Article:
Di Donato, S. orcid.org/0000-0003-1256-0761, Pauling, J.D., Ramjug, S. et al. (149 more authors) (2025) Temporal trends in vascular medication use in 8079 patients with systemic sclerosis: insights to inform future trials and therapeutic strategies from the EUSTAR cohort. Rheumatology. keaf290. ISSN: 1462-0324

https://doi.org/10.1093/rheumatology/keaf290

Temporal trends in vascular medication use in 8,079 patients with Systemic Sclerosis: insights to inform future trials and therapeutic strategies from the EUSTAR cohort

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Introduction:

Systemic sclerosis (SSc) is characterised by widespread vascular damage resulting in digital and systemic vasculopathic sequelae. Although there are effective treatments available, vascular disease remains a significant cause of morbidity and mortality in

SSc. Our aim was to describe patterns of vascular medication use in SSc, including examination for potential changes over time.

Methods:

A cross-sectional study of SSc patients enrolled in the EUSTAR database meeting 2013 ACR/EULAR SSc criteria. Patients were divided into two time periods: 2012-2017 and 2018-2022. We analysed the prescription patterns of endothelin receptor antagonists (ERA), phosphodiesterase type-5 inhibitors (PDE5i), calcium channel blockers (CCB), intravenous iloprost, and antiplatelet therapies. Logistic regression was used to evaluate temporal trends and interaction effects.

Results:

8079 patients were included. Significant increases over time were observed in the use of ERA (7% to 12%, p<0.001), PDE5i (5.4% to 7.2%, p=0.064), CCB (20% to 32%, p<0.001), and anti-platelet therapies (15% to 20%, p<0.001). There was a notable decrease in iloprost use (3.1% to 0.3%, p<0.001). The prevalence of active digital ulcers (DU) decreased (16% to 13%, p=0.040), while a history of DU (24% to 30%, p<0.001) increased. Year-by-year and nonlinear increases were noted for ERA and CCB whereas nonlinear increase was observed for PDE5i. Year-by-year and nonlinear decrease was observed for Iloprost prescription.

Conclusion:

A significant change has occurred over time in vascular medication use in SSc patients, with increased utilisation of ERA, PDE5i, CCB, and anti-platelet therapies, suggesting the adoption of more proactive and/or preventive treatment strategies.

Key words: Systemic sclerosis; Scleroderma; Vascular; Medication; Prescription; Temporal

Rheumatology key messages:

- Vascular therapy in SSc has shifted from reactive treatment toward more preventive, long-term approaches.
- Prescription rates of ERA, PDE5i, and CCB increased over time, while Iloprost use declined sharply.
- Future SSc trial designs for vascular drugs will need to take into account the evolving prescription practices.

INTRODUCTION

Systemic sclerosis (SSc) represents a multifaceted disease characterized by progressive vascular damage ('vasculopathy'), adaptive and humoral immune dysregulation, and fibrosis of the skin and internal organs, together resulting in multi-organ loss of function [1]. Specifically, vasculopathy is often an early and cardinal feature of the disease [2,3], affecting multiple vascular beds and associated with significant morbidity and mortality [3–6].

Digital vasculopathy, manifesting as Raynaud's phenomenon (RP), is observed in>95% of patients and often represents the first disease manifestation, sometimes occurring decades before skin involvement [7,8]. Furthermore, persistent digital ischaemia may result in irreversible tissue loss, from the development of acral digital ulcers (DU) and critical digital ischaemia (gangrene) [6,9]. Another common manifestation is digital pitting scars (PS), represented by often painful areas of concave depression with hyperkeratosis, typically occurring on the fingertips, and believed to be part of the ischaemic-fibrotic spectrum of SSc- vasculopathy [10].

Systemic vasculopathy can lead to severe complications such as pulmonary arterial hypertension (PAH) and scleroderma renal crisis (SRC) [11]. Primary pan-cardiac involvement in SSc, increasingly recognised as related to microvascular damage, can have a major impact on prognosis. In addition, other complications are part of the spectrum of vascular disease in SSc, including cutaneous telangiectasia, associated with marked body image dissatisfaction, and gastric antral vascular ectasia, a potentially life-threatening condition, that can result in major gastrointestinal bleeding.

Pharmacological treatment of SSc vasculopathy has progressed by targeting complementary pathways, including prostacyclin and nitric oxide augmentation, endothelin antagonism, and general vasoactive strategies. Main therapeutic classes include endothelin receptor antagonists (ERA), phosphodiesterase type-5 inhibitors (PDE5i), prostanoids, and calcium channel blockers (CCB) [12]. Importantly, targeting common disease effector pathways by combination therapies is beneficial in the context of the different vascular complications of SSc, especially PAH and DUs [13–15].

More recently, Selexipag (a non-prostanoid prostacyclin receptor agonist) has been approved for SSc-PAH [16] although not effective on SSc-RP in a randomised, placebo-controlled trial [17]. Nonetheless, encouraging findings in favour of this drug for SSc-DUs and RP have emerged [18,19]. Despite these advancements, unmet needs concerning vascular treatments for SSc remain in real world practice, as highlighted by recent studies showing that only 60% of patients receive at least one vasoactive therapy, and the use of specific treatments, such as prostanoids and ERAs, is limited to a minority of cases [20].

These medications reduce frequency and severity of vascular complications by addressing core SSc mechanisms. Moreover, vascular injury is pathogenically linked

to fibrotic complications in SSc through processes such as endothelial-mesenchymal transition [21–23], vascular remodelling [24,25], and tissue ischemia, representing a significant therapeutic target [26]. A unified endovascular phenotype in SSc has been proposed, in which the judicious use of vascular-acting therapies may provide benefit to multiple vascular beds [3,4,9,27].

Against this background, our analysis aimed to describe trends in vascular medication use in SSc, focusing on CCB, PDE-5i, ERA, and iloprost. These therapies represent the cornerstone of treatment for digital vasculopathy (namely RP and DU) with a 'strength of recommendation of 'A', according to EULAR recommendations [28].

METHODS

Study design and patients

Our study was a cross-sectional analysis of patients enrolled in the prospective, multicenter, international European Scleroderma Trials and Research group (EUSTAR) cohort database [29,30]. We censored data after the first recorded visit for each patient. The primary focus of the analysis was on the medications (ERA, PDE5i, CCB, and iloprost) deployed in the management of SSc-associated vasculopathy. The local ethics committee of each EUSTAR centre approved the study, in compiance with the Declaration of Helsinki. Informed written consent was provided by all participants.

Patients aged 18 years or older who fulfilled the 2013 American College of Rheumatology (ACR)/EULAR criteria for SSc [31] were eligible for inclusion only if they had complete documented status of specified vascular disease manifestations: 1) baseline history of DU, 2) active DU, and 3) the presence of PS.

We grouped our data into two time periods: 2012-2017 and 2018-2022, to provide a pragmatic description of the changes in the use of the specified vascular medications

(ERA, PDE5i, CCB, and iloprost) over the course of the preceding decade. The choice of these time periods aligns with significant events in the pharmaceutical landscape. In 2017, new SSc guidelines significantly endorsed ‘advanced’ treatments for digital vasculopathy, specifically by recommending PDE5i for RP and DUs. Additionally, Bosentan lost its patent shortly after this threshold, with generic versions available in early 2019. Similarly, Sildenafil saw generic versions enter the market in December 2017.

These developments likely influenced prescribing patterns and the availability of these medications, justifying our selected timeframes and enabling a comprehensive analysis of trends in vascular medication use over the last decade.

Data collection

The structure of the EUSTAR database and the collected variables within it have been well described in the extant literature [10,30,32]. We selected patient demographic and disease-related clinical features relevant to the objectives of our study. In the 2012-2017 cohort, 79.3% of all database patients were excluded, while in the 2018-2022 cohort, 52.7% were excluded. A comparative analysis of included and excluded patients for each period revealed no significant differences in available baseline characteristics (data not shown).

Statistical analysis

Categorical data were reported as absolute numbers and percentages and compared using Fisher’s exact test or Pearson’s Chi-squared test, as appropriate. Continuous data were reported as means (SD) or medians (IQR), normality was assessed with Shapiro-Wilk’s significance test, with graphical check through density plots and QQ plots. Homogeneity of variance for continuous variables was assessed using F-test and their comparisons were performed with Student’s t-test or Wilcoxon’s test, as

appropriate. For all statistical tests, a two-tailed p-value<0.05 was considered statistically significant. Type I error from multiple comparisons between the two time periods was controlled using false discovery rate correction. Logistic regression methods were used to analyse trends in drug prescriptions from 2012 to 2023. Year of baseline visit was converted into a progressive variable from 0 (2012) to 11 (2023) - 'Year progressive'- and prescription status for each medication was coded as a binary outcome. Acceptable collinearity of independent variables was assessed using the Variance Inflation Factor, with a threshold set at 5. Initial univariate logistic regressions assessed the association of each drug with every other drug and with the year. Covariates significant in univariate models were advanced to the multivariable stage. Before advancing significant variables to the multivariable model, Bonferroni correction was applied to the results of the univariate analyses to minimize type I errors. For multivariable analysis, logistic regression models incorporating interaction terms between significant drugs and the year variable were built. Each drug was analysed as a drug of interest, with models structured to elucidate the effects of co-prescriptions and year on prescription probabilities. To account for potential non-linearity in prescription trends over time, the 'Year progressive' variable was modelled using a penalized spline. This allows for the estimation of both linear and non-linear components of year as a continuous variable, providing a more flexible approach to capturing deviations from a strictly linear trend in prescribing patterns.

RESULTS

Patients' demographics and disease features

Patient and disease-related characteristics are presented in Table 1. The median (IQR) age and disease duration of the included patients were 55 (46-65) years and 105 (46-190) months, respectively and did not differ significantly across the two groups. The 2018-2022 cohort had a slightly shorter median (IQR) disease duration compared to the earlier cohort (104 [46-189] vs 114 [49-198] months, p=0.069). Additionally,

there was a higher proportion of patients with limited cutaneous systemic sclerosis (lcSSc) in the 2018-2022 cohort compared to 2012-2017 (63% vs 67%, p=0.038). Disease subsets, autoantibody profiles, and baseline mRSS were comparable between the two cohorts. Although the overall prevalence of PAH was lower in the 2018-2022 cohort, this was not statistically significant (12% in 2012-17 vs 9.5% in 2018-22, p=0.12). No clinically significant important differences were observed concerning the presence of interstitial lung disease, FVC (97% vs 95%, p=0.069), or diffusion capacity measures. The presence of telangiectasia remained stable also over time (59% vs 61%, p=0.4), as well as SRC (1.4% vs 1.6%, p=0.8) for 2012-2017 and 2018-2022, respectively.

The prevalence of active DUs significantly decreased over time between the two time periods (16% vs 13%, p=0.040). Whereas, both a history of DUs (24% vs 30%, p<0.001), history of gangrene (0.7% vs 3.9%, p<0.001), and the presence of PS (21% vs 26%, p<0.001) showed an increase over the study period. Although there was a small increase observed in the frequency of active gangrene over time, this did not reach statistical significance (0.6% vs 1.5%, p=0.063).

Temporal changes in vascular medication use

The use of ERA saw a substantial increase from 2012-2017 to 2018-2022 (7% vs 12% respectively, p<0.001). Similarly, PDE5i usage increased during the same periods (5.4% vs 7.2% respectively, p=0.064), as well as CCB prescription (20% vs 32% respectively, p<0.001). There was a notable decrease in Iloprost utilisation (3.1% vs 0.3%, p<0.001). The proportion of patients on vascular medications for each year and stratified by vascular drug is reported in Figure 1.

The combination of CCB with ERA saw a significant increase (2.1% vs 4.8%, p<0.001), while the association of PDE5i and ERA (1.9% vs 2.7%, p=0.3) and the combined use

of CCB and PDE5i (2.3% vs 2.6%, p=0.8) showed only modest absolute, but statistically non-significant, increases. Importantly, compared to 2012-2017, the prescription of anti-platelet therapies showed a significant increase in the 2018-2022 timeframe (15% vs 20% respectively, p<0.001). The distribution of recorded baseline visits by month is reported, grouped by the two 5-year periods, as imbalances in autumn/winter visits could influence the results (Supplementary Table S1 and Supplementary Figure S1). To this matter, differences in the geographical distribution of patients between the two cohorts, reflecting the geographical expansion of the EUSTAR centres, do not appear to systematically favour one group over the other in terms of colder or warmer climate. Therefore, the impact of climate-related distribution changes on the likelihood of RP/digital vasculopathy, and by consequence on vascular medication treatments, remains minimal (Supplementary Table S2 and Supplementary Table S3). Considering that therapeutic changes in the guidelines primarily affected ERA and PDE5i, we categorized patients into “ERA only”, “PDE5i only”, “Combination therapy (ERA + PDE5i)”, and the overall cohort to better assess their clinical characteristics, the prevalence of digital vasculopathic complications, and PAH (Supplementary Table S4). This stratification allows for a clearer understanding of the clinical profile of patients requiring more aggressive vasodilator therapy and the potential impact of evolving prescription patterns.

In logistic regression analyses, ERA prescription showed a linear yearly increase with a prescription odds ratio (OR) of 6.8 per year (p<0.001) with a further significant nonlinear increase in prescription (coefficient 0.51, p<0.001) in univariate analysis (Table 2). After adjusting for other medications and interactions in multivariable analysis, a significant nonlinear increase in prescription was observed (coefficient 0.68, p=0.005) without a significantly linear pattern (Table 2). Similarly, the use of PDE5i increased nonlinearly over time, with a significant nonlinear positive coefficient of 0.61 (p<0.001) in univariate analysis, confirmed after adjusting for other

medications and interactions in the multivariable model (1.20, p<0.001) (Table 3). CCB usage showed a growth trend as well, with an OR of 3.75 (p<0.001) per year and a nonlinear significant increase over time with a positive coefficient of 0.71 (p<0.001) in the univariate model. In the multivariable analysis, the prescription OR per year for CCB was 3.61 (p<0.001) with a significant nonlinear increase over time (coefficient 0.66, p<0.001) (Table 4). Iloprost prescription showed a year-by-year and a further nonlinear reduction over time with a yearly prescription OR of 0.0001 (p<0.001) with a strong significant nonlinear reduction over time with a coefficient of -13.0 (p<0.001) (Table 5). A post-hoc analysis was performed for Iloprost prescription in patients with a history of DUs to explore its relationship with ERA prescription, as these are known to prevent new DUs. Even in this population Iloprost prescription showed a significant reduction over time (Supplementary Figure S2), with a yearly prescription OR of 0.001 (p<0.001) (Supplementary Table S5).

Vascular medication combination therapy

When adjusting the vasoactive drug prescription for concomitant vascular medications, ERA prescription was shown to be positively associated with the concomitant use of PDE5i (OR 14.2, p<0.001) (Table 2). Accordingly, a higher likelihood for prescription of PDE5i was conferred by concomitant use of ERA (OR 11.0, p<0.001) and concomitant CCB use (OR 4.10, p=0.033) (Table 3). Lastly, CCB prescription odds were significantly higher in the presence of concomitant PDE5i (OR 5.38, p=0.018) or anti platelets (OR 2.59, p=0.015) prescriptions (Table 4).

Interaction effects in multivariable models

In interaction analyses, despite the positive association between ERA and PDE5i prescription (OR 14.2, p<0.001), this combination was found to be diminished nonlinearly over time with a coefficient of -1.7 (p=0.008) (Table 2). Likewise, the odds of prescribing a PDE5i in combination with either ERA or CCB also demonstrated a

nonlinear decreasing pattern over time with year by CCB nonlinear interaction coefficient of -1.3 (p=0.003) and a year by ERA nonlinear interaction coefficient of -1.4 (p=0.005), respectively (Table 3). In line with these analyses, the odds of prescribing a CCB in concomitance with a PDE5i has reduced nonlinearly over time (year by PDE5i nonlinear coefficient -2.0, p<0.001) (Table 4). Lastly, the prescription of CCB in combination with both PDE5i and anti-platelet agents has significantly increased over time in a nonlinear manner (year by PDE5i by anti-platelets nonlinear coefficient 3.1, p=0.011) (Table 4).

DISCUSSION

We present a comprehensive analysis of the temporal trends in the prescription of vascular medications in patients with SSc enrolled in the multinational EUSTAR cohort, as well as the overall prevalence of vascular manifestations of the disease over the last decade, revealing several shifts in clinical practice. However, distinguishing whether these changes reflect evolving clinical practices or a response to changes in disease manifestations potentially influenced by other treatments, such as immunosuppressive therapies, more integrated care approaches, and earlier diagnosis, remains challenging. Furthermore, the examined drug classes are known to confer benefit across multiple vascular beds in SSc and we were not able to confidentially determine the primary vascular indication for their prescription. To maintain the focus on prescribing trends over time rather than on the influence of specific indications, we did not adjust for PAH or DU, as such adjustments would obscure the temporal association we aimed to investigate. Notably, the interaction effects observed between different drug combinations offer novel ‘real world’ insights into the evolving management strategies for SSc-related vascular disease.

The most important finding resides in the progressive increase in the use of CCB, ERA, and PDE5i drug therapies which also temporally aligns with the reduced incidence of

active DUs and Iloprost utilisation, possibly corresponding to a decrease in the need for acute interventions such as hospitalizations for prostanoid infusions, and possibly influenced by the COVID pandemic [33]. A striking drop in Iloprost prescription occurred in 2020 and the following years, coinciding with the onset of the COVID pandemic, where restrictions on non-urgent admissions likely played a substantial role. Notably, Iloprost use has not returned to pre-pandemic levels, suggesting that the pandemic may have accelerated an ongoing shift in clinical practice towards alternative long-term vasoactive therapies such as PDE5i and ERA. This shift may not only reflect an improvement in outpatient management strategies [34] but also a transition from reactive to more proactive and preventative treatment strategy in managing SSc-associated vascular disease.

Noticeably, the diminishing positive association of ERA with PDE5i over the years, as well as the general reduction of prescriptions concerning PDE5i in combination with either ERA or CCB suggest a potential shift in therapeutic preferences towards the use of ERA and PDE5i as interchangeable monotherapies. This trend may reflect an adaptation to the availability of emerging clinical evidence [27]. Despite the apparent reduction in combination prescriptions over time, the presence of ERA or PDE5i still confers a high OR for the prescription of the other. This indicates that these medications have remained strongly prescribed in *combination* for SSc complications. However, as these drugs are also broadly prescribed over time for SSc-vasculopathy as monotherapy (probably thanks to lower costs and availability/generalised uptake by treating clinicians), this trend likely mimics an apparent reduction in combination prescriptions. Therefore, while combination therapies are apparently declining, driven by an absolute increase in monotherapy, ERA and PDE5i practically remain common combination choice for SSc-vasculopathy. These data may also be influenced by the intrinsic heterogeneity of the EUSTAR database. To this matter, differences in the geographical distribution of patients between the two cohorts, reflecting the

geographical expansion of the EUSTAR centres, do not appear to systematically favor one group over the other in terms of colder or warmer climate. Therefore, the impact of climate-related distribution changes on the likelihood of RP/digital vasculopathy, and by consequence on vascular medication treatments, remains minimal.

Our analysis revealed a rise in popularity of anti-platelet therapies, with a marked increase of this class of drug prescription in the last 5 years. This is particularly true in conjunction with CCBs. These latter presented a three-fold increase in their prescription likelihood in the presence of anti-platelets agents, which could suggest how anti-platelets are perceived to potentially enhance the efficacy of CCBs (probably through micro-thrombosis prevention). We were unable to assess whether the increase in anti-platelet prescriptions was influenced by underlying cardiovascular comorbidities, as this information was not systematically available for the majority of patients. Therefore, we could not determine whether these treatments were primarily prescribed for SSc-related vascular dysfunction or for concomitant cardiovascular disease. Nevertheless, there is no reason to suspect a higher prevalence of cardiovascular disease in the later cohort, given that the demographic characteristics remained comparable between the two periods. Significantly, the combination of PDE5i and anti-platelet therapies showed a significant increase over time in combination with CCBs. Historically, the limited evidence base, including a lack of robust efficacy data for anti-platelet agents in SSc, has limited their use despite a strong therapeutic rationale for such treatments [35,36] . Recent emerging data has challenged this therapeutic nihilism, including from the EUSTAR database, has found evidence for anti-platelet therapy, including for DU disease [37] . These findings may underscore a broader trend towards more refined and possibly patient-tailored treatment approaches [38,39] . Our descriptive analysis is of value to investigators planning a trial of vasoactive therapy considering permitted background treatments.

Despite these positive trends in vascular disease epidemiology and medication prescription observed in our study, the ongoing burden of severe manifestations such as digital gangrene and pulmonary arterial hypertension amongst some SSc patients, indicates ongoing challenges and substantial unmet needs in treatment efficacy. Future research should focus on defining specific endotypes of vascular disease in SSc and exploring the potential of combination therapies to address these resistant manifestations in a selected and more severe SSc population.

This study leveraged data from the multinational EUSTAR database, employing a cross-sectional design to explore the patterns of medication usage at patients' first recorded visit and across different years. By focusing on patients with available data concerning digital vasculopathy at baseline, our study provides an understanding of the real-world application of these therapeutic agents and their association with clinical outcomes. Furthermore, this analysis identified trends in the prescribing practices over time, providing insights into the evolving landscape of SSc management. The large sample size and extended observation period provide a robust background for understanding these trends. However, the imbalanced numbers between the first and the second groups and the potential for selection bias represent limitations of the study. Our analyses did not suggest any systematic differences between the two five-year cohorts, but it cannot be assumed that no unknown differences may have been present. Another limitation of our study is the inability to fully account for the specific clinical indications behind each prescription and the lack of data regarding past exposure to these classes of treatments. It is likely that there are patients within the EUSTAR cohort who have previously tried CCB but had not continued treatment at the time of entry to the EUSTAR database e.g., on account of adverse effects and/or lack of efficacy.

Finally, comparing the absolute numbers of our cohort with another large-scale study from Germany, which revealed that up to 60% of patients received at least one vasodilator therapy, might cause our findings to appear low [20]. However, in the German study a significant proportion of patients was treated with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers [20], which were not classified as vasodilative agents in our study. Conversely, the prevalence of CCB use in the German study was even lower than our reported rate. This highlights how differences in the inclusion criteria, as well as possible different regulations for prescriptions, can influence the real-world use of such therapies. Additionally, the intrinsic potential for reporting bias which can occur in large registries may lead to a tendency for the underreporting of medication use in general [40], which could account for the seemingly low prevalence in our sample.

In conclusion, our study benchmarks the significant progress made to date and the remaining unmet needs concerning SSc vascular disease. Future research, informed by our findings, could explore the development of risk prediction models to unlock novel approaches towards systemic vascular disease modification in SSc.

Funding:

No funding was received for this study.

Data availability statement:

Data are available upon reasonable request.

Acknowledgments:

EUSTAR Collaborators: Serena Guiducci, Silvia Bellando Randone, Ulrich Walker, Florenzo Iannone, Oliver Distler, Radim Becvar, Otylia Kowal Bielecka, Maurizio Cutolo, Vasiliki Liakouli, Elise Siegert, Simona Rednic, Jerome Avouac, Carlomaurizio

Montecucco, László Czirják, Michele Iudici, Katja Perdan-Pirkmajer, Bernard Coleiro, Dominique Farge Bancel, Kristofer Andréasson, Mislav Radic, Alexandra Balbir-Gurman, Nicolas Hunzelmann, Luca Idolazzi, Christopher, Denton, Jörg Henes, Vera Ortiz-Santamaria, Johannes Pflugfelder, Dorota Krasowska, Ivan Foeldvari, José António Pereira da Silva, Bojana Stamenkovic, Maria De Santis, Lidia P. Ananieva, Philipp Klemm, Ulf Müller-Ladner, Klaus Søndergaard, Simone Negrini, Gabriella Szücs, Anna-Maria Hoffmann-Vold, David Launay, Valeria Riccieri, Ana Maria Gheorghiu, Christina Bergmann, Francesca Ingegnoli, Vanessa Smith, Mette Mogensen, Maria Rosa Pozzi, Felix Lauffer, Marie Vanthuyne, Juan Jose Alegre-Sancho, Martin Aringer, Ellen De Langhe, Branimir Ani, Sule Yavuz, Svetlana Agachi, Alberto Cauli, Kamal Solanki, Esthela Loyo, Edoardo Rosato, Figen Yargucu Zhini, Rosario Foti, Britta Maurer, Marzena Olesinska, Jorge Juan González Martín, Emmanuel Chatelus, Ira Litinsky, Lesley Ann Saketkoo, Eduardo Kerzberg, Breno Valdetaro Bianchi, Ivan Castellví, Massimiliano Limonta, Maura Couto, Camillo Ribi, Antonella Marcoccia, Thierry Martin, Lorinda S Chung, Tim Schmeiser, Dominik Majewski, Anna Wojteczek, Vera Bernardino, Gabriela Riemekasten, Yair Levy, Elena Rezus, Rossella Talotta, Sara Bongiovanni, Marek Brzosko, Hadi Poormoghim, Ina Kötter, Giovanna Cuomo, Oscar Massimiliano Epis, Petros Sfikakis, Daniel Furst, Ana-Maria Ramazan, Jeska de Vries-Bouwstra, Alain Lescoat, Julia Spierings, Fabiola Atzeni, Masataka Kuwana, Arsene Mekinian, Mickaël Martin, Yoshiya Tanaka, Carmen-Pilar Simeón-Aznar, Philipp Klemm, Ulf Müller-Ladner, Magda Pârvu, Nicoletta Del Papa, Kastriot Kastrati, Jennifer Ben Shimol, Enrico Selvi, Tomas Soukup, Yasushi Kawaguchi, Andre Nuñez Conde, Marija Geroldinger-Simic, Ignasi Rodríguez-Pintó, Percival D. Sampaio-Barros, Ulrich Gerth, Marta Dzhus, Duygu Temiz Karadag, Anastas Batalov, Knarik Ginosyan, Vahan Mukuchyan, Valentina Vardanyan, Armine Haroyan, Len Harty, Mariela Geneva-Popova, Mohammad Naffaa, Cristina Maglio, Okada Masato, Futoshi Iwata.

Conflicts of interest:

MH: research funding and speaker fees from Janssen, outside of the submitted work. SDD: None. GB: None. PA: speakers fees from Bristol Myers Squibb, Bohringer Ingelheim, research funding from Bristol Myers Squibb, Bohringer Ingelheim, Roche, Novartis, CSL Behring, Janssen- Cilag, CSL Vifor, Gruppo Italiano Lotta alla Sclerodermia (GILS), European Scleroderma Trials and Research Group (EUSTAR). JP: speaker fees from Janssen and Boehringer Ingelheim; consultancy fees from Janssen, Boehringer Ingelheim, AstraZeneca, IsoMab, Sojournix Pharma, and Permeatus Inc. Educational support from CSL Vifor. MET: speaker fees from Abbvie and Boehringer Ingelheim; consultancy fees from Abbvie, Janssen, Boehringer Ingelheim, Lilly, and UCB. EJ: None. YA: consulting fees from Boehringer, Topadur, Horizon, Argenx, AstraZeneca, Medsenic. CSM: speaker fees from Boehringer Ingelheim, Janssen, Roche, LIBBS, and Bristol Myers Squib. GM: speaker fees from Bohringer Ingelheim; research funding from Pfizer, Abbvie. MK: has received consulting fees from Argenx, AstraZeneca, Boehringer Ingelheim, Chugai, GlaxoSmithKline, Kissei, Mochida, and Novartis. EZ: consultancy, speaking, and lecture fees from Boehringer Ingelheim and Janssen. LM: None. FPC: None. AB: None. MDB: None. SR: None. PC: None. LA : None. FDG: consultin fees from GlaxoSmithKline, Boehringer Ingelheim, Roche, CSL Behring, Corbus, Acceleron, Horizon, Arxx Therapeutics, Lilly, Novartis, Certa Therapeutics, and Zurbio; speaker fees from Janssen, GlaxoSmithKline, and Boehringer Ingelheim. MM: None. MV: research funding from Boehringer Ingelheim, Ferrer, Galapagos, and Janssen Pharmaceutical Companies of Johnson & Johnson; consulting fees from Boehringer Ingelheim and Janssen Pharmaceutical Companies of Johnson & Johnson; speaker fees from Boehringer Ingelheim, Bristol-Myers Squibb, GSK, Janssen Pharmaceutical Companies of Johnson & Johnson, MSD, Novartis, and Roche.

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Table 1. Patient and disease-related demographic characteristics of the overall included study population. ACE: Angiotensin Converting Enzyme; ANA: antinuclear antibody; CCB: Calcium Channel Blocker; DLCO: Diffusing Capacity of the Lungs for Carbon Monoxide; DUs: digital ulcers; ERA: Endothelin Receptor Antagonist; FVC: Forced Vital Capacity; HRCT: High-Resolution Computed Tomography; ILD: Interstitial Lung Disease, KCO: Carbon Monoxide Transfer Coefficient; PDE5i: Phosphodiesterase-5 inhibitor.

Characteristic	Overall, N = 8,079[1]	2012-2017, N = 985[1]	2018-2022, N = 7,094[1]	p-value[2]
Age (median)	55 (46, 65)	55 (45, 64)	56 (46, 65)	0.069
Sex				0.6
Female	6,813 (84%)	822 (83%)	5,991 (84%)	
Leroy subset				0.038
lcSSc	4,432 (63%)	593 (67%)	3,839 (63%)	
dcSSc	2,564 (37%)	292 (33%)	2,272 (37%)	
Disease duration in months (median)	105 (46, 190)	114 (49, 198)	104 (46, 189)	0.069
ANA positive	6,255 (96%)	756 (95%)	5,499 (96%)	0.7
Anti-Scl-70	2,252 (38%)	257 (36%)	1,995 (38%)	0.4
Anticentromere	2,302 (40%)	286 (42%)	2,016 (40%)	0.4
mRSS	6 (3, 12)	6 (4, 11)	6 (3, 12)	>0.9
History of DUs	2,371 (29%)	238 (24%)	2,133 (30%)	<0.001
Active DUs	1,066 (13%)	154 (16%)	912 (13%)	0.040
History of Gangrene	287 (3.6%)	7 (0.7%)	280 (3.9%)	<0.001
Active Gangrene	110 (1.4%)	6 (0.6%)	104 (1.5%)	0.063

Telangiectasia	4,541 (61%)	479 (59%)	4,062 (61%)	0.4
Pitting scars	2,073 (26%)	206 (21%)	1,867 (26%)	<0.001
Pulmonary Artery Hypertension	339 (10%)	82 (12%)	257 (9.5%)	0.12
Scleroderma Renal Crisis	123 (1.6%)	13 (1.4%)	110 (1.6%)	0.8
ILD at HRCT scan	164 (47%)	105 (47%)	59 (48%)	0.9
FVC (%)	95 (79, 109)	97 (81, 111)	95 (79, 109)	0.069
DLCO (%)	68 (54, 81)	69 (51, 81)	68 (54, 81)	0.8
KCO (%)	78 (65, 89)	78 (66, 89)	78 (65, 89)	0.6
ACE inhibitors use	618 (8.0%)	74 (7.8%)	544 (8.0%)	0.9
Angiotensin receptor blockers	436 (5.6%)	51 (5.4%)	385 (5.7%)	0.8
CCB	2,368 (31%)	193 (20%)	2,175 (32%)	<0.001
PDE5i	538 (6.9%)	51 (5.4%)	487 (7.2%)	0.064
ERA	893 (12%)	66 (7.0%)	827 (12%)	<0.001
Intravenous iloprost	41 (0.6%)	27 (3.1%)	14 (0.3%)	<0.001
Anti platelets	1,504 (19%)	138 (15%)	1,366 (20%)	<0.001
CCB + PDE5i (combined)	198 (2.6%)	22 (2.3%)	176 (2.6%)	0.8
CCB + ERA (combined)	345 (4.5%)	20 (2.1%)	325 (4.8%)	<0.001
PDE5i + ERA (combined)	200 (2.6%)	18 (1.9%)	182 (2.7%)	0.3
CCB + ERA + PDE5i (combined)	69 (0.9%)	10 (1%)	59 (0.9%)	0.4
1 Median (IQR); n (%)				
2 Wilcoxon rank sum test or Pearson's Chi-squared test.				
False discovery rate correction for multiple testing				

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Table 2. Univariate and multivariable logistic regression with interactions to explain the change in prescription of Endothelin Receptors Antagonists. CCB: Calcium channel blocker; ERA: Endothelin receptor antagonist; PDE5i: Phosphodiesterase type-5 inhibitor.

Characteristic	OR[1]	95% CI[1]	p-value[2]	OR[1]	95% CI[1]	p-value
Year progressive						
Linear component	6.8	2.78, 17.9	<0.001	3.20	0.87, 13.6	0.10
Nonlinear component	0.51**	0.22, 0.79**	<0.001	0.68**	0.2, 1.1**	0.005
Phosphodiesterase 5 Inhibitors (PDE5i)	5.56	4.59, 6.73	<0.001	14.2	2.62, 71.4	0.001
Calcium Channel Blockers (CCB)	1.50	1.30, 1.74	<0.001	0.94	0.18, 3.87	>0.9
Antiplatelets agents	2.25	1.93, 2.62	<0.001	0.76	0.11, 3.87	0.8
Iloprost	2.11	0.94, 4.26	0.2			
Year progressive * PDE5i						
*Linear component * PDE5i*				0.26	0.01, 6.91	0.4
*Nonlinear component * PDE5i*				-1.7**	-2.9, -0.5**	0.006
Year progressive * CCB						
*Linear component * CCB*				2.53	0.17, 56.9	0.5
*Nonlinear component * CCB*				-0.16**	-1.0, 0.69**	0.7
PDE5i * CCB				0.77	0.04, 13.5	0.9
Year progressive * Antiplatelet agents						
*Linear component * Antiplatelet agents*				8.39	0.35, 362	0.2
*Nonlinear component * Antiplatelet agents*				-0.19**	-1.2, 0.82**	0.7
PDE5i * Antiplatelet agents				0.45	0.01, 13.3	0.6
CCB * Antiplatelet agent				1.40	0.08, 25.2	0.8
Year progressive * PDE5i * CCB						
*Linear component * PDE5i * CCB*				0.33	0.00, 97.4	0.7
*Nonlinear component * PDE5i * CCB*				1.5**	-0.57, 3.6**	0.2
Year progressive * PDE5i * Antiplatelet agents						
*Linear component * PDE5i * Antiplatelet agents*				10.1	0.01, 18.4	0.5
*Nonlinear component * PDE5i * Antiplatelet agents*				0.54**	-2.0, 3.1**	0.7
Year progressive * CCB * Antiplatelet agents						
*Linear component * CCB * Antiplatelet agents*				0.35	0.00, 81.5	0.7
*Nonlinear component * CCB * Antiplatelet agents*				-0.56**	-2.0, 0.91**	0.5
PDE5i * CCB * Antiplatelet agents				0.46	0.00, 297	0.8
Year progressive * PDE5i * CCB * Antiplatelet agents						
*Linear component * PDE5i * CCB * Antiplatelet agents*				6.02	0.00, 34.3	0.8
*Nonlinear component * PDE5i * CCB * Antiplatelet ag.*				-0.77**	-4.7, 3.3**	0.7

Characteristic	OR[1]	95% CI[1]	p-value[2]	OR[1]	95% CI[1]	p-value
Year progressive						
Linear component	2.11	0.77, 6.29	0.2	2.80	0.56, 17.9	0.2
Nonlinear component	0.61**	0.26, 0.95**	<0.001	1.20**	0.67, 1.80**	<0.001
Endothelin Receptor Antagonists (ERA)	5.56	4.59, 6.73	<0.001	11.0	2.57, 45.5	<0.001
Calcium Channel Blockers (CCB)	1.35	1.13, 1.62	0.006	4.10	1.10, 15.0	0.033
Iloprost	2.21	0.83, 4.91	0.4			
Antiplatelet agents	1.18	0.95, 1.46	0.6			
Year progressive * ERA						
*Linear component * ERA*				0.53	0.03, 8.82	0.7
*Nonlinear component * ERA*				-1.4**	-2.5, -0.44**	0.005
Year progressive * CCB						
*Linear component * CCB*				0.18	0.01, 2.31	0.2
*Nonlinear component * CCB*				-1.3**	-2.2, -0.44**	0.003
ERA * CCB				0.75	0.05, 9.38	0.8
Year progressive * ERA * CCB						
*Linear component * ERA * CCB*				0.30	0.00, 46.5	0.6
*Noninear component * ERA * CCB*				1.5**	-0.13, 3.2**	0.070

[1] OR = Odds Ratio, CI = Confidence Interval ; [2] Bonferroni correction for multiple testing.
* Represents the interaction term.
** The nonlinear component of "Year progressive" represents the deviation from linearity and is derived from a natural spline transformation. Coefficient for this component has not been exponentiated and do not correspond to odds ratio but describes the (positive) non-linear effect of time progression.

Table 3. Univariate and multivariable logistic regression with interaction to explain the change in prescription of Phosphodiesterase Type-5 inhibitors. CCB: Calcium channel blocker; ERA; Endothelin receptor antagonist.

Table 4. Univariate and multivariable logistic regression with interactions to explain the change in prescription of Calcium Channel Blockers. ERA; Endothelin receptor antagonist; PDE5i: Phosphodiesterase type-5 inhibitor.

Characteristic	OR[1]	95% CI[1]	p-value[2]	OR[1]	95% CI[1]	p-value
Year progressive						
Linear component	3.75	2.14, 6.70	<0.001	3.61	1.76, 7.64	<0.001
Nonlinear component	0.71**	0.52, 0.91**	<0.001	0.66**	0.40, 0.92**	<0.001
Endothelin Receptor Antagonists (ERA)	1.50	1.30, 1.74	<0.001	1.18	0.27, 4.18	0.8
Phosphodiesterase 5 Inhibitors (PDE5i)	1.35	1.13, 1.62	0.006	5.38	1.29, 22.0	0.018
Antiplatelets agents	3.06	2.73, 3.44	<0.001	2.59	1.19, 5.55	0.015
Iloprost	1.21	0.62, 2.28	>0.9			
Year progressive * ERA						
*Linear component * ERA*				1.63	0.14, 26.4	0.7
*Nonlinear component * ERA*				-0.15**	-1.0, 0.74**	0.7
Year progressive * PDE5i						
*Linear component * PDE5i*				0.16	0.01, 2.53	0.2
*Nonlinear component * PDE5i*				-2.0**	-3.1, -0.87**	<0.001
ERA * PDE5i				0.65	0.04, 10.6	0.8
Year progressive * Antiplatelet agents						
*Linear component * Antiplatelet agents*				1.58	0.35, 7.29	0.6
*Nonlinear component * Antiplatelet agents*				-0.05**	-0.55, 0.46**	0.9
ERA * Antiplatelet agents				1.40	0.10, 19.6	0.8
PDE5i * Antiplatelet agents				0.18	0.01, 3.22	0.3
Year progressive * *ERA * PDE5i*						
*Linear component * ERA * PDE5i*				0.47	0.00, 121	0.8
*Nonlinear component * ERA * PDE5i*				1.5**	-0.55, 3.6**	0.15
Year progressive * ERA * Antiplatelet agents						
*Linear component * ERA * Antiplatelet agents*				0.36	0.00, 55.6	0.7
*Nonlinear component * ERA * Antiplatelet agents*				-0.68**	-2.2, 0.82**	0.4
Year progressive * PDE5i * Antiplatelet agents						
*Linear component * PDE5i * Antiplatelet agents*				2.99	0.00, 23.8	0.7
*Nonlinear component * PDE5i * Antiplatelet agents*				3.1**	0.76, 5.7**	0.011
ERA * PDE5i * Antiplatelet agents				0.71	0.00, 326	>0.9
Year progressive * ERA * PDE5i * Antiplatelet agents						
*Linear component * ERA * PDE5i * Antiplatelet*				2.93	0.00, 3.35	0.9
*Nonlinear component * ERA * PDE5i * Antiplatelet*				-1.3**	-5.2, 2.6**	0.5

[1] OR = Odds Ratio, CI = Confidence Interval. [2] Bonferroni correction for multiple testing.

* Represents the interaction term.

*** The nonlinear component of "Year progressive" represents the deviation from linearity and is derived from a natural spline transformation. Coefficient for this component has not been exponentiated and do not correspond to odds ratio but describes the (positive) non-linear effect*

of time progression.

Table 5. Univariate logistic regression to explain the association of the prescription of intravenous Iloprost with time and other vascular medications.

Characteristic	OR[1]	95% CI[1]	p-value[2]
Endothelin Receptor Antagonists	2.11	0.94, 4.26	0.049
Phosphodiesterase 5 inhibitors	2.21	0.83, 4.91	0.074
Calcium Channel Blockers	1.21	0.62, 2.28	0.6
Year progressive			
Linear component	0.0001	0.00001, 0.0052	<0.001
Nonlinear component	-13.0**	-19.0, -7.6**	<0.001
Anti platelets	1.45	0.68, 2.87	0.3
[1] OR = Odds Ratio, CI = Confidence Interval			
[2] Bonferroni correction for multiple testing			
*** The nonlinear component of "Year progressive" represents the deviation from linearity and is derived from a natural spline transformation. Coefficient for this component has not been exponentiated and do not correspond to odds ratio but describes the (positive) non-linear effect of time progression.*			

Figure 1. Proportion of patients on vascular medications over time (2012-2022), stratified by Drug Class. CCB (Calcium Channel Blockers), ERA (Endothelin Receptor Antagonists), PDE5i: Phosphodiesterase 5 inhibitors).

Alt text:

Line chart showing the proportion of SSc patients receiving CCB, ERA, PDE5i, and Iloprost from 2012 to 2022, with increasing trends for CCB, ERA, and PDE5i, and a sharp decline for Iloprost since 2019.