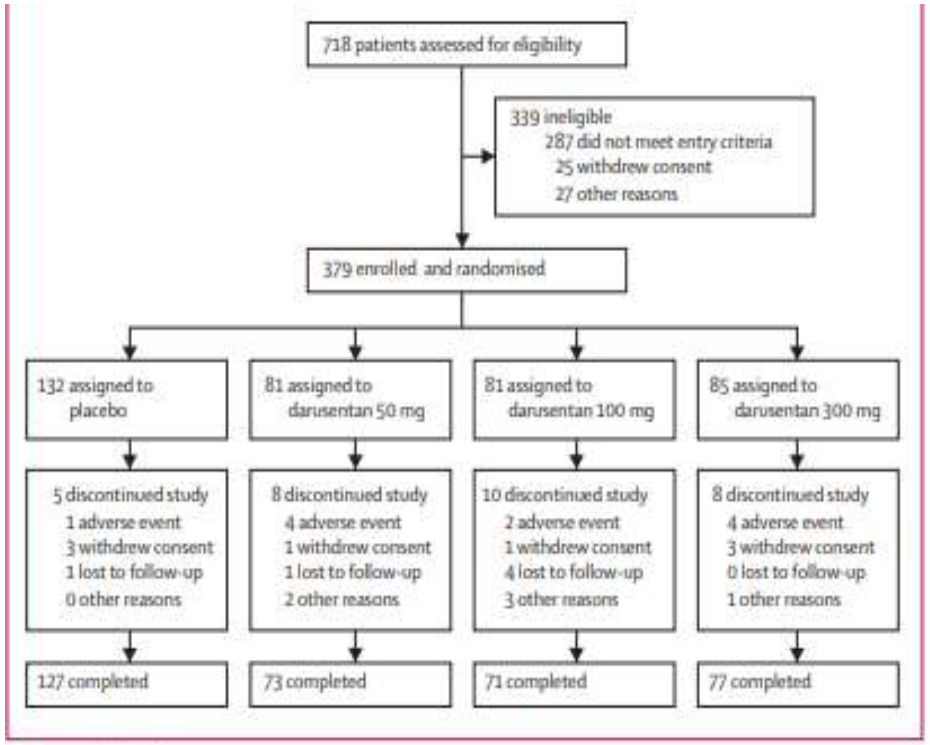
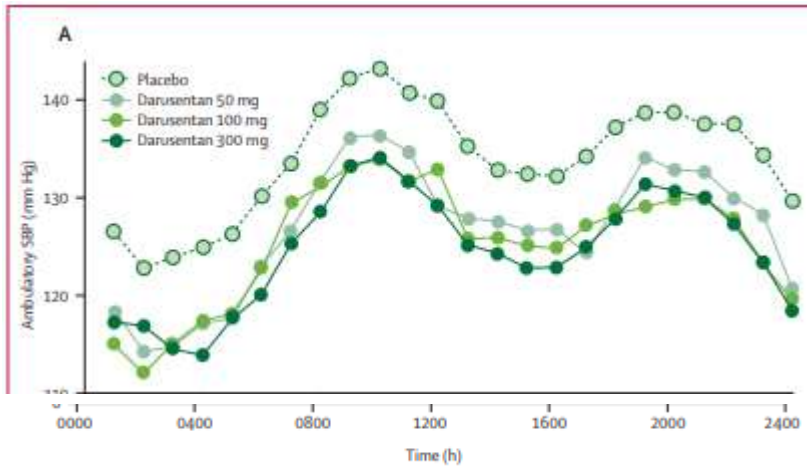


Figure 1: Trial profile

	Placebo (n=132)	Darusentan 50 mg (n=81)	Darusentan 100 mg (n=81)	Darusentan 300 mg (n=85)	All patients (N=379)
Age (years)	62 (9)	62 (8)	62 (9)	61 (10)	62 (9)
Women	72 (55%)	38 (47%)	40 (49%)	41 (48%)	191 (50%)
Black	27 (21%)	16 (20%)	14 (17%)	18 (21%)	75 (20%)
Body-mass index (kg/m²)	32 (6)	33 (5)	31 (6)	31 (5)	32 (5)
eGFR (mL/min/1·73 m²)	80 (23)	81 (21)	76 (20)	78 (20)	79 (21)
≥Four antihypertensive drugs	75 (57%)	50 (62%)	50 (62%)	45 (53%)	220 (58%)
Diuretic drugs	131 (99%)	81 (100%)	81 (100%)	84 (99%)	377 (99%)
ACEI or ARB	127 (96%)	78 (96%)	78 (96%)	84 (99%)	367(97%)
Calcium-channel blocker	96 (73%)	64 (79%)	56 (69%)	65 (77%)	281 (74%)
β blocker	85 (64%)	51 (63%)	56 (69%)	58 (68%)	250 (66%)
Other antihypertensive drugs	25 (19%)	16 (20%)	23 (28%)	15 (18%)	79 (21%)

(Weber MA Lancet 2009)

Resistant Hypertension



All three darusentan doses produced significant reductions in both systolic and diastolic blood pressures

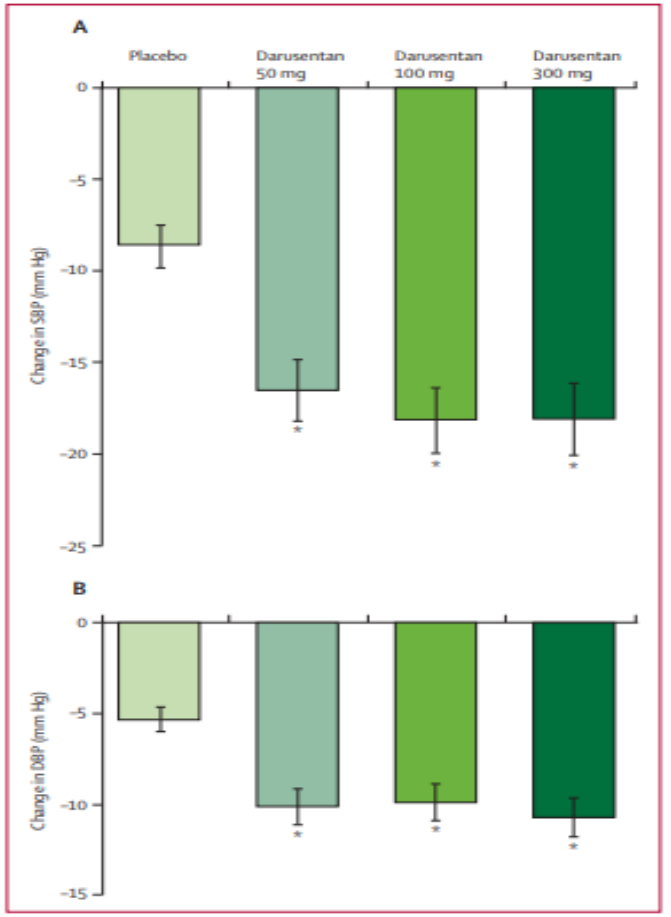


Figure 2: Changes from baseline in clinic seated blood pressure after 14 weeks of treatment

Oedema or fluid retention occurred in 67 (27%) patients given darusentan compared with 19 (14%) given placebo.
One patient in the placebo group died (sudden cardiac death), and 5 patients in the three darusentan dose groups combined had cardiac-related serious adverse events

Conclusion The use of this drug accompanied by effective diuretic therapy seems to represent a new and effective strategy for dealing with treatment-resistant hypertension.

At the end of the study (14W):
143/81 mm Hg with placebo,
134/77 mm Hg with darusentan 50 mg,
134/76 mm Hg (17/11) with darusentan 100 mg,
134/76 mm Hg (17/11) with darusentan 300 mg

(Weber MA Lancet 2009)

Resistant Hypertension

The Parallel-Group, Phase 3 Study with **Aprocitentan** in Subjects with Resistant Hypertension (PRECISION)

= Sitting systolic blood pressure > 140 mm Hg despite taking standardized background therapy consisting of three antihypertensive drugs, including a diuretic

Three sequential parts:

- part 1 was the 4-week double-blind, randomised, and placebo-controlled part, in which patients received aprocitentan 12·5 mg, aprocitentan 25 mg, or placebo in a 1:1:1 ratio
- part 2 was a 32-week single (patient)-blind part, in which all patients received aprocitentan 25 mg
- part 3 was a 12-week double-blind, randomised, placebo-controlled withdrawal part, in which patients were re-randomised to aprocitentan 25 mg or placebo in a 1:1 ratio

The primary and key secondary endpoints were changes in office systolic blood pressure from baseline to week 4 and from withdrawal baseline to week 40, respectively

(Schlaich M Lancet 2022)

Resistant Hypertension

	Aprocitentan 12·5 mg (n=243)	Aprocitentan 25 mg (n=243)	Placebo (n=244)
Age at screening, years			
Mean age at screening	61·2 (10·3)	61·7 (10·4)	62·2 (11·2)
18 to <65	143 (59%)	136 (56%)	130 (53%)
65 to <75	78 (32%)	85 (35%)	86 (35%)
≥75	22 (9%)	22 (9%)	28 (11%)
Gender			
Men	144 (59%)	145 (60%)	145 (59%)
Women	99 (41%)	98 (40%)	99 (41%)
Geographical area			
Europe	153 (63%)	143 (59%)	152 (62%)
North America	76 (31%)	81 (33%)	75 (31%)
Asia or Australia	14 (6%)	19 (8%)	17 (7%)
Race or ethnicity			
White	203 (84%)	200 (82%)	202 (83%)
Black or African American	28 (12%)	28 (12%)	26 (11%)
Asian	11 (5%)	14 (6%)	13 (5%)
Other†	1 (0)	1 (0)	3 (1%)
BMI at screening, kg/m²			
Mean BMI	33·6 (6·2)	34·3 (6·8)	33·3 (5·6)
Low to overweight (<30)	75 (31%)	70 (29%)	79 (32%)
Obese (30 to <40)	135 (56%)	132 (54%)	132 (54%)
Severely obese (≥40)	33 (14%)	41 (17%)	33 (14%)
Estimated glomerular filtration rate at baseline between 15 and <60 mL/min per 1·73 m²	55 (23%)	61 (25%)	46 (19%)
Urine albumin-creatinine ratio at baseline, mg/g‡			
<30	144 (60%)	155 (65%)	154 (65%)
30 to 300	63 (26%)	55 (23%)	56 (24%)
>300	34 (14%)	28 (12%)	28 (12%)
Medical history			
Diabetes	131 (54%)	137 (56%)	127 (52%)
Ischaemic heart disease	73 (30%)	79 (32%)	73 (30%)
Congestive heart failure	48 (20%)	51 (21%)	44 (18%)
Sleep apnoea syndrome	33 (14%)	39 (16%)	31 (13%)
Stroke§	20 (8%)	21 (9%)	16 (7%)
≥4 antihypertensive drugs at screening*	151 (62%)	158 (65%)	151 (62%)
Unattended automated office blood pressure at baseline, mm Hg			
Systolic blood pressure	153·2 (8·8)	153·3 (9·0)	153·3 (9·0)
Diastolic blood pressure	87·9 (9·4)	87·7 (9·7)	87·1 (9·9)
Ambulatory blood pressure monitoring at baseline, mm Hg¶			
24 h systolic blood pressure	137·7 (13·3)	137·6 (15·2)	137·1 (13·6)
24 h diastolic blood pressure	83·5 (8·7)	82·5 (10·0)	82·5 (9·1)

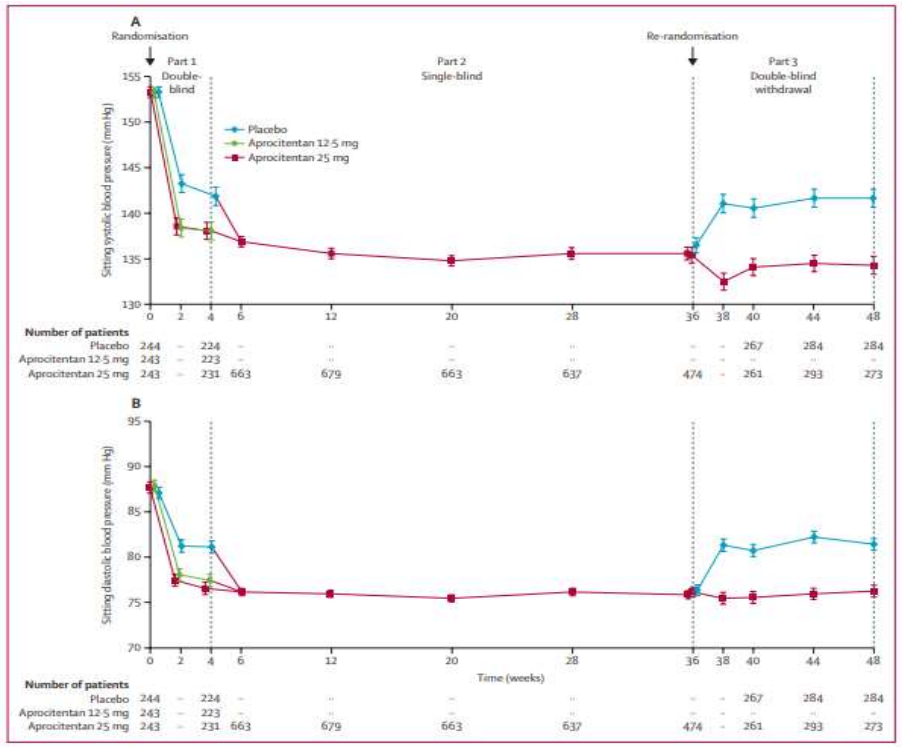


Figure 2: **Sitting systolic and diastolic blood pressures measured as unattended automated office blood pressure over time**
Blood pressure was measured at trough, before taking the study treatment and the standardised background antihypertensive therapy. Bars are standard error of the mean. Values are offset from each other for readability.

704 (96%) completed part 1 of the study
of these, 613 (87%) completed part 2
of these, 577 (94%) completed part 3 of the study

The change in office SBP at 4 weeks was

- –15·3 mm Hg for aprocitentan 12·5 mg,
- –15·2 mm Hg for aprocitentan 25 mg,
- –11·5 mm Hg for placebo,

for a difference versus placebo
of –3·8 (1·3) mm Hg (p=0·0042) and - 3·7 mm Hg (–6·7 to –0·8, p=0·0046),respectively

(Schlaich M Lancet 2022)

Resistant Hypertension

	Aprocitentan 12·5 mg	Aprocitentan 25 mg	Placebo
Part 1: Double-blind	243	245	242
Patients with at least one event	30 (12·3%)	47 (19·2%)	7 (2·9%)
Oedema or fluid retention	22 (9·1%)	45 (18·4%)	5 (2·1%)
Anaemia or haemodilution	9 (3·7%)	3 (1·2%)	0
Hepatic disorder	0	1 (0·4%)	2 (0·8%)
Part 2: Single-blind	..	704	..
Patients with at least one event	..	185 (26·3%)	..
Oedema or fluid retention	..	128 (18·2%)	..
Anaemia or haemodilution	..	63 (8·9%)	..
Hepatic disorder	..	16 (2·3%)	..
Part 3: Double-blind withdrawal	..	310	303
Patients with at least one event	..	18 (5·8%)	15 (5·0%)
Oedema or fluid retention	..	8 (2·6%)	4 (1·3%)
Anaemia or haemodilution	..	6 (1·9%)	4 (1·3%)
Hepatic disorder	..	4 (1·3%)	7 (2·3%)

Data are n or n (%). Events are defined using the Medical Dictionary for Regulatory Activities (version 24.1). Safety analyses were done according to the received treatment group.

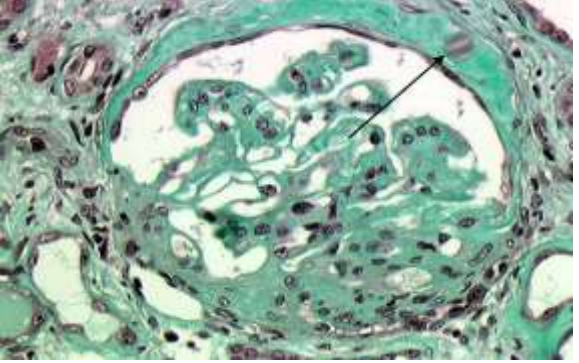
Table 2: Treatment-emergent adverse events of special interest

The eGFR decreased slightly with aprocitentan in part 1 versus placebo, stabilised in part 2, and decreased further in the aprocitentan group in part 3 while remaining stable in the placebo group

Slight increases in N-terminal pro-brain natriuretic peptide (NT-proBNP) and mid-regional pro-atrial natriuretic peptide (MR-proANP) were observed in part 1 with aprocitentan, followed by stabilisation during part 2 and reversal during part 3

Conclusion **In patients with resistant hypertension, aprocitentan was well tolerated and superior to placebo in lowering blood pressure at week 4 with a sustained effect at week 40**

(Schlaich M Lancet 2022)

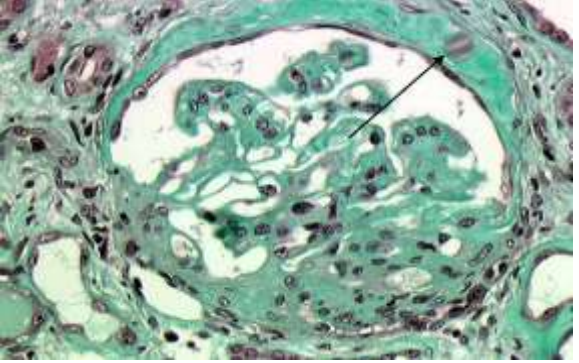


Diabetic Nephropathy

Table 1 Baseline characteristics of included studies

Ref.	Patients No.	Interventions (dose/d)	Treatment period (wk)	Age mean (SD)	Sex, *n* (%) female	eGFR [mean (SD) mL/min/1.73 m²]	UACR, mg/g creatinine median (Q1 to Q3) or mean (SD)	SBP, mmHg mean (SD)	DBP, mmHg mean (SD)	Hemoglobin A1c, % mean (SD)	Study type	NCT number
Heerspink *et al*[12], 2019	2648	Atrasentan 0.75 mg	53 mo? (follow-up 2.2 years)	I: 64.8 (8.6)	25%	44.0 (13.7)	792 (462-1480)	136.5 (15.2)	75.0 (9.9)	7.8 (1.5)	RCT	NCT01858532
				C: 64.7 (8.7)	26.60%	43.7 (13.7)	805 (444-1451)	136.2 (14.8)	74.8 (10.0)	7.8 (1.5)		
Kohan *et al*[7], 2011	89	Atrasentan 0.25 mg, 0.75 mg, 1.75 mg	8	I: 63 (12) 67 (9) 64 (13)	41% 36% 27%	31 (4) 34 (6) 33 (5)	350 (194-1226) 360 (209-726) 433 (157-998)	134 (14) 137 (15) 135 (11)	75 (8) 74 (8) 75 (9)	7.6 (1.0) 7.6 (1.2) 7.3 (1.1)	RCT	N/A
				C: 61 (8)	17%	34 (5)	515 (170-1477)	138 (14)	78 (8)	7.4 (0.9)		
Mann *et al*[8], 2010	1392	Avosentan 25, 50 mg	48	I: 61.2 (8.8) 61.0 (9.1)	30.8% 32.8%	29.9 (6.2) 30.4 (6.5)	1422 (728.9-2425.3) 1472 (758.5-2515)	137.1 (13.8) 137.0 (14.3)	77.9 (9.2) 77.5 (8.6)	8.0 (1.5) 8.1 (1.6)	RCT	NCT00120328
				C: 60.8 (8.9)	33.80%	30.1 (6.2)	1531 (794.3-2823.9)	135.4 (15.1)	77.2 (9.5)	8.0 (1.5)		
Rafnsson *et al*[13], 2011	28	Bosentan 250 mg	4	I: 62 (8)	18.00%	28.9 (7.4)	415 (681.6)	149 (24)	81 (10)	7.4 (1.1)	RCT	NCT01357109
				C: 63 (9)	20.80%	31.5 (4.0)	409 (512.7)	151 (25)	78 (9)	8.0 (1.4)		
Wenzel *et al*[14], 2009	286	Avosentan 5, 10, 25, and 50 mg	12	I: 60.8 (10.0) 58.4 (10.0)	34% 30%	31.3 (7.0) 32.2 (5.0)	N/A	N/A	N/A	N/A	RCT	N/A
				C: 58.4 (10.0)	13%	30.5 (5.0)	N/A	N/A	N/A	N/A		
Zeeuw *et al*[9], 2014	211	Atrasentan 0.75 mg or 1.25 mg	12	I: 65.0 (9.8) 64.5 (8.8)	N/A	N/A	878 (515-1682) 826 (481-1389)	138 (14) 136 (15)	75 (10) 74 (9)	7.5 (1.5) 7.7 (1.4)	RCT	NCT01356849 NCT01424319
				C: 64.3 (9.0)	N/A	N/A	671 (410-1536)	136 (14)	72 (10)	7.4 (1.3)		

(Zhang World Journal of Diabetes 2020)



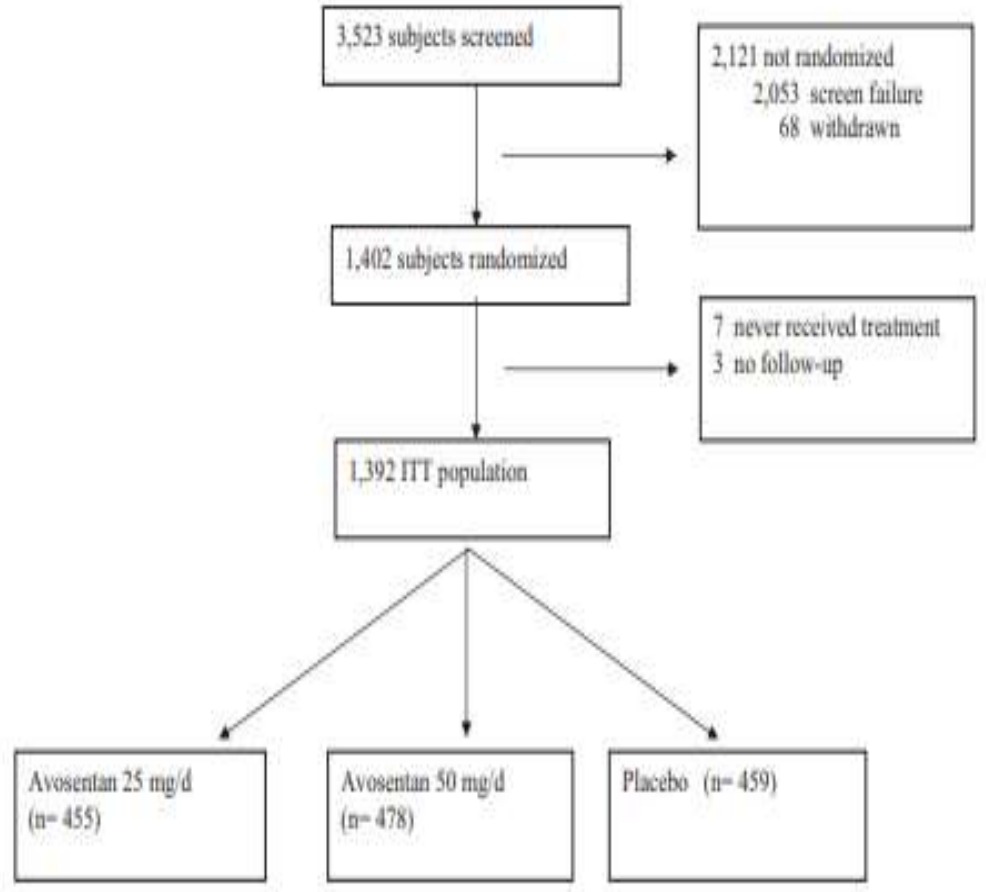
Diabetic Nephropathy

Receptor Antagonist Avosentan on Time to Doubling of Serum Creatinine, End Stage Renal Disease or Death in Patients With Type 2 Diabetes Mellitus and Diabetic Nephropathy

ASCEND study

multicenter, multinational, double-blind, placebo controlled trial.
1392 participants with type 2 diabetes
oral avosentan (25 or 50 mg) or placebo during 42 months

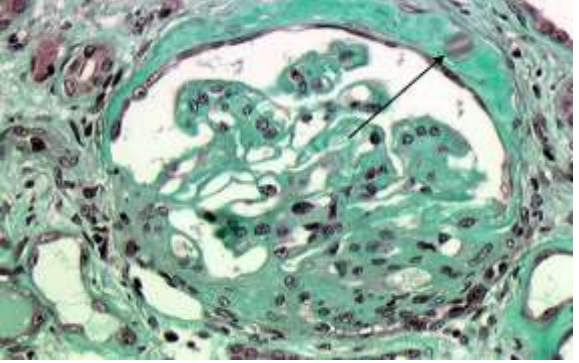
Overt nephropathy =
urine ACR 35 mg/mmol (309 mg/g)
and
serum creatinine level between115 and 265 mmol/L in men and between 106 and 265 mmol/L in women.



The composite primary outcome was the time to doubling of serum creatinine, ESRD, or death.

Secondary outcomes included changes in albumin-to-creatinine ratio (ACR) and cardiovascular outcomes

(Mann et al JASN 2010)



Diabetic Nephropathy

Trial was stopped prematurely after a median follow-up of 4 months (maximum 16 months) because of an excess of cardiovascular events with avosentan.

No difference in the frequency of the primary outcome between groups

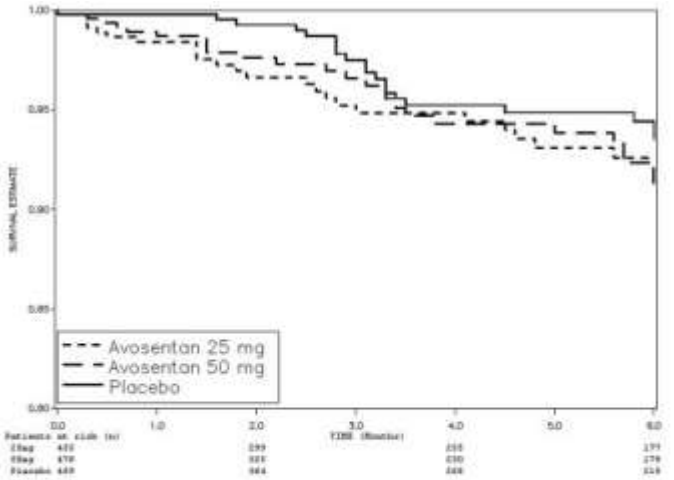


Figure 2. Kaplan-Meier plot shows time to doubling of serum creatinine, ESRD, or death in patients who had type 2 diabetes and diabetic nephropathy and were treated with avosentan 25 mg/d, avosentan 50 mg/d, or placebo (n = 1392). There were no significant differences among groups. The plots were truncated at 6 months because of premature termination of the trial.

Avosentan significantly reduced ACR: avosentan 25 mg/d, 50 mg/d, and placebo, the median reduction in ACR was

- 44.3%
- 49.3 %
- 9.7%,respectively.

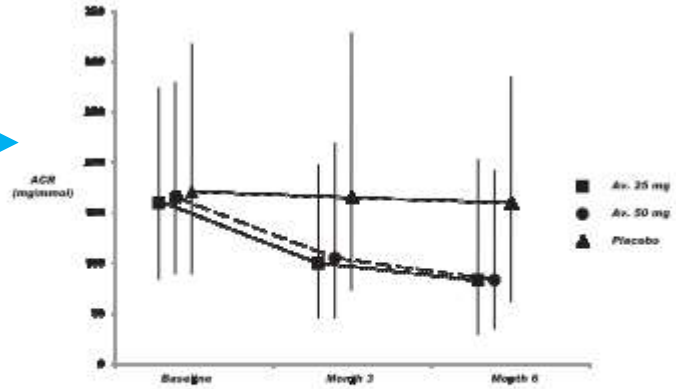
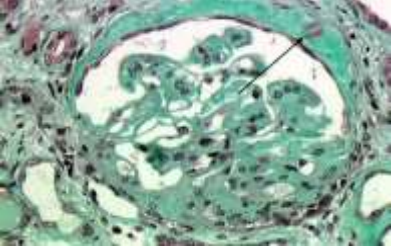


Figure 3. Urine ACR changed significantly ($P < 0.0001$; see Table 3) in the avosentan (av)-treated groups during the first 6 months of the trial. Medians and interquartile ranges are given. Similar differences were found for fractional excretion of urine albumin (see Supplemental Appendix 2).

(Mann et al JASN 2010)



Diabetic Nephropathy

Table 5. Frequency of adverse events relating to fluid overload as reported by the clinical investigators on adverse event forms (not adjudicated)

Signs of Fluid Overload (*n* [%])	Avosentan 25 mg (*n* = 455)	Avosentan 50 mg (*n* = 478)	Placebo (*n* = 459)	*P*	
				Avosentan 25 mg *versus* Placebo	Avosentan 50 mg *versus* Placebo
Peripheral edema	78 (17.1)	80 (16.7)	77 (16.7)	0.706	0.822
Other edema	42 (9.2)	55 (11.5)	25 (5.4)	0.053	0.006
Fluid overload	28 (6.2)	26 (5.4)	5 (1.1)	<0.001	0.001
Dyspnea	31 (6.8)	34 (7.1)	15 (3.3)	0.052	0.197
Acute pulmonary edema	9 (2.0)	8 (1.7)	4 (0.9)	0.286	0.184
CHF	27 (5.9)	18 (3.8)	10 (2.2)	0.003	0.107

Adverse events led to discontinuation of trial medication significantly more often for avosentan than for placebo (19.6 and 18.2 versus 11.5% for placebo), dominated by fluid overload and congestive heart failure; death occurred in

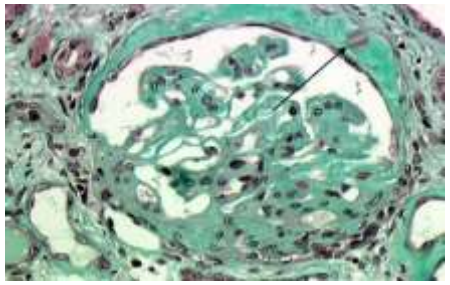
- 21 (4.6%),
- 17 (3.6%;),
- 12 (2.6%)

Avosentan 25 mg/d (n= 455)		Avosentan 50 mg/d (n= 478)		Placebo (n= 459)	
Primary outcome	37	Primary outcome	41	Primary outcome	44
Death	21	Death	17	Death	12
CV outcome	68	CV outcome	71	CV outcome	47
CHF	27	CHF	29	CHF	10
Fluid overload	204	Fluid overload	219	Fluid overload	141

Conclusion

Avosentan reduces albuminuria when added to standard treatment in people with type 2 diabetes and overt nephropathy but induces significant fluid overload and congestive heart failure

(Mann et al JASN 2010)



Diabetic Nephropathy

Prospective randomized, double-blind, placebo-controlled clinical trial
efficacy and safety of atrasentan for the reduction of residual albuminuria in subjects with type 2 DN who were receiving stable doses of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs).

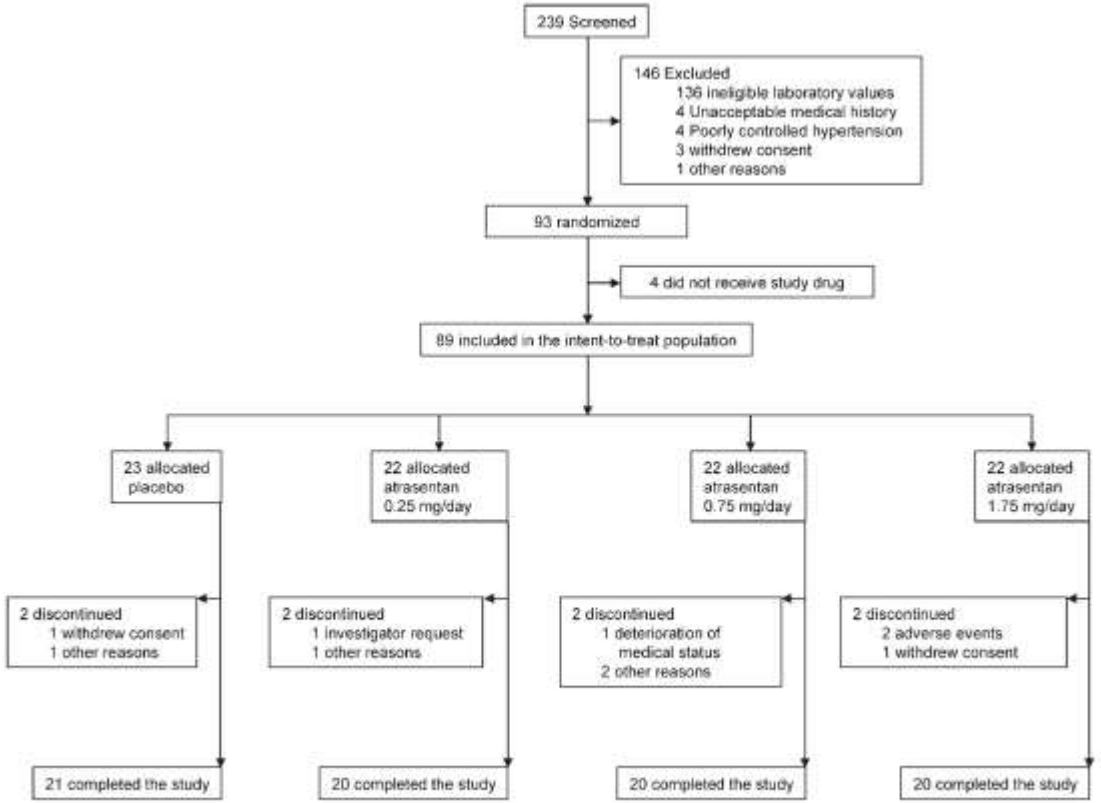


Figure 1. Disposition of subjects during the study. Subjects may have had more than one reason for discontinuation.

eGFR >20 ml/min and a urinary albumin-to-creatinine ratio (UACR) of 100 to 3000 mg/g

placebo

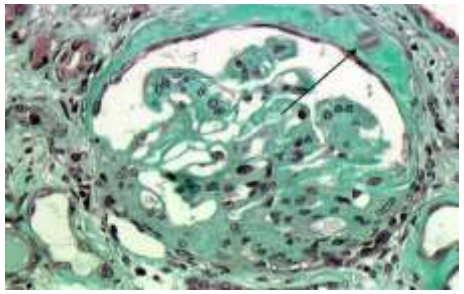
or

atrasentan (0.25, 0.75, or 1.75 mg daily)

for 8 weeks

primary efficacy measure was change from baseline to each post baseline observation in UACR over the course of the treatment period.

(Kohan et al JASN 2011)



Diabetic Nephropathy

Compared with the 11% reduction in the mean of the UACR from baseline to final observation in the placebo group during the study, the mean of UACR decreased by
21, 42, and 35% in the 0.25-, 0.75-, and 1.75-mg atrasentan groups (P = 0.291, P = 0.023, and P = 0.073, respectively

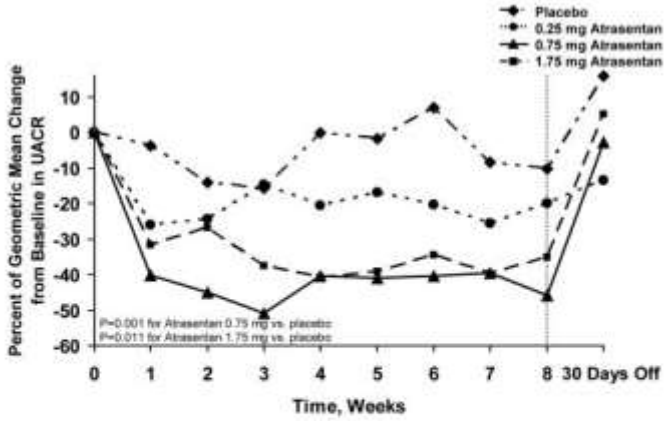


Figure 2. Atrasentan treatment significantly reduces albuminuria. Effect of atrasentan on change in UACR from baseline. Significant reductions in UACR were seen with the 0.75-mg dose ($P = 0.001$ versus placebo by repeated measures analysis) and 1.75-mg dose ($P = 0.011$ versus placebo by repeated-measures analysis). UACR returned toward baseline values after 30 days from drug discontinuation.

In the placebo group, 17% of subjects achieved > 40% reduction in UACR from baseline
compared with
30% , 50 %, and 38% in the 0.25-, 0.75-, and 1.75-mg atrasentan groups, respectively (P = 0.029 for 0.75 mg versus placebo)

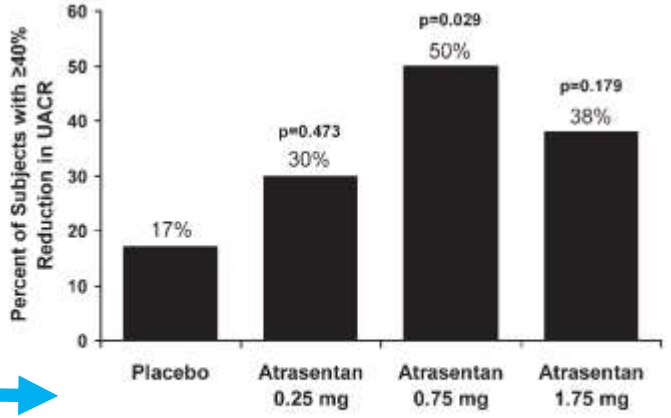


Figure 3. Atrasentan treatment significantly increases the percentage of subjects achieving ≥ 40% reduction in UACR compared to placebo.

(Kohan et al JASN 2011)

Diabetic Nephropathy

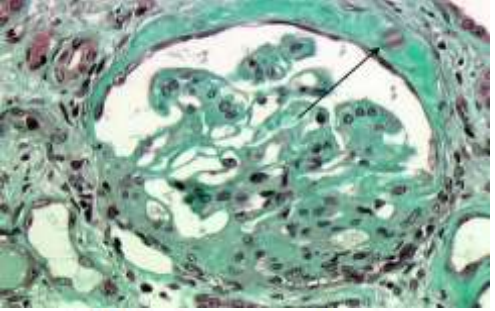


Table 4. Treatment-emergent adverse events in study subjects

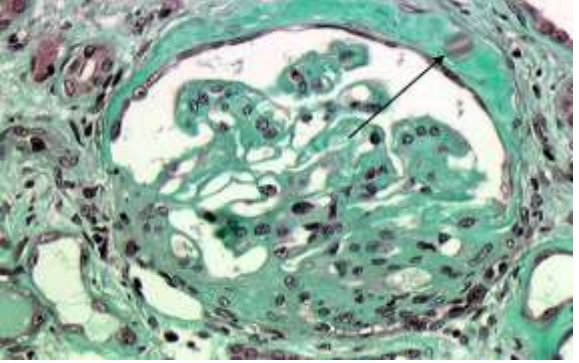
Subjects Experiencing, *N* (%)	Placebo (*n* = 23)	Atrasentan 0.25 mg (*n* = 22)	Atrasentan 0.75 mg (*n* = 22)	Atrasentan 1.75 mg (*n* = 22)
Any adverse event	13 (57%)	16 (73%)	16 (73%)	19 (86%)[a]
Any adverse event at least possibly related to study drug	5 (22%)	8 (36%)	6 (27%)	13 (59%)[b]
Any severe adverse event	0	1 (5%)	0	1 (5%)
Any serious adverse event	0	1 (5%)	3 (14%)	1 (5%)
Any adverse event leading to discontinuation of study drug	0	0	2 (9%)	2 (9%)
Deaths	0	0	0	0
Most commonly reported adverse effects[c]				
peripheral edema	2 (9%)	3 (14%)	4 (18%)	10 (46%)[d]
diarrhea	2 (9%)	1 (5%)	3 (14%)	0
dizziness	0	3 (14%)	2 (9%)	1 (5%)
urinary tract infection	1 (4%)	0	2 (9%)	3 (14%)
headache	0	2 (9%)	1 (5%)	2 (9%)
cough	1 (4%)	1 (5%)	2 (9%)	0
hypertension	1 (4%)	1 (5%)	1 (5%)	1 (5%)
hypoglycemia	0	3 (14%)	0	1 (5%)
hypotension	1 (4%)	0	1 (5%)	2 (9%)

[a] $P = 0.047$ versus placebo.
[b] $P = 0.016$ versus placebo.
[c] Reported in ≥5% of subjects.
[d] $P = 0.007$ versus placebo.

Conclusion

Atrasentan, at the doses tested, safe and effective in reducing residual albuminuria and may ultimately improve renal outcomes in patients with type 2 diabetic nephropathy.

(Kohan et al JASN 2011)



Diabetic Nephropathy

Phase IIB clinical trialrandomized, double blind, parallel-designed, placebo-controlled, 12-week, multicenter studies (ATRASENTAN)

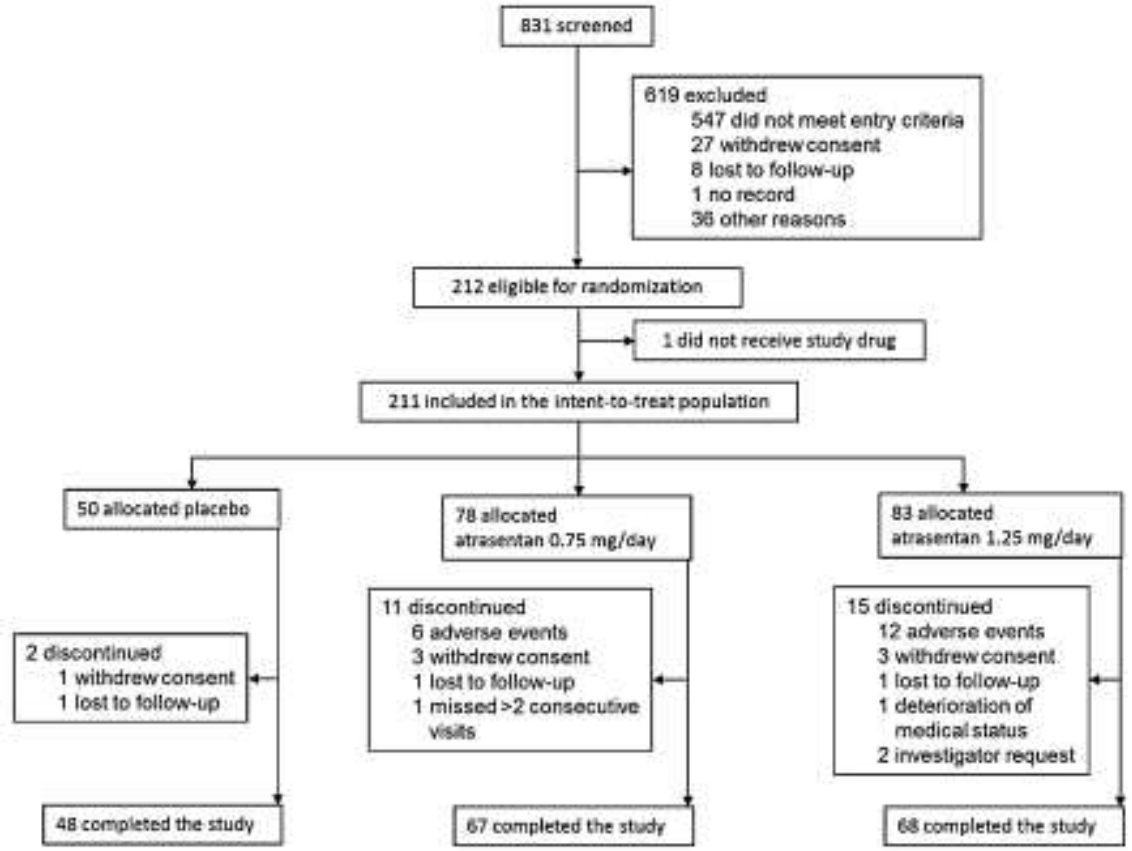


Figure 1. Consolidated Standards of Reporting Trials diagram. This is a summary of the disposition of study participants.

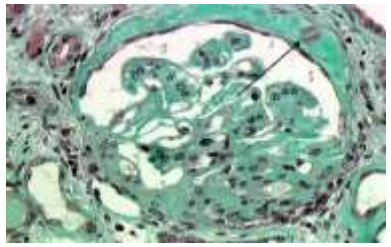
211 patients with type 2 diabetes

urine albumin/creatinine ratios of 300–3500 mg/g
and
eGFRs of 30–75 ml/min per 1.73 m2

placebo (n=50) or to 0.75 mg/d (n=78) or 1.25 mg/d (n=83) atrasentan for 12 weeks

The primary efficacy endpoint was the change from baseline to week UACR.

(De Zeeuw JASN 2014)



Diabetic Nephropathy

Compared with placebo, 0.75 mg and 1.25 mg atrasentan reduced

- urine albumin/ creatinine ratios by an average of 35% and 38%
- albuminuria > 30% in 51% and 55% of participants, respectively.
- eGFR measurements did not change

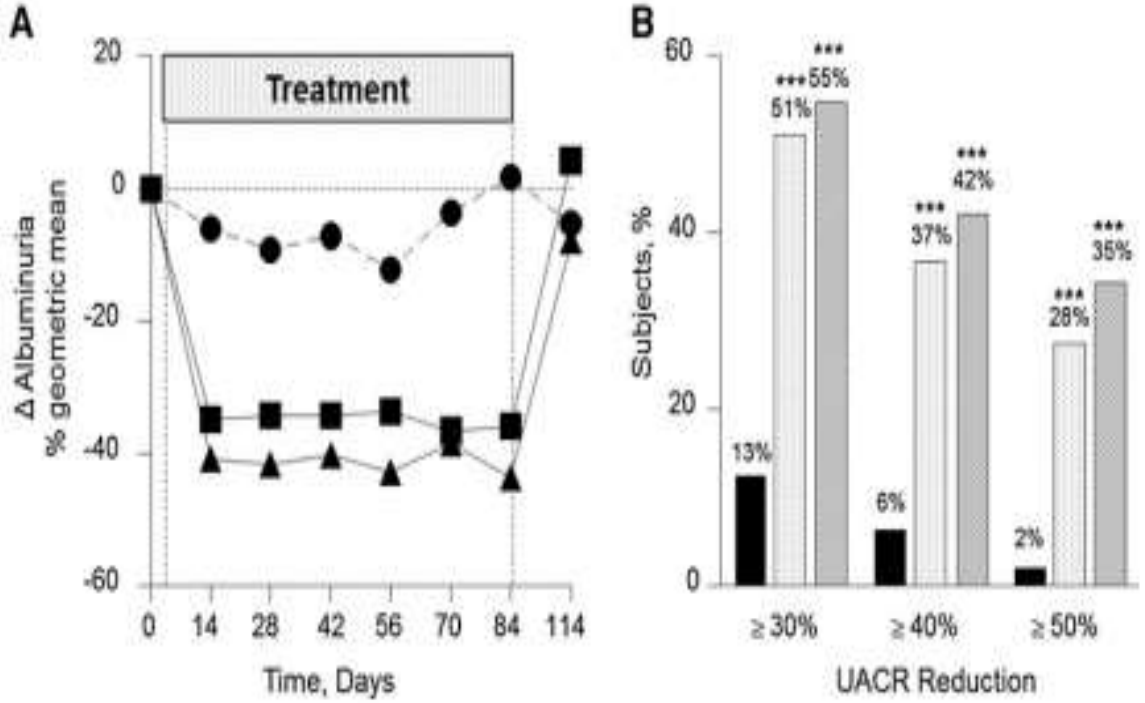
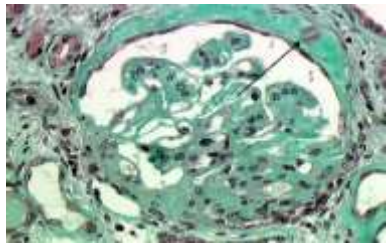
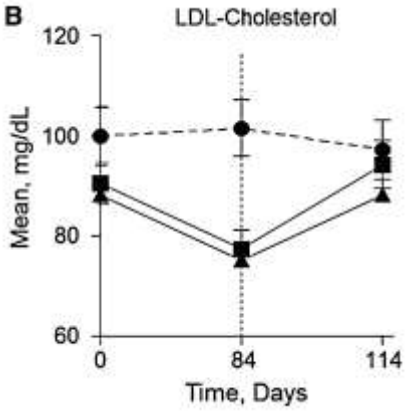


Figure 2. Atrasentan treatment significantly decreases albuminuria. (A) UACR change in the percent geometric mean from baseline to recovery for the placebo (●), 0.75 mg/d atrasentan (■), and 1.25 mg/d atrasentan (▲) groups. (B) Degree of UACR reduction from baseline to final in the placebo (squares), 0.75 mg/d atrasentan (open bars), and 1.25 mg/d atrasentan (filled bars) groups. ***$P<0.001$.

(De Zeeuw JASN 2014)

Diabetic Nephropathy





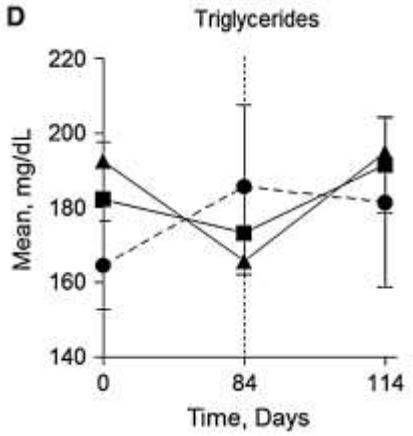
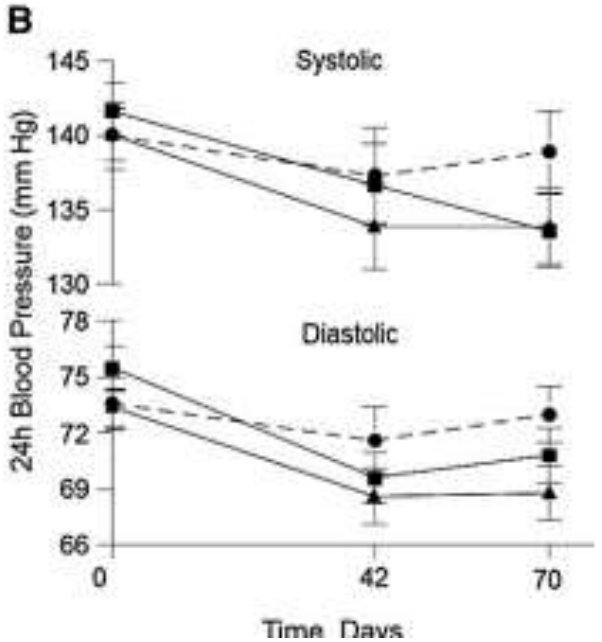


Figure 4. Atrasentan treatment exerts lipid-lowering effects. Mean changes in total cholesterol (A), LDL cholesterol (B), HDL cholesterol (C), and triglycerides (D) after placebo (●), 0.75 mg/d atrasentan (■), and 1.25 mg/d atrasentan (▲) treatment for 12 weeks and after recovery.

24-hour systolic and diastolic BP
LDL cholesterol,
triglyceride levels

decreased significantly in both treatment groups

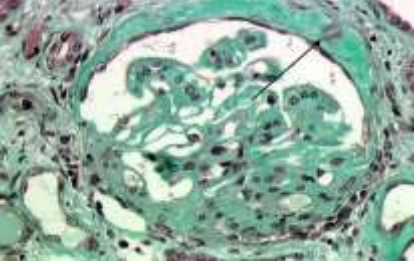


After stopping atrasentan for 30 days
measured parameters returned to pretreatment levels

Conclusion

Atrasentan reduced albuminuria and improved BP and lipid spectrum with manageable fluid overload–related adverse events in patients with type 2 diabetic nephropathy receiving RAS inhibitors

(De Zeeuw JASN 2014)



Diabetic Nephropathy

Atrasentan and renal events in patients with type 2 diabetes and chronic kidney disease (SONAR): a double-blind randomised, placebo-controlled trial

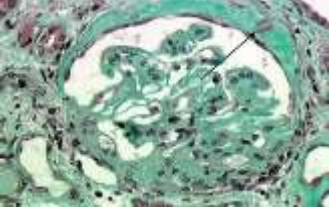
- 18–85 years with
- type 2 diabetes,
- estimated glomerular filtration rate (eGFR) 25–75 mL/min
- a urine albumin-to-creatinine ratio (UACR) of 300–5000 mg/g
- who had received maximum labelled or tolerated renin–angiotensin system inhibition for at least 4 weeks

Participants were given atrasentan 0·75 mg orally daily during an enrichment period before random group assignment.

Those with a UACR decrease of at least 30% with no substantial fluid retention during the enrichment period (responders) were included in the double-blind treatment period

The primary endpoint was a composite of doubling of serum creatinine (sustained for ≥30 days) or end-stage kidney disease at 42 months

(Heerspink Lancet 2019)



Diabetic Nephropathy

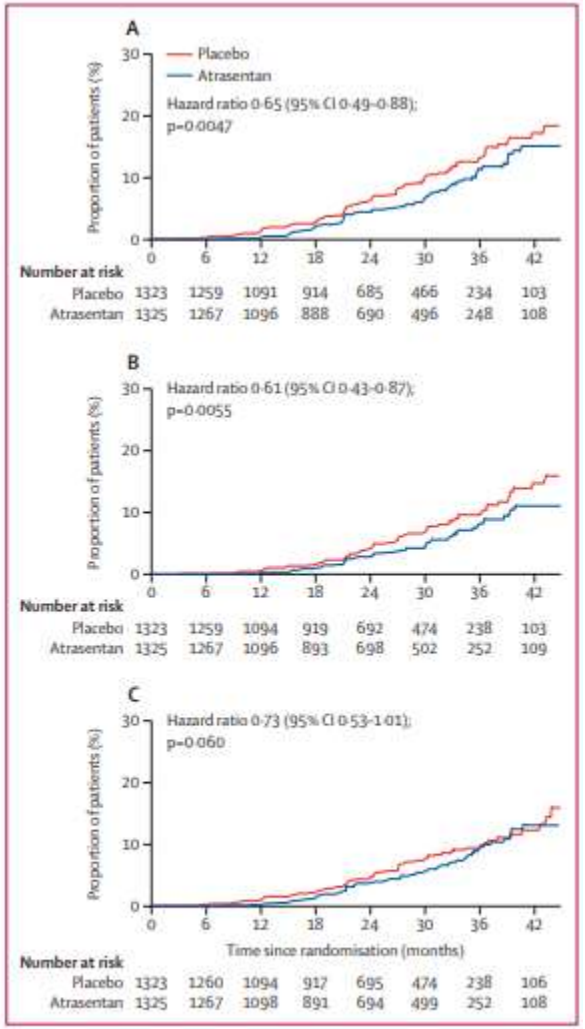
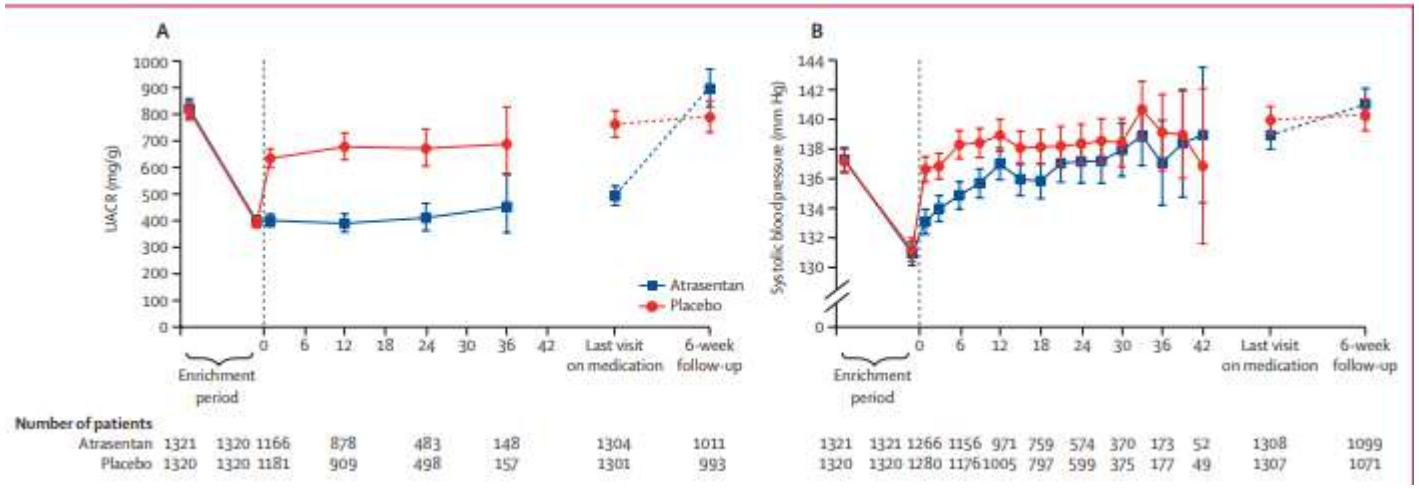


Figure 3: **Effects of atrasentan on the primary composite renal outcome and its components in responders**

Composite primary renal outcome (A), doubling of serum creatinine (B), and end-stage kidney disease (C) in the intention-to-treat population of responders. Calculated by Cox proportional hazard regression models.

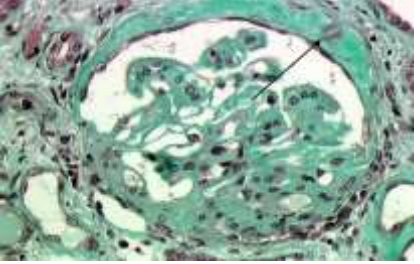


11 087 patients were screened; 5117 entered the enrichment period, 2648 patients were responders and were randomly assigned to the atrasentan group (n=1325) or placebo group (n=1323)

Median follow-up was 2·2 years

79 (6·0%) of 1325 patients in the atrasentan group and 105 (7·9%) of 1323 in the placebo group had a primary composite renal endpoint event (hazard ratio [HR] 0·65 p=0·0047)

(Heerspink Lancet 2019)



Diabetic Nephropathy

	Atrasentan (n=1321)	Placebo (n=1320)	p value*
Any serious adverse event	479 (36·3%)	430 (32·6%)	0·049
Adverse events leading to discontinuation	137 (10·4%)	122 (9·2%)	0·360
Deaths	58 (4·4%)	52 (3·9%)	0·630
Treatment-emergent adverse events of interest			
Hypervolaemia or fluid retention	483 (36·6%)	426 (32·3%)	0·022
Cardiac failure†	72 (5·5%)	51 (3·9%)	0·064
Anaemia	244 (18·5%)	136 (10·3%)	<0·0001
Vasodilation	126 (9·5%)	118 (8·9%)	0·638
Cardiac toxicity	147 (11·1%)	130 (9·8%)	0·310
Serious adverse events (>1% in either group)			
Acute kidney injury	32 (2·4%)	28 (2·1%)	0·696
Pneumonia	32 (2·4%)	22 (1·7%)	0·216
Congestive cardiac failure	23 (1·7%)	15 (1·1%)	0·252
Acute myocardial infarction	21 (1·6%)	21 (1·6%)	1·0
Coronary artery disease	18 (1·4%)	17 (1·3%)	1·0
Anaemia	16 (1·2%)	10 (0·8%)	0·325
Hypoglycaemia	14 (1·1%)	8 (0·6%)	0·284
Urinary tract infection	16 (1·2%)	7 (0·5%)	0·092
Cardiac failure	13 (1·0%)	8 (0·6%)	0·381
Cataract	16 (1·2%)	8 (0·6%)	0·150
Hyperkalaemia	13 (1·0%)	13 (1·0%)	1·0

Data are n (%). *Fisher's exact test. †Cardiac failure events included all investigator-reported treatment-emergent adverse events.

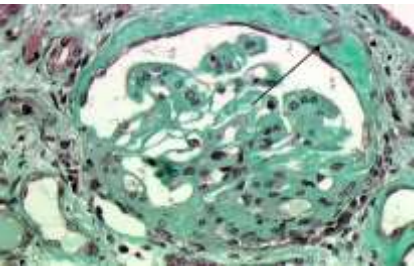
Table 3: **Adverse events during double-blind treatment period**

Fluid retention and anaemia adverse events, were more frequent in the atrasentan group than
in the placebo group

Conclusion

Patients with type 2 diabetes and CKD selected for a substantial UACR reduction and minimal clinical signs of sodium retention during short-term treatment with atrasentan had a significantly lower risk of doubling of serum creatinine or end-stage kidney disease during long-term treatment with this endothelin receptor antagonist compared with placebo.

(Heerspink Lancet 2019)



Diabetic Nephropathy

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META-ANALYSIS

Endothelin receptor antagonists for the treatment of diabetic nephropathy: A meta-analysis and systematic review

Li Zhang, Shuai Xue, Jie Hou, Guang Chen, Zhong-Gao Xu

The inclusion criteria were as follows:

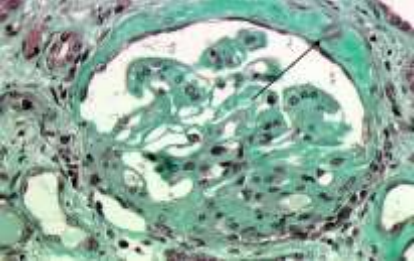
(1) Patients 18 to 85 years old;

(2) Diagnosed with DM for at least 4 wk;

(3) Albuminuria: urinary albumin-to-creatinine ratio (UACR) > 3 mg/mmoL

(4) Measured eGFR > 15 mL/min per 1.73 m2 or serum creatinine (sCr) < 3 mg/dL.

(Zhang World Journal of Diabetes 2020)



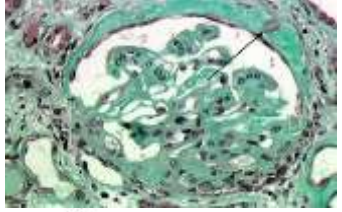
Diabetic Nephropathy

The present meta-analysis included a total of 5271 participants (3331 and 1940 in the experimental and control groups, respectively)

Table 1 Baseline characteristics of included studies

Ref.	Patients No.	Interventions (dose/d)	Treatment period (wk)	Age mean (SD)	Sex, *n* (%) female	eGFR [mean (SD) mL/min/1.73 m²]	UACR, mg/g creatinine median (Q1 to Q3) or mean (SD)	SBP, mmHg mean (SD)	DBP, mmHg mean (SD)	Hemoglobin A1c, % mean (SD)	Study type	NCT number
Heerspink *et al*[12], 2019	2648	Atrasentan 0.75 mg	53 mo? (follow-up 2.2 years)	I: 64.8 (8.6)	25%	44.0 (13.7)	792 (462-1480)	136.5 (15.2)	75.0 (9.9)	7.8 (1.5)	RCT	NCT01858532
				C: 64.7 (8.7)	26.60%	43.7 (13.7)	805 (444-1451)	136.2 (14.8)	74.8 (10.0)	7.8 (1.5)		
Kohan *et al*[7], 2011	89	Atrasentan 0.25 mg, 0.75 mg, 1.75 mg	8	I: 63 (12) 67 (9) 64 (13)	41% 36% 27%	31 (4) 34 (6) 33 (5)	350 (194-1226) 360 (209-726) 433 (157-998)	134 (14) 137 (15) 135 (11)	75 (8) 74 (8) 75 (9)	7.6 (1.0) 7.6 (1.2) 7.3 (1.1)	RCT	N/A
				C: 61 (8)	17%	34 (5)	515 (170-1477)	138 (14)	78 (8)	7.4 (0.9)		
Mann *et al*[8], 2010	1392	Avosentan 25, 50 mg	48	I: 61.2 (8.8) 61.0 (9.1)	30.8% 32.8%	29.9 (6.2) 30.4 (6.5)	1422 (728.9-2425.3) 1472 (758.5-2515)	137.1 (13.8) 137.0 (14.3)	77.9 (9.2) 77.5 (8.6)	8.0 (1.5) 8.1 (1.6)	RCT	NCT00120328
				C: 60.8 (8.9)	33.80%	30.1 (6.2)	1531 (794.3-2823.9)	135.4 (15.1)	77.2 (9.5)	8.0 (1.5)		
Rafnsson *et al*[13], 2011	28	Bosentan 250 mg	4	I: 62 (8)	18.00%	28.9 (7.4)	415 (681.6)	149 (24)	81 (10)	7.4 (1.1)	RCT	NCT01357109
				C: 63 (9)	20.80%	31.5 (4.0)	409 (512.7)	151 (25)	78 (9)	8.0 (1.4)		
Wenzel *et al*[14], 2009	286	Avosentan 5, 10, 25, and 50 mg	12	I: 60.8 (10.0) 58.4 (10.0)	34% 30%	31.3 (7.0) 32.2 (5.0)	N/A	N/A	N/A	N/A	RCT	N/A
				C: 58.4 (10.0)	13%	30.5 (5.0)	N/A	N/A	N/A	N/A		
Zeeuw *et al*[9], 2014	211	Atrasentan 0.75 mg or 1.25 mg	12	I: 65.0 (9.8) 64.5 (8.8)	N/A	N/A	878 (515-1682) 826 (481-1389)	138 (14) 136 (15)	75 (10) 74 (9)	7.5 (1.5) 7.7 (1.4)	RCT	NCT01356849 NCT01424319
				C: 64.3 (9.0)	N/A	N/A	671 (410-1536)	136 (14)	72 (10)	7.4 (1.3)		

(Zhang World Journal of Diabetes 2020)



Diabetic Nephropathy

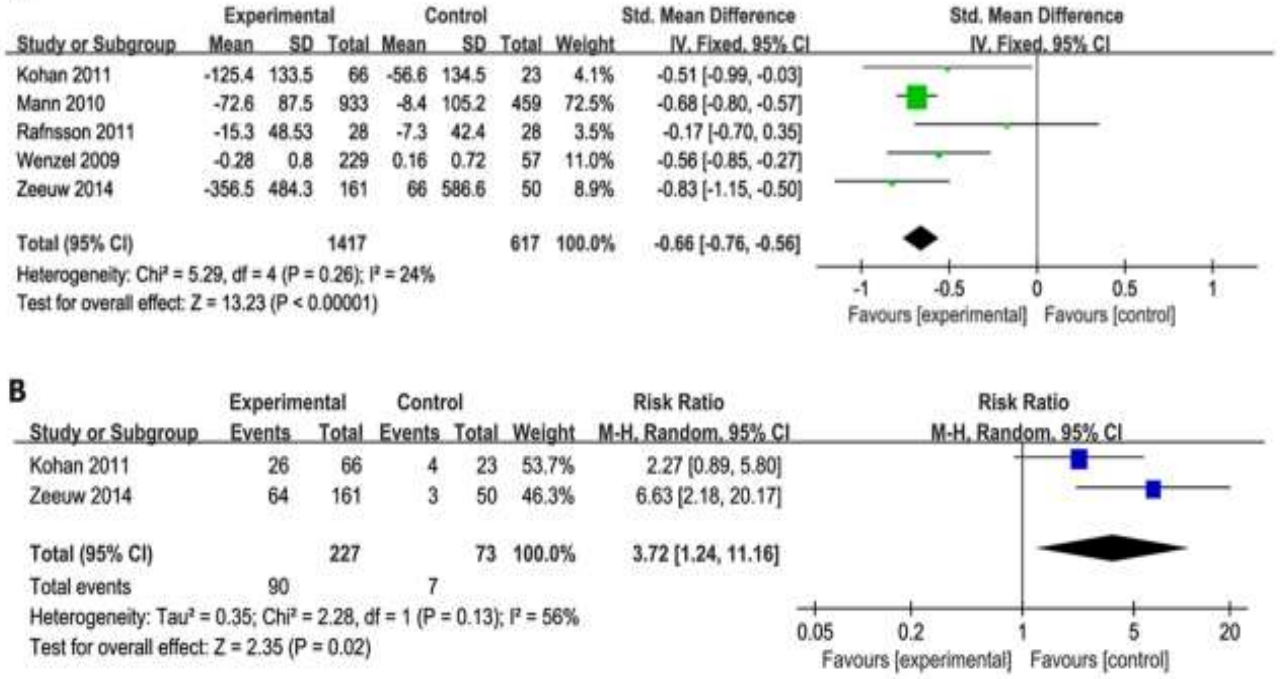


Figure 3 Forest plot of comparisons of the risk ratio between experimental and control groups. A: In terms of the urinary albumin-to-creatinine ratio (UACR)/urinary albumin ejection rate changes from baseline; B: In terms of the 40% reduction in UACR. SD: Standard deviation.

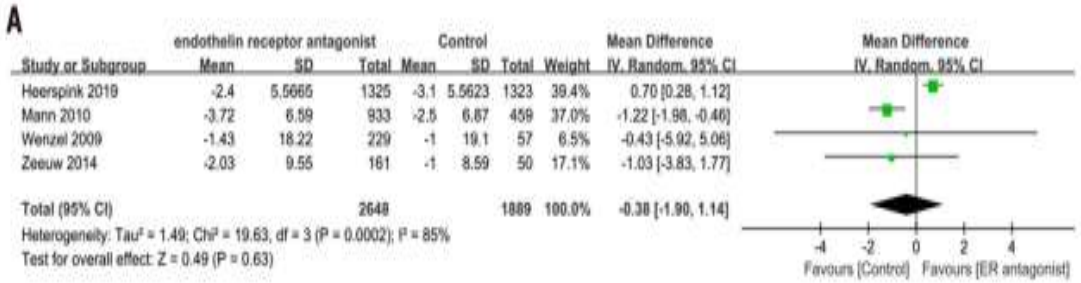


Figure 4 Forest plot of comparisons between experimental and control groups. A: In terms of the estimated glomerular filtration rate change from baseline; B: In terms of the ratio of serum creatinine doubling; C: In terms of the onset of end-stage renal. SD: Standard deviation.

No significant difference in eGFR change from baseline between the experimental and control groups
(P = 0.63)

No significant difference in AEs (P = 0.08) and mortality (P = 0.23)
However, the intervention group had a higher incidence of SAEs than the control group (P = 0.0009)

Conclusion ER antagonists group showed a significantly greater reduction in albuminuria and more patients with 40% reduction in urinary albumin-to-creatinine ratio than the control group (P < 0.0001 and P = 0.02, respectively)

(Zhang World Journal of Diabetes 2020)

Chronic kidney disease

Zibotentan in combination with dapagliflozin compared with dapagliflozin in patients with chronic kidney disease (ZENITH-CKD): a multicentre, randomised, active-controlled, phase 2b, clinical trial

Adults (≥18 to ≤90 years) with an estimated GFR (eGFR) > 20 mL/min and a urinary albumin-to-creatinine ratio (UACR) of 150–5000 mg/g

were randomly assigned (2:1:2) to 12 weeks of daily treatment with

- zibotentan 1·5 mg plus dapagliflozin 10 mg
- zibotentan 0·25 mg plus dapagliflozin 10 mg
- dapagliflozin 10 mg plus placebo

The primary endpoint was a change from baseline UACR (zibotentan 1·5 mg plus dapagliflozin vs dapagliflozin plus placebo) at week 12

(Heerspink Lancet 2023)

Chronic kidney disease

1492 participants
For the main analysis, 449 (30%) participants,

- mean age 62·8 years ,
- 138 [31%] female,
- 305 [68%] White,
- mean eGFR 46·7 mL/min
- median UACR 565·5 mg/g

received treatment with

- ➢ zibotentan 1·5 mg plus dapagliflozin (n=179 [40%]),
- ➢ zibotentan 0·25 mg plus dapagliflozin (n=91 [20%])
- ➢ or dapagliflozin plus placebo (n=177 [40%]).

Type 2 DB 59 % 57% 58%

	Dapagliflozin 10 mg plus placebo (n=177)	Zibotentan 0·25 mg plus dapagliflozin 10 mg (n=91)	Zibotentan 1·5 mg plus dapagliflozin 10 mg (n=179)
Age, years	63·6 (11·60)	61·3 (12·72)	62·7 (12·33)
Sex			
Female	55 (31%)	28 (31%)	55 (31%)
Male	122 (69%)	63 (69%)	124 (69%)
Race			
White	125 (71%)	56 (62%)	124 (69%)
Black or African American	22 (12%)	7 (8%)	17 (9%)
Asian	26 (15%)	18 (20%)	26 (15%)
Other	4 (2%)	10 (11%)	10 (6%)
Weight, kg	85·5 (18·2)	83·8 (16·5)	85·9 (16·9)
BMI, kg/m²	30·2 (5·4)	29·6 (5·0)	30·1 (5·0)
Current nicotine user	25 (14%)	12 (13%)	22 (12%)
Blood pressure, mm Hg			
Systolic	137·6 (17·6)	136·5 (17·8)	136·4 (16·1)
Diastolic	79·9 (9·8)	79·6 (10·5)	78·9 (9·4)
eGFR, mL/min per 1·73 m²	45·2 (20·7)	48·4 (23·5)	47·4 (23·4)
eGFR ≥60	32 (18%)	22 (24%)	45 (25%)
eGFR 45 to <60	41 (23%)	19 (21%)	27 (15%)
eGFR 30 to <45	62 (35%)	28 (31%)	61 (34%)
eGFR <30	42 (24%)	22 (24%)	46 (26%)
Haemoglobin, g/L	132·0 (16·7)	131·7 (16·5)	130·3 (16·2)
Serum potassium, mmol/L	4·60 (0·46)	4·64 (0·48)	4·64 (0·52)
Median UACR	577·0 (279·5–1150·6)	526·7 (212·1–1287·0)	566·8 (235·6–1202·7)
UACR >1000, mg/g	58 (33%)	32 (35%)	55 (31%)
Type 2 diabetes	105 (59%)	52 (57%)	104 (58%)
Chronic kidney disease cause			
Cystic kidney disease	1 (<1%)	0	3 (2%)
Type 2 diabetes and chronic kidney disease	93 (53%)	44 (48%)	88 (49%)
Ischaemic or hypertensive nephropathy	32 (18%)	20 (22%)	30 (17%)
Chronic glomerulonephritis	20 (11%)	10 (11%)	25 (14%)
IgA nephropathy	7 (4%)	4 (4%)	8 (4%)
Other	13 (7%)	6 (7%)	17 (9%)
Unknown	13 (7%)	11 (12%)	19 (11%)
Other	17 (10%)	6 (7%)	14 (8%)

(Heerspink Lancet 2023)

Chronic kidney disease

The effect of zibotentan plus dapagliflozin compared with dapagliflozin plus placebo in reducing UACR was consistent across subgroups defined by baseline type 2 diabetes status and eGFR level

At week 12, the difference in UACR versus dapagliflozin plus placebo was

–33·7% p<0·0001) for zibotentan 1·5 mg plus dapagliflozin and

–27·0% (90% CI –38·4 to –13·6;
p=0·0022) for zibotentan 0·25 mg plus dapagliflozin

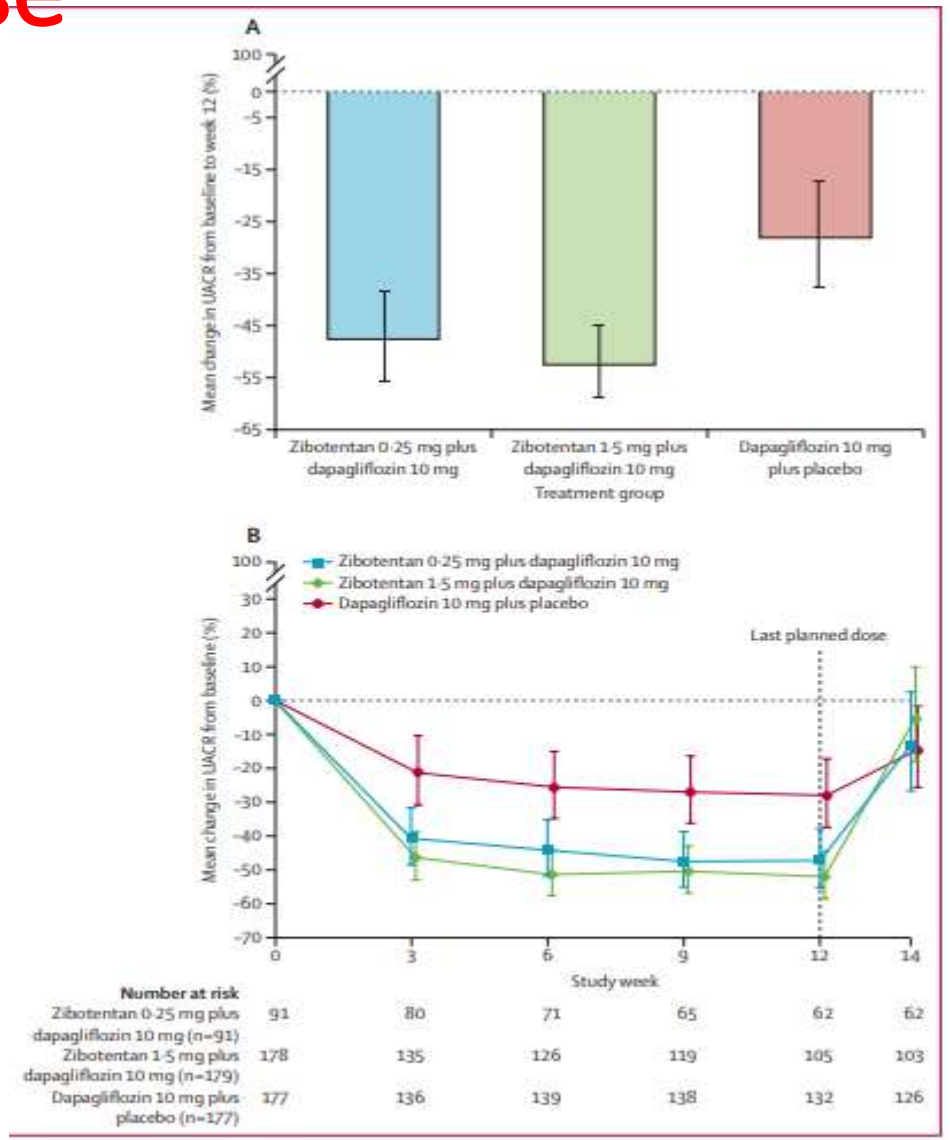
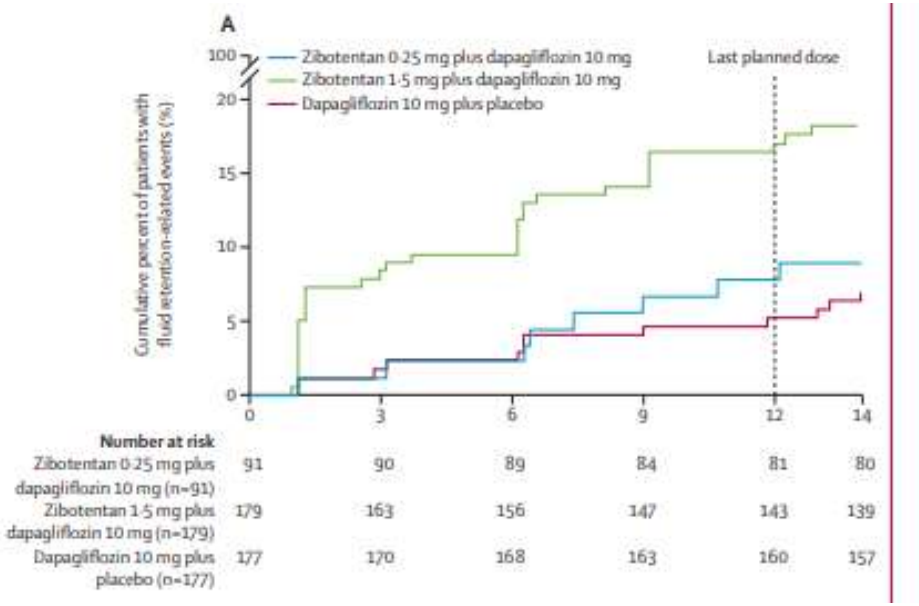
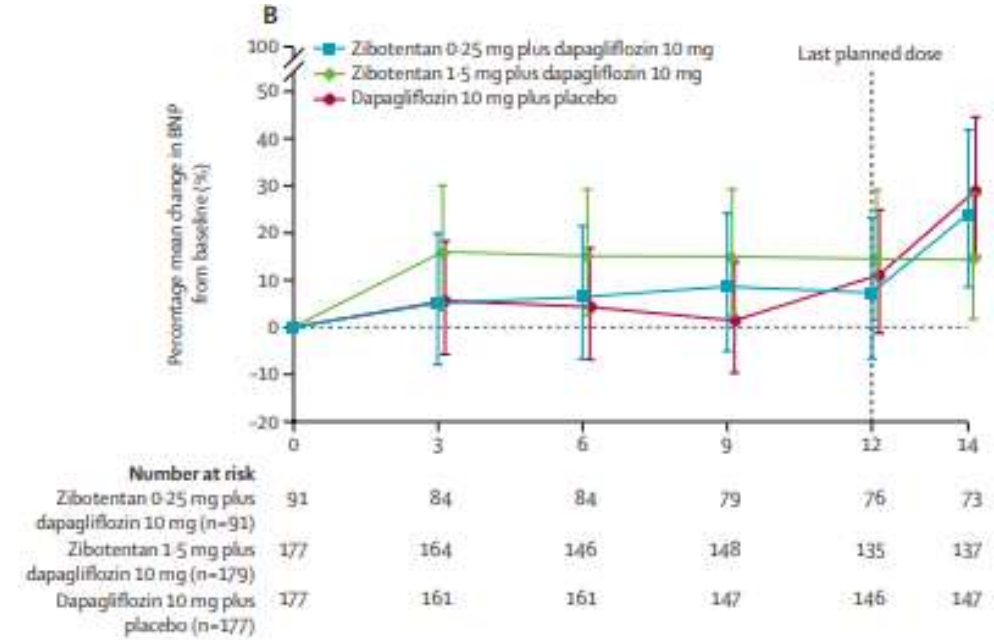


Figure 2: Mean change in UACR
(A) Bar graph of the percentage mean change in UACR from baseline to week 12 in the dapagliflozin 10 mg plus placebo, zibotentan 1·5 mg plus dapagliflozin 10 mg, and zibotentan 0·25 mg plus dapagliflozin 10 mg groups. (B) UACR trajectory over time in the three treatment groups. Vertical bars indicate the 90% CIs of the mean at given timepoints. UACR=urinary albumin-to-creatinine ratio.

(Heerspink Lancet 2023)

Chronic kidney disease





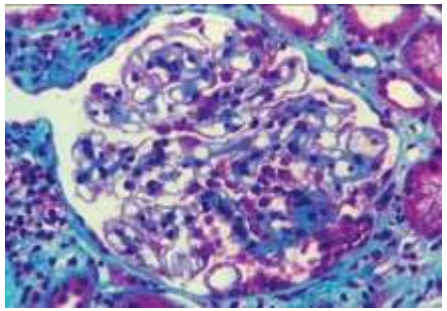
Fluid-retention events were observed in

- 33 (18%) of 179 participants in the zibotentan 1·5 mg plus dapagliflozin group,
- 8 (9%) of 91 in the zibotentan 0·25 mg plus dapagliflozin group,
- 14 (8%) of 177 in the dapagliflozin plus placebo group

Conclusion

Combined treatment with low-dose zibotentan and dapagliflozin yielded a robust and significant reduction in albuminuria, with an acceptable safety profile when compared with placebo combined with dapagliflozin.

(Heerspink Lancet 2023)



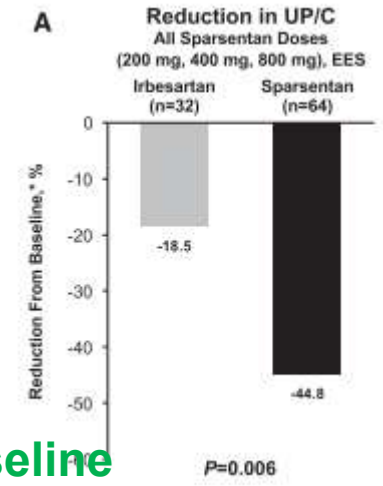
FSGS

In this phase 2, randomized, double-blind, active-control Efficacy and Safety of Sparsentan (RE-021), a Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients with Focal Segmental Glomerulosclerosis (FSGS): DUET study

Patients aged 8–75 years with biopsy-proven FSGS, eGFR >30 ml/min, and urinary protein-to-creatinine ratio (UP/C) >1.0 g/g received sparsentan (200, 400, or 800 mg/d) or irbesartan (300 mg/d) for 8 weeks,

Table 1. Baseline demographics and characteristics (FAS)

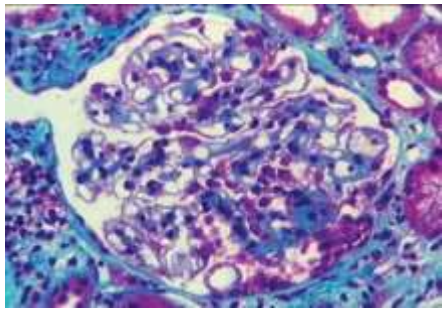
Characteristics	Irbesartan (*n*=36)	Sparsentan, All D (*n*=73)
Age, *n* (%)		
Pediatric, ≥8 to ≤18 yr	10 (28)	13 (18)
Adult, >18–75 yr	26 (72)	60 (82)
Sex, *n* (%)		
Female	17 (47)	32 (44)
Male	19 (53)	41 (56)
Race, *n* (%)		
Asian	1 (3)	5 (7)
Black	7 (19)	8 (11)
White	26 (72)	57 (78)
Other	2 (6)	3 (4)
Ethnicity, *n* (%)		
Hispanic/Latino	6 (17)	14 (19)
Non-Hispanic/non-Latino	30 (83)	59 (81)
Body mass index, kg/m^2, mean (SD)	28.7 (6.4)	28.4 (6.1)
Immunosuppression at baseline, *n* (%)	13 (36)	21 (29)
eGFR, ml/min per 1.73 m^2, mean (SD)	74.5 (44.7)	74.4 (37.3)
UP/C ratio, g/g, median (range)	3.12 (0.9–10.7)	3.61 (0.4–18.7)
ACE inhibitor or ARB use before washout, *n* (%)	32 (89)	59 (81)
Use of ≥1 diuretic/antihypertensive agent, *n* (%)	20 (56)	40 (55)
Diuretics	9 (25)	26 (36)
Additional antihypertensive treatments	16 (44)	29 (40)



Conclusion Sparsentan-treated patients had greater reductions in UP/C than irbesartan-treated patients did when all doses (45% versus 19%; P=0.006) or the 400 and 800 mg doses (47% versus 19%; P=0.01)

The primary endpoint was a change from baseline UACR sparsentan vs placebo) at week 8

(Trachtman H JASN 2018)



FSGS

Longer-term efficacy and safety outcomes from a 108-week, randomized, phase 3 clinical trial that compared sparsentan with the active control irbesartan in patients with FSGS DUPLEX study

Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

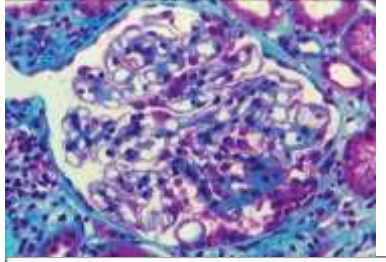
Characteristic	Sparsentan (N=184)	Irbesartan (N=187)
Age		
Mean — yr	41.7±16.5	41.5±17.3
Range — yr	9–74	9–75
<18 yr — no. (%)	16 (8.7)	19 (10.2)
Median time from FSGS diagnosis to informed consent (IQR) — yr	2 (1–6.5)	3 (1–6)
Male sex — no. (%)	101 (54.9)	99 (52.9)
Hispanic or Latino ethnic group — no. (%)†	34 (18.5)	44 (23.5)
Race — no. (%)†		
Asian	23 (12.5)	28 (15.0)
Black	17 (9.2)	12 (6.4)
White	137 (74.5)	138 (73.8)
Other	10 (5.4)	13 (7.0)
eGFR — ml/min/1.73 m²‡	63.3±28.6	64.1±31.7
Median urinary protein-to-creatinine ratio (IQR)§	3.1 (2.3–4.5)	3.0 (2.1–4.7)
Blood pressure — mm Hg		
Systolic	133±15	131±15
Diastolic	86±11	82±10
Serum albumin level — g/liter	34.9±7.4	34.9±7.5
Blood potassium level — mmol/liter	4.32±0.46	4.31±0.44
Documented history of nephrotic syndrome — no. (%)¶	55 (29.9)	62 (33.2)
FSGS-associated genetic variants — no./total no. (%)‖		
Monogenic variants in podocyte structure or function proteins**	15/173 (8.7)	18/179 (10.1)
COL4A3–5 variants	12/173 (6.9)	15/179 (8.4)
High-risk *APOL1* variants	9/173 (5.2)	5/179 (2.8)
Previous use of renin–angiotensin–aldosterone system inhibitors — no. (%)††	152 (82.6)	143 (76.5)
Use of immunosuppressive agents for renal indications at baseline — no. (%)‡‡	50 (27.2)	46 (24.6)
Use of diuretics at baseline — no. (%)‡‡	68 (37.0)	73 (39.0)
Moderate or severe edema — no. (%)	9 (4.9)	6 (3.2)

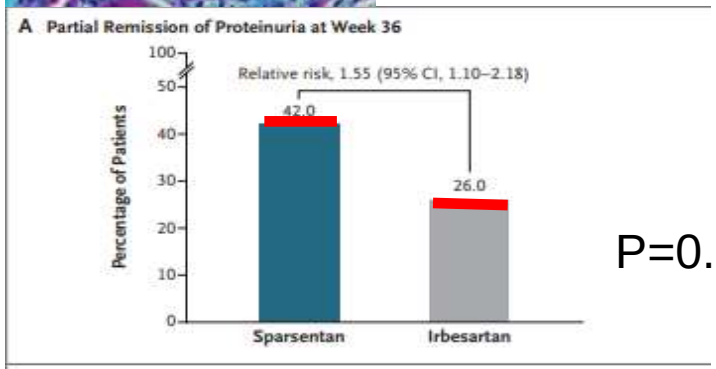
The surrogate efficacy end point assessed at the prespecified interim analysis at 36 weeks was the FSGS partial remission of proteinuria end point (defined as a urinary protein-to-creatinine ratio of ≤1.5 [with protein and creatinine both measured in grams] and a >40% reduction in the ratio from baseline)

Primary efficacy end point was the estimated glomerular filtration rate (eGFR) slope at the time of the final analysis W112

(Rheault MN NEJM 2023)

FSGS





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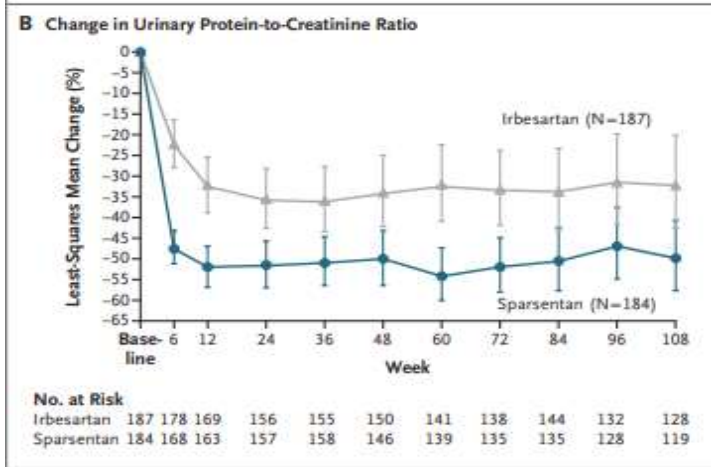


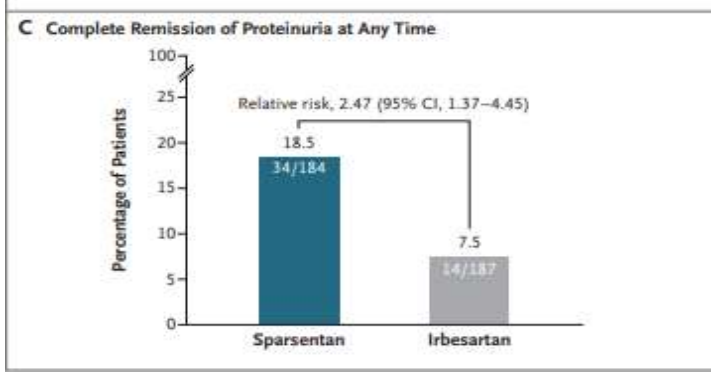


Table 2. The eGFR Slope and Change in eGFR.

Variable	Sparsentan (N=184)	Irbesartan (N=187)	Difference	P Value
Least-squares mean eGFR slope (95% CI) — ml/min/1.73 m²/yr				
eGFR total slope*	−5.4 (−6.9 to −3.9)	−5.7 (−7.2 to −4.3)	0.3 (−1.7 to 2.4)	0.75
eGFR chronic slope†	−4.8 (−6.3 to −3.3)	−5.7 (−7.2 to −4.2)	0.9 (−1.3 to 3.0)	0.42
Least-squares mean change in eGFR from baseline to week 112 (95% CI) — ml/min/1.73 m²‡	−10.4 (−12.6 to −8.1)	−12.1 (−14.4 to −9.9)	1.8 (−1.4 to 4.9)	

* The eGFR total slope was the slope from day 1 to week 108.
† The eGFR chronic slope was the slope from week 6 to week 108.

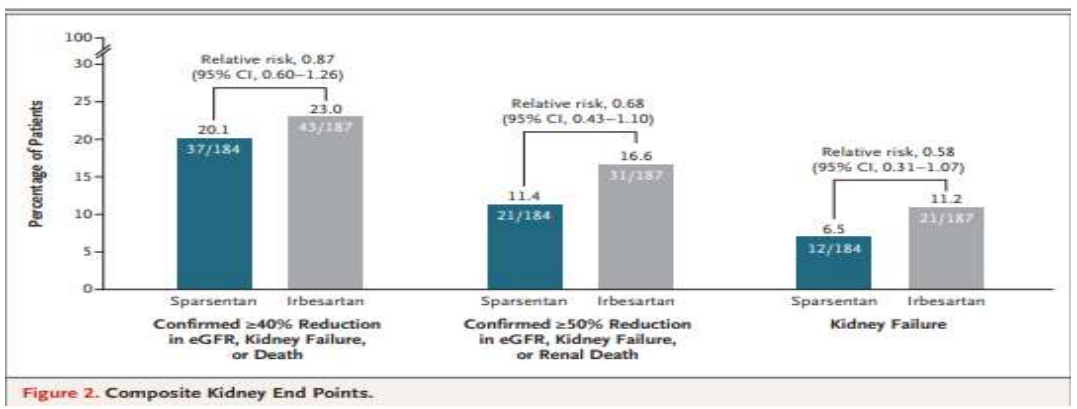
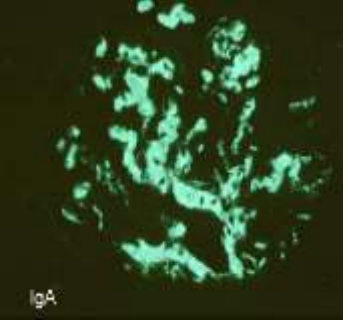


Figure 2. Composite Kidney End Points.

Conclusion no significant between-group differences in eGFR slope at 108 weeks, despite a greater reduction in proteinuria with sparsentan than with irbesartan

(Rheault MN NEJM 2023)



IgA Nephropathy

Randomized, double-blind, active-control Efficacy and Safety of Sparsentan a Dual Endothelin Receptor and Angiotensin Receptor Blocker, in Patients with IgA N

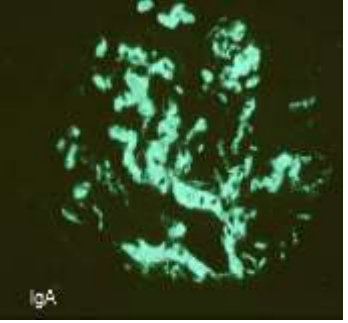
- ≥ 18 ans
- Biopsy proven IgAN
- Proteinuria ≥ 1,0 g/24h
- eGFR ≥ 30 ml/min
- SBP≤ 150 mm Hg
- DBP ≤ 100 mm Hg
- Despite meximised renin angiotensin system inhibitor for at least 12 Weeks

Primary efficacy end point of prespecified interim analysis = primary proteinuria efficacy end point at 36 Weeks

	Sparsentan (n=202)	Irbesartan (n=202)
Age at informed consent, years	46·6 (12·8)	45·4 (12·1)
Sex	400 mg	300 mg
Male	139 (69%)	143 (71%)
Female	63 (31%)	59 (29%)
Race*		
Asian	67 (33%)	49 (24%)
Black or African American	1 (<1%)	3 (1%)
White	130 (64%)	142 (70%)
Other	4 (2%)	9 (4%)
Ethnicity†		
Hispanic or Latino	17 (8%)	16 (8%)
Not Hispanic or Latino	185 (92%)	186 (92%)
Age at IgA nephropathy diagnosis, years‡	40·2 (13·4)	39·0 (12·4)
Time from initial kidney biopsy to informed consent, years§	6·4 (6·5)	6·4 (7·1)
History of hypertension	144 (71%)	140 (69%)
Blood pressure, mm Hg		
Systolic	128 (14·4)	130 (12·4)
Diastolic	82 (10·6)	83 (10·6)
Urine protein–creatinine ratio, g/g	1·3 (0·8–1·8)	1·2 (0·9–1·7)
Urinary protein excretion, g/day	1·8 (1·2–2·8)	1·8 (1·3–2·6)
Urine albumin–creatinine ratio, g/g	1·0 (0·7–1·5)	1·1 (0·7–1·5)
eGFR, mL/min per 1·73 m²¶	56·9 (24·4)	57·1 (23·6)
eGFR category		
≥90 mL/min per 1·73 m²	26 (13%)	25 (12%)
≥60 to <90 mL/min per 1·73 m²	49 (24%)	48 (24%)
≥45 to <60 mL/min per 1·73 m²	45 (22%)	49 (24%)
≥30 to <45 mL/min per 1·73 m²	67 (33%)	75 (37%)
≥15 to <30 mL/min per 1·73 m²	15 (7%)	5 (2%)
Serum albumin, g/L	41·2 (3·9)	41·7 (3·8)
ACE inhibitor or ARB at maximum labelled dose at screening‖	131 (65%)	125 (62%)
Baseline concomitant medication use**		
Antihypertensive medications††	88 (44%)	83 (41%)
Lipid-lowering medications	112 (55%)	111 (55%)

(Heerspink Lancet 2023)

IgA Nephropathy



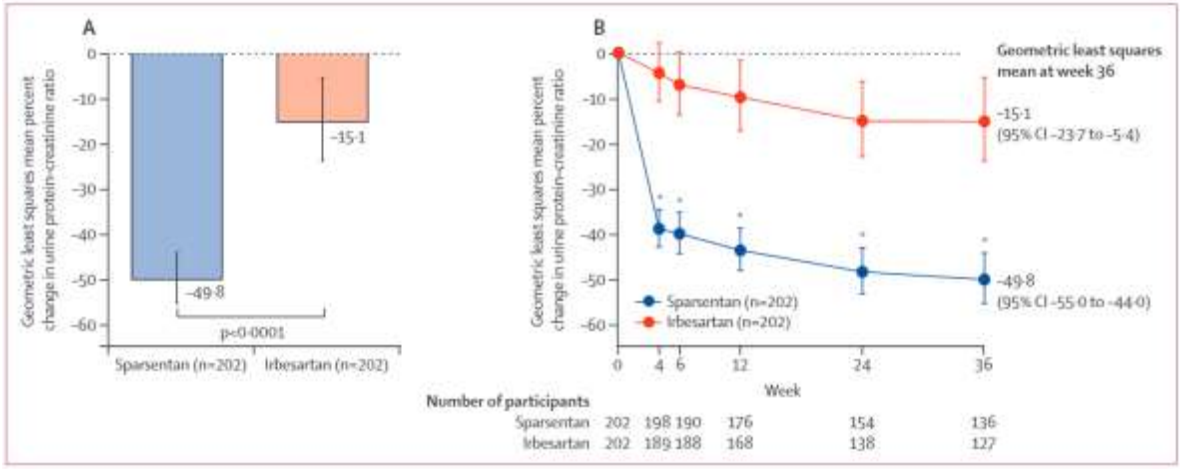


Figure 2: Percent change from baseline in urine protein–creatinine ratio in the sparsentan vs irbesartan treatment groups at week 36 (primary efficacy endpoint) and by visit
(A) At week 36. (B) By visit. Error bars show 95% CIs. Urine protein–creatinine ratio is based on 24-h urine samples. On-treatment urine protein–creatinine ratio at scheduled visits through to week 94 were included in the model. For percent change from baseline in urine protein–creatinine ratio for sparsentan vs irbesartan, geometric least squares mean ratio (sparsentan/irbesartan)=0·59, 95% CI 0·51–0·69; p<0·0001. *p<0·0001 for sparsentan vs irbesartan at each week.

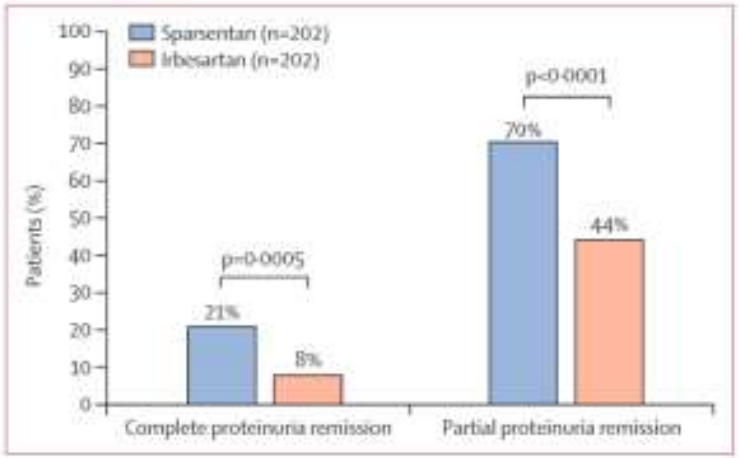


Figure 3: Percentage of patients with complete and partial remission of proteinuria at any time during treatment in the double-blind period

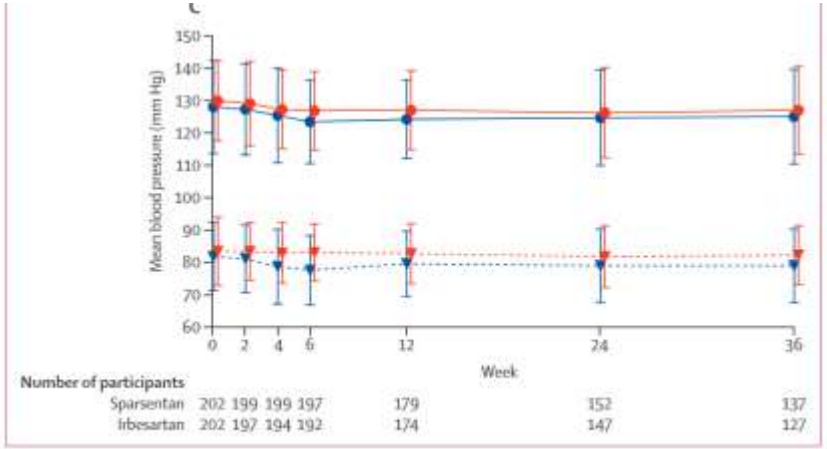


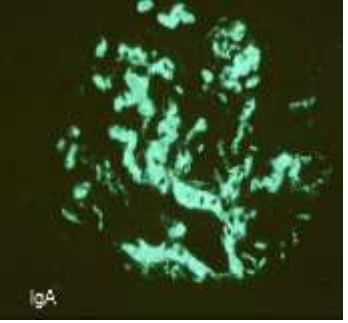
Figure 4: Change in SBP, change in DBP, and blood pressure by visit in the sparsentan and irbesartan treatment groups

Conclusion

Statistical significant effect on sparsentan compared to Ibersartan on UPCR level after 36 W of treatment

(Heerspink Lancet 2023)

IgA Nephropathy



	Sparsentan group (n=202)	Irbesartan group (n=202)	Between-group difference (95% CI)	p value
Key secondary efficacy endpoints*				
Chronic slope from week 6 to week 110, mL/min per 1·73 m² per year	-2·7 (-3·4 to -2·1)	-3·8 (-4·6 to -3·1)	1·1 (0·1 to 2·1)	0·037
Total slope from day 1 to week 110, mL/min per 1·73 m² per year	-2·9 (-3·6 to -2·2)	-3·9 (-4·6 to -3·1)	1·0 (-0·03 to 1·94)	0·058
Other secondary efficacy endpoint†				
Absolute change from baseline to week 110, mL/min per 1·73 m²	-5·8 (-7·4 to -4·2)	-9·5 (-11·2 to -7·9)	3·7 (1·5 to 6·0)	·
Prespecified exploratory endpoint†				
Absolute change from baseline to week 114, mL/min per 1·73 m²	-6·1 (-7·7 to -4·5)	-9·0 (-10·7 to -7·2)	2·9 (0·5 to 5·3)	·

Data are least-squares mean change (95% CI) in eGFR unless otherwise stated. eGFR=estimated glomerular filtration rate. *Assessed in the full analysis set. †Assessed in patients in the full analysis set who completed the study treatment.

Table 2: Change in eGFR

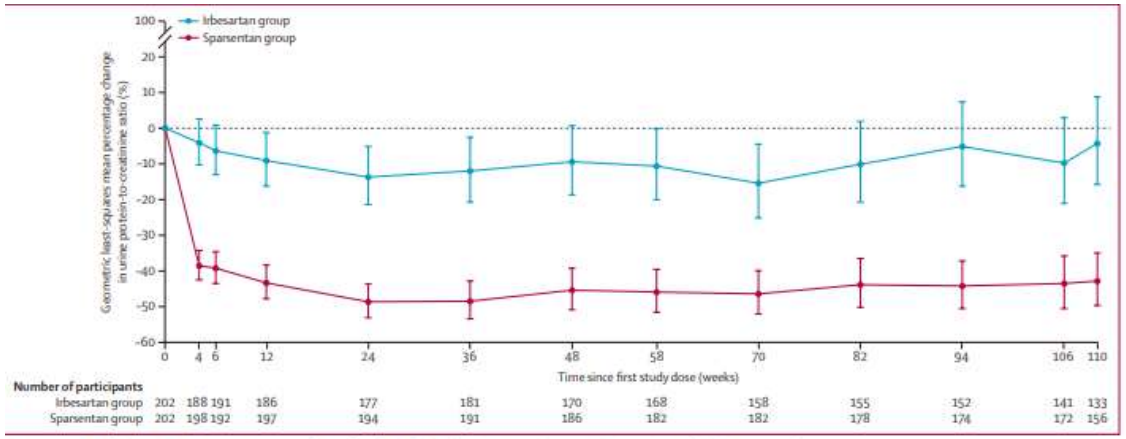


Figure 5: Geometric least-squares mean percentage change from baseline in the urine protein-to-creatinine ratio at each visit up to week 110

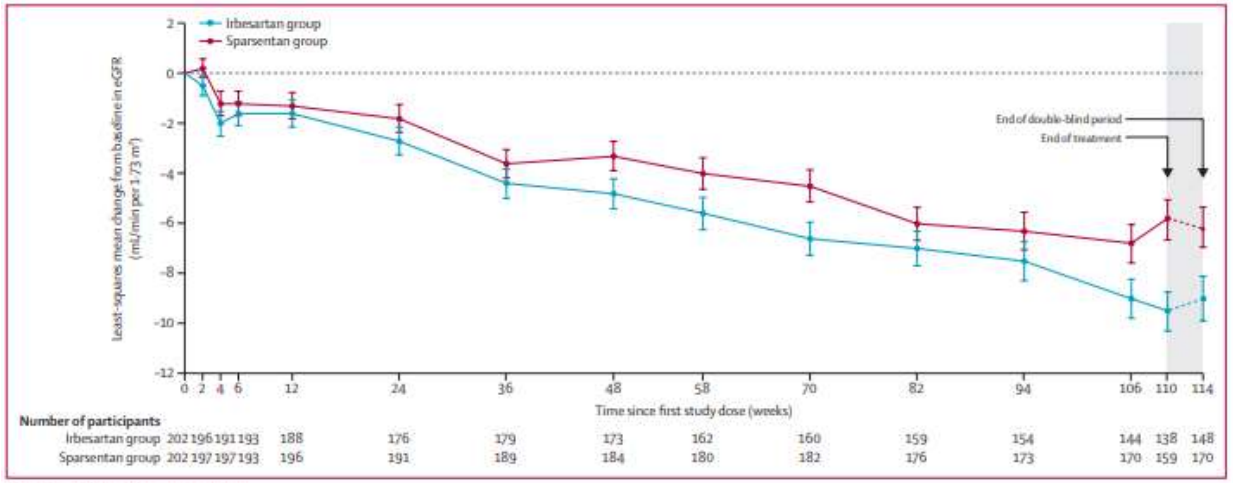


Figure 2: eGFR by visit up to week 114

Conclusion

The totality of data from PROTECT suggests that sparsentan is an effective and safe treatment for IgA nephropathy that delivers meaningful clinical benefit beyond RAS inhibition alone.

(Rovin B Lancet 2023)

Conclusion

Table 3. Renal effects displayed by selective endothelin receptor antagonists (ERAs) in different randomized controlled trials.

N	Study Population	Diabetes (%)	Baseline GFR (mL/min/1.73 m^2)	Intervention/Control/ Follow-Up	Kidney Endpoints	Albuminuria/Proteinuria Reduction	BP Reduction (ERA-Placebo)	GFR Difference (ERA-Placebo)	Author/Study/Year
379	GFR > 30 mL/min/ 1.73 m^2. Resistant hypertension.	153 (40%)	79.0	Darusentan 50, 100 or 300 mg/daily Placebo 3.5 months	NR	30.4 mg/g (UACR)	−9.9 mmHg in SBP(95%CI: −12.3–−5.7) −4.6 mmHg in DBP (95%CI: −7.0–−2.2)	−3.7 (95%CI: −6.9–−0.5)	Weber, M.A. et al. [91] 2009
1392	21–80 years. Creatinine 1.2–3 mg/dL. UACR ≥ 309 mg/g. Diabetic.	1392 (100%)	33.3	Avosentan 25 or 50 mg/daily Placebo 4 months	HR 0.87 (95%CI 0.6–1.2) [a]	565.5 mg/g (UACR) 31.7% UACR reduction *	−5.1 mmHg in SBP−3.7 mmHg in DBP	0.15 (95%CI: −1.3–1.9)	Mann, J.F.E. et al. [36] ASCEND 2010
89	GFR > 20 mL/min/ 1.73 m^2. UACR 100–3000 mg/g. Type 2 diabetes.	89 (100%)	52.8	Atrasentan 0.25, 0.75, 1.25 mg/daily Placebo 2 months	NR	27.5% UACR reduction * Not significant reduction with 0.25 mg	−8.2 mmHg in SBP−6.6 mmHg in DBPNot significant reduction with 0.25 mg	NR	Kohan, D.E. et al. [92] 2011
27	18–70 years. CKD stages 1 to 4. Non-diabetic.	0 (0%)	54.0	Sitaxsentan 100 mg/daily Placebo and nifedipine 30 mg/daily 1.5 months	NR	0.56 g/day (24-h proteinuria) 336.3 mg/g (UPCR)	≈−5 mmHg reduction in SBP and DBP	NR	Dhaun, N. et al. [93] 2011
211	>18 years. GFR 30 to 75 mL/min/1.73 m^2. UACR 300–5000 mg/g. Type 2 diabetes.	211 (100%)	49.3	Atrasentan 0.75 or 1.25 mg/daily Placebo 3 months	NR	301.5 mg/g (UACR)	0.5 mmHg in SBP (95%CI: −5.0–6.0) 1 mmHg in DBP (95%CI: −2.8–4.8)	−0.5 (95%CI: −5.3–4.3)	Zeeuw, D. et al. [18] RADAR 2014
2648	18–85 years. GFR 25 to 75 mL/min/1.73 m^2. UACR 300–5000 mg/g. Type 2 diabetes Responders (30% decrease in UACR).	2648 (100%)	43.9	Atrasentan 0.75 mg/daily Placebo 26.4 months	HR 0.65 (95%CI 0.5–0.9) [b]	33.6% UACR reduction * (95%CI: 29.1–38.2)	−1.6 mmHg SBP reduction (95%CI: 0.7–2.5)	0.65 (95%CI: 0.3–1.0)	Heerspink, et al. [19] SONAR 2019
13	>18 years. Systemic sclerosis. CKD stages 2 to 3a.	0 (0%)	52.4	Zibotentan 10 mg/daily Placebo 6.5 months	NR	NR	NR	4.3 (95%CI: 2.6–11.3)	Stern, et al. [24] ZEBRA 1 2022

[a] Doubling of serum creatinine, end-stage kidney disease or death. [b] Doubling of serum creatinine, end-stage kidney disease or death due to kidney failure. * UACR percentage reduction compared to place (the reduction observed in the placebo group has been subtracted to the reduction in the active treatment groups). BP: Blood Pressure; SBP: systolic blood pressure; DBP: Diastolic blood Pressure; CKD: Chronic Kidney Disease; GFR: Glomerular Filtration Rate; UACR: urine albumin-to-creatinine ratio; UPCR: urine protein-to-creatinine ratio; NR: not reported.

Potential interest in a broad spectrum of renal diseases

Key therapeutic option to reduce proteinuria level

Effect on CKD progression remains uncertain

Conclusion

Drug	Route	Dose	Approved indication (potential indications based on clinical studies)	Contra-indications	Half-life (hours)	Bio-availability	Metabolism	Excretion	Adverse effects
Selective ET_A antagonists									
Ambrisentan	Oral	5–10 mg daily	PAH	Moderate/severe hepatic impairment, pregnancy, IPF	13.6–16.5	NR	CYP3A4, CYP3A5, CYP2C19	Biliary	Fluid retention (22%), anaemia (7%), liver injury (3%)
Atrasentan	Oral	0.75–1.25 mg daily	(DKD, metastatic prostate cancer [NS])	NR	24	NR	CYP3A4	NR	Fluid retention (37%), anaemia (19%)
Avosentan	Oral	5–50 mg daily	(DKD)	NR	7.5–15	72–81	NR	Biliary	Fluid retention (17%), heart failure (5%), anaemia (12%)
Darusentan	Oral	50–300 mg daily	(Resistant hypertension)	NR	16–18	NR	NR	Biliary	Fluid retention (27%), anaemia (NR)
Sitaxentan	Oral	25–100 mg daily	(PAH)	NR	8.4	70–100	CYP2C9, CYP3A4	Urine (50%–60%)	Fluid retention (9%), liver injury (2%), headache (15%–26%)
Zibotentan	Oral	5–15 mg daily	(Metastatic prostate cancer [NS]) CKD	NR	5–23	NR	CYP3A4	Urine (35%–77%)	Fluid retention (14%–17%), headache (33%–100%)
Nonselective ET_A/ET_B antagonists									
Bosentan	Oral	62.5–250 mg twice daily	PAH (ILD [NS], COPD [NS], chronic heart failure [NS])	Moderate/severe hepatic impairment, pregnancy	5.6	41%	CYP2C9, CYP3A4	Biliary	Liver injury (11%), fluid retention (10%), anaemia (6%), drug interactions (bosentan induces CYP2C9 and CYP3A4)
Macitentan	Oral	10 mg daily	PAH	Moderate/severe hepatic impairment, pregnancy	16 (48 for active metabolite)	NR	CYP3A4, CYP2C8, CYP2C9, CYP2C19	Urine	Fluid retention (22%), anaemia (13%), liver injury (3%)
Aprocitentan	Oral	5–50 mg daily	(Hypertension)	NR	47.4–53.2	NR	Not dependent on CYP	Urine and faeces	Hypertension (3%), headache (4%), fluid retention (2%)
Tezosentan	IV	1–50 mg/h	(PAH [NS], acute heart failure [NS])	NR	6 min (initial), 3 h (terminal)	Not applicable	NR	NR	Headache (32%), hypotension (23%)
Dual ET_A/AT_1 antagonist									
Sparsentan	Oral	200–800 mg daily	(FSGS, IgAN)	NR	NR	NR	NR	NR	Headache (19%), hypotension (12%), fluid retention (12%)

Abbreviations: AT1, angiotensin II type 1 receptor; CYP, cytochrome P450 enzymes; DKD, diabetic kidney disease; ET_A, endothelin receptor A; ET_B, endothelin receptor B; FSGS, focal segmental glomerulosclerosis; IgAN, IgA nephropathy; IPF, idiopathic pulmonary fibrosis; IV, intravenous; NR, not reported; NS, results from trials showed no significant benefit from endothelin receptor antagonism; liver injury defined as liver aminotransferases ≥3 times the upper limit of normal; PAH, pulmonary arterial hypertension.

Promising results in

DKD

HTA

IGAN (reduction of eGFR decline)

Interest of combination ERA and ISGLT2

- Synergisitc effect
- Reduction of side effects (fluid retention)