

Novel Treatments for Proteinuria and Hypertension: Is there a Role for Endothelin Inhibitors ?

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DISCLOSURES

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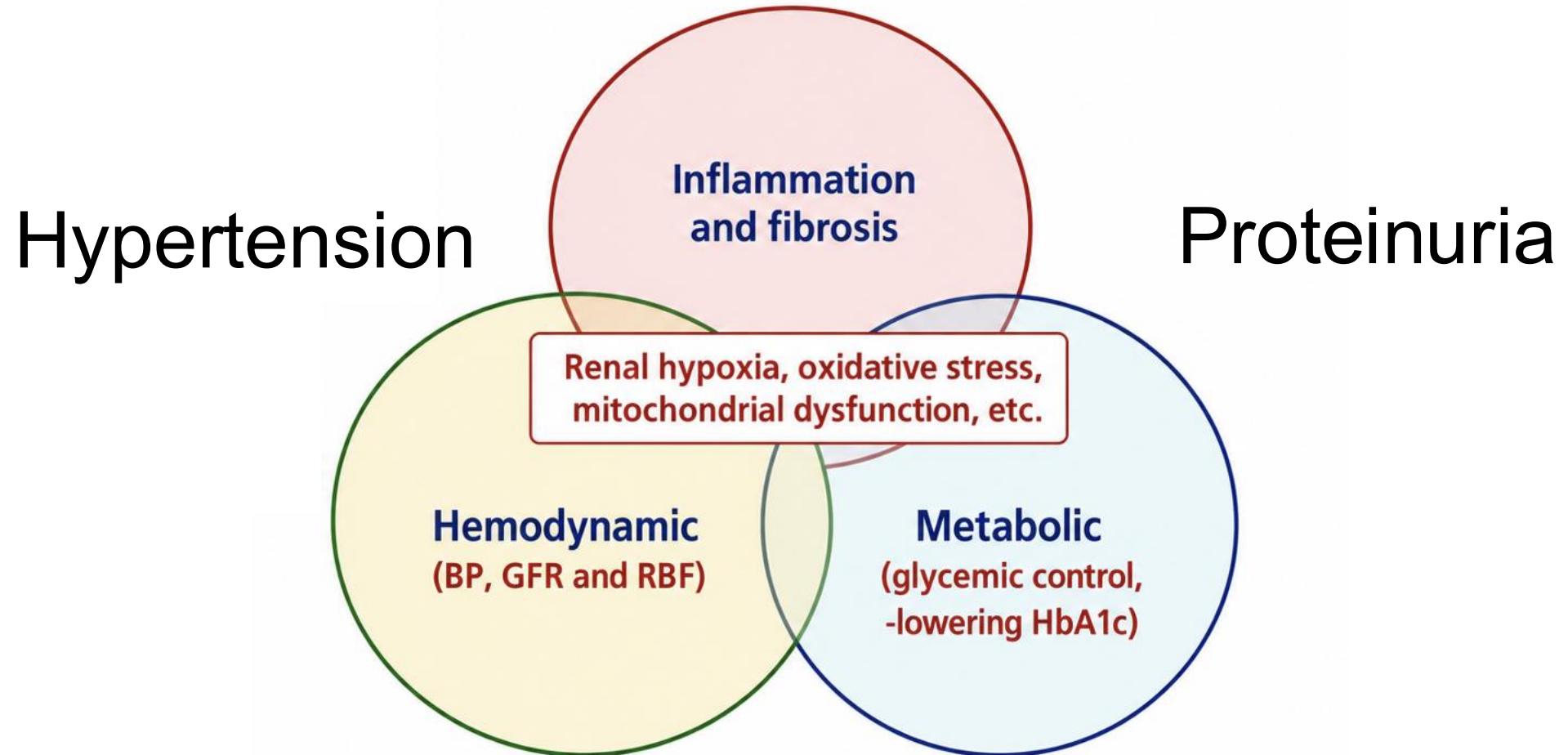


LEARNING OBJECTIVES

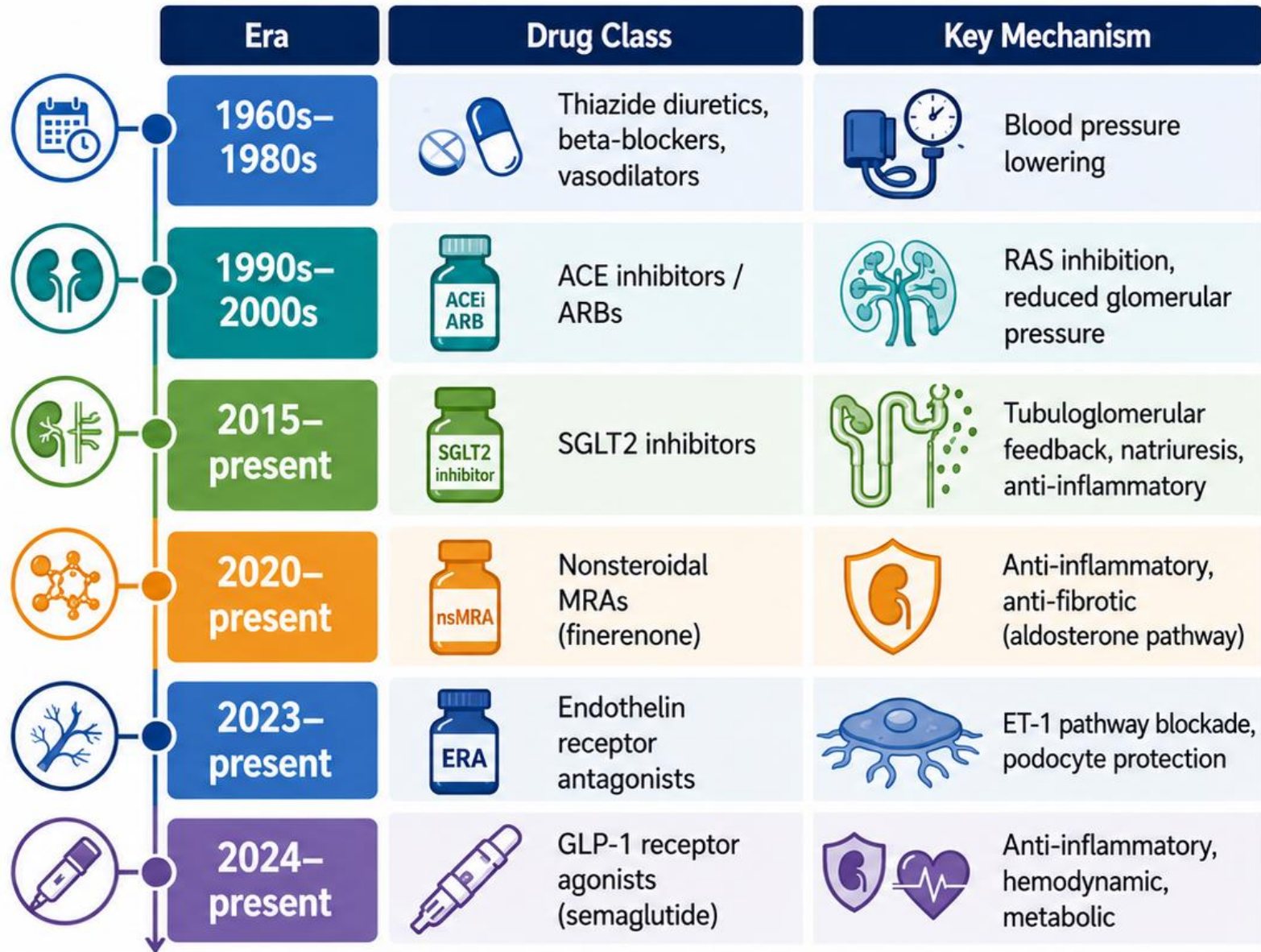
- Describe the role of endothelin-1 signaling in hypertension, proteinuria, and kidney injury
- Explain how vascular endothelial growth factor signaling pathway inhibitors (VSPIs) cause kidney toxicity
- Evaluate the rationale and emerging evidence for endothelin receptor antagonists, in VSPI-associated hypertension and proteinuria.



DRIVERS OF KIDNEY IMPAIRMENT

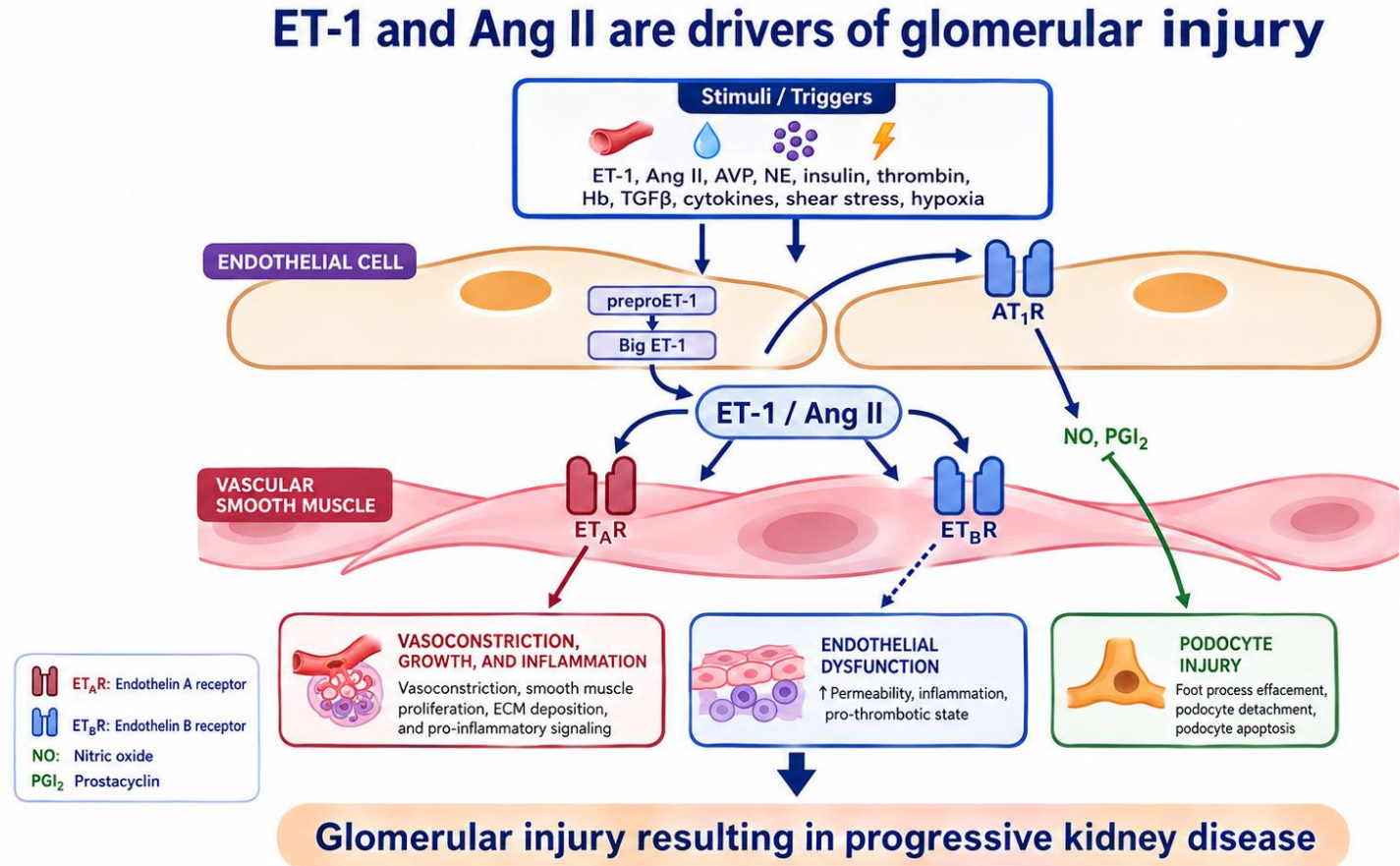


EVOLUTION OF KIDNEY PROTECTIVE THERAPIES

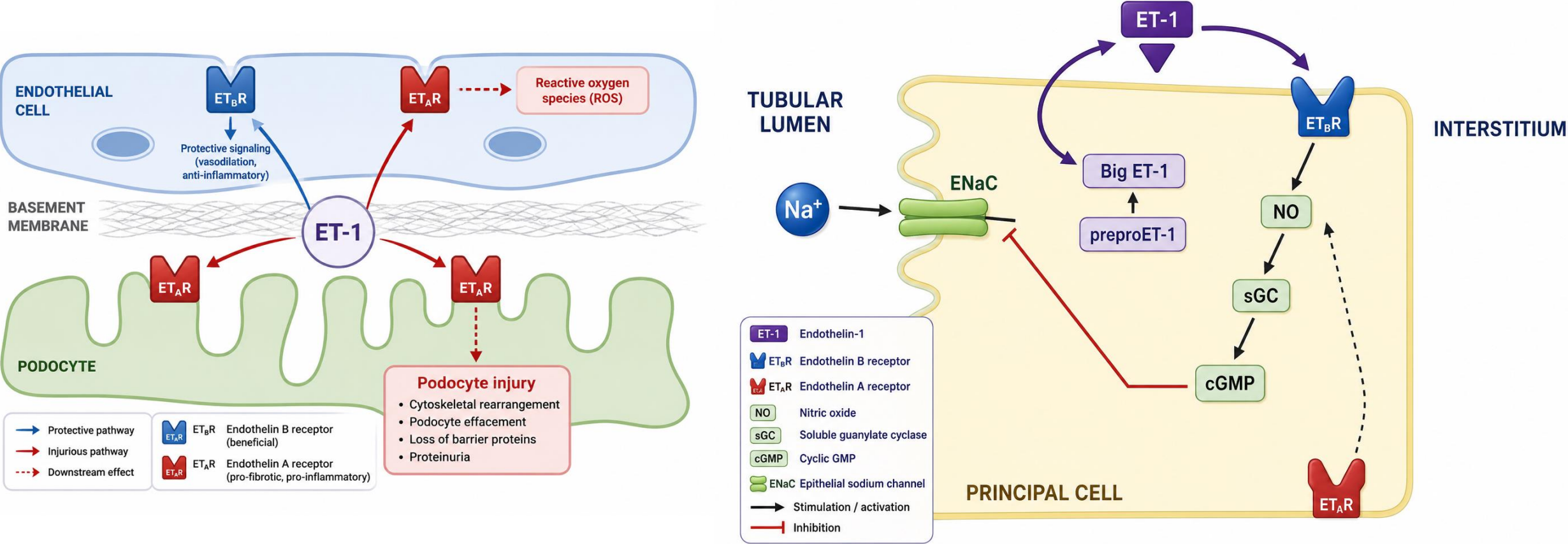


ROLE OF ENDOTHELIN-1

Endothelin-1 acting primarily through the ETA receptor, promotes vasoconstriction, glomerular hyperfiltration, podocyte injury, mesangial expansion, inflammation, and fibrosis



EFFECTS OF ENDOTHELIN-1



ENDOTHELIN RECEPTOR ANTAGONISTS

Trial	Agent	Population	N	Duration	Key Result
Bosentan Hypertension (1998)	Bosentan	Essential hypertension	293	4 wk	SBP -7.4–10.3 mmHg vs placebo
DORADO (2009)	Darusentan	Resistant hypertension	379	14 wk	SBP -10 mmHg vs placebo
DORADO-AC (2010)	Darusentan	Resistant hypertension	849	14 wk	SBP -7 mmHg vs placebo
PRECISION (2022)	Aprocitentan	Resistant hypertension	730	48 wk	SBP -3.8 mmHg vs placebo
PRECISION-CKD (2025)	Aprocitentan	Resistant hypertension with CKD	147	36 wk	SBP -16.6 mmHg; UACR -59.6%



ENDOTHELIN RECEPTOR ANTAGONISTS

Trial	Agent	Population	N	Duration	Key Result
Atrasentan (2011)	Atrasentan	DKD	89	8 wk	UACR reduced 42% vs 11% with placebo
RADAR (2014)	Atrasentan	DKD	211	12 wk	UACR reduced 35–38% vs placebo
SONAR (2019)	Atrasentan	DKD	3,668	2.2 yr	35% reduction in kidney events (HR 0.65; P=0.005)
AFFINITY (2025)	Atrasentan	IgAN, FSGS, Alport syndrome	20*	12 wk	IgAN subgroup: 48% reduction in proteinuria
ALIGN (2025)	Atrasentan	IgAN	340	36 wk	UPCR reduced 38.1% vs 3.1% with placebo (P<0.001)
Atrasentan + SGLT2 inhibitor (2026)	Atrasentan	IgAN	54	12 wk	25.3% additional reduction in UPCR vs placebo
DUET (2018)	Sparsentan	FSGS	109	8 wk	Greater proteinuria reduction than irbesartan
PROTECT (2023)	Sparsentan	IgAN	406	110 wk	UPCR reduced 42.8% vs 4.4%; slower chronic eGFR decline (P=0.04)
DUPLEX (2023)	Sparsentan	FSGS	371	108 wk	Partial remission 42% vs 26% (P=0.009); primary eGFR endpoint not significant



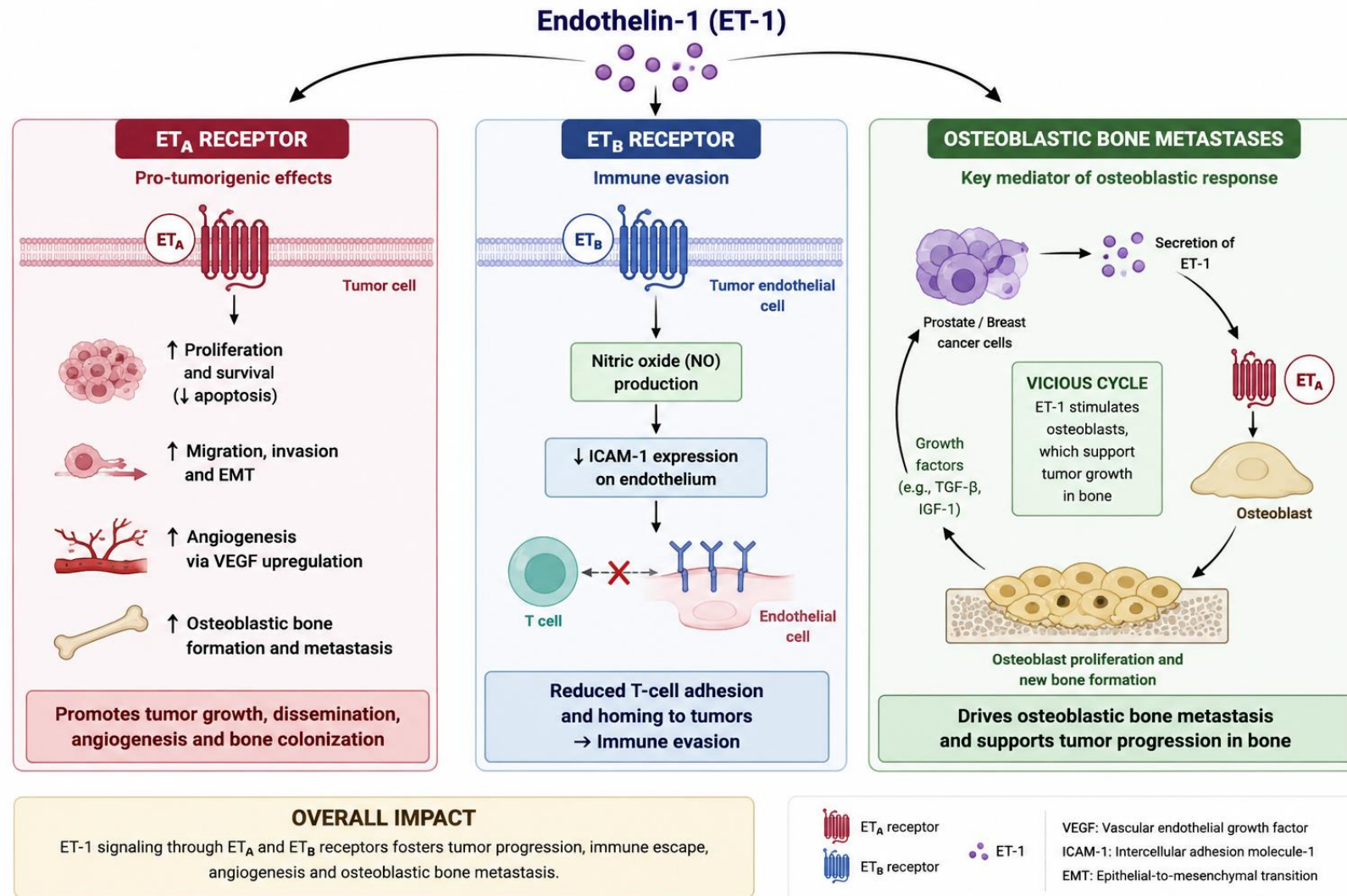
FDA-APPROVED ENDOTHELIN RECEPTOR ANTAGONISTS

	Sparsentan	Atrasentan	Aprocitentan
Drug class	Dual endothelin angiotensin receptor antagonist	Selective endothelin receptor antagonist	Dual endothelin receptor antagonist
Receptor targets	ETA + AT ₁	ETA	ETA + ETB
ETA selectivity	>500-fold over ETB	>1,800-fold over ETB	Non-selective
Indications	- Slow kidney function decline in adults with primary IgAN - Reduce proteinuria in adults and pediatric patients (≥8 years) with FSGS	Reduce proteinuria in adults with IgAN with UPCR ≥1.5 g/g	Treatment of hypertension in adults whose blood pressure remains uncontrolled despite treatment with other antihypertensive medications.
Side effects	- Fluid retention and anemia - Hepatotoxicity - Embryo-fetal toxicity; requires liver-test and pregnancy monitoring	- Fluid retention and anemia - Possible adverse effect on spermatogenesis	Fluid retention and anemia

He Q, Lin J, Mo C, Li G, Lu J, Sun Q, Cao L, Gan H, Sun Q, Yao J, Lian S, Wang W. Endothelin receptor antagonists (ERAs) can potentially be used as therapeutic drugs to reduce hypertension caused by small molecule tyrosine kinase inhibitors (TKIs). Front Pharmacol. 2025 Jan 9;15:1463520.



ROLE OF ENDOTHELIN-1 IN CANCER



Bagnato A et al. The endothelin axis in cancer. *Int J Biochem Cell Biol.* 2008;40(8):1443-51.

Rosanò L, et al. Endothelin 1 in cancer: biological implications and therapeutic opportunities. *Nat Rev Cancer.* 2013 Sep;13(9):637-51.

TRIALS OF ENDOTHELIN-1 ANTAGONISTS IN PATIENTS WITH CANCER

Trial	Agent	Cancer	N	Key Result
ENTHUSE M0	Zibotentan	Non-metastatic CRPC	1,421	No improvement in overall survival
ENTHUSE M1	Zibotentan	mCRPC	594	No survival benefit
ENTHUSE M1C	Zibotentan + docetaxel	mCRPC	1,174	No improvement in overall survival
Carducci et al.	Atrasentan	mCRPC	809	No significant improvement in disease progression or survival
SWOG S0421	Atrasentan + docetaxel	mCRPC	1,038	No improvement in overall survival or progression-free survival
Chiappori et al.	Atrasentan	Advanced NSLC	44	No survival benefit
Groenewegen et al.	Atrasentan + IFN- α	mRCC	32	Improved OS in patients with decreasing VEGF and increasing ET-1 levels.
Kefford et al 2007	Bosentan	Metastatic melanoma	80	No improvement in progression-free or overall survival
Kefford et al 2010	Bosentan + dacarbazine	Metastatic melanoma	84	No improvement in response or survival



ET-1 antagonist has not been associated with increased cancer progression in clinical trials.

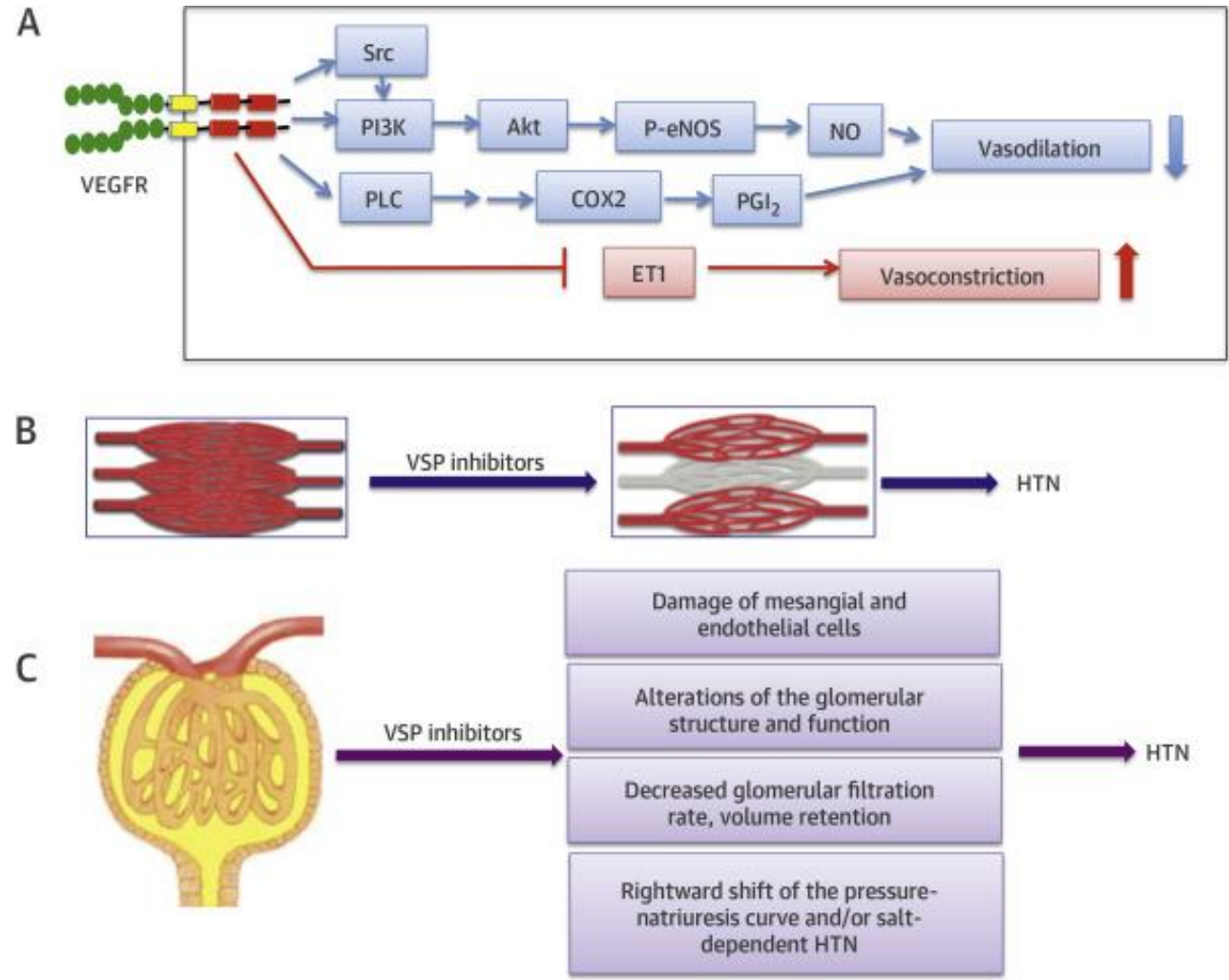
CANCER THERAPY-ASSOCIATED HYPERTENSION AND PROTEINURIA

Drug Class	Representative Agents
Anti-VEGF monoclonal antibodies	Bevacizumab, Ramucirumab
VEGF-trap	Aflibercept
VEGF receptor tyrosine kinase inhibitors (TKIs)	Sunitinib, Sorafenib, Pazopanib, Axitinib, Lenvatinib, Cabozantinib
Proteasome inhibitors	Carfilzomib

VEGF signaling pathway inhibitor (VSPI) increases ET-1 signaling



EFFECTS OF VSPI ON THE KIDNEY



PILOT STUDY OF SPARSENTAN FOR VSPI ASSOCIATED PROTEINURIA

Clinical question

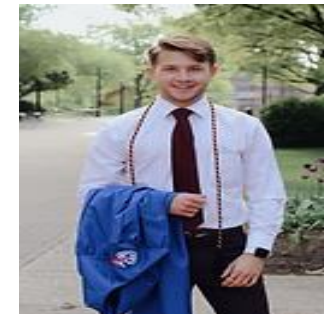
Can dual endothelin/angiotensin receptor blockade reduce high-grade proteinuria during VEGF-pathway cancer therapy?

Study objective

Evaluate whether sparsentan reduces high-grade proteinuria in adult oncology patients receiving vascular endothelial growth factor signaling pathway inhibitors.

Primary Endpoint

Proportion of patients achieving a **$\geq 25\%$ reduction in proteinuria at Day 60** compared with 1:1 matched historical controls.



N = 20

Patients with active cancer treatment

60 days

Open-label treatment

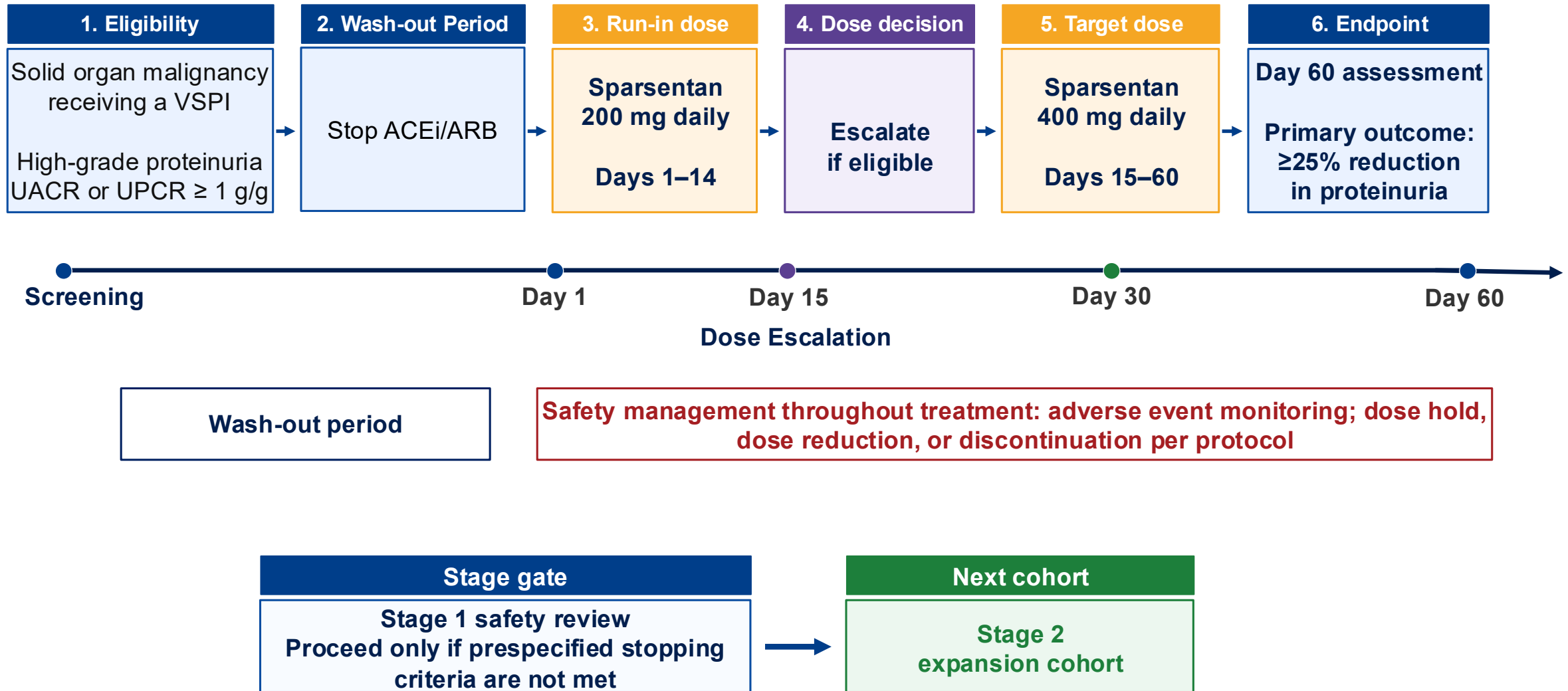
Endpoint

Safety and Efficacy

Goal

Support cancer therapy continuation

SCHEMATIC OF PILOT TRIAL



INCLUSION AND EXCLUSION

Inclusion

- 1 Adult oncology patient**
Age ≥ 18 with active malignancy receiving a vascular endothelial growth factor pathway inhibitor.
- 2 Recent exposure**
VEGF pathway inhibitor started within 21 days before screening.
- 3 New high-grade proteinuria**
Urine protein-to-creatinine or albumin-to-creatinine ratio ≥ 1.0 g/g, or $\geq 2+$ dipstick.
- 4 Stage 1 cohort**
Initial safety cohort before expansion to Stage 2.

Exclusion

- ! Kidney safety**
eGFR < 45 , active acute kidney injury, or high-grade proteinuria predating therapy.
- ! Medication safety**
Contraindication to sparsentan, ARBs, endothelin receptor antagonists, or prohibited interacting medications.
- ! Electrolyte risk**
Potassium > 5.0 mEq/L before screening.
- ! Major comorbidity**
NYHA class II-IV heart failure, recent significant cardiovascular/cerebrovascular disease, or major liver disease.
- ! Other**
Solid organ transplantation history or body weight < 50 kg.



PRELIMINARY RESULTS

Characteristic	1	2	3	4
Age, y	63	61	68	56
Sex	F	F	M	F
Cancer type	Ovarian	Ovarian	HCC	Ovarian
VSPI	Bevacizumab	Bevacizumab	Lenvatinib	Bevacizumab
Baseline creatinine, mg/dL	0.8	0.9	1.0	0.8
Baseline eGFR, mL/min/1.73 m ²	87	74	82	82
Baseline UACR, mg/g	2632	2482	5493	1699
Serum albumin, g/dL	3.7	3.6	3.5	4.4
Blood pressure, mmHg	145/65	158/76	171/81	122/79
ACEi/ARB prior	Lisinopril	Lisinopril	Losartan	No
SGLT2 inhibitor	No	No	No	No

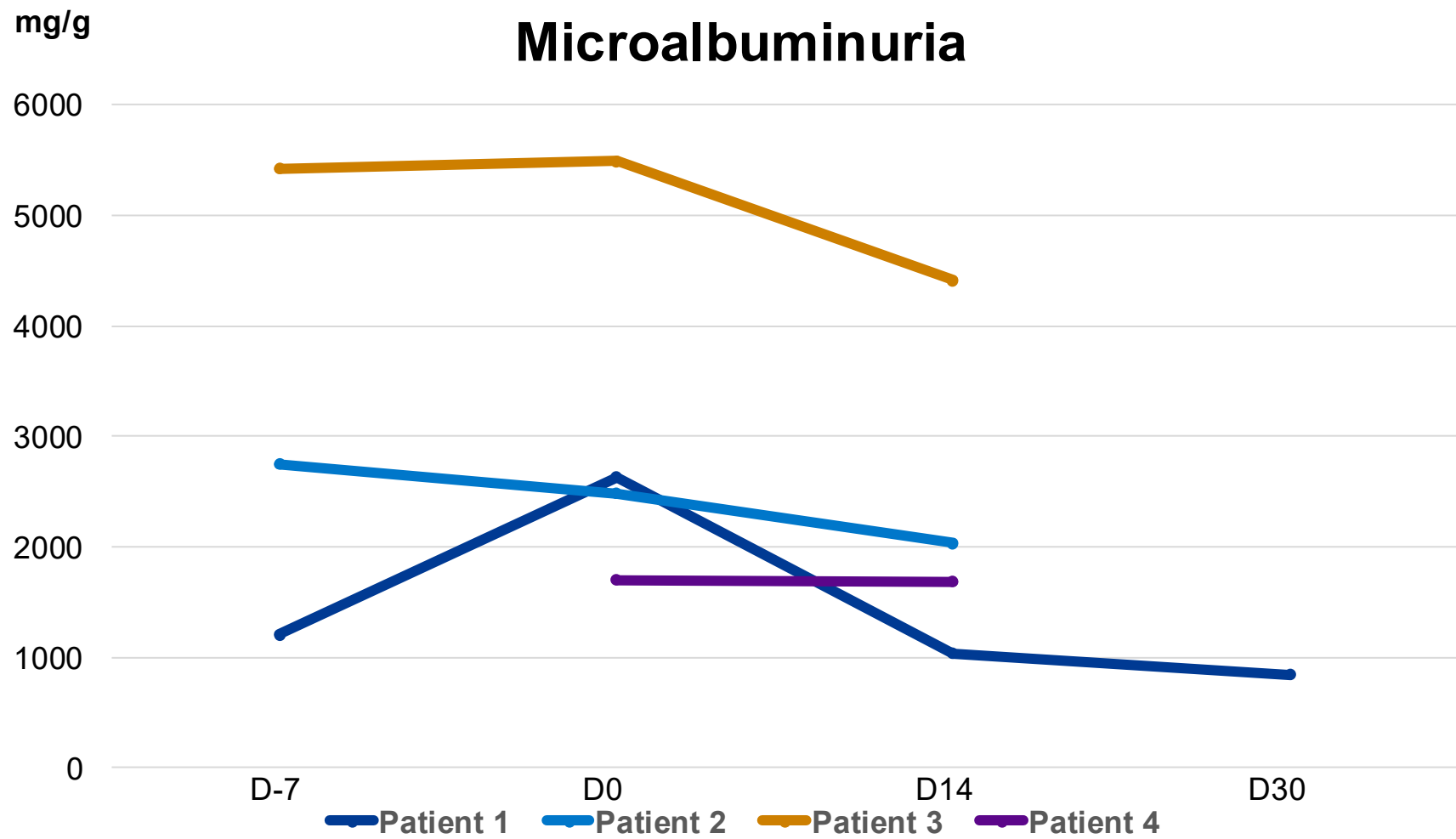


PRELIMINARY RESULTS

- 2 out of 4 reported worsening fatigue although it did not interfere with their daily activities
- None with worsening swelling, dizziness, hyperkalemia, AKI, abnormal LFTs or anemia

Patient	D-7 (ACEi/ARB)	D0	Day 15	Day 30	Day 60	%change (D0 vs D15)
Microalbuminuria (mg/g Cr)						
1	1202	2632	1037	839		61%
2	2748	2482	2029			18%
3	5422	5493	4415			20%
4	-	1699	1692			0%
Blood pressure (mmHg)						
1	168/75	168/78	165/70	134/63		-1.8/-10.3
2	146/72	162/78	118/58			-27.2/-25.6
3	165/92	166/84	142/80			-14.5/-4.8
4	-	137/90	130/86			-5.1/-4.4



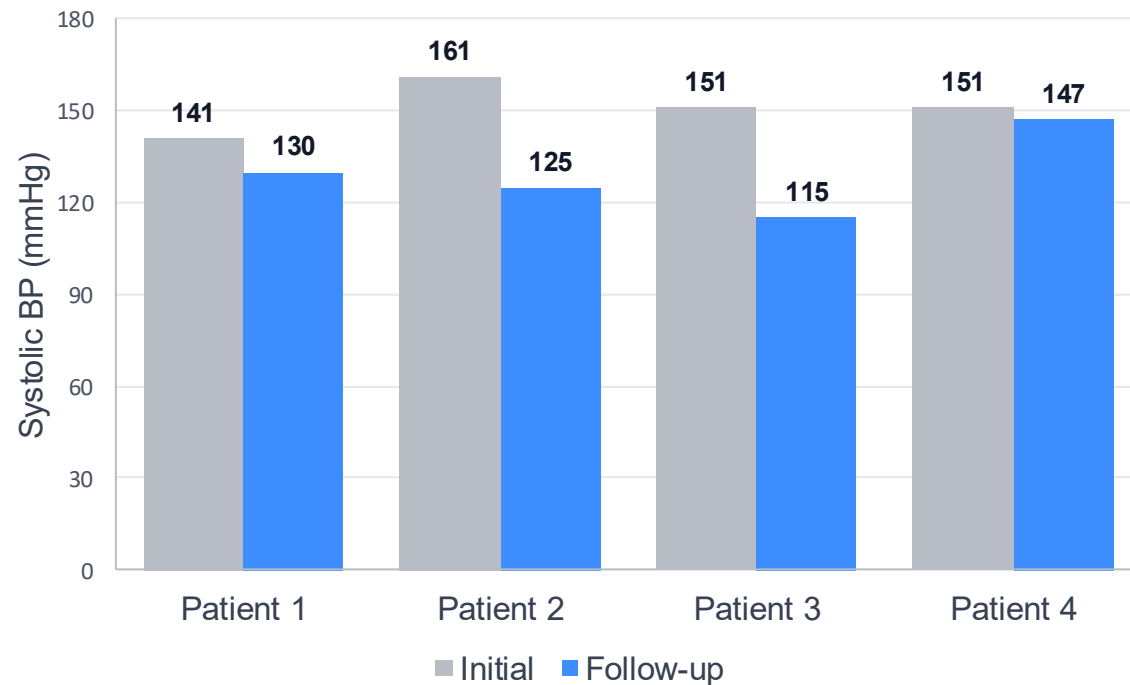


APROCITENTAN

Case series of VSPI-associated hypertension and/or proteinuria; aprocitentan was added to existing antihypertensive therapy.



Systolic blood pressure before and after aprocitentan



Proteinuria declined in both patients with available follow-up: 9→0.98 and 1→0.3 g/g Cr.

-22 mmHg

Mean reduction in
systolic BP

3 of 4

Continued the same
VSPI

Patient 3 switched therapy after biopsy-proven TMA

3 patients stopped ACEi because of hyperkalemia.



Aprocitentan may control VSPI toxicity and preserve cancer therapy.

CONCLUSIONS

- VSPIs increase ET-1 signaling and commonly cause hypertension and proteinuria
- ET-1 promotes vasoconstriction, sodium retention, inflammation, and fibrosis. Endothelin receptor antagonists can reduce BP and proteinuria
- Endothelin blockade may mitigate hypertension and proteinuria, potentially allowing patients to continue cancer therapy without significant adverse effects

