A multi-national survey to identify clinicians' perspectives concerning Proton Pump inhibitors in patients with systemic sclerosis

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ABSTRACT

Objectives: Proton Pump Inhibitors (PPIs) are widely used in SSc for gastroesophageal reflux disease (GERD). However, there is little evidence to support their empirical use and long-term safety has been questioned. Our objective was to better describe clinicians' attitudes toward PPIs prescription and use in SSc patients.
Methods: Clinicians involved in the care of SSc patients were invited through international physician networks and social media to participate in an online survey.
Results: Responses from 227 clinicians from 36 countries were evaluable. The majority 'agreed' (41.4 %) or 'strongly agreed' (45.4 %) that GERD is a major cause of morbidity in SSc. Lifestyle modifications are seldom (16 %) considered effective. Only half 'agreed' (43 %) or 'strongly agreed' (11 %) there is solid evidence supporting PPIs efficacy in SSc. The most common reasons for PPIs prescription were symptomatic GERD unresponsive to lifestyle modification (95 %), objective evidence of GERD (82 %), and hoarseness or respiratory symptoms (71 %). There are variable concerns about PPIs long-term safety in SSc. The three highest (mean) reasons (0–10, here 10 is 'very concerned') were: small intestinal bacterial overgrowth (5.5), osteoporosis (5.4), and drug interactions (5.2). There are significant differences in attitudes towards surgery for refractory GERD, and concerns about potential complications. PPIs may have a putative role for disease modification (e.g., ILD and calcinosis), and the role of immunosuppression is uncertain for GI (gastrointestinal) disease in SSc.
Conclusion: PPIs are frequently prescribed in SSc. Side effects are a recognized concern, especially regarding long-term therapy. There is significant variation in attitudes towards surgical intervention. Future research and practical treatment recommendation for PPIs in SSc are urgently needed.

Section snippets

PPIs are commonly prescribed in SSc and there are important safety concerns about long-term use.

The maximal PPIs dosage and combination therapy is often

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prescribed for refractory GERD in SSc.

Physicians reckon PPIs may have a putative disease-modifying effect in SSc for interstitial lung disease and calcinosis.

Introduction

Gastrointestinal (GI) involvement affects the majority (>90 %) of patients with systemic sclerosis (SSc) throughout the course of their disease [1], and is associated with significant disease-related morbidity and mortality [2–4]. In particular, oesophageal disease is almost universal, and often presents as gastroesophageal reflux disease (GERD), and other troublesome GI symptoms (e.g., dysphagia) [5,6].

The importance of GI involvement for patients with SSc has been recently highlighted and confirmed [7]. Effective treatment of GERD in SSc patients remains a major clinical challenge and a clear unmet need in the disease. A major frustration is that many patients are refractory to standard (including high-dose) treatment approaches used in the general population. Furthermore, uncontrolled GERD may lead to serious potential sequelae including (but not limited to) stricture formation, pre-malignant alterations (i.e., Barrett's esophagus), and malignant evolution [8,9]. Moreover, GERD has been reported to be centrally implicated in the pathogenesis of SSc-associated interstitial lung disease (ILD) [10,11].

Non-pharmacological interventions are mandatory in *all* patients with SSc. Lifestyle modifications and education include acid food avoidance, smoking cessation, alcohol reduction, weight control, small and frequent meals, and eating several hours before lying down in a supine position [12,13]. However, these interventions are rarely fully effective in controlling symptoms, and therefore, a pharmacological approach is very often required in patients with SSc.

Proton Pump inhibitors (PPIs) are considered by far the single class of drugs that has had the greatest impact in controlling GERD symptoms in SSc, changing everyday life of many patients. However, to date, treatment recommendations for the use of PPIs in SSc have been based largely on learned experience in the general population, and expert consensus [14]. Specifically, there are no large, specific randomized controlled trails [15]. Furthermore, in patients with SSc, the use of maximum dose of PPIs is frequent, often ineffective, and with objective evidence of continued reflex disease (e.g., as disclosed on endoscopy) [16] despite patient compliance with therapy, and with minimal or no symptoms [17,18].

Of particular relevance to patients with SSc, significant safety concerns have been raised in the general population about the long-term safety of PPIs treatment. These include (but are not limited to) increased risk of infections, cardiovascular and kidney diseases, hypomagnesemia, interaction with other drug therapies, reduced intestinal absorption of vitamins and minerals, and dementia [19–21]. In addition, specific SSc considerations have been raised about long-term PPIs use including increased risk of calcinosis, small intestinal bacterial overgrowth, diarrhoea, osteoporosis and increased risk of fractures [22]. However, on the contrary, a potential beneficial effect has been reported for SSc-associated interstitial lung disease, as it has been postulated that recurrent microaspiration may drive the development and/or progression of interstitial lung disease [23]. Furthermore, surgery is seldom performed due to concerns about potential complications. Moreover, the optimal surgical procedure for refractory GERD in patients with SSc is yet to be defined [24].

Against this background, the aim of our survey was to examine clinicians' awareness of GERD and their perspectives concerning PPIs use in patients with SSc.

Methods

Study design

A dedicated Steering Board was assembled which consisted of clinicians with an interest in SSc (GB, CC, AMP, SBR, LD, MH, MMC, ZM, and FP), patient representation (IG), respiratory (BR) and surgical colleagues (PM-C), and with methodological expertise (AA). The resulting group developed a bespoke survey to explore clinicians' attitudes concerning the use of PPIs for controlling GERD and other upper GI symptoms in patients with SSc.

The survey consisted of a series of questions (see **supplementary materials**) that included basic clinician-reported demographic, specialty, SSc experience (years of practice, how many SSc patients under their care), GERD awareness and management, PPIs therapy (duration, drugs, modalities of prescription, efficacy), PPIs side effects, and surgical intervention. For inclusion, respondents were required to be at least 18 years old. The survey was launched on the 28th of November 2022 and was live for four weeks. The link to the survey was widely distributed including through social media (e.g., Twitter®) and patient-led organizations (listed in the acknowledgment section).

Statistical analyses

Data were imported from the survey platform into SPSS® software. Descriptive statistics were used to summarize the data. Absolute and relative frequencies were calculated and depicted in tabular and graphical form. Data are presented as the number and percentage of all available responses to each question throughout the manuscript.

Results

Clinician demographics and SSc experience

The survey was completed by the majority (N = 182; 80 %) of 227 respondents and most of them were between 30 and 50 years (N = 127; 55.9 %). There was an equal distribution between male and females (N = 108; 47.6 % and N = 117; 51.5 %, respectively). There was broad international representation with responses from 36 countries, among which the most common were from Italy (N = 49; 21.6 %), UK (N = 39; 17.2 %), and the US (N = 34; 15 %). The majority of respondents were rheumatologists (N = 160; 70.5 %), followed by internists (N = 24; 10.6 %), gastroenterologists (N = 17; 7.5 %), and pneumologists/respiratory physicians (N = 12; 5.3 %). Time practicing since completion of training was variable: 11–20 years (N = 63; 27.8 %), 0–5 years (N = 55; 24.2 %), 21–30 years (N = 42; 18.5 %), 6–10 years (N = 39; 17.2 %), and more than 30 years (N = 28; 12.3 %). The majority (N = 196; 86 %) of respondents practice was based in a University hospital. Over half (N = 124; 54.6 %) of respondents reported that they had at least 50 patients with SSc under their care (Table 1).

GERD awareness and management

The majority of respondents either agreed (N = 94; 41.4 %) or strongly agreed (N = 103; 45.4 %) that GERD is a major cause of morbidity in patients with SSc (N = 18; 7.9 % neutral, N = 11; 4.8 % disagreed, and N = 1; 0.4 % strongly disagreed). Oesophageal dysmotility (N = 206; 91 %) and hypotensive lower esophageal sphincter (N = 169; 74 %) were considered two of the major pathogenetic causes of GERD symptoms in SSc. Furthermore, oesophageal fibrosis (N = 99; 44 %), autonomic disfunction (N = 91; 40 %) and smooth muscle atrophy (N = 82; 36 %) were also considered as important.

The majority of clinicians either 'agreed' (N = 114; 53 %) or 'strongly agreed' (N = 34; 16 %) that SSc patients with GERD should be tested for *Helicobacter pylori* infection; however, about one-quarter (N = 50; 23 %) were 'neutral' to this proposal. There was significant variation between

Table 1
Characteristics of survey respondents.

	Clinician characteristics	N (%)
Age (years)	18–30	21 (9.3 %)
	30–50	127 (55.9 %)
	50–70	69 (30.4 %)
	>70	10 (4.4 %)
Gender	Male/female	108 (47.6 %)/117
	Other/prefer not to specify	(51.5 %)
		1 (0.4 %)/1 (0.4 %)
Country	Italy	49 (21.6 %)
	United Kingdom	39 (17.2 %)
	United States of America	34 (15.0 %)
	Iran	12 (5.3 %)
	Australia	9 (4.0 %)
	Sweden	9 (4.0 %)
	Canada	8 (3.5 %)
	Switzerland	8 (3.5 %)
	France	6 (2.6 %)
	Spain	6 (2.6 %)
	Other	47 (20.7 %)
Primary Specialty	Rheumatology	161 (70.5 %)
	Internal Medicine	24 (10.6 %)
	Gastroenterology	17 (7.5 %)
	Pneumologist/respiratory	12 (5.3 %)
	physician	3 (1.3 %)
	Gastrointestinal surgery	2 (0.9 %)
	General Medicine	1 (0.4 %)
	Nurse	8 (3,5 %)
	Other*	
Practice after training (years)	0–5	55 (24.2 %)
	6–10	39 (17.2 %)
	11–20	63 (27.8 %)
	21–30	42 (18.5 %)
	>30	28 (12.3 %)
Workplace	University hospital	196 (86.0 %)
	General (non-university/	27 (12.0 %)
	teaching hospital)	2 (1.0 %)
	General practitioner/family	18 (8.0 %)
	practice clinic	
	Private practice	
Number of SSc patients cared for	<25	73 (32.2 %)
	25–50	30 (13.2 %)
	50–100	28 (12.3 %)
	100–200	34 (15.0 %)
	>200	62 (27.3 %)

* Allergology and Immunology, Cardiology, Dermatology, Geriatrics, Immunology, Nephrology, Paediatric Rheumatology.

respondents whether patients with SSc and GERD should always be referred to a Gastroenterologist: 'strongly agreed' (N = 24; 11 %), 'agreed'; (N = 65; 30 %), 'neutral' (N = 54; 25 %), 'disagreed' (N = 67; 31 %), or 'strongly disagreed' (N = 7; 3 %). Furthermore, over half of respondents either 'strongly disagreed' (N = 39; 17 %) or 'disagreed' (N = 106; 47 %) that lifestyle modifications and non-pharmacological management of GERD alone are effective in controlling GERD symptoms in SSc ('neutral' N = 46; 20 %, 'agreed' N = 28; 12 %, 'strongly agreed' N = 8; 4 %).

Over half of respondents either 'strongly disagreed' (N = 54; 24 %) or 'disagreed' (N = 94; 41 %) that immunosuppression is an effective treatment option for GI manifestations in SSc, however one-quarter (N = 61; 27 %) were 'neutral' ('agreed' N = 15; 7 % and 'strongly agreed' N = 3; 1 %). Again, around half either 'strongly agreed' (N = 25; 11 %) or 'agreed' (N = 97; 43 %) that there is solid evidence in the literature supporting the efficacy of PPIs in patients with GERD; one-third were 'neutral' (N = 73; 32 %), and only around one-fifth either strongly 'disagreed' (N = 5; 2 %) or 'disagreed' (N = 27; 12 %).

PPIs therapy

PPIs prescribing practice

Most respondents prescribe PPIs either 'often' (N = 46; 20.3 %), 'very often' (N = 116; 51.1 %), or 'always' (N = 50; 22 %), and with less than 10 % prescribing either 'rarely' or 'never' (N = 12; 5.3 % and N = 3; 1.3 %, respectively). The main reasons for prescribing PPIs were "symptomatic GERD unresponsive to lifestyle modification" (N = 216; 95 %), "objective evidence of GERD (e.g., esophagitis on endoscopy)" (N = 186; 82 %), and "hoarseness or respiratory symptoms (e.g., dry cough) where GERD is suspected to be implicated" (N = 162; 71 %). Other reasons were "regurgitation" (N = 124; 55 %), "dysphagia" (N = 103; 45 %), and "symptomatic GERD unresponsive to H2 blocker" (N = 96; 42 %) (Table 2). A wide range of PPIs are prescribed (Fig. 1), most commonly pantoprazole (N = 169; 74 %), omeprazole and esomeprazole (both N = 163; 72 %), and lansoprazole (N = 155; 68 %). Less commonly prescribed PPIs were rabeprazole (N = 65; 28 %) and dexlansoprazole (N = 44; 19 %). Clinicians frequently either 'often' (N = 94; 41.4), 'very often' (N = 68; 30 %) or 'always' (N = 19; 8.4 %) prescribe the maximum dose of PPIs (or even higher) in patients with refractory GERD ('rarely' N = 38; 16.7 % and 'never' N = 8; 3.5 %).

PPIs SSc disease modification

Around half (N = 96; 44 %) of respondents were neutral concerning whether PPIs may reduce the progression of interstitial lung disease in at least some SSc patients. However, many either 'agreed' (N = 81; 37 %) or 'strongly agreed' (N = 9; 4 %), and fewer 'disagreed' (N = 27; 12 %) or 'strongly disagreed' (N = 4; 2 %). Similarly, around half (N = 93; 42.9 %) were 'neutral' to whether all SSc patients should be on high-dose PPIs long-term after lung transplantation; whereas, around half either 'agreed' (N = 84; 38.7 %) or 'strongly agreed' (N = 24; 11.1 %), and the minority 'disagreed' (N = 15; 6.9 %) or 'strongly disagreed' (N = 1; 0.5 %). Again, around half of respondents were 'neutral' to whether patients with refractory calcinosis should have their PPIs dose and/or frequency reduced, and one-fifth either 'agreed' (N = 49; 22.6 %) or 'strongly agreed' (N = 1; 0.5 %); and one-quarter 'disagreed' (N = 55; 25.3 %) or 'strongly disagreed' (N = 7; 3.2 %).

PPIs efficacy

PPIs efficacy is reported to be evaluated with patient-reported symptoms in the majority (N = 212; 93 %) of cases; in one-third either by endoscopy (N = 79; 35 %) or patient-reported outcome measures/instruments (N = 69; 30 %), and less commonly by pHmetry (N = 21; 9 %) or manometry (N = 19; 8 %) (Fig. 2). The majority of clinicians wait until 6 weeks to evaluate whether PPIs are effective for GERD before considering dose changes (0–6 weeks: N = 43; 18.9 %; 6 weeks to 3 months: N = 120; 52.9 %; 3–6 months: N = 49; 21.6 %; 6–12 months: N = 5; 2.2 %; and >12 months: N = 3; 1.3 %).

Table 2
Reasons for prescribing PPIs in patients with SSc.

Reason	N (%)
Symptomatic GERD unresponsive to lifestyle modification	216 (95 %)
Objective evidence of GERD (e.g., oesophagitis on endoscopy)	186 (82 %)
Hoarseness or respiratory symptoms (e.g., dry cough) where GERD is suspected to be implicated	162 (71 %)
Regurgitation	124 (55 %)
Dysphagia	103 (45 %)
Symptomatic GERD unresponsive to H2 blocker	96 (42 %)
Preventive measure due to other ongoing medications	87 (38 %)
Concern for microaspiration post lung transplant	79 (35 %)
Proven hiatal hernia	50 (22 %)
Other *(oesophageal hypomotility, oesophageal dilation on CT scan, hypertensive oesophagus on manometry)*	4 (2 %)

PPIs: Proton Pump Inhibitors; GERD: Gastroesophageal Reflux Disease; CT: Computed Tomography.

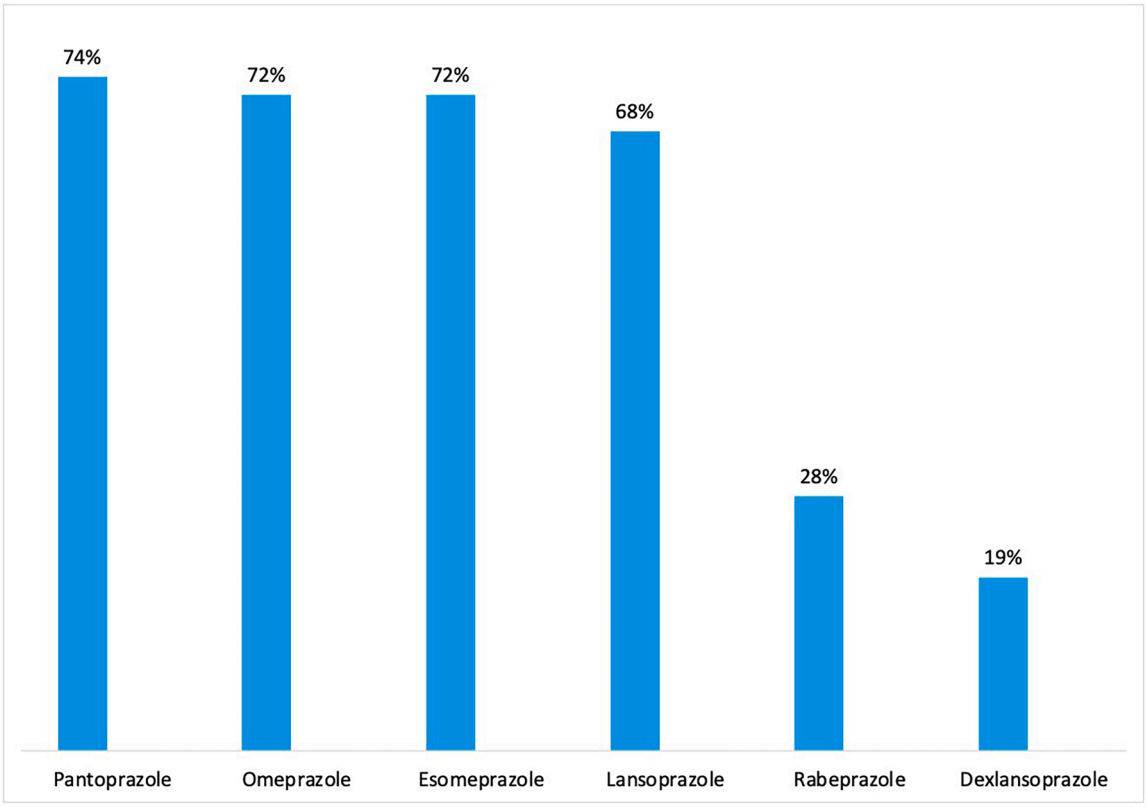

Fig. 1. Type of Proton Pump Inhibitors prescribed and their relative frequencies.

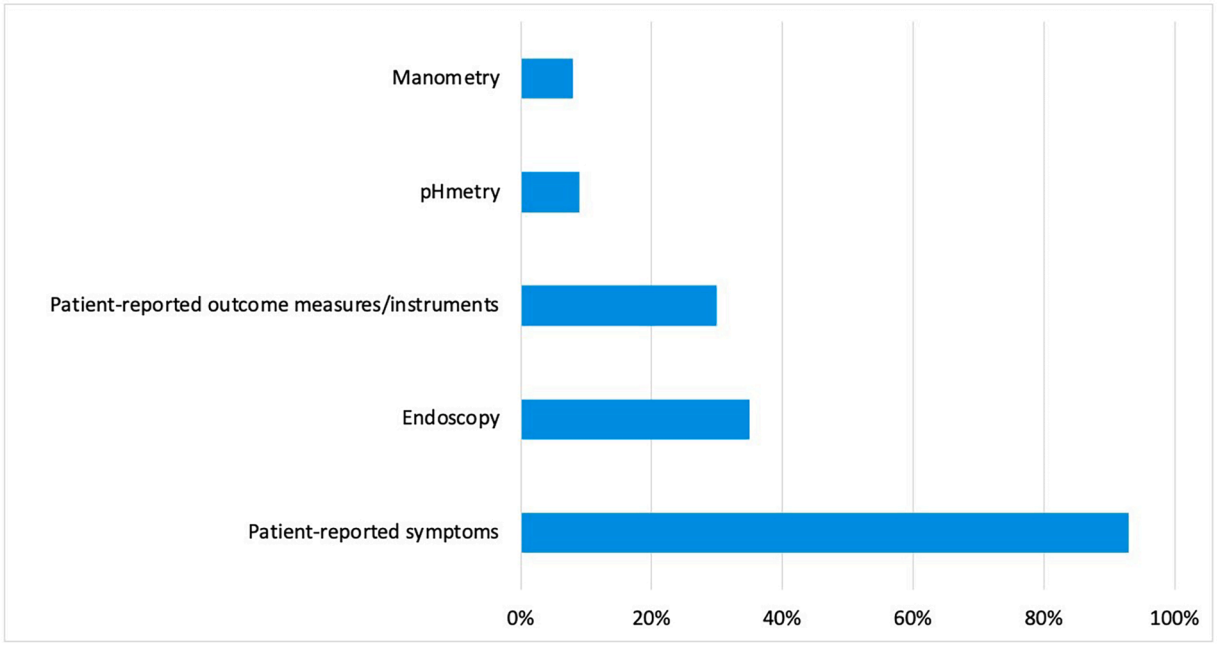

Fig. 2. Strategies used to evaluate the efficacy of Proton Pump Inhibitors treatment.

Refractory GERD and PPIs combination therapy

Most respondents either 'agreed' (N = 140; 62 %) or 'strongly agreed' (N = 47; 21 %) that in patients who do not respond to maximum PPIs dose then they would recommend further diagnostic modalities or investigations such as endoscopic evaluation ('neutral' N = 26; 12 %, 'disagreed' N = 14; 6 %, and 'strongly disagreed' N = 0; 0 %). In patients who do not respond to once-daily PPIs, over half (N = 129; 56.8 %) would recommend twice-daily PPIs prescription.

Other treatment strategies included adding other anti-acid medication such as e.g., TUMS, sucralfate, or sodium alginate/sodium bicarbonate (N = 31; 13.7 %), other promotility agent (N = 31; 13.7 %) or a Histamine-2 receptor antagonist (H2Ras) (N = 21; 9.3 %). Most either 'agreed' (N = 144; 63 %) or 'strongly agreed' (N = 47; 21 %) that patients with SSc with refractory GERD on PPIs should be prescribed other

therapies, such as a prokinetic agents if there is dysphagia and/or evidence of dysmotility ('neutral' $N = 34$; 15 %, 'disagreed' $N = 2$; 1 %, 'strongly disagreed' $N = 0$; 0 %)

Controlled GERD on PPIs treatment

Most respondents either 'disagreed' ($N = 123$; 54 %) or 'strongly disagreed' ($N = 35$; 15 %) that PPIs should be discontinued in patients with SSc if their symptoms have completed resolved on therapy; one-fifth ($N = 38$; 17 %) were 'neutral', and the minority 'agreed' ($N = 26$; 12 %) or 'strongly agreed' ($N = 5$; 2 %). Furthermore, two-thirds either 'agreed' ($N = 138$; 61 %) or 'strongly agreed' ($N = 10$; 4 %) that the PPIs dose should be reduced in patients with well-controlled GERD; one-quarter ($N = 53$; 23 %) were 'neutral', and the minority 'disagreed' ($N = 24$; 11 %) or 'strongly disagreed' ($N = 2$; 1 %). Over half of respondents either 'disagreed' ($N = 119$; 52 %) or 'strongly disagreed' ($N = 20$; 9 %) that PPIs should be switched to H2 receptor antagonists in patients with SSc and stable GERD; one-third were 'neutral' ($N = 71$; 31 %), and the minority 'agreed' ($N = 15$; 7 %) or 'strongly agreed' ($N = 2$; 1 %).

Side effects

There was significant heterogeneity about whether the long-term use of PPIs in SSc is of concern: 'strongly agreed' ($N = 6$; 3 %), 'agreed' ($N = 76$; 34 %), 'neutral' ($N = 81$; 36 %), 'disagreed' ($N = 56$; 25 %), and 'strongly disagreed' ($N = 8$; 4 %). Clinicians were most concerned about a wide range of potential PPIs side effects (0–10, where 10 being 'very concerned') as depicted in Fig. 3. The most common (mean, SD) were small intestinal bacterial overgrowth (5.5, 2.5), osteoporosis and increased risk of fracture (5.4, 2.5), drug interactions (5.2, 2.5), hypomagnesemia (4.7, 2.4), and diarrhoea (4.6, 2.5).

Surgery

Over half ($N = 113$; 52 %) of respondents were 'neutral' whether GI surgery (e.g., fundoplication) in patients with SSc with refractory GERD was associated with significant improvements in symptoms, one-third either 'disagreed' ($N = 57$; 26 %) or 'strongly disagreed' ($N = 13$; 6 %), and the minority 'agreed' ($N = 28$; 13 %) or 'strongly agreed' ($N = 6$; 3 %). Over half either 'agreed' ($N = 98$; 45.2 %) or 'strongly agreed' ($N = 13$; 6 %) were concerned about frequent complications from surgery in patients with SSc for refractory GERD; however, around half ($N = 99$; 45.6 %) were 'neutral', and few 'disagreed' ($N = 6$; 2.8 %) or 'strongly disagreed ($N = 1$; 0.5 %).

Discussion

A wide range of PPIs are frequently prescribed in patients with SSc and generally considered an effective therapy; however, many clinicians have significant safety concerns about long-term use. Our survey confirms that clinicians consider that GERD is a major cause of morbidity in patients with SSc. Furthermore, the pathogenetic causes leading to upper GI involvement are multifactorial and complex. Non-pharmacological management is seldom considered alone as ineffective in controlling GERD symptoms in patients with SSc. In fact, the majority of respondents almost always prescribe PPIs and with no clear preference among the different available agents.

There is significant heterogeneity in clinical practice concerning the management of upper GI symptoms including GERD in patients with SSc. Moreover, PPIs are prescribed at maximum dosage in the presence of refractory GERD and combination therapy is often prescribed. However, to date, there are only limited recommendations concerning practical PPIs prescribing and most derive from SSc experts' opinion. For example, the British Society of Rheumatology guideline for the treatment of SSc (currently under revision) states that 'PPIs and H2Ras are recommended for treatment of GERD and dysphagia and may require long-term administration' [25,26]. Furthermore, the EULAR SSc recommendations highlighted that 'in asymptomatic patients with SSc, PPIs should be used with caution since long-term therapy with PPIs might lead to nutritional deficiencies, possibly due to reduced intestinal absorption, or increased risk of infections' [15]. In addition, experts ($n = 170$) from the Scleroderma Clinical Trials Consortium and the Canadian Scleroderma Research group guidance state with high agreement (94 %) that high-dose PPIs therapy should be deployed for GERD/upper GI dysmotility [27]. Therefore, there is a clear need to define the optimal therapeutic strategy for PPIs in patients with SSc, including in patients with apparently stable disease to minimize potential long-term side effects.

Lifestyle modifications are often neglected and should be considered as mandatory in the management of GERD in SSc. Furthermore, the potential role for surgical intervention is seldom discussed, although patients strongly indicated that they would consider this approach. Nonetheless, concerns about potential side effects should also be discussed. Another novel finding from our survey is that there is varying

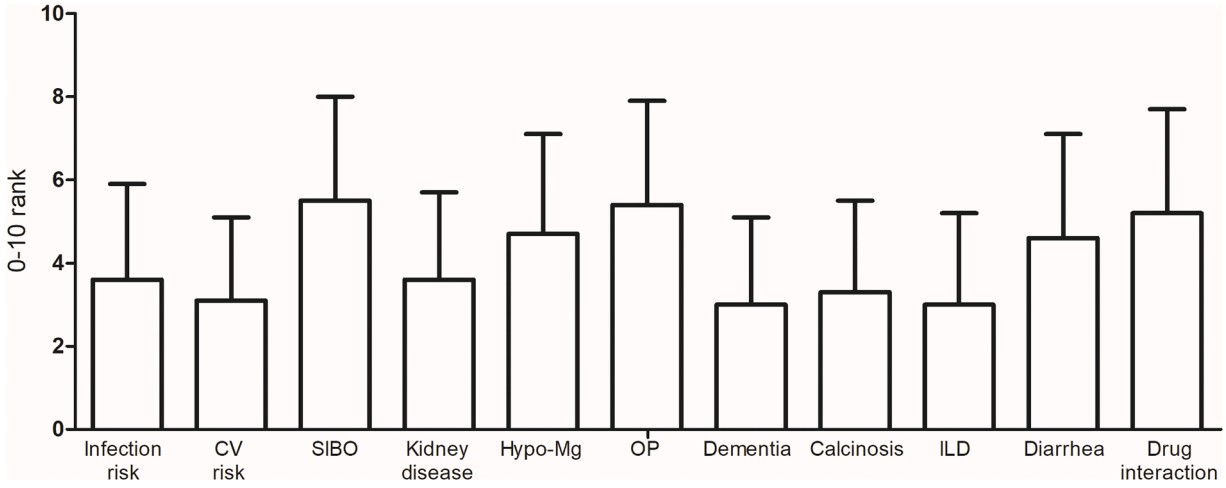

Fig. 3. Respondents' opinion about Proton Pump inhibitors' safety profile.
Answers were provided ranking the concern from 0 (not concerned) to 10 (very concerned) for each listed adverse event. The column height shows the mean value, and the bars show the standard deviation.
List of abbreviations shown in the figure: CV, cardiovascular; SIBO, small intestine bacterial overgrowth; Mg, magnesium; OP, osteoporosis (also including the risk of fractures); ILD, interstitial lung disease.

consensus whether PPIs could potentially be used therapeutically as a putative form of disease-modification e.g., prevention progression of ILD (including after lung transplantation) and calcinosis.

Our study benefited from significant target audience engagement with >200 clinicians who responded to our survey and whose answers were fully evaluable. However, there are some relevant aspects to highlight. First, our survey was distributed primarily through international SSc physician networks and social media, and therefore, there could be an intrinsic bias in the target audience. However, there was a wide distribution observed in the age of respondents, and with good geographical representation. Furthermore, data (including respondent characteristics) were self-reported and not subject to confirmatory review. Finally, the survey was written in the English language which could lead to a potential bias in the respondents who undertook (and completed) the survey. Future research should consider the impact of the experience/number of patients with SSc under their clinical care and PPI prescribing

In conclusion, our survey confirms that clinicians dealing with SSC consider GERD a frequent, well-known and troublesome manifestation of GI involvement of the disease. Moreover, it can be linked with other important manifestation of the disease, such as ILD. PPIs are considered an effective therapy for GERD in many patients with SSc; however, long-term safety is a concern by clinicians. Our survey highlights the heterogeneity in the use, prescription and monitoring of PPI therapy in everyday clinical practice suggesting that future research and practical treatment recommendations for PPIs in patients with SSc are strongly needed, including refractory GERD. Furthermore, the role of combination therapy, treatment strategies in apparently stable disease, PPIs as true disease modifying agents, the role of immunosuppression and surgical intervention for GI disease in SSc, should all be further explored.

Ethics statement

All subjects gave their informed consent for using their anonymous responses before starting the survey. The study was conducted in accordance with the Declaration of Helsinki and it was impossible at any time to link responses to individuals.

Declaration of competing interest

None declared by any of the authors.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2024.152419.

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