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# Bosentan Does Not Affect Renal Resistive Index in Scleroderma/ Systemic Sclerosis Patients

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**Keywords**
Systemic sclerosis · Renal hemodynamics · Endothelin · Pulse pressure · Chronic kidney disease

**Abstract**
***Introduction:*** If properly evaluated, chronic kidney disease can be found in up to 50% of patients with systemic sclerosis (SSc). The renal resistive index (RRI) is a marker of intrarenal vascular resistance and can predict SSc-associated vasculopathy. This study aimed to determine the impact of bosentan, a nonselective endothelin-1 receptor antagonist, on RRI and kidney function in SSc patients with recurrent digital ulcers. ***Methods:*** Twenty-one patients (age 57 ± 9 years, 19 females) were recruited in a 16-week prospective open-label uncontrolled study. Standardized procedures were used to measure general clinical and laboratory characteristics, systolic, diastolic, and mean arterial pressure (MAP), pulse pressure (PP), diastolic to systolic blood pressure (D/S) ratio, and urinary endothelin-1 levels. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used to calculate kidney function as an estimated glomerular filtration rate (eGFR). RRI was measured by Doppler ultrasound as the average of three samplings of intrarenal blood flow in different kidney regions of both kidneys. Patients with secondary causes of kidney disease or kidney diseases associated with albuminuria were excluded. ***Results:*** Bosentan treatment for 16 weeks did not change RRI (0.731 ± 0.049–0.730 ± 0.054, $p = 0.925$), but increased urine endothelin-1 to creatinine ratio (0.27 ± 0.15–0.49 ± 0.57 pg/mg, $p = 0.032$) and reduced MAP (123 ± 10–101 ± 11 mm Hg, $p < 0.001$), PP (76 ± 11–68 ± 10 mm Hg, $p = 0.003$), D/S ratio (0.563 ± 0.044–0.538 ± 0.031, $p = 0.006$), and eGFR (92 ± 20–84 ± 24 mL/min/1.73 $m^2$, $p = 0.003$). ***Discussion/Conclusion:*** In conclusion, in patients with SSc complicated by digital ulcers and normal to mildly diminished kidney function, bosentan had no effect on intrarenal hemodynamics, but reduced blood pressure levels and kidney function.

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## Introduction

Although scleroderma renal crisis (SRC) is not related to a progressive kidney dysfunction, it is the most reported kidney complication of SSc and involves less than 10% of patients [1]. However, progressive kidney damage

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characterizes patients with systemic sclerosis (SSc) [2] and, beyond SRC, when glomerular filtration rate is appropriately estimated [3, 4], subclinical kidney impairment can be found in about one-third of patients with SSc [4]. After excluding secondary causes of kidney disease, such as overlap syndromes or drug-induced kidney adverse effects, kidney impairment in SSc consists of reduced estimated glomerular filtration rate (eGFR) with or without increased urinary protein excretion. In these isolated forms of kidney dysfunction, subclinical vascular damage with enhanced vasoconstriction and reduced intrarenal vascular resistance seems to play a central pathophysiological role [5, 6].

Non-proteinuric chronic kidney disease has been shown in patients with SSc [7]. Although the pathogenesis is unknown, it seems to involve intrarenal hemodynamics and reduced eGFR [8]. In this context, the renal resistive index (RRI), assessed by Doppler ultrasound, has been considered a reliable marker of kidney disease presence and progression [9]. In fact, RRI is high in patients with SSc without clinical symptoms of kidney damage [7] and it correlates to kidney function, the presence of SSc-associated vasculopathy, and SRC severity [10, 11]. Because RRI has been associated with eGFR decline and long-term mortality in patients with non-proteinuric kidney disease [12], this index might also have a role as a prognostic marker in non-proteinuric SSc patients with reduced kidney function [13].

Several humoral mediators have been involved in SSc-associated vasculopathy, and, in particular, endothelin plays an important role [14]. Endothelin-1 acts as a potent vasoconstrictor of small arteries and arterioles, and it is involved in mesangial cell activation and extracellular matrix deposition in the kidney [15, 16]. Moreover, endothelin-1 is involved in the pathogenesis of classical SSc-associated vasculopathy, such as digital ulcers and pulmonary arterial hypertension. Bosentan, an endothelin-1 nonselective competitive antagonist at endothelin-A and endothelin-B receptors, is licensed by the Italian Drug Agency for the treatment of SSc-associated vascular complications [17, 18]. Endothelin-1 is elevated in patients with SSc, and its plasma levels are associated with the occurrence of SRC [19]. Also, in a published clinical case, bosentan restored kidney function in a patient who needed dialysis as a consequence of SRC [20]. Because endothelin-1 is involved in regulating intrarenal hemodynamics and the pathogenesis of SSc-associated vasculopathy, it has been hypothesized that bosentan might have a kidney protective effect in these patients. Bosentan, by inhibiting receptor-mediated endothelin-1 effect in kidney tissue, could improve intrarenal hemodynamics and increase eGFR in patients with non-proteinuric kidney disease.

The aim of this study was to evaluate the effect of bosentan on RRI and kidney function in patients with SSc who plan to use bosentan to treat recurrent digital ulcers without signs of chronic kidney disease. Urine endothelin-1 to creatinine ratio was measured before and after bosentan administration to assess the drug's effect on blocking endothelin-1 binding to its receptors.

## Materials and Methods

Outpatients followed at the Rheumatology Division of the Academic Hospital of Udine in Italy were prospectively enrolled in this open-label uncontrolled prospective study. Inclusion criteria were both sexes, age equal to or greater than 18 years, a diagnosis of limited or diffuse cutaneous SSc according to the American College of Rheumatology and European League Against Rheumatism Classification Criteria [21], and the presence of SSc-associated active digital ulcers with the indication to start bosentan. Patients were evaluated by an expert rheumatologist who performed a general examination, assessed SSc severity by the modified Rodnan's skin score [22], and prescribed initial organ damage screening such as pulmonary artery pressure measurement by standard echocardiography. For study purposes, patients' kidney function was evaluated by a nephrologist who recorded anamnestic and pharmacological data, performed a detailed diagnostic evaluation of kidney disease before commencing bosentan, and reevaluated the patients' kidney function 16 weeks later. Patients who had a history of glomerular or tubular kidney disease, proteinuria or urinary albumin levels equal to or higher than 30 mg/day, gross or microscopic hematuria, renal artery stenosis, polycystic kidney disease, active urinary tract infection, obstructive kidney disease, or a between-kidney longitudinal diameter difference of more than 1 cm, or who did not sign the informed consent form, did not complete 4 months of treatment, or had incomplete data, were excluded. Bosentan dosage was started at 62.5 mg twice daily for 4 weeks, and then increased to 125 mg twice daily for a total of 16 weeks. The primary outcome of the study was to assess the bosentan effect on reducing RRI by at least 0.05 (effect size); the secondary outcome was the bosentan effect on eGFR after 16 weeks of treatment.

Renal ultrasound examination was performed with a duplex Doppler apparatus after a 12-h fasting period, as previously shown [12]. Briefly, a 3.5-MHz convex phased array probe and color Doppler mapping were used to identify the renal arteries. The Doppler angle was kept lower than 60° and as close as possible to zero to measure peak systolic velocity (PSV) and end-diastolic velocity (EDV) at the level of renal arteries and intrarenal medium-sized arteries. The RRI was calculated according to the formula (PSV-EDV)/PSV, where PSV and EDV were measured in cm/s 3 times at the superior, medium, and inferior regions of both kidneys and expressed as the mean value of all measures. For the purposes of this study, the RRI value considered for each patient was the average of the RRI of the right and left kidneys. According to previous studies, a value greater than 0.70 can be considered high and pathological [13, 23].

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Patients' blood pressure was measured in accordance with the European Society of Hypertension and European Society of Cardiology Guidelines for the Management of Arterial Hypertension [24]. Briefly, before starting the blood pressure measurement, patients were seated comfortably in a quiet environment for 5 min. Systolic and diastolic blood pressure (SBP and DBP, respectively) were assessed in the dominant arm with an automated oscillometric sphygmomanometer (M2 HEM-7121-E, OMRON, Kyoto, Japan). Three blood pressure readings were collected, 1 to 2 min apart, and additional readings were taken only if the first two readings deviated by more than 10 mm Hg. The blood pressure taken into account was the average of the previous two consecutive readings. Pulse pressure (PP) was defined as the difference between SBP and DBP, whereas mean arterial pressure (MAP) was defined as one-third of the SBP added to two-thirds of the DBP. The diastolic to systolic blood pressure (D/S) ratio was also calculated as an important determinant of RRI [25]. Blood pressure was measured just before the RRI evaluation in all patients.

Standard routine laboratory tests (hemoglobin, platelet count, serum glucose, serum total cholesterol, serum C-reactive protein [CRP], erythrocyte sedimentation rate [ESR], serum and urinary creatinine, and autoimmunity testing [anti-topoisomerase I, anticentromere, and anti-RNA polymerase III antibodies]) were performed by the certified biochemical laboratory of the Academic Hospital of Udine. For the measurement of urinary endothelin-1 levels, the urine sample was obtained by collecting the first morning urine in a sterile container. This sample was then centrifuged for 5 min at a speed of 3,000 rpm at a temperature of 4°C. The obtained supernatant was then stored at −80°C pending the assay. The latter was performed with an immuno-enzymatic method (Human Endothelin-1 Immunoassay QuantiGlo® Kit, R&D Systems, Inc., Minneapolis, MN, USA). To minimize the confounding effect of renal blood flow and urine concentration on endothelin-1 levels, we calculate the urine endothelin-1 to creatinine ratio. The glomerular filtration rate was estimated (eGFR) by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26]. Kidney function was categorized according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification, which defines mildly decreased kidney function as an eGFR lower than 90 mL/min/1.73 $m^2$ and moderately decreased kidney function an eGFR lower than 60 mL/min/1.73 $m^2$ in at least two measurements lasting more than 3 months [27].

This study was performed adhering to the principles established in the Declaration of Helsinki. All patients read the consent document and gave their informed consent to using clinical data for research at the first visit. Before collecting data for the database, it was anonymized. The Institutional Review Board of the University of Udine approved the study protocol (protocol number 141/2022).

*Statistical Analysis*

Patients' data were summarized as mean and standard deviation for normally distributed variables or as median and interquartile range (IQR) for skewed ones. Discrete or qualitative variables were summarized as counts and percentages. Correlation analysis was performed by calculating the Pearson's or Spearman's correlation coefficient for normally or not-normally distributed variables, respectively. Variables' mean difference before and after bosentan treatment was assessed by the two-tailed Student's *t* test or the Wilcoxon signed-rank test for paired samples according to variable distribution. The comparison of proportions was performed with the Fisher's exact test. Univariate and multivariate analyses were performed with linear or logistic regression models for continuous or binomial independent variables, respectively. To analyze factors associated with RRI or eGFR change, a sensitive analysis was performed after dividing patients who reduced or did not reduce RRI or eGFR after treatment. A sample size of 15 patients was estimated based on an expected RRI change (effect size) of 0.05 for the primary outcome, considering a population standard deviation of RRI of 0.07, a within-patient correlation of 0.60 based on previous studies [12, 13, 28], and a type I and II error probability of 5% and 20%, respectively. A probability of accepting the null hypothesis equal to or lower than 0.05 or a 95% confidence interval that does not cross the zero point were considered statistically significant to determine a true difference. The statistical analysis was performed with R software version 4.2.1 (R Core Team, R Foundation for Statistical Computing, Vienna, Austria) [29].

## Results

At enrollment, 27 patients were included in the study, but six were dropped because of exclusion criteria. Of those excluded, 5 patients presented a secondary cause of kidney damage, and 1 had incomplete data. The included patients were 90% females of middle age with a normal body mass index, and about 19% were active smokers. The laboratory profile of the study group showed hemoglobin levels close to the low normal limit of 12.0 g/dL, a normal platelet count, glycemic profile, and cholesterol levels, and low inflammatory activity according to CRP and ESR values. Two-thirds of patients had elevated RRI (greater than 0.70), about one-third had mildly reduced kidney function (eGFR <90 mL/min/1.73 $m^2$), and less than 10% had moderately reduced kidney function (eGFR <60 mL/min/1.73 $m^2$). No patients had eGFR lower than 45 mL/min/1.73 $m^2$. About one-third of patients were affected by diffuse cutaneous SSc, and the other two-thirds by limited cutaneous SSc. Half of patients had a 10-year lasting disease; disease skin activity was low to mild (median Rodnan's skin score of 8); and no 1 patient presented echocardiographic signs of pulmonary hypertension. All patients presented with recurrent digital ulcers and showed hypertension at baseline; no patient was taking antihypertensive drugs or any other drug impairing hemodynamics, and no one had a history of diabetes, dyslipidemia, or cardiovascular events. Baseline clinical and laboratory characteristics of the study group are presented in Tables 1 and 2.

Variables directly associated with baseline RRI were SBP, PP, and D/S ratio, whereas the only variable directly associated with baseline eGFR was diffuse cutaneous SSc.

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**Table 1.** General clinical and laboratory characteristics of the study group at baseline

| | |
|---|---|
| *Generic variables* | |
| Age, years | 57±9 |
| Sex (female/male) | 19/2 |
| Active smokers, *n* (%) | 4 (19) |
| Body mass index, kg/m$^2$ | 24.6±4.9 |
| Serum hemoglobin, g/dL | 12.0±1.4 |
| Platelet count, 10$^3$/mm$^3$ | 249±62 |
| Serum glucose, mg/dL | 84±7 |
| Serum total cholesterol, mg/dL | 178±30 |
| Serum C-reactive protein, mg/L | 3.4 (1.2–4.8) |
| ESR, mm/h | 27 (23–38) |
| eGFR lower than 90 mL/min/1.73 m$^2$, *n* (%) | 8 (38) |
| eGFR lower than 60 mL/min/1.73 m$^2$, *n* (%) | 2 (9.5) |
| Systolic pulmonary arterial pressure, mm Hg | 29±4 |
| *SSc-associated variables* | |
| Disease duration, years | 10 (8–14) |
| Rodnan's skin score | 8 (4–17) |
| Disease subsets, *n* (%) | |
| Limited cutaneous | 13 (62) |
| Diffuse cutaneous | 8 (38) |
| Specific autoantibody, *n* (%) | |
| Anti-topoisomerase I antibody | 11 (52) |
| Anticentromere antibody | 7 (33) |
| Anti-RNA polymerase III antibody | 2 (9.5) |

Age and ESR were inversely associated with baseline eGFR (Table 3). Patients with diffuse cutaneous SSc were younger than those with limited cutaneous (51 ± 12 and 60 ± 5 years, respectively), and multivariate age correction nullified the direct relationship between diffuse cutaneous SSc and eGFR ($p = 0.232$). Age correction also reduced the relationship between baseline eGFR and log-transformed ESR ($p = 0.073$).

Bosentan treatment for 16 weeks did not change RRI (median difference after-before treatment: 0.015; IQR: −0.028 to 0.033), but it reduced SBP and DBP, MAP, PP, urinary creatinine, and eGFR and increased serum creatinine levels (Table 2). Urine endothelin-1 to creatinine ratio was increased after bosentan treatment (median difference 0.06 pg/mg, IQR −0.04 to 0.24 pg/mg, Table 2). To analyze factors associated with RRI reduction, the study group was divided into patients with reduced or no RRI after bosentan treatment (Table 4). With respect to baseline, the mean RRI reduction in patients with reduced RRI was 0.04, whereas the mean RRI increased by 0.03 in the other group. Diffuse cutaneous SSc was more prevalent in patients with reduced RRI than in the other group. No other variables showed a difference between patients with and without RRI reduction. No variables were associated with RRI reduction by the logistic regression model (Table 5). By considering reduced eGFR as a binomial independent factor, variables inversely associated with it were SBP and DBP and MAP after bosentan treatment (Table 5).

## Discussion

In patients with recurrent digital ulcers and normal or mildly decreased kidney function without albuminuria, a 16-week bosentan treatment did not alter baseline RRI. Based on prior research, we estimated that bosentan would have a 0.05 effect size on baseline RRI; nevertheless, the observed effect in this study was remarkably far from even a lower value, suggesting that bosentan may have a very negligible impact on RRI in our patients. Bosentan, on the other hand, was successful in raising the urine endothelin-1 to creatinine ratio, indicating that it effectively reduced endothelin-1's ability to bind to its receptors. In the sensitive analysis, urinary endothelin-1 tended to increase to a comparable level in both groups of patients with and without RRI reduction following bosentan treatment, which is intriguing and suggests that the effect of bosentan on endothelin-1 appeared independent of that of intrarenal hemodynamic change.

Trombetta et al. [30] previously demonstrated a lack of efficacy of bosentan in the RRI of SSc patients. The authors demonstrated that adding bosentan to a cyclic iloprost infusion to treat SSc patients with Raynaud's phenomenon did not change RRI after a 4-year treatment while improving nailfold capillary number and fingertip blood perfusion as compared to iloprost alone. This suggests that bosentan has no effect on kidney circulation, but it can improve in the long-term vascular structure and the capillary blood flow in other altered vascular regions. However, because no other studies have examined the effect of bosentan on intrarenal hemodynamics in SSc patients, the reason for the lack of an effect on lowering RRI can only be speculative. Akaishi et al. [25] previously demonstrated that the D/S ratio, a metric of arterial stiffness, was the best independent predictor of RRI. We found a strong direct association between baseline RRI, PP, and D/S ratio in our study, which validates prior data [25, 28, 31]. However, the D/S ratio changed little after bosentan treatment, suggesting a slight reduction in arterial stiffness. We reasoned that such a small change could not have an influence on intrarenal hemodynamics. Other factors could be connected to bosentan's non-selective dual inhibitory action on endothelin binding to

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**Table 2.** Within-patient difference of variables before and after 16-week bosentan treatment

| Variable | Before | After | *p* value |
|---|---|---|---|
| SBP, mm Hg | 173±15 | 146±17 | <0.001 |
| DBP, mm Hg | 97±9 | 79±9 | <0.001 |
| MAP, mm Hg | 123±10 | 101±11 | <0.001 |
| PP, mm Hg | 76±11 | 68±10 | 0.003 |
| D/S ratio | 0.563±0.044 | 0.538±0.031 | 0.006 |
| Serum creatinine, mg/dL | 0.77±0.19 | 0.89±0.26 | 0.003 |
| Urinary creatinine, mg/dL | 61±20 | 55±18 | 0.009 |
| eGFR, mL/min/1.73 $m^2$ | 92±20 | 84±24 | 0.003 |
| RRI | 0.731±0.049 | 0.730±0.054 | 0.925 |
| Urinary endothelin-1, pg/mL | 0.14±0.07 | 0.23±0.24 | 0.054 |
| Urine endothelin-1 to creatinine ratio, pg/mg | 0.27±0.15 | 0.49±0.57 | 0.032 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; D/S, diastolic to systolic blood pressure ratio; eGFR, estimated glomerular filtration rate by CKD-EPI equation; RRI, renal resistive index; *p*, probability.

**Table 3.** RRI and eGFR baseline correlation analysis with other factors

| Variable | RRI | | eGFR | |
|---|---|---|---|---|
| | *r* | *p* value | *r* | *p* value |
| Age, years | 0.266 | 0.244 | −0.584 | 0.005 |
| Female (yes/no) | −0.080 | 0.731 | −0.302 | 0.183 |
| Active smokers (yes/no) | 0.195 | 0.397 | 0.100 | 0.664 |
| Body mass index, kg/$m^2$ | 0.103 | 0.658 | −0.102 | 0.659 |
| SBP, mm Hg | 0.539 | 0.012 | −0.119 | 0.608 |
| DBP, mm Hg | 0.140 | 0.546 | −0.092 | 0.691 |
| MAP, mm Hg | 0.350 | 0.120 | −0.114 | 0.624 |
| PP, mm Hg | 0.622 | 0.003 | −0.087 | 0.707 |
| D/S ratio | −0.485 | 0.026 | 0.033 | 0.888 |
| Serum hemoglobin, g/dL | 0.266 | 0.244 | 0.223 | 0.331 |
| Platelet count, $10^3/mm^3$ | −0.011 | 0.962 | −0.241 | 0.292 |
| Serum glucose, mg/dL | 0.215 | 0.350 | 0.067 | 0.773 |
| Serum total cholesterol, mg/dL | 0.312 | 0.168 | −0.116 | 0.617 |
| Serum creatinine, mg/dL | 0.269 | 0.239 | −0.934 | <0.001 |
| eGFR, mL/min/1.73 $m^2$ | −0.288 | 0.206 | – | – |
| Serum C-reactive protein, mg/L | 0.042 | 0.856 | −0.281 | 0.218 |
| ESR, mm/h | 0.253 | 0.268 | −0.499 | 0.021 |
| Urinary endothelin-1, pg/mL | 0.241 | 0.293 | −0.157 | 0.496 |
| Urine endothelin-1 to creatinine ratio, pg/mg | 0.233 | 0.310 | −0.059 | 0.799 |
| RRI | – | – | −0.287 | 0.206 |
| SSc-disease duration, years | 0.025 | 0.915 | −0.336 | 0.137 |
| Rodnan's skin score | −0.170 | 0.461 | 0.213 | 0.355 |
| Systolic pulmonary arterial pressure, mm Hg | −0.053 | 0.820 | 0.314 | 0.166 |
| Diffuse cutaneous SSc (yes/no) | 0.259 | 0.257 | 0.477 | 0.029 |
| Anti-topoisomerase I antibody (yes/no) | −0.011 | 0.964 | 0.194 | 0.400 |
| Anticentromere antibody (yes/no) | −0.016 | 0.946 | −0.058 | 0.801 |
| Anti-RNA polymerase III antibody (yes/no) | −0.165 | 0.474 | 0.009 | 0.969 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; D/S, diastolic to systolic blood pressure ratio; eGFR, estimated glomerular filtration rate by CKD-EPI equation; SSc, systemic sclerosis; RRI, renal resistive index; *r*, correlation coefficient; *p*, probability.

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**Table 4.** Sensitive analysis according to RRI reduction or not after treatment

| Variable | RRI not reduced | RRI reduced | *p* value |
|---|---|---|---|
| | *n* = 12 | *n* = 9 | – |
| RRI | 0.033±0.017 | −0.038±0.022 | <0.001 |
| Age, years | 58±8 | 54±11 | 0.415 |
| Female, *n* (%) | 11 (92) | 8 (89) | 0.999 |
| Active smokers, *n* (%) | 3 (25) | 1 (11) | 0.603 |
| Body mass index, kg/m$^2$ | 23.7±3.1 | 25.8±6.7 | 0.401 |
| SBP before treatment, mm Hg | 169±15 | 179±14 | 0.113 |
| SBP after treatment, mm Hg | 142±16 | 152±17 | 0.166 |
| DBP before treatment, mm Hg | 96±9 | 99±9 | 0.524 |
| DBP after treatment, mm Hg | 76±9 | 82±9 | 0.187 |
| MAP before treatment, mm Hg | 120±10 | 126±11 | 0.257 |
| MAP after treatment, mm Hg | 98±11 | 105±11 | 0.159 |
| PP before treatment, mm Hg | 73±13 | 81±7 | 0.079 |
| PP after treatment, mm Hg | 66±10 | 71±11 | 0.275 |
| D/S ratio before treatment | 0.572±0.054 | 0.551±0.021 | 0.229 |
| D/S ratio after treatment | 0.539±0.032 | 0.537±0.032 | 0.912 |
| Serum hemoglobin, g/dL | 11.9±1.4 | 12.1±1.4 | 0.740 |
| Platelets, 10$^3$/mm$^3$ | 252±75 | 245±41 | 0.778 |
| Serum glucose, mg/dL | 83±5 | 86±9 | 0.363 |
| Serum total cholesterol, mg/dL | 181±33 | 176±29 | 0.714 |
| Serum creatinine before treatment, mg/dL | 0.78±0.16 | 0.76±0.24 | 0.766 |
| Serum creatinine after treatment, mg/dL | 0.85±0.19 | 0.88±0.29 | 0.805 |
| eGFR before treatment, mL/min/1.73 m$^2$ | 90±18 | 95±24 | 0.586 |
| eGFR after treatment, mL/min/1.73 m$^2$ | 83±19 | 87±27 | 0.727 |
| Log ESR, mm/h | 26 (23–35) | 30 (23–38) | 0.887 |
| Log serum C-reactive protein, mg/L | 3.4 (1.1–5.8) | 2.0 (1.3–4.6) | 0.754 |
| Urine endothelin-1 to creatinine ratio before treatment, pg/mg | 0.28±0.16 | 0.25±0.15 | 0.671 |
| Urine endothelin-1 to creatinine ratio after treatment, pg/mg | 0.54±0.70 | 0.44±0.46 | 0.523 |
| RRI before treatment | 0.718±0.053 | 0.748±0.040 | 0.151 |
| RRI after treatment | 0.750±0.052 | 0.710±0.047 | 0.079 |
| SSc-disease duration, years | 10 (8–14) | 8 (8–18) | 0.668 |
| Rodnan's skin score | 8 (4–14) | 9 (6–17) | 0.593 |
| Systolic pulmonary arterial pressure, mm Hg | 29±4 | 30±5 | 0.588 |
| Diffuse cutaneous SSc subtype, *n* (%) | 2 (17) | 6 (67) | 0.032 |
| Anti-topoisomerase I antibody, *n* (%) | 4 (33) | 7 (78) | 0.081 |
| Anticentromere antibody, *n* (%) | 5 (42) | 2 (22) | 0.642 |
| Anti-RNA polymerase III antibody, *n* (%) | 1 (8.3) | 1 (11) | 0.999 |

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; D/S, diastolic to systolic blood pressure ratio; eGFR, estimated glomerular filtration rate by CKD-EPI equation; SSc, systemic sclerosis; RRI, renal resistive index; *p*, probability.

type A and B receptors. Despite the fact that type A receptors cause vasoconstriction in the kidney cortical circulation, type B receptors cause the opposite in the medulla [32]. As a result, the net effect of bosentan on RRI, measured as the average of multiple samplings in different regional blood flows, may be null.

In this study, we chose SSc patients with digital ulcers because bosentan is indicated and reimbursed in these patients by the Italian Drug Agency, and the presence of digital ulcers is a marker of vascular dysfunction and blood flow impairment [33]. In middle-aged subjects, an RRI value higher than 0.70 has been considered abnormal [28], and it has frequently been seen in middle-aged patients with SSc [13, 33]. Additionally, in several investigations [9, 33], an elevated RRI has been linked to the existence of a more advanced SSc-related vasculopathy. Our findings support these observations because all of our patients presented with recurrent digital ulcers as an advanced vascular consequence of SSc and had a mean baseline RRI greater than 0.70. These results imply that RRI may be a

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**Table 5.** Sensitive analysis by univariate logistic regression

| Variable | Reduced RRI | | Reduced eGFR | |
|---|---|---|---|---|
| | OR (95% CI) | *p* value | OR (95% CI) | *p* value |
| Age (every 1 SD), years | 0.86 (0.31–2.24) | 0.751 | 0.43 (0.08–1.34) | 0.217 |
| Female (yes/no) | 0.90 (0.03–25.1) | 0.944 | NA | NA |
| Active smokers (yes/no) | 0.30 (0.01–2.86) | 0.332 | 1.64 (0.16–37.2) | 0.696 |
| Body mass index (every 1 SD), kg/m$^2$ | 1.76 (0.70–5.70) | 0.267 | 1.30 (0.50–3.88) | 0.603 |
| SBP before treatment (every 1 SD), mm Hg | 2.81 (1.04–10.5) | 0.070 | 0.43 (0.12–1.16) | 0.127 |
| SBP after treatment (every 1 SD), mm Hg | 2.01 (0.80–5.93) | 0.160 | 0.23 (0.07–0.79) | 0.032 |
| DBP before treatment (every 1 SD), mm Hg | 1.45 (0.60–3.86) | 0.427 | 0.29 (0.05–0.91) | 0.070 |
| DBP after treatment (every 1 SD), mm Hg | 1.95 (0.78–5.88) | 0.181 | 0.26 (0.06–0.77) | 0.035 |
| MAP before treatment (every 1 SD), mm Hg | 2.02 (0.80–6.24) | 0.163 | 0.31 (0.07–0.94) | 0.071 |
| MAP after treatment (every 1 SD), mm Hg | 2.06 (0.81–6.43) | 0.157 | 0.23 (0.04–0.72) | 0.032 |
| PP before treatment (every 1 SD), mm Hg | 3.51 (1.12–21.1) | 0.081 | 0.75 (0.23–1.92) | 0.574 |
| PP after treatment (every 1 SD), mm Hg | 1.71 (0.70–4.93) | 0.262 | 0.41 (0.12–1.08) | 0.101 |
| D/S ratio before treatment (every 1 SD) | 0.55 (0.14–1.43) | 0.277 | 0.90 (0.36–2.28) | 0.813 |
| D/S ratio after treatment (every 1 SD) | 0.95 (0.37–2.51) | 0.906 | 0.96 (0.35–2.42) | 0.933 |
| Serum hemoglobin (every 1 SD), g/dL | 1.13 (0.58–2.24) | 0.724 | 0.67 (0.31–1.31) | 0.258 |
| Platelet count (every 1 SD), $10^3$/mm$^3$ | 0.98 (0.84–1.13) | 0.782 | 1.06 (0.92–1.25) | 0.460 |
| Serum glucose (every 1 SD), mg/dL | 1.63 (0.67–4.46) | 0.296 | 0.44 (0.14–1.16) | 0.120 |
| Serum total cholesterol (every 1 SD), mg/dL | 0.85 (0.34–2.06) | 0.712 | 0.47 (0.14–1.25) | 0.158 |
| Serum creatinine before treatment (every 1 SD), mg/dL | 0.89 (0.34–2.19) | 0.791 | 0.89 (0.35–2.41) | 0.806 |
| Serum creatinine after treatment (every 1 SD), mg/dL | 1.13 (0.45–2.90) | 0.781 | 2.32 (0.83–10.5) | 0.170 |
| eGFR before treatment (every 1 SD), mL/min/1.73 m$^2$ | 1.16 (0.48–3.02) | 0.738 | 1.45 (0.57–3.96) | 0.437 |
| eGFR after treatment (every 1 SD), mL/min/1.73 m$^2$ | 1.20 (0.49–3.16) | 0.694 | 0.59 (0.19–1.47) | 0.284 |
| Log serum c-reactive protein (every 1 log), mg/L | 1.05 (0.41–2.71) | 0.920 | 1.40 (0.53–4.10) | 0.505 |
| Log ESR (every 1 log), mm/h | 0.84 (012–5.32) | 0.845 | 3.52 (0.54–37.0) | 0.224 |
| Urinary endothelin-1 before treatment (every 1 SD), pg/mL | 1.14 (0.44–3.10) | 0.768 | 0.68 (0.21–1.69) | 0.424 |
| Urinary endothelin-1 after treatment (every 1 SD), pg/mL | 1.12 (0.43–2.96) | 0.804 | 0.16 (0.01–0.75) | 0.088 |
| RRI before treatment (every 1 SD) | 1.58 (0.65–4.35) | 0.334 | 0.39 (0.11–1.08) | 0.097 |
| RRI after treatment (every 1 SD) | 0.39 (0.11–1.06) | 0.095 | 0.74 (0.28–1.80) | 0.506 |
| SSc-disease duration (every 1 SD), years | 0.74 (0.21–2.19) | 0.584 | 0.73 (0.19–2.30) | 0.606 |
| Rodnan's skin score (every 1 SD) | 1.88 (0.65–6.29) | 0.261 | 2.34 (0.76–8.72) | 0.159 |
| Systolic pulmonary arterial pressure (every 1 SD), mm Hg | 1.07 (0.87–1.35) | 0.555 | 0.93 (0.73–1.14) | 0.491 |
| Diffuse cutaneous SSc subtype (yes/no) | 6.75 (1.04–62.8) | 0.060 | 1.88 (0.29–16.4) | 0.528 |
| Anti-topoisomerase I antibody (yes/no) | 4.08 (0.70–29.1) | 0.131 | 1.78 (0.29–12.2) | 0.538 |
| Anticentromere antibody (yes/no) | 0.30 (0.03–1.94) | 0.227 | 0.53 (0.08–3.73) | 0.515 |
| Anti-RNA polymerase III antibody (yes/no) | NA | NA | NA | NA |

SBP, systolic blood pressure; DBP, diastolic blood pressure; MAP, mean arterial pressure; PP, pulse pressure; D/S, diastolic to systolic blood pressure ratio; eGFR, estimated glomerular filtration rate by CKD-EPI equation; SSc, systemic sclerosis; RRI, renal resistive index; OR, odds ratio; CI, confidence interval; SD, standard deviation; *p*, probability; NA, not applicable because of a too low proportion in one group.

measure of the overall health of the microcirculation in SSc patients and that a high RRI may indicate latent intrarenal vascular damage before the manifestation of classic kidney disease signs, such as albuminuria or a decline in kidney function. This could explain the reason for the relative high prevalence of kidney disease in SSc patients when glomerular filtration rate is appropriately estimated [4].

In this study, we observed that bosentan treatment was associated at the same time with systemic blood pressure reduction and kidney function decline. In addition, in the sensitive analysis, the lower the SBP, DBP, or mean blood pressure after bosentan treatment, the higher the probability of kidney function decline, thus linking blood pressure reduction to kidney function decline. Bosentan has been shown to reduce systemic blood pressure in patients with resistant hypertension [34] or with diabetes complicated by albuminuria [35], but in all of these studies, its effect on blood pressure was not associated with any change in creatinine levels. This might suggest that in our SSc



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patients, high RRI indicates damaged intrarenal circulation with impaired capacity to adapt to changes in renal blood flow, as can be observed in ischemic kidney disease with or without renal artery stenosis [12, 36]. In ischemic kidney disease, renal blood flow is sustained by angiotensin II, and ACE-inhibitors reduce eGFR because they counteract this compensatory mechanism [37]. Analogously, in SSc patients, the renal blood flow seems to be sustained by endothelin-1. An interesting experimental model has been shown in the spontaneously hypertensive rat in which the authors found an overexpression of endothelin type A receptor in the glomeruli and smooth muscle cells of intrarenal arteries and an upregulation of the type B receptor only in the glomeruli that were responsible for the reduced MAP and eGFR after bosentan treatment [38].

Several mechanisms have been suggested as responsible for the kidney disease in the ischemic kidney despite renal artery stenosis, mechanisms that can also be enhanced in SSc patients. In particular, increased production of reactive oxygen species and oxidative stress, increased kidney fibrosis and matrix turnover, and the ischemia/reperfusion injury phenomenon seem to play a central pathophysiological role [36, 39]. Regarding this point, the intravenous infusion of the antioxidant N-acetyl-cysteine in SSc patients without advanced vasculopathy was able to reduce RRI, suggesting the importance of oxidative stress in regulating intrarenal hemodynamics in not complicated SSc patients [40].

This study had several limits to discuss. The first important limit was the lack of a control group. A control group would have been useful to assess the real effects of treatment on outcomes by excluding casual variations and quantifying the regression to the mean phenomenon, typical of a prospective study. However, regarding the main outcome of this study, the lack of even a small change in RRI with bosentan would not have been interpreted differently with a control group. On the other hand, bosentan effects on blood pressure and kidney function without a control group must be taken cautiously. The second important limit was that blood pressure was measured before RRI evaluation and not at the same time as RRI evaluation. Therefore, systemic hemodynamics could not reflect the instant hemodynamic situation at the moment of RRI evaluation. However, whether or not this could have affected our results is not clear. Probably, the use of other noninvasive methods of continuous systemic blood pressure evaluation, such as ambulatory or beat-to-beat blood pressure monitoring, might have better represented the relationship between intrarenal and systemic hemodynamic changes [41, 42]. Third, we did not have data about albuminuria after bosentan treatment. Therefore, we were not able to assess new-onset albuminuria as a marker of kidney damage progression. However, we considered 16 weeks of bosentan treatment too short for observing significant effects on kidney damage beyond eGFR changes [43]. Forth, we used bosentan because of its indication in patients with recurrent digital ulcers. Therefore, we included only patients with a documented advanced SSc-associated vasculopathy in which bosentan and other vasodilator substances have already failed to modify RRI. Further studies should assess bosentan or other endothelin-1 receptor antagonist effects on kidney protection in early disease, probably when RRI is lower than 0.70.

In conclusion, despite urinary endothelin-1 rises and systemic blood pressure decreases, bosentan treatment for 16 weeks has no effect on the RRI of patients with recurrent digital ulcers and normal to mildly decreased kidney function. The high baseline RRI and the declining kidney function in response to reduced blood pressure suggest subclinical intrarenal vascular damage with the characteristics of ischemic kidney disease without renal artery stenosis, even though SSc patients with recurrent digital ulcers do not exhibit any symptoms of chronic kidney disease. Endothelin-1 may act as a significant compensatory mechanism in these patients to maintain the renal blood flow. Whether long-term effects of endothelin-1 receptor antagonists on blood pressure levels and kidney function could exert or not a beneficial effect on kidney disease progression should be the aim of future studies.

## Statement of Ethics

All authors have read and adhered to the journal's ethical standards statement for submitted manuscripts. The research was conducted in accordance with the Declaration of Helsinki's guiding principles. At the initial appointment, all patients read the consent document and gave their written informed consent to the use of their clinical data for research. Before data for the database were collected, they were anonymized. The Institutional Review Board of the University of Udine has authorized protocol number 141/2022.

## Conflict of Interest Statement

The authors affirm that they have no conflicts of interest to disclose regarding the information in this publication.

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## Author Contributions

E.D.P., G.C., M.B., I.G., G.F.F., E.G., S.D.V., and G.R. contributed to the elaboration of the study protocol, the clinical evaluation of the participating patients, the evaluation of the results, and the discussion/conclusions of the study itself. B.T. contributed by performing all the protocol-required laboratory biohumoral assays.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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