Relationship between calcium channel blockers and skin fibrosis in patients with systemic sclerosis

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ABSTRACT

Objective. *Recent experimental evidence suggests that calcium channel blockers (CCBs) may have anti-fibrotic effects on liver and pulmonary fibrosis. We aimed to investigate whether use of CCBs was associated with the skin fibrosis in patients with systemic sclerosis (SSc).*

Methods. *Based on the 5-year follow-up data from the Canadian Scleroderma Research Group registry, we used the generalised estimating equations (GEE) model to assess the relationship between use of CCBs and the primary outcome of skin fibrosis measured by the modified Rodnan skin score (mRSS). We also used GEE models to explore the associations between use of CCBs and risk of secondary outcomes including digital ulcers, pulmonary fibrosis, calcinosis, and scleroderma renal crisis.*

Results. *There were 1547 patients (1330 females) with SSc included in this study. Their mean age was 55.5 years and there were 606 patients taking CCBs at baseline. No significant difference in mRSS between the use versus non-use of CCBs was found in the multivariable analysis: mean difference = -0.19 (95% confidence interval: -0.62, 0.23), p-value = 0.37. Use of CCBs was not significantly related to risk of secondary outcomes, with an odds ratio (OR) of 1.13 for digital ulcers, 0.94 for pulmonary fibrosis, 0.90 for calcinosis and 1.69 for scleroderma renal crisis, respectively.*

Conclusion. *No significant associations between use of CCBs and skin fibrosis, digital ulcers, pulmonary fibrosis, calcinosis and scleroderma renal crisis were found in patients with SSc. More evidence from other well-designed studies would be required to confirm these findings.*

Introduction

Skin thickening and tightening along with Raynaud's phenomenon (RP) are the most common characteristics of systemic sclerosis (SSc) (1). Medications such as CCBs are commonly prescribed for symptomatic benefit in RP (2, 3). Recent experimental evidence suggests that CCBs may have anti-fibrotic effects on liver and pulmonary fibrosis (4, 5). However, there are no reported studies demonstrating whether CCBs have any association with inhibiting fibrosis in SSc patients. We initiated a 5-year follow-up study of patients registered in the Canadian Scleroderma Research Group (CSRG) with the primary objective of determining whether CCBs were associated with skin fibrosis in SSc. The secondary objective was to evaluate the relationship between use of CCBs and digital ulcers, pulmonary fibrosis, calcinosis, and scleroderma renal crisis (SRC).

Patients and methods

Patients with SSc enrolled in the CSRG registry between 2004 and 2015 from 19 centers across Canada were included in this study. Patients in the CSRG registry must meet the criteria including: 1) confirmation of SSc by a rheumatologist; 2) ≥18 years; 3) English or French speaking; and 4) being compliant with study procedures and visits (6). Over 98% of CSRG patients meet the 2013 ACR/EULAR classification criteria for SSc (7).

At the registry visits, study rheumatologists recorded whether the patients took CCBs currently for the baseline visit and since their last follow-up visit. Our primary outcome was the severity of skin fibrosis assessed by study rheumatologists using the modified Rodnan skin score (mRSS) over the 5-year follow-up period (8). The total mRSS score ranges from 0 to 51, with

a higher skin score implying more severe skin involvement. The secondary outcomes included digital ulcers, pulmonary fibrosis, calcinosis, and SRC. The potential covariates adjusted for in the analyses included patients' time of follow-up, baseline age, gender, study center, BMI, ethnicity, education, marital status, smoking, drinking, SSc duration, diffuse SSc subset, years since onset of RP symptom, years since onset of non-RP symptom, rheumatoid arthritis, pulmonary hypertension, use of other anti-hypertensive drugs (such as angiotensin-converting-enzyme inhibitor and angiotensin receptor blocker) and immunomodulators.

To assess the association between the use of CCB and outcomes which were repeatedly measured over 5-year study period, the linear and logistical generalised estimating equations (GEE) models with unstructured correlation structures were conducted for the continuous and dichotomous outcomes respectively (9). Univariate and multivariable regression models were conducted in the analyses, in which the covariates were chosen to fit the final multivariable models with a variance inflation factor of <4 and through univariate analyses using the cut-off *p*-value of <0.2. Results from the models were presented as mean difference with corresponding 95% confidence interval (CI), and odds ratio (OR) and 95% CI, for continuous and dichotomous outcomes respectively.

We conducted two sensitivity analyses by: 1) performing structured multivariable GEE analyses using an autoregressive correlation structure and robust standard error estimators, and 2) using ten multiple imputations to impute the missing values on outcomes. Two subgroup analyses in multivariable models were conducted including: 1) sex; and 2) different disease duration (*i.e.* at baseline SSc duration ≥5 years *vs*. SSc duration <5 years).

Results

There were 1547 SSc patients (1330 females) included in this study (Table I). These patients contributed 5601 observations in the registry over the 5-year follow-up, with a mean number of registry visits of 3.2 (SD: 1.4) and a mean time of follow-up of 3.8 years (SD: 3.0), respectively. There were 606 (40%) patients currently taking CCBs at baseline. The mean age was 55.5 years at baseline, and the SSc duration was 7.3 years since their first diagnosis. There were 217 (14%) patients with active digital ulcers, 421 (28%) pulmonary fibrosis, 334 (22%) calcinosis, and 60 (4%) SRC, respectively. The baseline mean mRSS was 9.8 (SD: 9.6), in which no significant difference in mRSS was found between CCB users and non-CCB users (*p*-value = 0.70).

Table I. Baseline characteristics and comparison between CCB users and non-CCB users.

Characteristics	All patients (n=1547)	CCB users (n=606)	Non-CCB users (n=921)	*p*-value
Age (years): mean (SD)	55.5 (12.19)	56.5 (12.52)	54.9 (11.90)	0.015[1]
Female sex: n (%)	1330 (85.97)	515 (84.98)	799 (86.75)	0.33[2]
Ethnicity: n (%)				
Caucasian	1283 (89.16)	523 (91.92)	748 (87.49)	0.008[2]
Non-caucasian	156 (10.84)	46 (8.08)	107 (12.51)	
Education level: n (%)				
High school or less	734 (51.40)	302 (53.55)	425 (49.88)	0.18[2]
More than high school	694 (48.60)	262 (46.45)	427 (50.12)	
Married: n (%)	996 (69.50)	388 (68.55)	600 (70.18)	0.52[2]
BMI (kg/m^2): mean ± SD	25.7 (5.69)	25.8 (5.78)	25.7 (5.63)	0.71[1]
Smoker: n (%)	202 (14.10)	81 (14.29)	118 (13.82)	0.80[2]
Alcohol drinking: n (%)	760 (53.94)	311 (55.54)	443 (52.86)	0.33[2]
SSc duration since first diagnosis (years): mean (SD)	7.3 (8.17)	7.5 (7.86)	7.2 (8.38)	0.41[1]
Time of follow-up (years): mean (SD)	3.8 (2.98)	3.9 (2.98)	3.8 (2.96)	0.91[1]
Diffuse SSc subset: n (%)	523 (34.73)	209 (35.30)	313 (34.32)	0.70[2]
Rheumatoid arthritis: n (%)	60 (3.94)	12 (2.00)	48 (5.22)	0.002[2]
RP: n (%)	1367 (95.66)	552 (98.05)	803 (94.03)	<0.001[2]
Years since onset of RP symptom: mean (SD)	13.5 (12.35)	13.8 (12.61)	13.4 (12.18)	0.48[1]
Years since onset of non-RP symptom: mean (SD)	9.7 (9.39)	9.9 (9.43)	9.6 (9.37)	0.43[1]
Pulmonary hypertension: n (%)	217 (14.29)	94 (15.61)	123 (13.44)	0.24[2]
Use of other anti-hypertensive drugs: n (%)	492 (31.80)	222 (36.63)	270 (29.32)	0.003[2]
Use of immunomodulators: n (%)	504 (32.58)	207 (34.16)	297 (32.25)	0.44[2]
Digital ulcer: n (%)	217 (14.20)	106 (17.52)	110 (11.94)	0.002[2]
Pulmonary fibrosis: n (%)	421 (27.88)	171 (28.79)	249 (27.24)	0.51[2]
SSc renal crisis: n (%)	60 (3.94)	33 (5.49)	26 (2.83)	0.009[2]
Calcinosis: n (%)	334 (22.08)	129 (21.54)	204 (22.37)	0.70[2]
Modified Rodnan skin score (0-51): mean (SD)	9.8 (9.56)	9.9 (9.18)	9.7 (9.81)	0.70[1]

CCB: calcium channel blockers; SD: standard deviation; BMI: body mass index; SSc: Scleroderma; RP: Raynaud's phenomenon.
[1]Based on Student's *t*-test; [2]Based on Chi-square test.

During follow-up, the mean mRSS was 9.1 (SD: 9.1), 8.6 (SD: 9.0), 8.3 (SD: 8.4), 8.4 (SD: 8.6), and 8.7 (SD: 8.8) for Year 1, 2, 3, 4, and 5 post-baseline, respectively. As presented in Table II, no significant difference on mRSS was found between use and non-use of CCBs in the univariate analysis: mean difference =-0.31 (95% CI: -0.66, 0.05), *p*-value = 0.09. Likewise, in the unstructured multivariable GEE model, there was no significant difference on mRSS between the groups: mean difference =-0.19 (95% CI: -0.62, 0.23), *p*-value = 0.37. No significant relationship was found in univariate analyses for secondary outcomes. Similar findings were also observed from multivariable analyses: OR = 1.13 (95% CI: 0.87, 1.45) for digital ulcers, OR = 0.94 (95% CI: 0.72, 1.19) pulmonary fibrosis, OR = 0.90 (95% CI: 0.78, 1.04) calcinosis, and OR = 1.69 (95% CI: 0.87, 3.27) SRC.

As shown in Table III, similar results to the primary analyses were found from sensitivity analyses, where use of CCBs was not significantly related to any of the outcomes. Significant associations were observed between use of CCBs and mRSS in men (mean difference = -2.57, 95% CI: -3.48, -1.67) and risk of calcinosis in the patients

Table II. Relationship between CCB and outcomes in univariate and multivariable analyses.

Covariates	mRSS		Digital ulcers		Pulmonary fibrosis		Calcinosis		Scleroderma renal crisis	
	Univariate analysis[1]	Multivariable analysis[1]	Univariate analysis[1]	Multivariable analysis[1]	Univariate analysis[1]	Multivariable analysis[1]	Univariate analysis[1]	Multivariable analysis[1]	Univariate analysis[1]	Multivariable analysis[1]
Use of CCB	-0.31 (-0.66, 0.05), 0.09	-0.19 (-0.62, 0.23), 0.37	1.16 (0.96, 1.36), 0.09	1.13 (0.87, 1.45), 0.36	0.98 (0.87, 1.12), 0.85	0.94 (0.72, 1.19), 0.57	0.93 (0.82, 1.07), 0.30	0.90 (0.78, 1.04), 0.18	1.79 (1.12, 2.86), 0.02	1.69 (0.87, 3.27), 0.13
Age (years)[2]	0.12 (0.10, 0.15), < 0.001	0.03 (0.01, 0.06), 0.006	1.03 (1.02, 1.04), < 0.001	1.03 (1.02, 1.04), < 0.001	1.01 (1.00, 1.02), 0.004	1.02 (1.01, 1.03), 0.006	1.01 (1.00, 1.02), 0.18	1.01 (0.99, 1.02), 0.52	0.99 (0.95, 1.05), 0.16	1.00 (0.98, 1.02), 0.95
Female sex	-4.07 (-5.11, -3.02), <0.001	-1.91 (-2.98, -0.83), 0.001	0.65 (0.48, 0.89), 0.006	0.86 (0.63, 1.19), 0.37	0.56 (0.41, 0.76), < 0.001	0.57 (0.39. 0.82), 0.002	1.31 (0.97, 1.77), 0.08	1.21 (0.87, 1.69), 0.26	0.67 (0.32, 1.35), 0.18	0.83 (0.40, 1.63), 0.61
Ethnicity										
Caucasian	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Non-caucasian	0.75 (-0.46, 1.97), 0.23	-[3]	1.18 (0.82, 1.70), 0.36	-[3]	1.49 (1.10, 2.02), 0.01	1.33 (0.89, 2.00), 0.16	0.97 (0.71, 1.34), 0.85	-[3]	3.85 (2.13, 6.94), < 0.001	1.61 (0.82, 3.16), 0.17
Education level										
High school or less	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
More than high school	-0.13 (-0.89, 0.63), 0.74	-[3]	1.00 (0.80, 1.27), 0.96	-[3]	0.75 (0.61, 0.91), 0.004	0.82 (0.63, 1.07), 0.15	0.95 (0.78, 1.16), 0.62	-[3]	0.88 (0.51, 1.50), 0.63	-[3]
Married	-0.33 (-1.15, 0.49), 0.43	-[3]	0.96 (0.74, 1.23), 0.74	-[3]	1.13 (0.91, 1.40), 0.28	-[3]	1.05 (0.84, 1.30), 0.69	-[3]	0.71 (0.41, 1.23), 0.22	-[3]
BMI (kg/m^2)[2]	-0.11 (-0.18, -0.04), 0.001	-0.04 (-0.10, 0.04), 0.23	0.96 (0.93, 0.98), < 0.001	0.97 (0.95, 0.99), 0.01	1.02 (0.99, 1.04), 0.08	1.02 (0.99, 1.04), 0.18	0.95 (0.93, 0.97), < 0.001	0.97 (0.95, 0.98), 0.001	0.97 (0.91, 1.03), 0.17	0.97 (0.92, 1.02), 0.17
Smoking	-0.75 (-1.78, 0.30), 0.15	1.51 (0.48, 2.53), 0.004	1.28 (0.93, 1.76), 0.13	1.12 (0.81, 1.56), 0.51	1.72 (1.21, 2.42), 0.004	2.05 (1.33, 3.17), 0.001	1.05 (0.79, 1.39), 0.75	-[3]	0.92 (0.45, 2.07), 0.84	-[3]
Drinking	0.62 (-0.14, 1.38), 0.11	0.33 (-0.37, 1.03), 0.35	0.94 (0.74, 1.19), 0.60	-[3]	0.72 (0.59, 0.87), 0.002	0.66 (0.51, 0.86), 0.003	1.20 (0.98, 1.47), 0.07	1.27 (1.03, 1.57), 0.03	0.87 (0.51, 1.43), 0.50	-[3]
SSc duration (years) [2]	-0.08 (-0.12, -0.03), 0.001	0.02 (-0.04, 0.08), 0.49	1.02 (1.00, 1.03), 0.007	1.06 (1.04, 1.08), < 0.001	1.01 (1.00, 1.02), 0.19	1.03 (1.01, 1.05), 0.02	1.05 (1.04, 1.06), < 0.001	1.03 (1.01, 1.04), 0.001	1.03 (0.99, 1.06), 0.17	1.04 (0.99, 1.08), 0.13
Time of follow-up (years)[2]	-0.32 (-0.43, -0.20), <0.001	-0.09 (-0.21, 0.02), 0.11	1.00 (0.97, 1.04), 0.85	-[3]	1.00 (0.96, 1.05), 0.87	-[3]	1.02 (0.99, 1.06), 0.14	1.03 (0.99, 1.07), 0.16	1.04 (0.94, 1.15), 0.43	-[3]
Diffuse subsets	9.65 (9.01, 10.29), < 0.001	-[4]	2.90 (2.31, 3.64), < 0.001	-[4]	2.41 (1.97, 2.95), < 0.001	-[4]	1.44 (1.18, 1.75), < 0.001	-[4]	4.84 (2.83, 8.28), < 0.001	-[4]
Rheumatoid arthritis	0.50 (-1.45, 2.44), 0.62	-[3]	0.98 (0.53, 1.84), 0.97	-[3]	1.31 (0.77, 2.27), 0.32	-[3]	1.35 (0.76, 2.39), 0.30	-[3]	2.13 (0.71, 6.36), 0.18	1.21 (0.25, 6.05), 0.83
Years since onset of RP symptom (years)[2]	-0.13 (-0.23, -0.02), 0.02	-0.08 (-0.21, 0.04), 0.25	0.99 (0.98, 1.00), 0.05	0.97 (0.92, 1.02), 0.24	0.99 (0.98, 1.00), 0.008	0.98 (0.97, 1.01), 0.06	1.02 (1.02, 1.03), < 0.001	1.02 (0.98, 1.04), 0.23	0.97 (0.95, 1.00), 0.06	0.99 (0.97, 1.02), 0.67
Years since onset of non-RP symptom (years)[2]	-0.11 (-0.15, -0.07), < 0.001	-[4]	1.00 (0.99, 1.02), 0.42	-[4]	1.00 (0.99, 1.01), 0.71	-[4]	1.04 (1.03, 1.05), < 0.001	-[4]	0.95 (0.92, 0.99), 0.02	-[4]
Pulmonary hypertension	0.33 (-0.73, 1.37), 0.55	-[3]	1.21 (0.88, 1.66), 0.24	-[3]	2.49 (1.93, 3.21), < 0.001	1.07 (0.87, 1.31), 0.54	1.14 (0.87, 1.50), 0.34	-[3]	1.97 (1.07, 3.65), 0.03	1.33 (0.74, 2.40), 0.34
Use of other anti-hypertensive drugs	0.26 (-0.03, 0.55), 0.08	0.42 (0.07, 0.76), 0.02	1.21 (1.03, 1.42), 0.02	1.34 (1.12, 1.60), 0.001	1.09 (0.97, 1.23), 0.18	1.02 (0.79, 1.31), 0.89	1.10 (0.97, 1.25), 0.14	1.09 (0.95, 1.26), 0.22	6.12 (3.57, 10.51), < 0.001	9.48 (4.92, 17.71), < 0.001
Use of immunomodulators	0.49 (0.18, 0.81), 0.002	0.13 (-0.31, 0.57), 0.56	0.94 (0.79, 1.12), 0.47	-[3]	1.19 (1.04, 1.37), 0.01	1.54 (1.20, 1.98), 0.001	1.22 (1.06, 1.40), 0.01	1.23 (1.05,1.45), 0.01	1.24 (0.78, 1.98), 0.37	-[3]

CCB: calcium channel blockers; mRSS: Modified Rodnan skin score; BMI: body mass index.
[1]Results were shown as Statistics (95% confidence interval), p-value; Statistics were mean difference for primary outcome and odds ratio for secondary outcomes, respectively.
[2]Results for per 1-ponit increase. [3] Not included in the multivariable analysis due to the p-value > 0.2 found in the univariate analysis.
[4]Not included in the multivariable analysis due to the variance inflation factor of ≥ 4.

with SSc duration of <5 years (OR = 0.62, 95% CI: 0.45, 0.86) (Table IV). Significant subgroup differences in the associations between CCBs and mRSS by sex (p-value <0.001) and risk of calcinosis by disease duration (p-value = 0.002) were found. No significant relationship was observed in other subgroup analyses.

Discussion

Using data from the CSRG registry, we found no significant associations between use of CCBs and clinical outcomes including skin fibrosis, digital ulcers, pulmonary fibrosis, calcinosis and SRC in patients with SSc.

Some recent studies have investigated the anti-fibrotic effect of CCBs *in vitro* and *in vivo*. CCBs were protective against liver fibrosis in mouse models, which may be due to the increased level of antioxidant defense (5). Likewise, another study showed that CCBs could disrupt calcium signaling in pulmonary fibroblasts and prevent the bleomycin-induced fibrotic impairment of lung function (4). No published clinical studies in SSc patients evaluate the association between use of CCBs and skin fibrosis. Given CCBs are widely prescribed in SSc, a significant association may potentially suggest a new avenue towards anti-fibrotic therapy and management of SSc. Nevertheless, in this study, no significant relationship was found between use of CCBs and skin fibrosis, though there was a trend towards decreased mRSS in CCB-users (Table III). On the other hand, use of CCBs was unexpectedly observed to be non-significantly related with increased risks of digital ulcers and SRC (Table III). Part of the interpretation may be because those with more severe disease not fully accounted for by the measured covariates, were more likely to receive CCB therapy. It may also reflect our lack of knowledge of the disease pathophysiology and patients' response to CCBs. Furthermore, no data on the daily dosages or consumption frequency of CCBs were available in the CSRG registry; such data would assist with understanding the dose-response relationship between CCBs and the outcomes to further interpret the findings. Similarly, we could not investigate drug interactions between CCBs and other medications that patients were taking, in which the interactions may potentially account for the results. The elements of an observational study including non-trial design and potential unmeasured confounding (10) may weaken the strength of evidence of these findings. Therefore more research is needed to further corroborate these results.

Nonetheless, in subgroup analyses, CCBs were found to be significantly related with decreased mRSS in men and risk of calcinosis in patients with SSc duration of <5 years (Table IV). The subgroup differences in mRSS by sex and risk of calcinosis by disease duration were significant. Of note, the overall findings were always better estimates than the apparent results observed within a subgroup (11). The subgroup analyses were *a posteriori* analyses without specified prior hypotheses, which could weaken the strength of evidence of the results (12). Therefore, these subgroup findings were served as exploratory analyses

Table III. Results for associations between use of CCB and outcomes from sensitivity analyses.

Outcomes	Analyses using structured multivariable GEE model		Analyses using multiple imputation	
	Statistics[1] (95% CI)	p-value	Statistics[1] (95% CI)	p-value
Primary outcome				
mRSS	-0.28 (-0.75, 0.17)	0.20	-0.17 (-0.64, 0.27)	0.43
Secondary outcomes				
Digital ulcers	1.26 (0.93, 1.67)	0.13	1.23 (0.82, 1.83)	0.16
Pulmonary fibrosis	0.85 (0.49, 1.48)	0.56	0.93 (0.73, 1.19)	0.58
Calcinosis	0.87 (0.73, 1.05)	0.14	0.95 (0.78, 1.12)	0.55
Scleroderma renal crisis	2.00 (0.92, 4.35)	0.09	1.88 (0.85, 4.17)	0.18

CCB: calcium channel blockers; GEE: generalised estimating equations; mRSS: Modified Rodnan skin score; CI: confidence interval.
[1]Statistics were mean difference for primary outcome and odds ratio for secondary outcomes, respectively.

Table IV. Results for associations between use of CCB and outcomes from subgroup analyses using unstructured multivariable GEE models.

Outcomes	Scleroderma duration			Sex		
	Duration >= 5 years[1]	Duration < 5 years[1]	p-value for subgroup	Women[1]	Men[1]	p-value for difference subgroup difference
Primary outcome						
mRSS	0.08 (-0.43, 0.61), 0.74	-0.32 (-0.79, 0.16), 0.18	0.44	0.01 (-0.35, 0.38), 0.96	-2.57 (-3.48, -1.67), < 0.001	< 0.001
Secondary outcomes						
Digital ulcers	1.19 (0.88, 1.59), 0.25	1.07 (0.83, 1.37), 0.62	0.59	1.11 (0.84, 1.45), 0.48	1.21 (0.73, 2.02), 0.46	0.77
Pulmonary fibrosis	0.92 (0.65, 1.35), 0.72	1.03 (0.73, 1.47), 0.85	0.66	1.16 (0.88, 1.53), 0.28	0.60 (0.28, 1.26), 0.17	0.11
Calcinosis	0.99 (0.83, 1.19), 0.93	0.62 (0.45, 0.86), < 0.001	0.002	0.89 (0.76, 1.04), 0.15	0.90 (0.48, 1.66), 0.71	0.97
Scleroderma renal crisis	1.91 (0.67, 5.57), 0.24	1.55 (0.72, 3.35), 0.27	0.12	0.65 (0.30, 1.43), 0.28	1.80 (0.74, 4.39), 0.19	0.93

CCB: calcium channel blockers; GEE: generalised estimating equations; mRSS: Modified Rodnan skin score.
[1]Results were shown as Statistics (95% confidence interval), p-value; statistics were mean difference for primary outcome and odds ratio for secondary outcomes, respectively.

to assist in generating hypotheses and guiding future research directions.

Some limitations exist in this study. First, we could not capture other unmeasured information from the CSRG registry, which would potentially lead to biased findings. Further data on the CCBs including drug use patterns and drug interactions were lacking, which precluded more investigations for this study. The total mRSS was used to measure both the extent and degree of skin fibrosis in patients with SSc. Thus the relationship between CCBs and the extent of skin thickening could not be distinguished from the association between CCBs and the degree of skin fibrosis (13). Moreover, we only adjusted for the combination of other anti-hypertensive drugs in multivariable analyses, rather than the various individual medications, mainly due to insufficient power to detect significant differences. Additionally, no adjustment for use of endothelin-1 receptor antagonists was performed in the analyses because no such data were collected in CSRG registry.

To our knowledge, this is the first large multicenter clinical study assessing the relationship between use of CCBs and skin fibrosis in SSc patients. These patients were considered to be representative of the spectrum of SSc in general clinical practice, which could enhance the generalisability of the findings (14). Moreover, rigorous statistical analyses were conducted to fully employ the data and support the robustness of our findings.

In conclusion, in this study using the 5-year follow-up data from the CSRG registry, no significant associations between use of CCBs and skin fibrosis, digital ulcers, pulmonary fibrosis, calcinosis and SRC were found in patients with SSc. More evidence from other well-designed studies would be required to confirm these findings.

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Competing interests

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