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ORIGINAL RESEARCH

Vasodilator drugs and heart-related outcomes in systemic sclerosis: an exploratory analysis

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ABSTRACT

Background and aims Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by excessive extracellular matrix deposition and widespread skin and internal organ fibrosis including various cardiac manifestations. Heart involvement is one of the leading causes of death among patients with SSc. In this study, we aimed to assess the effect of various vasodilator treatments.

Methods We used data from a national multicentric prospective study using the French SSc national database. We estimated the average treatment effect (ATE) of sildenafil, bosentan, angiotensin-converting enzyme (ACE) inhibitors and iloprost on diastolic dysfunction, altered ejection fraction <50% and pulmonary arterial hypertension (PAH) using a causal method, namely the longitudinal targeted minimum loss-based estimation, to adjust for confounding and informative censoring.

Results We included 1048 patients with available data regarding treatment. Regarding sildenafil analyses, the ATE on diastolic dysfunction at 3 years was -2.83% (95% CI -4.06 ; -1.60 , $p < 0.00001$), and the estimated ATE on altered ejection fraction <50% was -0.88% (95% CI -1.70 ; -0.05 , $p = 0.037$). We did not find a significant effect on PAH. Regarding bosentan, ACE inhibitors and iloprost, none of them neither showed a significant effect on diastolic dysfunction, altered ejection fraction <50% or PAH.

Conclusions Using causal methods, our study is the first and largest suggesting that sildenafil might have benefits among SSc patients regarding diastolic dysfunction and altered ejection fraction occurrence. However, further studies assessing the effect of vasodilators on heart-related outcome among SSc patients are needed to confirm those exploratory results.

INTRODUCTION

Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterised by excessive

WHAT IS ALREADY KNOWN ON THIS TOPIC

- ⇒ Systemic sclerosis (SSc) patients frequently develop cardiac involvement such as diastolic dysfunction, reduced left ventricular ejection fraction and pulmonary arterial hypertension, significantly impacting morbidity and mortality.
- ⇒ Vasodilators such as sildenafil, bosentan, angiotensin-converting enzyme inhibitors and iloprost are commonly prescribed for vascular complications in SSc, but their effects on cardiac outcomes remain unclear.
- ⇒ Prior research has not thoroughly investigated the impact of these vasodilators on heart-related outcomes in SSc patients.

WHAT THIS STUDY ADDS

- ⇒ The study found that sildenafil use in SSc patients was associated with a reduced incidence of diastolic dysfunction and altered ejection fraction <50% over a 3-year period.
- ⇒ No significant effects on cardiac outcomes were observed with the use of bosentan, ACE inhibitors or iloprost.
- ⇒ These findings suggest a potential cardioprotective role for sildenafil in patients with SSc.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- ⇒ The results underscore the need for further research into sildenafil as a treatment option for cardiac involvement in SSc.

extracellular matrix deposition with widespread skin internal organ fibrosis and small and large arterial vasculopathy. Patients with

SSc exhibit various cardiac manifestations associated with different prognostic significance, making it difficult to estimate overall cardiac disease and its manifestations.¹ The relations between confounders, treatment European Scleroderma Trials and Research group (EUSTAR) international cohort estimated an overall 5.4% prevalence of reduced left ventricular ejection fraction (LVEF).² The presence of diastolic dysfunction in patients with SSc has been largely assessed in the literature, with a prevalence ranging from 17% to 30%.^{3–5} Furthermore, the onset of these manifestations can be either primary or secondary to other complications associated with SSc such as pulmonary arterial hypertension (PAH) or cardiovascular risk factors, though definitions of primary heart involvement in SSc patients still lack a standardised consensus.⁶ However, data from national death registries and the EUSTAR cohort suggest that nearly 30% of mortality is attributable to cardiac causes and/or pulmonary arterial damages among SSc patients⁷ and no treatment has proven to have an effect on heart involvement yet.⁸ Moreover, a significant part of SSc morbidity and disability is related to the acral ischaemic vasculopathy of the disease. This led to the proposition of specific vascular targeting drugs, including vasodilators, which are frequently co-prescribed with other drugs used for common cardiovascular comorbidities. The detailed and overall cardiac and pulmonary arterial outcomes achieved with these various pharmacological measures should be delineated

in SSc patients. Therefore, we aimed to take advantage of this French nationwide prospective SSc cohort to assess the effect of vasodilator treatments, that is, sildenafil, bosentan, angiotensin-converting enzyme (ACE) inhibitors and iloprost on diastolic dysfunction, altered ejection fraction <50% and PAH using a machine-learning based method to address for confounding.

PATIENTS AND METHODS

Study design

The French SSc national prospective database is a multi-centre observational study that enrolled consecutive SSc patients in 42 French hospital centres.⁹ The study collected data prospectively since 2010 using a standardised form, which was recorded in an online database (Clean Web). The inclusion criteria for patients with SSc were based on the American College of Rheumatology (ACR) 1980¹⁰ and/or 2013-ACR/EULAR SSc classification criteria.¹¹ We excluded patients with localised scleroderma, patient with no information regarding their heart status or treatment or patients with date inconsistencies (figure 1). The study was approved by the institutional ethical committee (Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé; approval no.13.145; Advisory Committee on Information Processing in Material Research in the Field of Health) and met the data

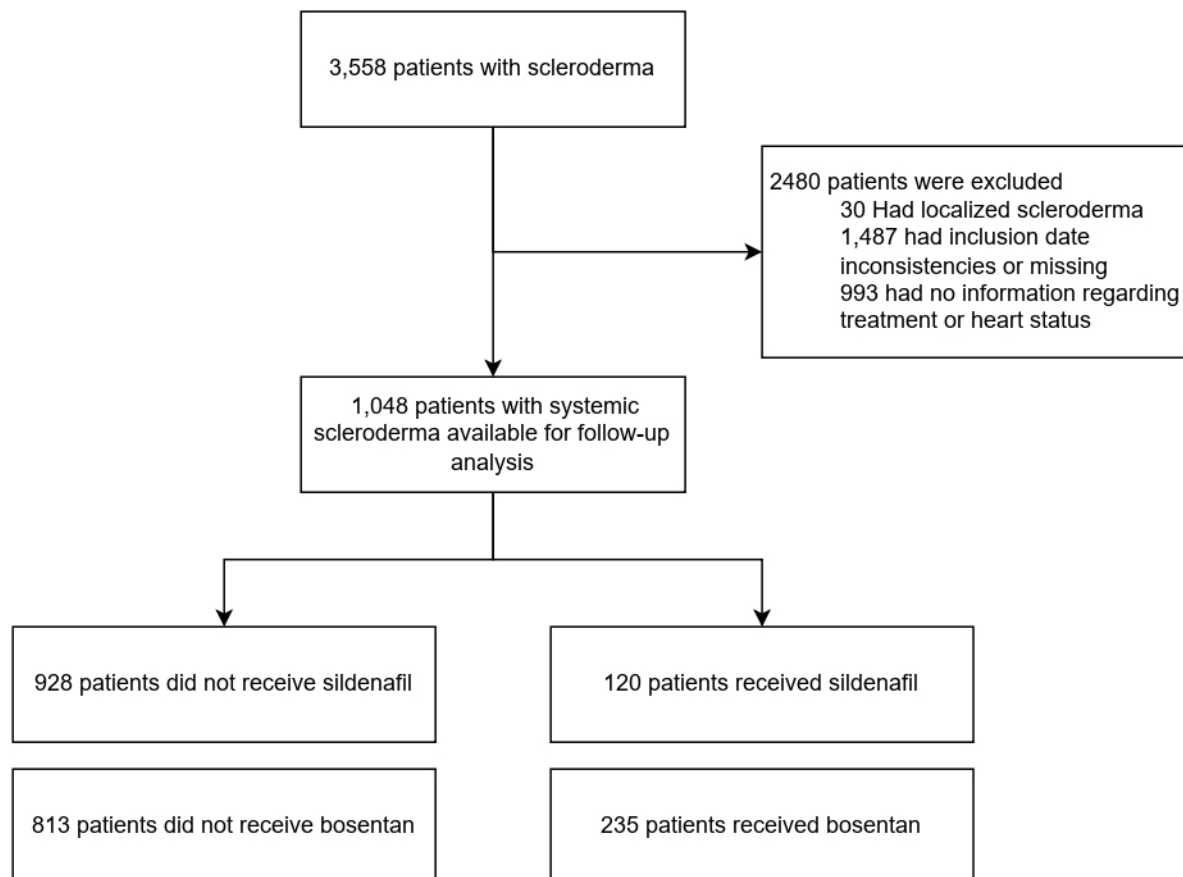


Figure 1 Flowchart.

protection requirements of the National Information science and Liberties Commission (recorded under no. 914607). Patients provided standard consent for the use of their data.

Data collection and outcomes

Data was extracted in May 2019 from the French database and included demographics, cardiovascular risk factors (smoking status, high blood pressure and body mass index (BMI)), associated diseases, dates of first Raynaud phenomenon (RP) and first non-RP symptoms, cutaneous subset and autoantibody status (such as anti-topoisomerase I, anti-centromere, anti-RNA polymerase III, anti-PM/Scl and other autoantibodies). We recorded the following data regarding organ involvements: ischaemic heart disease defined as any history of coronary artery disease or myocardial infarction, skin involvement measured by modified Rodnan skin score (mRSS); lung involvement as any interstitial lung disease (ILD) diagnosed on high-resolution CT or chest X-ray; ischaemic heart disease included patients with a history of coronary artery disease or myocardial infarction; muscle involvement including myalgia, muscle weakness and amyotrophy; digital ulcer (DU) defined as any history or active DU, digital tip ulcer, pitting scar or digital ischemia; and scleroderma renal crisis (SRC) defined by new onset hypertension ($\geq 150/85$ mm Hg) associated with a decrease in renal function defined by a decrement of at least 10% in the estimated glomerular filtration rate. Elevated creatine kinase was defined according to laboratory thresholds. Elevated natriuretic peptide was defined as brain natriuretic peptide (BNP) level >35 pg/mL or N-terminal pro-BNP >125 pg/mL. LVEF and diastolic function were assessed at baseline and through follow-up with transthoracic echocardiography (TTE). PAH was defined as mean pulmonary arterial pressure >25 mm Hg at rest measured by right heart catheterisation.

Disease duration was defined as the time between the first non-RP symptom reported by the patient and the inclusion visit. The following treatment administration were recorded: sildenafil, bosentan, ACE inhibitors, steroids, iloprost, mycophenolate mofetil, cyclophosphamide, tumour necrosis factor (inhibitors and rituximab). Patients were considered treated with iloprost if they received at least one perfusion of iloprost.

Statistical analysis

Continuous variables were expressed as medians (IQR), and qualitative variables were expressed as numbers (proportions). Qualitative variables and quantitative variables were compared using Fisher tests and Kruskal-Wallis tests, respectively. Then, we estimated the average treatment effect (ATE) at 3 years of four different treatments (sildenafil, bosentan, ACE inhibitors and iloprost) regarding three heart-related outcomes (diastolic dysfunction, altered ejection fraction $<50\%$, and PAH) using longitudinal targeted minimum loss-based estimation (LTMLE) and superlearning to adjust on

confounding and informative censoring.¹² The ATE is the adjusted mean difference of the interest outcome between patients who received treatment and those who did not. The LTMLE is a plug-in, semiparametric, double-robust estimator that has desirable statistical properties to estimate ATE: reducing the bias of an initial estimate by allowing for flexible estimation using nonparametric data-adaptive machine-learning methods to target an estimate closer to the true model specification.^{13 14} Those approaches might allow to explore associations that simpler regression such as the Cox model would not be able to capture.¹⁵ Using an ensemble of machine learning models through the super learner algorithm,¹⁶ we estimated two components of LTMLE: (1) the probability of treatment allocation and remaining uncensored conditional on covariates and (2) average counterfactual outcome if patients received treatment among three time points (at 1, 2 and 3 years of follow-up). We considered a set of baseline covariates that may be associated with treatment or the risk of cardiac related outcomes: age at inclusion, female sex, BMI, tobacco status, the presence of arterial hypertension, dyspnoea, muscle involvement, ILD, ischaemic heart disease, pericarditis, diastolic dysfunction, pulmonary arterial hypertension, LVEF 50% , history of past DU, anti-nuclear antibodies, anti-topoisomerase I antibodies, limited or diffuse form of SSc, diffusing capacity of the lung for carbon monoxide (DLCO) % of theoretical value, creatinine levels, the disease duration, any associated autoimmune disease, concomitant use of sildenafil, bosentan, iloprost, ACE inhibitors, steroids, cyclophosphamide, mycophenolate mofetil or rituximab (details provided in online supplemental table S1). For each outcome analysis, patient with prevalent outcome at baseline were excluded. Online supplemental figure S1 illustrates the relations between confounders, treatment and outcomes at years 1, 2 and 3. Analyses were performed using the SuperLearner and ltmle R packages.^{17 18} To account for missing data, we used multiple imputation with chained equations using the R 'MICE' package (V.3.5.0) in R and pooled across five imputed data sets. Further details are provided in online supplemental method S1 regarding LTMLE methodology.

Kaplan-Meier estimator was used to generate survival curves and compute survival rates. Event-free survivals were defined as the time from inclusion until the respective event or the date of last follow-up, right-censored at 3 years. Log-rank tests were used to compare outcome event-free survivals among patient with and without the treatment of interest (sildenafil, bosentan, ACE inhibitors and iloprost). All analyses were performed using R software V.4.2.2 for Mac (Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Over the 3558 patients of the French SSc national database, we included 1048 patients with available data regarding treatment and heart status (figure 1).

Baseline population and treatment

The median age of the total population was 55 years (IQR: 44; 65), mainly women (n=844, 80.5%). Regarding cardiovascular risk factors, 205 patients (21%) had arterial hypertension, and 342 patients were smokers (35.3%). Among them, 221 patients (22.0%) had a diffuse cutaneous SSc, with a median mRSs of 4² 11 and a median disease duration at baseline of 0.39 years (0.00; 4.35). Half of them had anti-centromere antibodies (n=433, 46.2%), a third had anti-topoisomerase I antibodies (n=267, 28.4%), and a few had anti-RNA pol3 antibodies (n=22, 5.8%). Regarding organ involvements, 378 patients had ILD (38.1%) with a median DLCO of 70% of theoretical value (IQR: 54; 81), 68 patients had pulmonary arterial hypertension at baseline (7.6%), 46 patients (6.1%) had left ventricular diastolic dysfunction, 40 patients (n=4.1%), 11 had atrio-ventricular block (1.4%), and 25 had arrhythmia (3.1%), with a median LVEF of 65% (IQR: 60; 70). Further details are available in table 1.

Among the cohort, 120 patients had sildenafil (11.5%), and 928 patients did not (88.5%). Patients with sildenafil had more frequently a diffuse cutaneous SSc (n=35, 31.2% vs n=186, 20.8%, p=0.015) with a higher disease duration at baseline (median in years (IQR): 1.57 (0.03; 6.51) vs 0.33 (0.00; 3.93), p=0.008), had more frequently past history of DUs (n=44, 45.4% vs n=260, 30.3%, p=0.004) and more frequently pulmonary arterial hypertension at baseline (n=30, 34.1% vs n=38, 4.7%, p<0.001). Also, 235 patients were treated with bosentan (22.4%), whereas 813 patients (77.6%) did not receive bosentan. Patients with bosentan were more frequently male (n=69 (29.4%) vs n=135 (16.6%), p<0.001), with more frequently diffuse cutaneous SSc (n=69, 31.1% vs n=152, 19.4%, p<0.001) with a higher disease duration at baseline (median in years (IQR): 1.11 (0.03, 5.57) vs 0.30 (0.00, 4.07), p=0.006). They had more frequently ILD (n=112, 51.4% vs n=266, 34.4, p<0.001) and more frequently pericarditis (n=48, 25.0% vs n=25, 3.3%, p=0.03). Further details are provided in table 1. Regarding other treatments, 257 patients (25.6%) received ACE inhibitor and 143 patients received iloprost (14.1%). Details of baseline characteristics are provided in online supplemental table S2.

Sildenafil and heart-related outcomes

Regarding the diastolic dysfunction survival analysis, three patients presented diastolic dysfunction at 3 years in the sildenafil group (3-year event rate: 2.67%; 95% CI 0; 5.61), whereas 40 patients presented diastolic dysfunction (3-year event rate: 4.89% (3.4; 6.37)) in the group without sildenafil (figure 2). The estimated ATE on diastolic dysfunction at 3 years was -2.83% (95% CI -4.06; -1.60, p<0.00001).

Regarding altered ejection fraction <50% survival analysis, one patient presented an altered EF <50% at 3 years in the sildenafil group (3-year event rate: 0.83% (95% CI 0; 2.45)) versus 13 patients in the other group (3-year event rate: 1.57% (95% CI 0.71; 2.41)). The estimated ATE on altered ejection fraction <50% at 3 years was -0.88% (95% CI -1.70; -0.05, p=0.037).

Regarding PAH, the estimated ATE on PAH at 3 years if patients received sildenafil was not significantly different from zero (ATE at 3 years (-0.939%; 95% CI -6.41; 4.53, p=0.74); 3-year event rate (n=3, 3.44% (95% CI 0; 7.2) and n=32, 3.92% (95% CI 2.57; 5.25))) in patients with and without sildenafil, respectively). Further details are available in table 2 and online supplemental table S3-S5.

Bosentan, angiotensin-converting enzyme (ACE) inhibitors and iloprost

Regarding bosentan analysis, we did not find any significant estimated average treatment difference at 3 years, either for diastolic dysfunction (ATE at 3 years: -0.31, 95% CI -3.69; 3.08, p=0.86), for reduced EF <50% (ATE at 3 years: -1.10%, 95% CI -2.71; 0.52, p=0.18) nor PAH (ATE at 3 years: -1.55%, 95% CI -3.40; 0.29, p=0.10). We did not find any significant estimated average treatment difference at 3 years regarding ACE inhibitors and iloprost among diastolic dysfunction, reduced EF <50% or PAH (table 2 and online supplemental table S3-S5). Figure 3 provides Kaplan-Meier curves of heart-related cumulative incidence among treated and untreated patients.

DISCUSSION

In our study, patients treated with sildenafil seemed to have less diastolic dysfunction and less LVEF <50% than those untreated, but we did not find any difference regarding PAH incidence. On the other hand, we did not find a significant effect on diastolic dysfunction, LVEF <50% or PAH among patients treated with bosentan, ACE inhibitors or iloprost.

To our knowledge, our study is the first one investigating the effects of vasodilators on heart-related outcomes in SSc patients. Clinical trials assessing cardioprotective treatments, such as anti-platelet therapy, anti-hypertensives or lipid-lowering drugs, require the recruitment of large cohorts of several thousand patients with regular and long duration follow-up. Those designs are impossible to build in autoimmune disease populations for various reasons, such as small cohort sizes or insufficient follow-up time to observe cardiovascular events of interest. This is why we use LTMLE, a plug-in, semiparametric, double-robust estimator, allowing us to estimate ATE while adjusting for confounders using nonparametric data-adaptive machine-learning methods to target an estimate closer to the true model specification.^{13 14 19} It allowed us to capture a supposed effect of sildenafil on diastolic dysfunction and altered EF >50%.

Vasodilators are widely used in SSc for various indications, especially for Raynaud's phenomenon, DUs and



Table 1 Baseline characteristics of SSc patients with and without sildenafil or bosentan

	Overall (n=1048)	No sildenafil (n=928)	Sildenafil (n=120)	P value*	No bosentan (n=813)	Bosentan (n=235)	P value†
Age, years median (IQR)	54.79 (43.66, 64.93)	54.66 (43.43, 64.61)	57.04 (47.81, 68.01)	0.185	55.26 (43.73, 64.55)	53.62 (43.56, 66.50)	0.915
Male, n (%)	204 (19.5)	177 (19.1)	27 (22.5)	0.391	135 (16.6)	69 (29.4)	<0.001
Tobacco use, n (%)	342 (35.3)	301 (34.8)	41 (40.2)	0.276	258 (34.2)	84 (39.4)	0.168
Body mass index (kg/m ²)	23.68 (20.96, 27.08)	23.59 (20.93, 27.06)	24.17 (21.21, 27.28)	0.181	23.72 (21.11, 26.92)	23.66 (20.57, 27.92)	0.624
Arterial hypertension, n (%)	205 (21.0)	177 (20.2)	28 (28.0)	0.091	155 (20.3)	50 (23.7)	0.294
Diffuse cutaneous SSc, n (%)	221 (22.0)	186 (20.8)	35 (31.2)	0.015	152 (19.4)	69 (31.1)	<0.001
Disease duration, median (IQR), years	0.39 (0.00, 4.35)	0.33 (0.00, 3.93)	1.57 (0.03, 6.51)	0.008	0.30 (0.00, 4.07)	1.11 (0.03, 5.57)	0.006
mRSS, median (IQR)	4.00 (2.00, 11.00)	4.00 (2.00, 10.00)	6.00 (2.00, 16.75)	0.168	4.00 (2.00, 9.00)	6.50 (3.00, 16.25)	<0.001
History of digital ulcers, n (%)	304 (31.8)	260 (30.3)	44 (45.4)	0.004	204 (27.1)	100 (49.0)	<0.001
Active digital ulcers, n (%)	171 (18.2)	150 (17.8)	21 (21.9)	0.33	112 (15.1)	59 (29.6)	<0.001
Telangiectasias, n (%)	481 (50.4)	421 (49.2)	60 (60.6)	0.034	359 (47.7)	122 (60.4)	0.001
Calcinosis, n (%)	154 (16.5)	133 (15.9)	21 (22.1)	0.143	108 (14.6)	46 (23.6)	0.005
Interstitial lung disease, n (%)	378 (38.1)	317 (36.0)	61 (55.5)	<0.001	266 (34.4)	112 (51.4)	<0.001
Pulmonary arterial hypertension, n (%)‡	68 (6.5)	38 (4.1)	30 (25.0)	<0.001	20 (2.5)	48 (20.4)	<0.001
History of coronary heart disease, n (%)	73 (8.4)	61 (7.9)	12 (13.5)	0.103	56 (8.2)	17 (9.1)	0.658
Scleroderma renal crisis, n (%)	24 (3.6)	20 (3.4)	4 (5.6)	0.316	13 (2.5)	11 (7.2)	0.011
Muscular involvement	146 (14.7)	131 (14.7)	15 (14.6)	>0.99	110 (14.1)	36 (17.0)	0.33
LVEF (%) ²	65.00 (60.00, 70.00)	65.00 (60.00, 70.00)	66.00 (61.00, 75.00)	0.013	65.00 (60.00, 70.00)	65.00 (60.00, 71.75)	0.092
Systolic PAP (mm Hg) ²	30.00 (26.00, 36.00)	30.00 (25.00, 35.00)	40.00 (30.00, 60.00)	<0.001	30.00 (25.00, 34.00)	37.00 (30.00, 55.50)	<0.001
Tricuspid regurgitation velocity (m/s)	2.48 (2.21, 2.70)	2.45 (2.21, 2.68)	2.70 (2.40, 3.74)	0.001	2.44 (2.20, 2.60)	2.70 (2.41, 3.62)	<0.001
Left ventricular diastolic dysfunction ²	46 (4.4)	39 (4.2)	7 (5.8)	0.474	32 (3.9)	14 (6.0)	0.205
Pericarditis§	40 (4.1)	31 (3.6)	9 (7.9)	0.04	25 (3.3)	15 (6.8)	0.03
Atrio-ventricular block, n (%)¶	11 (1.4)	9 (1.2)	2 (2.6)	0.281	6 (0.9)	5 (3.0)	0.057
Arythmia, n (%)**	25 (3.1)	18 (2.5)	7 (8.8)	0.008	13 (2.0)	12 (7.1)	0.002
FVC % of theoretical value, median (IQR)	99.00 (84.00, 112.25)	101.00 (85.00, 113.00)	88.00 (71.50, 101.50)	<0.001	102.00 (87.32, 114.00)	88.00 (71.25, 104.75)	<0.001
DLCO % of theoretical value, median (IQR)	70.00 (54.00, 81.00)	71.00 (58.00, 82.00)	46.00 (35.00, 62.00)	<0.001	72.00 (60.00, 83.00)	51.00 (36.00, 70.00)	<0.001
Elevated natriuretic peptide, n (%)††	119 (54.6)	90 (49.7)	29 (78.4)	0.002	76 (47.2)	43 (75.4)	<0.001
Serum creatinine, µmol/l, mean (SD)	71.00 (61.00, 82.00)	70.00 (61.00, 80.00)	76.50 (67.00, 96.25)	<0.001	69.00 (60.50, 80.00)	76.00 (64.75, 90.25)	<0.001
CRP, mg/L, mean (SD)	3.00 (2.00, 7.50)	3.00 (2.00, 7.00)	4.50 (3.00, 12.25)	0.001	3.00 (2.00, 6.00)	5.00 (2.00, 12.00)	<0.001
Elevated serum creatine kinase, n (%)	52 (44.8)	50 (47.2)	2 (20.0)	0.181	44 (48.9)	8 (30.8)	0.121

Continued

Table 1 Continued

	Overall (n=1048)	No sildenafil (n=928)	Sildenafil (n=120)	P value*	No bosentan (n=813)	Bosentan (n=235)	P value†
Anti-nuclear antibodies, n (%)	957 (96.7)	848 (96.5)	109 (98.2)	0.571	745 (96.8)	212 (96.4)	0.831
Anti-centromere antibodies, n (%)	433 (46.2)	383 (46.3)	50 (45.0)	0.84	343 (47.4)	90 (42.1)	0.185
Anti-topoisomerase I antibodies, n (%)	267 (28.4)	237 (28.5)	30 (28.0)	>0.99	194 (26.6)	73 (34.6)	0.03
Anti-RNA pol3 antibodies, n (%)	22 (5.8)	22 (6.5)	0 (0.0)	0.152	22 (7.6)	0 (0.0)	0.003
Anti-PM Scl antibodies, n (%)	2 (0.5)	1 (0.3)	1 (2.4)	0.208	2 (0.7)	0 (0.0)	‡
Sildenafil, n (%)	120 (11.5)	0 (0.0)	120 (100.0)	<0.001	23 (2.8)	97 (41.3)	<0.001
Bosentan, n (%)	235 (22.4)	138 (14.9)	97 (80.8)	<0.001	0 (0.0)	235 (100.0)	<0.001
ACE inhibitor, n (%)	257 (25.6)	215 (23.8)	42 (41.6)	<0.001	181 (22.9)	76 (35.8)	<0.001
Cyclophosphamide, n (%)	115 (11.3)	81 (8.8)	34 (33.7)	<0.001	65 (8.1)	50 (23.1)	<0.001
Steroids, n (%)	370 (36.0)	312 (33.9)	58 (53.7)	<0.001	263 (32.7)	107 (48.2)	<0.001
Iloprost, n (%)	143 (14.1)	106 (11.6)	37 (37.4)	<0.001	76 (9.5)	67 (31.5)	<0.001
Mycophenolate mofetil, n (%)	126 (12.4)	98 (10.6)	28 (30.1)	<0.001	82 (10.1)	44 (21.3)	<0.001
TNF inhibitors, n (%)	8 (0.8)	7 (0.8)	1 (1.2)	0.514	6 (0.7)	2 (1.0)	0.663
Rituximab, n (%)	29 (2.9)	20 (2.2)	9 (10.6)	<0.001	20 (2.5)	9 (4.5)	0.153

Bold indicates significant p-values.

*Statistical tests comparing patients with sildenafil versus patients without sildenafil.

†Statistical tests comparing patients with bosentan versus patients without bosentan.

‡Assessed by right-heart catheterisation.

§Assessed by transthoracic echocardiography or cardiac MRI.

¶Second or third degree, assessed by ECG.

**Auricular or ventricular arrhythmia, assessed by ECG.

††Defined by brain natriuretic peptide >35 pg/mL or N-terminal pro-brain natriuretic peptide >125 pg/mL.

‡‡Measured by transthoracic echocardiography.

ACE, angiotensin-converting enzyme; CRP, C-reactive protein; DLCO, diffusing capacity of the lung for carbon monoxide; FVC, forced vital capacity; IQR, interquartile range; LVEF, left ventricular ejection fraction; mPSS, modified Rodnan skin score; PAP, pulmonary artery pressure; SSc, systemic sclerosis; TNF, tumour necrosis factor.

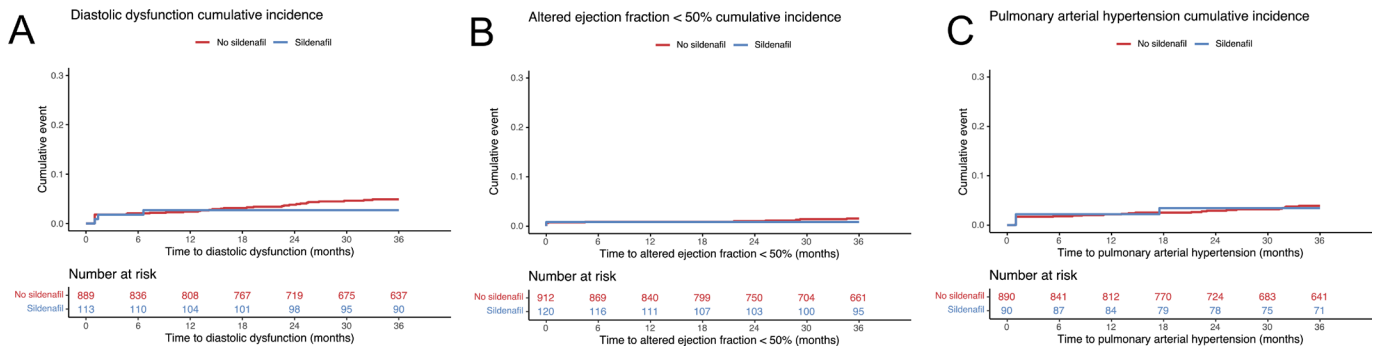


Figure 2 Kaplan-Meier: outcome incidence according to sildenafil treatment. (A) Diastolic dysfunction cumulative incidence according to sildenafil treatment group. (B) Altered left ventricular ejection fraction <50% cumulative incidence according to sildenafil treatment group. (C) Pulmonary arterial hypertension cumulative incidence according to sildenafil treatment group.

PAH.⁸ Two randomised controlled trials showed a benefit of bosentan for the reduction of the number of new DUs in SSc,^{20,21} and a meta-analysis based on three studies investigating sildenafil and tadalafil showed that patients with phosphodiesterase type 5 inhibitors had higher DU healing rate compared with placebo.²² Though the Sildenafil Effect on Digital Ulcer Healing in sClerodERma study investigating did not find any difference in time to DU healing among patients treated with sildenafil 20 mg three times per day for 12 weeks compared with placebo,²³ the unexpectedly high healing rate and the lower dosage used for sildenafil treatment compared with previous studies might explain the lack of results in the placebo group. Regarding PAH, the rationale for sildenafil and bosentan use is based on observational data and high-quality PAH randomised clinical trials, including connective tissue disorders patients, which showed mainly exercise capacity improvement.^{24–27} Regarding ACE inhibitors, EULAR recommendations suggest its use among patients with SRC though evidence showing benefit in survival is scarce in the literature.^{8,28–32}

Considering the population with heart disease but without SSc, ACE inhibitors were the first medication that demonstrated decreased mortality, morbidity and symptoms in patients with heart failure with reduced ejection fraction (HFrEF)^{33–36} but failed to show benefits among patients with heart failure with preserved ejection

fraction (HFpEF).³⁷ Regarding sildenafil, some early single-centre studies seemed promising in patients with HFpEF with improved exercise tolerance with prolonged therapy,^{38–40} but a recent multicentric randomised trial did not confirm those results.⁴¹ Studies investigating the sildenafil effect among patients with HFpEF have yielded unsatisfactory results, with few monocentric studies showing improvement in exercise capacity,⁴² but the multicentric Phosphodiesterase-5 Inhibition to Improve CLinical Status and EXercise Capacity in Diastolic Heart Failure (RELAX) study did not find any change in exercise capacity or clinical status among patients treated with sildenafil,⁴³ though, in our cohort, we found benefits for sildenafil regarding diastolic dysfunction and altered ejection fraction >50% at 3 years. This might be explained by the very specific mechanisms involved in SSc heart involvement. Pathophysiology of heart involvement in systemic is still unclear, but data suggest that SSc patients suffer from repeated cycles of myocardial ischemia-reperfusion due to abnormal vasoreactivity which might lead to myocardial fibrosis as seen on histopathological examination.^{44,45} Some studies assessed the effect of vasodilators on myocardial perfusion among SSc patients with thallium-201 adenosine single-photon emission computed tomography, positron emission tomography and cardiovascular MRI and suggest the coexistence of fixed organic lesions and reversible ischaemic lesions due

Table 2 Average treatment effect of sildenafil, bosentan, ACE inhibitor and iloprost on diastolic dysfunction, altered ejection fraction <50% and pulmonary arterial hypertension at 3 years

At 3 years						
Outcome	Diastolic dysfunction		Altered ejection fraction <50%		Pulmonary arterial hypertension*	
Treatment	Average treatment effect % (95% CI)	P value	Average treatment effect % (95% CI)	P value	Average treatment effect % (95% CI)	P value
Sildenafil	-2.83 (-4.06; -1.60)	< 0.00001	-0.88 (-1.70; -0.05)	0.0373	-0.94 (-6.41; 4.53)	0.74
Bosentan	-0.31 (-3.69; 3.08)	0.86	-1.10 (-2.71; 0.52)	0.18	-1.55 (-3.40; 0.29)	0.10
ACE inhibitor	-0.11 (-2.41; 2.20)	0.93	-0.41 (-2.05; 1.23)	0.63	0.25 (-1.55; 2.04)	0.79
Iloprost	-0.26 (-4.54; 4.01)	0.90	-1.11 (-2.89; 0.66)	0.18	-1.42 (-3.21; 0.38)	0.12

Bold indicates significant p-values.
 *Assessed by right-heart catheterisation.
 ACE, angiotensin-converting enzyme.

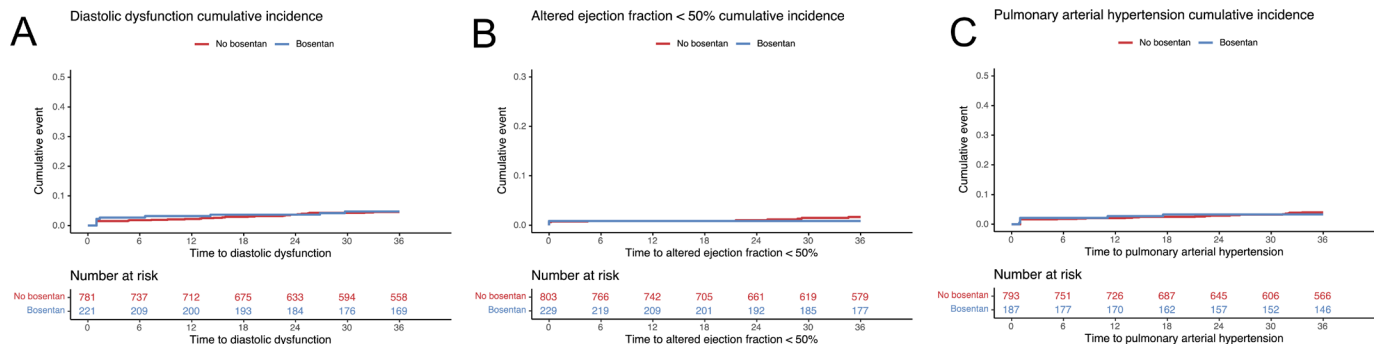


Figure 3 Kaplan-Meier: outcome incidence according to bosentan treatment. (A) Diastolic dysfunction cumulative incidence according to bosentan treatment group. (B) Altered left ventricular ejection fraction <50% cumulative incidence according to bosentan treatment group. (C) Pulmonary arterial hypertension cumulative incidence according to bosentan treatment group.

to vasospasm impairment.^{46–51} Those processes can lead to systolic or diastolic dysfunction in the early stages of the disease, long before it becomes clinically apparent, and eventually congestive heart failure.⁴⁵ Microcirculation impairment might explain the potential benefit of vasodilators such as sildenafil in our cohort and eventually prevent diastolic dysfunction due to myocardial damage provoked by repeated ischemia-reperfusion mechanism. Those results need to be confirmed by a prospective cohort specifically designed to assess diastolic dysfunction and altered ejection fraction among SSc patients. Besides, assuming vasodilators influence on reversible myocardial injury due to microcirculation impairment, it could be interesting to assess the impact of glifozins on diastolic dysfunction in SSc patients. Indeed, glifozins are the first class to have demonstrated a benefit among HFpEF patients with empagliflozin and dapagliflozin in the Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction and Dapagliflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure trials, respectively. The pathophysiological mechanisms explaining those benefits are not fully understood, but glifozins might have antifibrotic and antihypertrophic effects according to some animal models of HFpEF^{52–54} and reduced inflammation and oxidative stress attenuation,^{55,56} which might be interesting in myocardial fibrosis developed by SSc patients.

Limitations

Those results must be interpreted with caution for several reasons. First, even if we used LTMLE to adjust for confounders, our study is an exploratory analysis based on observational data. We probably could not consider all the potentials confounders, especially since the precise pathophysiology and epidemiology of cardiac involvement in scleroderma are not entirely clear.^{1 2 57} Second, we could not include time-dependent co-variables in the analysis due to missing data during follow-up. Confounders were only those assessed at baseline, so we censored the 3-year follow-up to not extrapolate too long from the initial assessment. Finally, as our cohort was a prospective observational study and was not originally

intended to specifically assess heart-related outcomes or the effect of a particular treatment, heart outcome assessment was not prespecified by a precise protocol but remained at the discretion of each local operator, particularly regarding the diastolic dysfunction. Moreover, we do not have the dosages of the various treatments or data to check patients' compliance.

To conclude, our study suggests that sildenafil might have benefits among SSc patients regarding diastolic dysfunction and altered ejection fraction occurrence. However, further studies assessing the effects of vasodilators on heart-related outcome in SSc patients are needed to confirm those exploratory results based on observational data.

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