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Prevention of Vascular Damage in Scleroderma and Autoimmune Raynaud's Phenomenon

A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Angiotensin-Converting Enzyme Inhibitor Quinapril

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Objective. **To evaluate the efficacy and tolerability of prolonged administration of quinapril, a long-acting angiotensin-converting enzyme inhibitor, in the management of the peripheral vascular manifestations of limited cutaneous systemic sclerosis (lcSSc) and in the prevention of the progression of visceral organ involvement in the disease.**

Methods. **This was a multicenter, randomized, double-blind, placebo-controlled study evaluating quinapril 80 mg/day, or the maximum tolerated dosage, in 210 patients with lcSSc or with Raynaud's phenomenon (RP) and the presence of SSc-specific antinuclear antibodies. Treatment was for 2–3 years. The primary outcome measure was the number of new ischemic ulcers appearing on the hands; secondary measures were the frequency and severity of RP attacks, skin score, treatments for ischemia, health status (measured by the Short Form 36 instrument), measures of kidney and lung function, and echocardiographic estimates of pulmonary artery pressure. An intent-to-treat analysis was used.**

Results. **Quinapril did not affect the occurrence of digital ulcers or the frequency or severity of RP episodes. It did not alter the treatments that were prescribed for either infected ulcers or severe RP symptoms. There was no apparent effect on the estimated tricuspid gradient. Health status was not affected by quinapril, and one-half of the patients who believed they had benefited from the trial treatment were in the placebo arm. Quinapril was not tolerated by one-fifth of the patients, with dry cough being the most frequent side effect.**

Conclusion. **Administration of quinapril for up to 3 years had no demonstrable effects on the occurrence of upper limb digital ulcers or on other vascular manifestations of lcSSc in this patient population.**

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Systemic sclerosis (SSc; scleroderma) is an autoimmune rheumatic disease of unknown etiology characterized by microvascular injury, excessive fibrosis of the skin, distinctive visceral involvement, including the lungs, heart, kidneys, and gastrointestinal tract, and progressive macrovascular pathology. It is an uncommon condition with an annual incidence of ~10 cases per million of the population of the UK (1). SSc has the highest disease-specific mortality of any rheumatic disease, and whatever the initial presentation, serious morbidity and mortality, especially from respiratory and cardiovascular complications, are common (2).

SSc is a heterogeneous disease, with distinctive clinical subsets that differ in disease pattern and outcomes. The most widely accepted system for clinical classification involves 2 subsets, limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), based on the extent of cutaneous involvement, which reflects to some extent the degree of visceral disease (3). The majority of patients (>60%) fall into the category of lcSSc. In these patients, as compared with those with dcSSc, visceral involvement is a late manifestation, occurring 10–30 years after the onset of Raynaud's phenomenon (RP), which is usually the first event. However, progressive vascular involvement is often a major feature in these patients, leading to manifestations such as recurrent painful digital ischemia and ulceration, severe gastrointestinal disease (4), particularly of the esophagus, and serious macrovascular complications, such as pulmonary hypertension (5).

There is compelling evidence that endothelial cell dysfunction plays a pivotal role in vascular injury, as reviewed by Flavahan et al (6). So far, the search for drugs to protect injured endothelial cells and to prevent platelet aggregation and subsequent release of platelet- and endothelium-derived mediators has been disappointing (7). For example, calcium-channel blockers are effective and are frequently used to treat RP (8–10), but there is no evidence that they influence the development of structural vascular abnormalities. In a randomized 12-week trial comparing nifedipine with losartan, an angiotensin II receptor antagonist, in patients with RP with or without SSc (11), losartan, but not the calcium-channel blocker, influenced serum markers of endothelial cell activation, vascular damage, and extracellular matrix turnover, suggesting an effect on the underlying pathologic processes.

Inhibition of angiotensin-converting enzyme (ACE) has revolutionized the management of scleroderma renal crisis, which previously had an almost invariably fatal outcome (12). There are anecdotal reports and open uncontrolled studies purporting that ACE inhibitors are effective in RP and affect digital blood flow (13,14). However, these encouraging observations were not substantiated by placebo-controlled studies. Of 4 placebo-controlled studies performed (15–18), only 1 showed a trend toward clinical improvement with ACE inhibition (16), while another (17) showed objective improvement in blood flow in the fingers. However, these studies were confined to testing captopril or enalapril, and there are no studies using newer ACE inhibitors that appear to have relatively greater effects on the peripheral vasculature. Furthermore, there are no data on the long-term effects of ACE inhibition on the progression of vascular disease in SSc.

Nevertheless, in addition to its effect in counteracting renin-driven hypertension, ACE inhibition potentially has effects on vascular function through a variety of mechanisms. For example, ACE inhibition plays a direct role in improving endothelial function in animal models of atherosclerosis (19), inhibits intimal hyperplasia after vascular injury (20), restores the normal vasodilatory response of coronary arteries in patients with coronary artery disease (21), and promotes vascular remodeling in patients with chronic hypertension (22). This effect on endothelial function is associated with increased availability of nitric oxide (23) and, since depressed levels of nitric oxide characterize the endothelial dysfunction seen in RP (24), ACE inhibition presents a possible treatment for SSc.

The purpose of this study, therefore, was to evaluate the efficacy and tolerability of the long-acting ACE inhibitor quinapril in the management of the peripheral vascular manifestations of lcSSc and in the prevention of the progression of visceral organ involvement in the disease.

PATIENTS AND METHODS

Patient population. The patients were at least 18 years of age and were classified as having lcSSc (3), with scleroderma limited to the hands, forearms, face, lower legs, and feet, or were classified as having autoimmune RP. The latter was defined as the presence of RP, documented objectively, insufficient clinical features for classification as SSc, but with SSc-associated autoantibodies, such as anticentromere antibody (ACA), anti–topoisomerase I, and anti–RNA polymerase antibody, or high-titer antinuclear antibody (ANA) or antinucleolar antibody in the absence of serologic findings specific for other connective tissue diseases (25).

Patients were excluded if they had a known allergy to, or intolerance of, ACE inhibitors, were women of childbearing age who were not using reliable contraception, had a history of angioedema, had significant impairment of renal or hepatic

function, had severe obstructive valvular heart disease, or had any other condition that would prevent compliance with treatment or adequate assessment. Patients were also excluded who did not speak English or Welsh or who spoke a language for which no approved translation of the Patient Information and Consent Form was available.

Drug treatment other than ACE inhibitors for underlying SSc and its complications, including immune-modulating agents, was permitted and was the prerogative of the patient's consultant in the participating center. This could include other vasodilator agents, such as calcium-channel blockers, α-adrenergic receptor blockers, and pentoxifylline. Intermittent intravenous iloprost or other prostacyclin preparation was permitted for severe digital ischemia but not for regular prophylactic treatment.

The study was conducted at 20 centers across England and Wales (16 district general hospitals and 4 tertiary referral centers). Approval of the Multicentre Research Ethics Committee (MREC Wales 00/09/19) was obtained, and each participating center received local ethics committee and research governance approval. All patients provided written informed consent, and the study was conducted according to the Declaration of Helsinki (2000 amendment) and according to the International Conference on Harmonisation Guidelines for Good Clinical Practice, as adopted by the European Union in 2001.

Study medication and dosage. Quinapril (20 mg) tablets and matching placebo tablets were provided in bulk by Pfizer (Kent, UK) and were down-packed into glass bottles at St. Mary's Pharmaceutical Unit (SMPU) in Cardiff. Patients started taking 1 tablet a day for the first 2 weeks, increasing by 1 tablet per day every 2 weeks, after blood pressure (BP) and serum creatinine levels were evaluated. The target dose was 80 mg/day, which was usually taken as 4 tablets each morning. If systolic BP fell to $<$80 mm Hg or the serum creatinine level rose by $>$30% above the baseline level, the study medication dosage was reduced and maintained at the reduced dosage throughout the trial. Reductions in dosage were allowed during the trial if side effects developed.

Study design. This was a multicenter, randomized, double-blind, placebo-controlled study. Study numbers were computer-generated in randomized permutated blocks of 10 at SMPU. Numbered packs of study medication in blocks of 10 were sent to each participating hospital, where patients were allocated a study number in order of recruitment. The code was broken after the last dose of study medication had been taken and the majority of data had been forwarded to the trial coordinator. The investigators, the assessors, and the patients were unaware of the treatment group assignment during the trial. Success of blinding was assessed after the end of the trial by asking assessors and patients their opinions as to treatment group assignment. Treatment was continued for at least 2 years but not more than 3 years. After baseline measurements, patients were assessed for drug efficacy, adverse events, and safety every 3 months for the duration of the study. Patients who discontinued the medication were assessed on an annual basis.

Outcome measures. The primary outcome measure was the rate of occurrence of new ischemic digital ulcers on the hands. Secondary outcome measures were as follows: self-reported visual analog scale (VAS; 0–100 mm) measurements of both the frequency and the severity of RP (detection of changes was maximized by showing patients their most recent VAS marks before they marked the scales [26]); introduction of vasodilators; use of intravenous iloprost to treat ischemic digital lesions; progression of the scleroderma skin score (27); progression of pulmonary and renal disease; occurrence of death, pulmonary hypertension, and significant macrovascular complications such as stroke or myocardial infarction; health status measured by the Short Form 36 healthy survey (used under license no. R3-082102-11646 from QualityMetric, Lincoln, RI).

Serum samples taken at the baseline visit for the Quinapril in Scleroderma (QUINS) trial were sent to a central laboratory for ANA analysis. They were initially screened using indirect immunofluorescence (IIF) on HEp-2 cells at a serum dilution of 1:40 and using polyvalent fluorescein isothiocyanate–conjugated secondary antibody. Two independent experienced observers interpreted IIF patterns. Positive samples were then further investigated for their autoantibody specificity using the most relevant technique. Ouchterlony immunodiffusion was performed using a commercial antigen source (Bio-Diagnostics, Upton-upon-Severn, UK) and rabbit thymus extract (Pel-Freez, Rogers, AR). Commercial enzyme-linked immunosorbent assays (The Binding Site, Birmingham, UK) were used for confirmatory purposes for anti–U1 RNP, anti-Sm, anti-Ro, anti-La, and anti–topoisomerase I. In-house immunoblotting was performed using K562 cells and a polyvalent alkaline phosphatase–conjugated secondary antibody. Radioimmunoprecipitation using ^{35}S-labeled K562 cells was then used to further investigate for anti–RNA polymerase antibodies, antinucleolar antibodies such as anti–U3 RNP, and other antibodies of as-yet-unidentified specificity.

A meeting of the study investigators was held to agree upon the definition of an active digital ulcer, which was defined as any lesion on the fingers with no epithelial surface, except for those due directly to trauma, which heal normally. The method of scoring skin thickness was demonstrated at the trial-initiation visit, and further training was provided as necessary by experienced staff. Annual estimates of the percentage of expected forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO) were used as measures of pulmonary function, and creatinine clearance was used as a measure of renal function. Echocardiograms were performed at baseline and at the end of the study to estimate pulmonary artery pressure. Although this was a multicenter study, the individual patient had baseline and final pulmonary function tests and echocardiography performed in the same laboratory.

Sample size. The original sample size calculation for the QUINS trial was based on an estimated average of 0.15 new ulcers per patient (the number of new ulcers that had developed in the 3 months before the baseline visit). Using this value in a power calculation, it was estimated that 160 patients in each treatment arm were required for 95% power at a 5% significance level to detect a 30% reduction per annum in the frequency of digital ulcers in the quinapril cohort. This took into account a withdrawal rate of 5% per annum. This level of improvement had been chosen, following discussions with the UK Scleroderma Study Group, as being a clinically significant effect of ACE inhibition. Before recruitment was closed, the mean number of new ulcers over the previous 3 months at the baseline assessment was 0.28. Assuming a 5% loss of patients

Table 1. Comparison of baseline characteristics of 380 eligible study patients, grouped according to whether they did or did not consent to study randomization*

	Nonconsenter group (n = 167)	Consenter group (n = 213)	Difference (nonconsenters minus consenters) (95% CI)
Female, no. (%)	143 (86)	182 (85)	0 (−7, 7)
Age, mean ± SD years	57 ± 12	54 ± 12	3.1 (1, 6)†
No. of organ systems involved, median (IQR)‡	2 (2, 4)	2 (2, 3)	0 (0, 1)
Disease duration, median (IQR) years§	10 (6, 17)	4 (1, 9)	5 (3, 6)¶

* 95% CI = 95% confidence interval; IQR = interquartile range.
† $P < 0.01$.
‡ Data are for 78 patients in the nonconsenter group; the other 89 patients did not consent to storage of this information in the UK Scleroderma Database.
§ Data are for 73 patients in the nonconsenter group; the other 94 patients did not consent to storage of this information in the UK Scleroderma Database.
¶ $P < 0.001$.

to followup each year, data would be available for ~180 patients, 90 per group, at the end of the 3-year trial. These data led to an estimate, based on the Poisson distribution, that the study would be able to detect a 25% reduction in the mean total number of ulcers in the treated group, using a 2-sided test at the 5% significance level with 80% power.

Statistical analysis. Analyses were on an intent-to-treat basis. Patient characteristics at baseline in the 2 randomized groups were summarized. For each safety and efficacy variable, a regression model was fitted to all the followup data. The regression model contained treatment (quinapril or placebo) and the baseline value of the variable. Robust Huber-White sandwich estimators of the regression coefficients were used, which take account of the observed correlation between the repeated assessments of the same patient. For all analyses, the alpha level was set at 0.05. Data from patients who had withdrawn from treatment were collected at annual visits for the duration of the study. Three patients did not start their study medication and did not provide any followup data. Major serologic subsets of SSc were examined for particular patterns of outcome, and the results for patients who tolerated the target dosage of 80 mg of quinapril daily were compared with those who took lower dosages. Diagnosis and ulcer history at baseline were also tested as subgroup variables. The statistical analysis was performed using Stata Release 9 software (28).

RESULTS

Data for this study were collected between March 2001 and January 2006. Enrollment into the trial was slower than expected, so the period of recruitment was extended, although the end date was retained. This allowed 213 patients to be recruited. Table 1 shows a comparison of the characteristics of the 213 patients who consented to be randomized into the trial, along with the 167 patients who did not consent. Data for age and sex were known for all patients, but information on the number of organ systems affected and disease duration was collected only from patients who had consented to storage of this information in the UK Scleroderma Database. The degree of involvement was assessed in 9 organ systems using a validated disease activity scale (29). Differences were calculated as values in the nonconsenter group minus values in the consenter group; thus, a positive value indicates a higher value in the

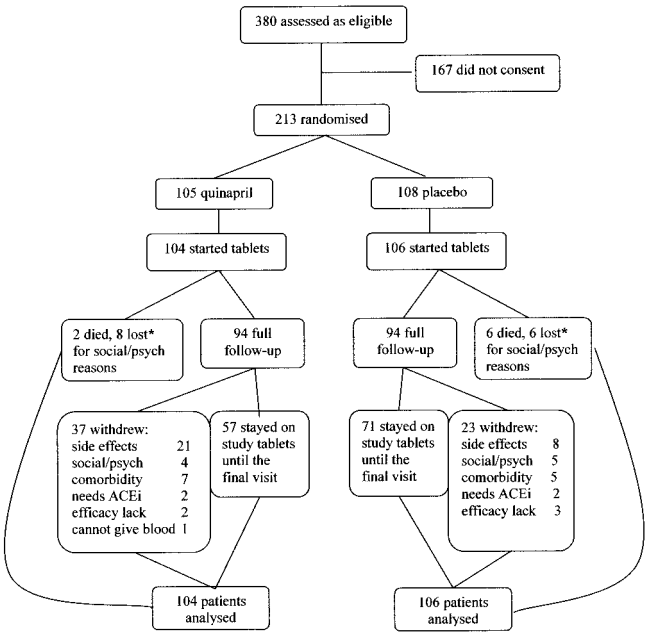

Figure 1. Flow diagram showing the distribution of study patients in the Quinapril in Scleroderma trial, from initial contact to completion of 3 years. *Lost was defined as failure to contribute any data to the final study visit. ACEi = angiotensin-converting enzyme inhibitor.

nonconsenter group. Nonconsenters were older and had a longer disease duration.

Of the 213 patients enrolled, 105 were randomly assigned to receive quinapril and 108 to receive placebo (Figure 1). Two patients assigned to receive placebo and 1 patient assigned to receive quinapril withdrew before taking any medication and were not included in the subsequent analyses. Of the remaining 210 patients, 109 were followed up for the full 3 years, and 101 patients were followed up for between 2 and 3 years.

As shown in Table 2, the baseline demographic and clinical characteristics of the 2 treatment groups were similar. The majority had lcSSc, but 13 of the patients taking quinapril (13%) and 11 taking placebo (10%) had RP and positive serologic results specific for scleroderma. Most of the patients were white (97%) and female (85%). The median disease duration, as measured from the first non-RP manifestation of SSc, in patients taking quinapril was 5 years and 4 years in patients taking placebo. Fifty patients (24%) had ulcers on their fingers. Often, the ulcers had been present for many months, and frequently, there were multiple ulcers. The mean number of ulcers per patient was 0.46 for those taking quinapril and 0.83 for those taking placebo. A new ulcer was defined as one that occurred within 3 months of the assessment. At baseline, the mean number of new ulcers in patients taking quinapril and those taking placebo was 0.35 and 0.23, respectively.

Of the 24 patients classified as having "autoimmune RP" (11% of the 210 randomized patients), 19 had SSc-associated autoantibodies (ACA in 8, anti–U1 RNP in 6, anti–topoisomerase I in 4, and anti–RNA polymerase II and III in 1). Five patients had high-titer ANA by IIF, which could not be further characterized. Eleven of the 24 patients with autoimmune RP (46%) had a history of ischemic digital ulcers, 2 (8%) developed new ulcers during the study, and 3 (13%) had unhealed ulcers at their final visit.

A total of 57 patients receiving quinapril and 71 receiving placebo were still taking the study medication at the final study visit (Figure 1). Forty-seven patients withdrew, died, or were lost to followup from the quinapril arm, but assessments were continued in all, although 10 patients did not contribute data to the final visit. Similarly, of the 35 patients who withdrew, died, or were lost to followup from the placebo arm, all were followed up, although 12 did not contribute data to the final visit. Only 2 patients, 1 in each arm of the trial, failed to contribute any data after the baseline visit.

Efficacy. For each outcome variable, a regression model was fitted to all the followup data. There were a total of 1,686 followup assessments, with an average of 8.0 assessments per patient. The treatment effects and 95% confidence intervals for the treatment effects are summarized in Table 3.

We observed small, but statistically significant, effects of quinapril treatment on blood pressure and serum creatinine. These were the expected physiologic effects of ACE inhibition. However, there were no

Table 2. Patient characteristics at trial entry and baseline values of outcome measures, by treatment group*

	Placebo (n = 106)	Quinapril (n = 104)
Diagnosis, no. (%)		
lcSSc	95 (90)	91 (87)
RP	11 (10)	13 (13)
Female, no. (%)	92 (87)	87 (84)
Caucasian, no. (%)	104 (98)	99 (95)
Age, mean ± SD years	55 ± 12	54 ± 12
Disease duration, median (IQR) years	4 (1, 9)	5 (2, 9)
No. of organ systems affected, median (IQR)	2 (2, 3)	3 (2, 3)
History of digital ulcers, no. (%)	77 (73)	62 (60)
Study medication titrated to full dose, no. (%)	98 (92)	74 (71)
Antibodies, no. (%)		
Anticentromere	49 (48)	48 (48)
Anti–topoisomerase I	12 (12)	7 (7)
Anti–U1 RNP	7 (7)	13 (13)
Digital ulcers, mean ± SD		
No. of new (<3 months) ulcers present	0.23 ± 0.68	0.35 ± 0.88
Total no. of ulcers present	0.83 ± 2.00	0.46 ± 1.05
RP attacks over the last 3 months, by VAS, mean ± SD mm		
Frequency	53 ± 27	56 ± 29
Severity	49 ± 27	52 ± 30
Skin score, mean ± SD	6 ± 5	5 ± 4
Blood pressure, mean ± SD mm Hg		
Systolic	130 ± 20	133 ± 20
Diastolic	77 ± 10	79 ± 11
Serum creatinine, mean ± SD μmoles/liter	77 ± 13	81 ± 16
Creatinine clearance, mean ± SD ml/minute	87 ± 34	86 ± 30
Urinary protein, mean ± SD gm/24 hours	0.11 ± 0.09	0.13 ± 0.11
Pulmonary studies		
FVC, mean ± SD % predicted	103 ± 17	106 ± 18
DLCO, mean ± SD % predicted	74 ± 16	74 ± 18
Pulmonary artery pressure >30 mm Hg, no. (%)	6 (6)	9 (9)
Short Form 36 health survey score, mean ± SD		
Physical	44 ± 11	44 ± 11
Mental	49 ± 10	49 ± 11

* lcSSc = limited cutaneous systemic sclerosis; RP = Raynaud's phenomenon; IQR = interquartile range; VAS = visual analog scale (0–100-mm scale); FVC = forced vital capacity; DLCO = diffusion capacity for carbon monoxide.

Table 3. Regression coefficients for treatment effect, adjusted for baseline values*

Variable	Treatment effect (quinapril minus placebo group)	95% CI
No. of new digital ulcers	−0.08	−0.23, 0.06
Total no. of digital ulcers	0.004	−0.18, 0.19
RP attack frequency, by VAS, mm	0.3	−5.6, 6.3
RP attack severity, by VAS, mm	0.1	−6.1, 6.3
Systolic blood pressure, mm Hg	−9	−12, −6†
Diastolic blood pressure, mm Hg	−4	−6, −3†
Serum creatinine, μmoles/liter	3.2	0.9, 5.5‡
Creatinine clearance, ml/minute	−1.2	−7.5, 5.2
Urinary protein, gm/24 hour	−0.004	−0.04, 0.03
FVC, % predicted	4.3	1.2, 7.4§
DLCO, % predicted	−0.8	−3.7, 2.0
Pulmonary artery pressure >30 mm Hg¶	1.7	0.6, 4.5
SF-36 health survey physical score	−0.7	−2.5, 1.0
SF-36 health survey mental score	0.6	−1.5, 2.7

* The regression model contained the treatment (quinapril or placebo) and the baseline value of the variable. Robust Huber-White sandwich estimators of the regression coefficients were used, which take into account the observed correlation between repeated assessments of the same patient. 95% CI = 95% confidence interval; RP = Raynaud's phenomenon; VAS = visual analog scale (0–100 mm); FVC = forced vital capacity; DLCO = diffusion capacity for carbon monoxide; SF-36 = Short Form 36.
† $P < 0.001$.
‡ $P < 0.006$.
§ $P < 0.007$.
¶ Treatment effect is expressed as an odds ratio (quinapril:placebo).

significant effects of treatment on either the occurrence of new digital ulcers or the total number of ulcers. Since the number of new ulcers had a non-Gaussian distribution with a large number of zero values, negative binomial regression models were also fitted. These confirmed that there was no treatment effect. Similarly, we could detect no effect of quinapril on the frequency or severity of RP episodes or other aspects of scleroderma, including health status, with the exception of the percent predicted FVC in the lung. The proportion of patients with an estimated tricuspid gradient on echocardiography of >30 mm Hg was similar in the 2 treatment groups. By the end of the trial, 8 patients had an estimated tricuspid gradient >40 mm Hg, suggestive of significant pulmonary hypertension. Four of these patients were in the quinapril arm of the trial and 4 in the placebo arm.

The possibility that quinapril was efficacious in certain groups of this heterogeneous population was tested by subgroup analyses for 4 factors. These were the inclusion category (lcSSc versus autoimmune RP), patients who had a history of digital ulcers versus those who did not, the 3 main serotypes in this cohort (ACA-positive, anti–U1 RNP–positive, and anti–topoisomerase I–positive patients), and patients who tolerated 80 mg/day of quinapril after titration versus those who could only tolerate a lower dose. The numbers of patients in these subgroups are shown in Table 2. Subgroup–treatment interactions were explored in regression models similar to those used to derive the data in Table 3. There were no significant interactions between subgroup and treatment (data not shown).

Furthermore, there was no indication that quinapril treatment reduced the morbidity associated with the ulcers or RP symptoms, since the number of patients receiving intravenous iloprost, the number of antibiotic treatments for digital ulcers, and the changes in vasodilator medication dosages were similar between the treatment groups, as shown in Table 4.

Fourteen patients in the quinapril group and 9 in the placebo group received 1 or more immunosuppressive drugs. In 4 patients in each group, these drugs were started during the trial. Agents included methotrexate (9 patients), azathioprine (8 patients), cyclophosphamide (6 patients), mycophenolate mofetil (2 patients), and tacrolimus (1 patient). The main clinical indications were polyarthritis, pulmonary disease, and myositis.

The only statistically significant treatment effect was on lung function. As expected in lcSSc patients, overall lung function was fairly well preserved (Table 2). Nevertheless, as shown in Table 3, an increase in the percent predicted FVC was observed in quinapril-treated patients, amounting to a mean difference of

Table 4. Treatment of severe Raynaud's disease and/or digital ulcers*

	Placebo (n = 106)	Quinapril (n = 104)	Difference (quinapril minus placebo), % (95% CI)
Intravenous iloprost, no. (%)	18 (17)	11 (11)	−6 (−16, 3)
Antibiotics for infected digital ulcers, no. (%)	24 (23)	20 (19)	−3 (−14, 8)
Increased dosage of vasodilator, no. (%)	10 (9)	8 (8)	−2 (−9, 6)
Decreased dosage of vasodilator, no. (%)	7 (7)	8 (8)	1 (−6, 8)

* P values were not significant. 95% CI = 95% confidence interval.

Table 5. Adverse events occurring during the trial*

	Placebo (n = 106)	Quinapril (n = 104)	Difference (quinapril minus placebo), % (95% CI)
AEs			
Total no. of AEs	484	505	
No. (%) of patients with ≥1 AE	82 (77)	92 (88)	11 (1, 21)†
No. of AEs probably or definitely related to treatment	5	41	
No. (%) of patients with ≥1 AE probably or definitely related to treatment	5 (5)	27 (26)	21 (12, 31)‡
SAEs			
Total no. of SAEs	40	23	
No. (%) of patients with ≥1 SAE	25 (24)	22 (21)	−2 (−14, 9)
No. (%) of patients with ≥1 SAE possibly related to treatment	1 (1); hemolytic anemia	1 (1); cholecystitis	0 (−3, 3)

* 95% CI = 95% confidence interval; AEs = adverse events; SAEs = serious adverse events.
† $P = 0.04$.
‡ $P < 0.001$.

~4%. This increase mainly occurred in those with lower levels of lung function (data not shown) and happened after 1 year of treatment. No effect of quinapril was seen on the DLco values.

Tolerability and safety. The overall incidence of adverse events reported by patients taking quinapril (88%) was statistically significantly higher than that reported by patients taking placebo (77%) (Table 5). Twenty-nine patients withdrew from the trial because of side effects suspected to be related to the study medication. Twenty-one were taking quinapril. The major side effect causing these patients to withdraw from the trial was a dry and/or persistent cough, which was experienced by 11 patients. Four withdrew because of headaches, 3 because of fatigue, 2 because of low blood pressure, 2 because of angioedema, and 1 each because of abdominal pain, vision problems, and high blood pressure (decision of the primary healthcare physician). Several patients experienced side effects of quinapril but continued to take the medication at full or reduced dosage. Fourteen developed these side effects during the 8-week titration period, but side effects also occurred later, up to 18 months from initiation of study medication.

No suspected unexpected serious adverse reactions to quinapril were observed. Eight patients died during the course of the trial. Two were taking quinapril, and 6 were taking placebo. One quinapril-treated patient died of ischemic heart disease 11 months after he withdrew from the trial because of a severe dry cough. He had taken quinapril for 6 months. The other patient, who withdrew from the trial because of deteriorating lung function, died 4 months later while in a tertiary center because of pulmonary hypertension. Causes of death of patients in the placebo arm were myocardial infarction, ischemic necrosis of the bowel, carcinoma of the breast, severe upper gastrointestinal hemorrhage, and pancreatitis, and 1 patient died of unknown causes.

Assessment of blinding. At the end of the trial, assessors were asked to give their opinion of their patients' treatment by selecting one of the following categories: quinapril, placebo, or don't know. Of the 154 opinions received from the assessors, 51 (33.1%) were correct concerning which 28 opinions were based on the side effects of quinapril. Using the same 3 options, patients were asked to give their opinions of their own treatment. One hundred twenty-two patients gave 63 correct opinions (51.6%): 34 correct opinions were from 58 patients who were taking quinapril (24 of which were due to side effects), and 29 correct opinions were from 64 patients who were taking placebo. Of the 25 patients who declared that their health had improved during the trial, 12 were in the placebo arm.

DISCUSSION

This multicenter, randomized, double-blind, placebo-controlled clinical trial examined the efficacy of ACE inhibition with quinapril for up to 3 years for the treatment of upper limb digital ulcers in patients with lcSSc. The duration of treatment, which lasted years rather than months, was chosen to abrogate the seasonal effects on vascular manifestations and, since most digital ulcers eventually heal, to enable us to focus on the occurrence of new ulcers. The trial had sufficient power to detect minor physiologic effects of ACE inhibition on

blood pressure and serum creatinine levels. Nevertheless, we could not detect a treatment effect on digital ulceration or on other manifestations of microvascular disease, which are so prominent in this subset of SSc. This lack of effect was unlikely to be due to insufficient statistical power and contrasts with the efficacy demonstrated for other agents, such as iloprost and bosentan, in studies that were of smaller scale and shorter term (30,31). Although there are anecdotal reports of ACE inhibition improving RP, for example in the context of renal crisis (32,33), the results here were consistent with short-term studies with agents such as captopril and enalapril that gave conflicting results for RP symptoms (13,14).

Digital ulcers, which are often very painful, are a common complication of scleroderma. In this study, they occurred in ~40% of patients during the course of the trial and were usually multiple. Several factors contribute to their etiology. These include local trauma, ischemia due to vascular disease, indurated tethered skin, and calcinosis. Similarly, a combination of factors, including epithelial dysfunction, infection, and poor blood flow, contribute to their persistence. Bosentan, an endothelin receptor antagonist, was previously shown to significantly reduce new digital ulcer formation in SSc and was more effective in patients who had ulcers at the baseline assessment (30). Subgroup analysis of this sort in our study, however, yielded negative results.

Similarly, there was no obvious treatment effect in the subgroup with "autoimmune RP." The decision was made to include autoimmune RP since our view was that lcSSc and autoimmune RP represent a continuum, with the RP patients anticipated to represent the milder end of the spectrum but still at risk of developing definite SSc. The inclusion criteria for this group of patients correspond to the criteria for the diagnosis of limited SSc proposed by LeRoy and Medsger in 2001 (25). Until these criteria are validated by prospective clinical studies, our approach might be open to criticism. However, these inclusion criteria were not questioned when the original trial protocol went out for international peer review.

In this study, quinapril also had no effect on the development of the important vascular complication of pulmonary arterial hypertension. The tricuspid gradient was assessed by echocardiography at baseline and at the end of the study. Of the 8 patients who developed an estimated tricuspid gradient >40 mm Hg, suggestive of significant pulmonary hypertension, 4 were in the quinapril arm of the trial and 4 in the placebo arm. These 8 patients were among the 161 lcSSc patients who had echocardiography at the final visit, giving an annual rate of onset of pulmonary arterial hypertension at 40 mm Hg of ~2% per year in this cohort. However, we do acknowledge that in terms of disease progression, the study was not very long and that the secondary end points, including the development of pulmonary hypertension, would require a much longer period of observation.

The only statistically significant effect of quinapril treatment was an increase in the FVC of the lungs. In view of the number of comparisons performed, this could be due to chance. There was no effect on the DLCO. The clinical significance of this novel observation is unknown, particularly since spirometry values were, for the most part, normal in this group of patients. However, the increase in FVC was most marked in those with the lowest values at baseline and became apparent only after 1 year of treatment. These results were not due to preferential withdrawal of patients taking quinapril who had a low percent predicted FVC, since the mean baseline values in those who withdrew because of a cough, others who withdrew, and all patients in the quinapril arm were 105.8%, 105.4%, and 105.9%, respectively. Concomitant therapy with immunosuppressive drugs also does not explain the difference. Whether or not the observed increase in FVC in patients taking quinapril has any clinical relevance needs further investigation. Endothelial cell injury may play a significant role in scleroderma lung disease (34), and recent studies indicate that the local renin–angiotensin system might be involved in the development of lung fibrosis (35–37).

In summary, this study showed no clinical effect of long-term quinapril treatment on the occurrence of upper limb digital ulcers in patients with lcSSc or on features of microvascular disease, such as RP. Similarly, there was also no apparent effect on the development of pulmonary hypertension. A possible beneficial effect on FVC was observed but is of uncertain significance.

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AUTHOR CONTRIBUTIONS

Drs. Gliddon and Maddison had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study design. Doré, Black, McHugh, Moots, Herrick, Maddison.
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Statistical analysis. Doré.

ROLE OF THE STUDY SPONSORS

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