

# A Multinational Survey Investigating the Unmet Needs and Patient Perspectives Concerning Proton Pump Inhibitors in Systemic Sclerosis

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**Objective.** Proton pump inhibitors (PPIs) are widely prescribed to treat gastroesophageal reflux disease (GERD) in Systemic Sclerosis (SSc). However, not all patients adequately respond to the treatment, and there are frequent concerns about the safety of long-term use of PPIs. Our aim was to identify the main problems/complaints of SSc patients on PPIs, as well as understand their unmet needs.

**Methods.** SSc patients treated with PPIs were invited through international patient associations and social media to participate in an online survey.

**Results.** We gathered 301 valid responses from 14 countries (United Kingdom 19.3% and United States 70.4%). Multiple PPIs use (two: 30% and three: 21% in series) was common. The majority (89%) reported improvement in gastrointestinal symptoms from receiving PPIs. Side effects attributed to receiving PPIs were uncommon (19%); however, most (79%) were potentially concerned. Around half (58%) had received lifestyle information, and most (85%) had searched online for information about PPIs. Only in the minority (12%) had a surgical approach been discussed; however, half (46%) indicated that they would be willing to undergo surgery to resolve their GERD symptoms but had important concerns.

**Conclusion.** Despite the frequent use of PPIs in patients with SSc, there is significant heterogeneity in prescription, and combination therapy (PPIs plus other medication for acid reflux) is not uncommon (approximately 40%). Patients have significant concerns about PPIs side effects. Education about PPIs is often neglected, and patients very frequently use online sources to obtain information on drug treatment. A surgical approach is infrequently discussed, and patients fear this potential therapeutic approach.

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### SIGNIFICANCE & INNOVATIONS

- Proton pump inhibitors (PPIs) are frequently used in patients with systemic sclerosis; however, there is significant heterogeneity in practice.
- Although PPIs are effective in the majority of patients who receive them, patients have significant concerns regarding long-term safety.
- Patient education about receiving PPIs is often neglected, and a surgical approach is not widely discussed.

## INTRODUCTION

Gastrointestinal (GI) involvement is almost universal (>90%) in patients with systemic sclerosis (SSc).<sup>1-3</sup> Upper GI tract dysfunction, often presenting with gastroesophageal reflux disease (GERD), is associated with important morbidity and represents one of the most troublesome complaints for patients with SSc.<sup>4-6</sup> Hypotony and inefficacy of the lower esophageal sphincter is one of the most important factors leading to GERD in patients with SSc.<sup>7,8</sup> However, other mechanisms are likely implicated (eg, autonomic dysfunction, dysmotility, and structural alterations to the esophagus).<sup>9,10</sup> Long-term uncontrolled GERD can also result in chronic inflammation of the GI tract, with potentially serious complications,<sup>11</sup> including stricture formation and malignant change.<sup>12,13</sup> Moreover, GERD and chronic microaspiration have been associated with interstitial lung disease (ILD) in SSc.<sup>14-16</sup>

In SSc, proton pump inhibitors (PPIs) represent one of the major achievements in the management of GI involvement, and are widely prescribed to successfully treat GERD in the general population, being often available “over the counter” without prescription. However, commonly standard doses of PPIs often achieve only a partial effect and/or are sometimes ineffective in patients with SSc.<sup>17</sup> Many patients with SSc still have objective (eg, on endoscopy) evidence of GERD also while receiving PPIs treatment despite apparently being well-controlled symptoms (eg, by patient report). Other patients are completely asymptomatic, and evidence of esophageal GI involvement is diagnosed coincidentally when performing investigations for other reasons; for example, esophageal dilation seen on computed tomography chest imaging investigating for ILD or on endoscopic examination done for other clinical reasons.

Despite the absence of randomized, placebo-control trials to guide the use of PPIs in SSc practice,<sup>18</sup> clinicians consider these drugs effective for GERD. Furthermore, the dosing, efficacy, and duration of PPIs therapy in SSc is largely unknown. To the best of our knowledge, only studies on small samples have shown symptomatic benefit over short periods of time.<sup>19,20</sup> Therefore, a significant safety concern is that it is not uncommon for patients with SSc to

receive long term maximal PPIs doses in clinical practice. Furthermore, broad-ranging safety concerns have been raised regarding the general population receiving PPIs<sup>21</sup> that may have a particular relevance to patients with SSc.<sup>22</sup> These include (but are not limited to) an increased risk of infection,<sup>23,24</sup> kidney injury, small intestinal bacterial overgrowth, osteoporosis, hypomagnesemia,<sup>22</sup> and cardiovascular disease.<sup>21</sup> Against this background, the aim of our study was to identify the main problems/complaints of patients with SSc on receiving PPIs, as well as understand their unmet needs.

## PATIENTS AND METHODS

**Study design and survey questions.** A steering board of clinicians with an interest in SSc (GB, CC, FP, AMP, SBR, LD, MMC, ZHM, and MH) was gathered together with a patient representative (IG), a pulmonologist (BR), a surgeon (PMC), a methodologist (AA), and nurse representatives (KEA and MRM). The board developed a survey to explore the unmet needs and perspectives of patients with SSc about receiving PPIs. The survey consisted of a series of questions (Supplementary Materials) that included patient demographics, PPIs therapy (duration, drug therapies, and modalities of assumption and prescription), efficacy of receiving PPIs (including use in combination), side effects (real and perceived), education and lifestyle, investigations, and surgery.

**Survey distribution and responses.** Patients were required to be at least 18 years old, diagnosed with SSc, and having received a PPIs treatment. The survey was launched on November 4, 2022, and was kept open for four weeks. The link to the survey was widely distributed to a large number of patients with SSc, including (but not limited to) through social media (eg, X, formerly known as Twitter) and patient-led organizations (listed in the Acknowledgments section). Our study did not require ethical approval because no identifiable information was collected throughout the duration of the survey; consent was implied through voluntary participation, and respondents could discontinue at any point.

**Statistical analysis.** 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 form. Data are presented as the number and percentage of all available responses to each question throughout the manuscript. The data underlying this article will be considered to be shared on reasonable request to the corresponding author.

**Ethics statement.** All patients 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.

## RESULTS

**Survey responses.** In 14 countries, a total of 301 valid responses were collected from individuals based in the United Kingdom ( $n = 58$ ; 19.3%) and United States ( $n = 212$ ; 70.4%), as well as from 12 other countries ( $n = 30$ , 9.8%; Supplementary Materials). For our present analysis, we present data from UK and US respondents.

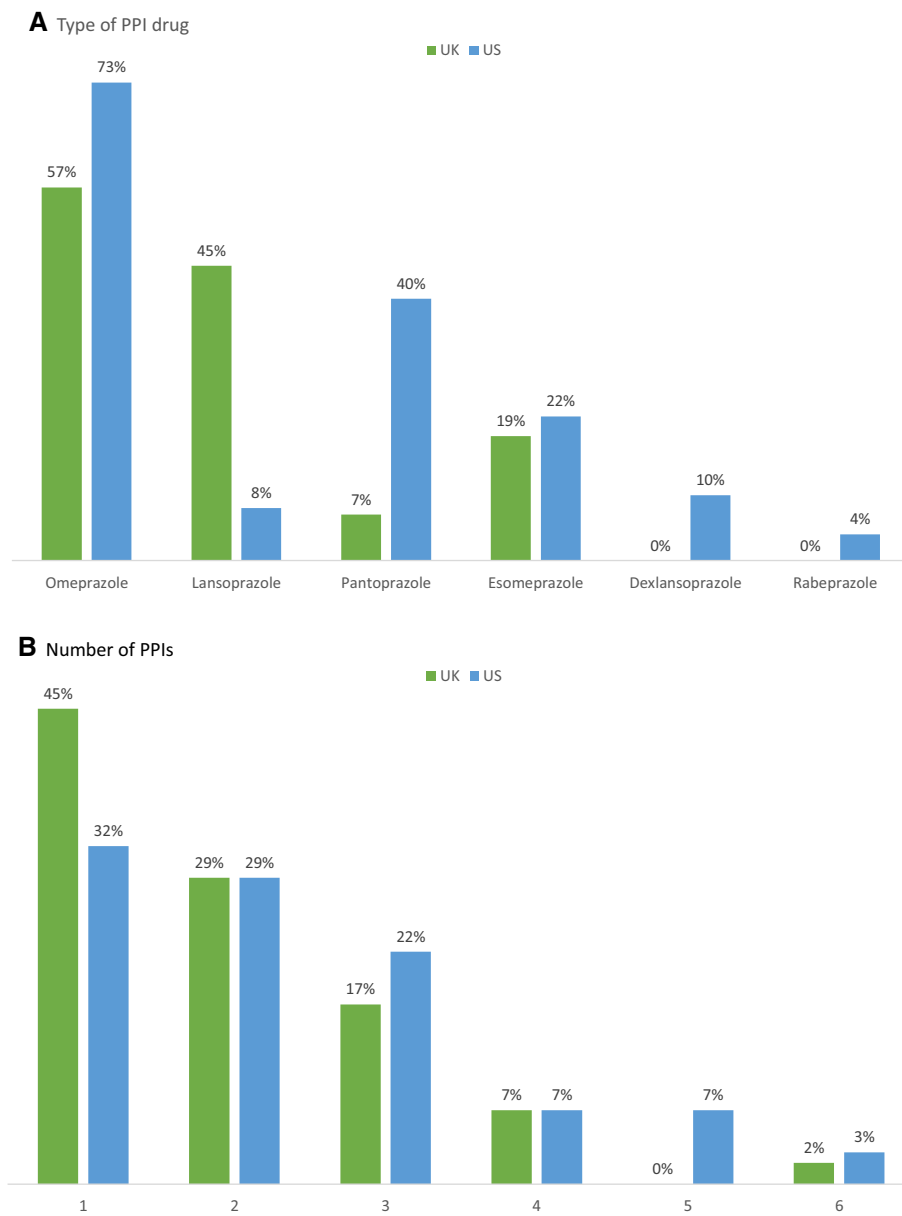
**Respondent demographics.** Respondent demographics are presented in Table 1. The majority were female (United Kingdom  $n = 56$ , 97%; United States  $n = 201$ , 95%), and around four-fifths were between 30 and 70 years of age (United Kingdom  $n = 50$ , 86%; United States  $n = 177$ , 84%). The majority were also White (United Kingdom  $n = 55$ , 95%; United States  $n = 181$ , 85%) and with other ethnic representation. Residential status and level of education are presented in

Table 1. One-third of patients (United Kingdom  $n = 18$ , 31%; United States  $n = 68$ , 32%) received care delivered by a SSc specialist in an academic medical center. There was a clear difference in the location of health care delivery between countries. Care provided by a general rheumatologist in a local hospital was more common in the United Kingdom ( $n = 30$ , 52%) compared to the United States ( $n = 27$ , 13%), whereas care via private practice was more common in the United States than in the United Kingdom ( $n = 64$ , 30%, vs  $n = 1$ , 2%). Shared care in a combination of a general rheumatologist and SSc specialist was less common and similar between countries (United Kingdom  $n = 9$ , 15%; United States  $n = 40$ , 19%). Very few (6% of US patients only) reported that their care was provided by other specialists (internal medicine, pneumology, gastroenterology, dermatology, or cardiology).

**PPIs therapy.** The majority of respondents (United Kingdom  $n = 51$ , 88%; United States  $n = 197$ , 93%) received PPIs for SSc-related GI symptoms. There were geographic differences in the type of PPIs received, and the most commonly prescribed (Figure 1) were as follows: omeprazole

**Table 1.** Survey respondents' characteristics

Characteristics	All ( $n = 301$ , $n$ (%))	United Kingdom ( $n = 58$ ), $n$ (%)	United States ( $n = 212$ ), $n$ (%)
Age, y			
18–30	5 (2)	2 (3)	1 (0.5)
30–50	73 (24)	15 (26)	46 (22)
50–70	182 (60)	35 (60)	131 (62)
>70	41 (14)	6 (10)	34 (16)
Gender			
Female	284 (95)	56 (97)	201 (95)
Male	16 (5)	2 (3)	11 (5)
Ethnicity			
American Indian or Alaska native	3 (1)	0 (0)	3 (1)
Asian	6 (2)	0 (0)	4 (2)
Black or African American	10 (3)	0 (0)	9 (4)
Hispanic or Latino	19 (6)	0 (0)	13 (6)
Native Hawaiian or other Pacific Islander	0 (0)	0 (0)	0 (0)
White	258 (86)	55 (95)	181 (85)
Other/prefer not to specify	5 (2)	2 (3)	1 (0.5)
Residence			
Rural	82 (27)	27 (47)	47 (22)
Urban	68 (23)	9 (15)	43 (20)
Suburbs	151 (50)	22 (38)	122 (58)
Education			
Primary school	3 (1)	3 (5)	0 (0)
High school	57 (19)	17 (29)	32 (15)
University	186 (62)	28 (48)	138 (65)
Other (master's degree, PhD)	55 (18)	10 (17)	42 (20)
Care			
General rheumatologist in local hospital	64 (21)	30 (52)	27 (13)
General rheumatologist in private practice	77 (26)	1 (2)	64 (30)
Scleroderma specialist in an academic medical center	92 (31)	18 (31)	68 (32)
Combination of general rheumatologist and scleroderma specialist	54 (18)	9 (15)	40 (19)
Other (internal medicine, pneumology, gastroenterology, dermatology, or cardiology)	14 (5)	0 (0)	13 (6)



**Figure 1.** (A) Type of PPIs taken and (B) number of PPIs used. PPI, proton pump inhibitor; UK, United Kingdom; US, United States.

(United Kingdom n = 33, 57%; United States n = 154, 73%), esomeprazole (United Kingdom n = 11, 19%; United States n = 46, 22%), pantoprazole (United Kingdom n = 4, 7%; United States n = 85, 40%), and lansoprazole (United Kingdom n = 25, 45%; United States n = 18, 8%), whereas dexlansoprazole (United Kingdom n = 0, 0%; United States n = 22, 10%) and rabeprazole (United Kingdom n = 0, 0%; United States n = 9, 4%) were used in a minority of patients. Over half (United Kingdom n = 32, 55%; United States n = 143, 68%) of respondents reported they had received multiple (including their current) PPIs medications over time, specifically two (United Kingdom n = 17, 29%; United States n = 62, 29%) or three (United Kingdom n = 10,

17%; United States n = 47, 22%) PPIs (Figure 1). The most common schedules of receiving PPIs were twice (United Kingdom n = 32, 55%; United States n = 97, 46%) and once a day (United Kingdom n = 20, 35%; United States n = 105, 49%), and a symptom-driven PPI approach was only reported in the minority of patients (United Kingdom n = 6, 10%; United States n = 10, 5%).

**Treatment efficacy and combination therapy.** In the majority of cases, respondents considered receiving PPIs to be effective in controlling GI symptoms (United Kingdom n = 49, 85%; United States n = 192, 91%; Table 2); in the majority (94%, both United Kingdom n = 46 and United States n = 182),

**Table 2.** Gastrointestinal symptoms that improved with receiving proton pump inhibitors

Symptoms	All (n = 301), n (%)	United Kingdom (n = 58), n (%)	United States (n = 212), n (%)
Heartburn or reflux	251 (94)	46 (94)	182 (94)
Regurgitating food or phlegm	58 (22)	9 (18)	45 (23)
Trouble swallowing solid or liquid food	45 (17)	6 (12)	37 (20)
Sensation of food getting stuck in the chest	37 (14)	8 (16)	25 (13)
Bloating, nausea, or vomiting	36 (13)	7 (14)	27 (14)
Early fullness after eating	18 (7)	2 (4)	14 (7)
A metallic taste in the mouth	15 (6)	3 (6)	10 (5)
Diarrhea	7 (3)	3 (6)	4 (2)
Constipation	5 (2)	0 (0)	5 (3)
Incontinence of stool	2 (1)	0 (0)	2 (1)

heartburn or acid reflux improved as well as food or phlegm regurgitation (United Kingdom n = 9, 18%; United States n = 45, 23%), bloating, nausea and vomiting (14%, both United Kingdom n = 7 and United States n = 27), and trouble swallowing solid or liquid food (United Kingdom n = 6, 12%; United States n = 37, 20%).

Many respondents (United Kingdom n = 18, 31%; United States n = 98, 46%) indicated that they received other medications for their GERD. Combination therapy (receiving PPIs plus another medication for acid reflux different from PPIs) was reported in around 40% (United Kingdom n = 21, 36%; United States n = 94, 44%) and was more effective than receiving PPIs alone in most respondents (United Kingdom n = 15, 71%; United States n = 68, 72%). One of the main concern of patients was the rebound of their symptoms if they stopped receiving PPIs (United Kingdom n = 48, 83%; United States n = 182, 86%). In over half of patients, symptoms initially improved and then returned despite the regular use of PPIs (United Kingdom n = 30, 52%; United States n = 93, 44%).

**PPIs side effects.** *Side effects attributed to receiving PPIs.* Less than one-quarter of respondents (United Kingdom n = 13,

22%; United States n = 34, 16%) reported some side effects attributed to receiving PPIs: weak bones (osteoporosis; United Kingdom n = 4, 31%; United States n = 15, 44%), calcium formation (“calcinosis”; United Kingdom n = 4, 31%; United States n = 6, 18%), kidney problems (United Kingdom n = 2, 15%; United States n = 3, 9%), and risk of cardiovascular events (United Kingdom n = 0, 0%; United States n = 3, 9%).

*Concerns about long-term side effects from receiving PPIs.* Respondents indicated significant concerns about long-term side effects from receiving PPIs (Table 3). The three most common concerns were weak bones (osteoporosis) (United Kingdom n = 26, 63%; United States n = 119, 69%), kidney problems (54%, both United Kingdom n = 22, and United States n = 93), and calcium formation, calcinosis (United Kingdom n = 15, 37%; United States n = 69, 40%).

**Lifestyle and education.** Around half (United Kingdom n = 24, 41%; United States n = 136, 64%) of respondents reported that they received information on lifestyle and dietary modification to manage their GERD symptoms. Most patients (around three-quarters) felt that this information has been either

**Table 3.** Perceived concerns of patients with SSc about the side effects of receiving proton pump inhibitors long term\*

Side effects	All (n = 301), n (%)	United Kingdom (n = 58), n (%)	United States (n = 212), n (%)
Weak bones	159 (66)	26 (63)	119 (69)
Kidney problems	131 (55)	22 (54)	93 (54)
Calcium formation (calcinosis)	93 (39)	15 (37)	69 (40)
Cardiovascular diseases	91 (38)	16 (39)	63 (36)
Diarrhea	56 (23)	10 (24)	37 (21)
Constipation	52 (22)	11 (27)	33 (19)
Infections	51 (21)	9 (22)	34 (20)
Arrhythmias	42 (18)	7 (17)	31 (18)
Sleeplessness	41 (17)	9 (22)	25 (14)
Dizziness	34 (14)	7 (17)	20 (12)
Flatulence	34 (14)	5 (12)	25 (14)
Allergic reactions	18 (7)	4 (10)	10 (6)

\* SSc, systemic sclerosis.

**Table 4.** Education and lifestyle measurement for gastroesophageal reflux disease in patients with SSc\*

Type of given advice	All (n = 301), n (%)	United Kingdom (n = 58), n (%)	United States (n = 212), n (%)
Avoid going to bed for at least two/three hours after eating	161 (92)	22 (92)	131 (96)
Sleep with head elevated	165 (95)	19 (79)	131 (96)
Avoid certain type of foods	156 (90)	18 (75)	18 (94)
Avoid smoking	102 (59)	15 (62)	13 (10)
Source of information			
Discussion with a health care professional	151 (87)	20 (83)	120 (88)
Written information	85 (49)	9 (37)	72 (53)
Directed to information on the internet	38 (21)	3 (12)	30 (22)

\* SSc, systemic sclerosis.

helpful (United Kingdom n = 6, 25%; United States n = 52, 38%) or somewhat helpful (United Kingdom n = 13, 54%; United States n = 60, 44%). Over 90% (Table 4) received information about avoiding going to bed for at least two/three hours after eating, sleeping with the head elevated, and avoiding certain types of food; around two-thirds were advised to avoid smoking (Table 4). The majority received information through discussion with a health care professional (United Kingdom n = 20, 83%; United States n = 120, 88%). However, a difference was observed in the provision of written information (United Kingdom n = 9, 37%; United States n = 72, 53%) and directing patients to available information on the internet (United Kingdom n = 3, 12%; United States n = 30, 22%; Table 4). Furthermore, many patients indicated that they used the internet to search for information relating to receiving PPI medications (United Kingdom n = 42, 72%; United States n = 191, 90%).

**Access to receiving PPIs.** The majority of respondents indicated that PPIs were prescribed to them by a health care professional (United Kingdom n = 58, 100%; United States n = 198, 90%), with only 10% of US patients (n = 22) reporting buying them over the counter. The prescription was paid or reimbursed by their National Health System in two-thirds (United Kingdom n = 38, and United States n = 137, both 65%). For some patients (United Kingdom n = 1, 2%; United States n = 32, 15%), reimbursement was dependent on the specific PPIs they received. Furthermore, many respondents (United Kingdom n = 11, 58%; United States n = 31, 72%) indicated they were (or would) still purchase PPIs without the benefit of financial assistance.

**Investigations for GERD.** The majority (United Kingdom n = 44, 76%; United States n = 186, 88%) reported that invasive testing (eg, upper endoscopy or ambulatory acid probe testing or esophageal manometry) was used to diagnose GERD. Among respondents who did not receive previous diagnostic tests, three-quarters (United Kingdom n = 10, 71%; United States n = 19, 73%) would consider undergoing invasive examinations if this could be helpful in optimizing their treatment/symptoms.

**Surgery.** The majority of respondents (United Kingdom n = 51, 88%; United States n = 184, 87%) reported that their specialist (rheumatologist or gastroenterologist) did not discuss surgery as a therapeutic option for GERD. However, around half of patients (United Kingdom n = 29, 50%; United States n = 93, 44%) indicated that they would be willing to undergo surgery (eg, fundoplication) to resolve their reflux symptoms. However, respondents did report concerns about undergoing surgery to resolve reflux symptoms (United Kingdom n = 48, 83%; United States n = 170, 80%). The most five common surgical concerns were as follows: failure of reflux symptoms to significantly improve (United Kingdom n = 36, 75%; United States n = 123, 72%), postoperative surgical complications (eg, blood clots and bleeding; United Kingdom n = 30, 62%; United States n = 114, 67%), worsening of reflux symptoms (eg, trouble with swallowing; United Kingdom n = 37, 77%; United States n = 103, 61%), possible new unexpected GI symptoms (United Kingdom n = 29, 60%; United States n = 112, 66%), and pain or discomfort from surgery (United Kingdom n = 25, 48%; United States n = 56, 33%). Other important concerns were anxiety related to hospitalization (United Kingdom n = 17, 35%; United States n = 37, 22%) and fear of not waking up after anesthesia (United Kingdom n = 14, 29%; United States n = 26, 15%), and death (United Kingdom n = 8, 17%; United States n = 23, 13%).

**DISCUSSION**

Our study benchmarks the significant impact that GERD has on patients with SSc and the frequent prescription of PPIs as a cornerstone in the management of SSc. The majority of patients consider receiving PPIs as highly effective; however, symptoms may be refractory to initial treatment and/or recur despite good initial response.

There is significant geographic heterogeneity in PPIs prescription concerning choice of drug therapy and frequency of administration, which is likely multifactorial in origin, including (but not limited to) differences in local prescription practices and

financial reimbursement systems. Furthermore, sequentially receiving PPIs and receiving a combination (PPIs plus another medication for acid reflux different from PPIs) were similar in both UK and US respondents, which highlights the unmet need for optimized treatment approaches for refractory GERD in many patients with SSc.

Although the long-term use of PPIs in patients with SSc raises a number of potentially serious safety concerns (through extrapolation of studies from the general population),<sup>21–24</sup> it was encouraging that the majority of respondents did not report any side effects while receiving PPIs. However, our data clearly highlight the need for a thorough patient education before receiving PPI medications because respondents identified a number of potential concerns (eg, osteoporosis and calcinosis). Of note, only around half of respondents had received information concerning lifestyle and dietary modifications to manage their GERD. Although there was a geographic difference in the way relevant information was provided to patients (ie, either by discussion with a health care professional [United Kingdom] or written information [United States]), both formats were considered beneficial by the majority of respondents. Health care professionals are increasingly directing patients to online sources of medical information, and patients themselves are increasingly using internet-based resources to inform health care use and treatment decisions<sup>25</sup>.

A surgical approach is infrequently discussed with patients. However, around half of respondents indicated that they would be willing to undergo surgery (eg, fundoplication) to resolve their reflux symptoms, although many had concerns about potential complications. Historically, many clinicians maintain a relatively nihilistic approach toward surgery for the esophagus in patients with SSc, including for GERD (eg, because of new or worsening of GERD or dysphagia). However, a recent systematic literature review found that fundoplication was overall a safe and effective procedure in patients with SSc. The evidence base supporting surgical intervention for GERD in patients with SSc is limited and generally of low quality. Although some negative outcomes have been reported and/or are feared (eg, worsening of dysphagia), the extant literature suggests that fundoplication appears to be generally a safe and effective approach in patients with SSc. Future research will need to focus on defining the indications, clinical criteria, and optimal timing for surgery.<sup>26</sup>

The strength of the present study is in the large number of patients involved who completed study-related surveys. However, there are a number of limitations to consider when interpreting the survey data. Patients were recruited with a self-reported diagnosis of SSc and, therefore, were not subject to confirmatory physician and/or chart review, including medications. Indeed, a minority of US patients indicated that they bought PPIs over the counter. Furthermore, there could be an intrinsic potential source of bias through distributing the survey via social media (eg, patients with more severe GERD symptoms could have been more likely to be exposed to the survey invitation). Although the

majority of respondents were from the United Kingdom and United States, our data (eg, demographic information) suggest that we have assembled a representative cohort of patients with SSc.

In conclusion, our survey highlights the burden of GERD in patients with SSc. Side effects directly attributed to receiving PPIs are uncommon, but patients are concerned about long-term safety. There is significant heterogeneity in patients with SSc who received PPIs, and receiving a combination of PPIs and other classes of medications is not uncommon. Symptoms often recur despite continuing to receive PPIs. Education about receiving PPIs is often neglected, and patients rely on online information. A surgical approach is still not widely considered as a therapeutic option, although many patients would consider this to resolve their reflux symptoms. Further research is required to define the precise therapeutic strategy to ameliorate GERD symptoms in patients with SSc and to confirm the safety of long-term use of PPIs in this patient population.

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## AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Hughes had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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