

ONLINE SUPPLEMENTARY DATA

Supplementary Table 1. Clinical variables values, in the two patient groups (ILO and ILO+BOSE), for each follow up year, with baseline and overall significant differences reported.

CLINICAL VARIABLES	STATISTICAL TEST	PATIENTS GROUP	T0	T1	T2	T3	T4	T0-T4 p R ² r
NEW DUs INCIDENCE	Cochran's Q Test	ILO+ BOSE	10/15	4/15	2/15	4/15	2/15	0.0042
DLCO %	Friedman's Test	ILO+ BOSE	64.3 ±16	64.5 ±21	67.6 ±19	73.2 ±27	70.2 ±28	0.46
		ILO	81.3 ±16 p=0.02	82.9 ±15	72.3 ±14	71 ±15	74.7 ±24	0.039
	Correlation	ILO+ BOSE ILO						0.15 0.55 -0.74 -0.9817 to 0.4050 CI 0.04 0.8 -0.89 -0.9931 to -0.05777
	Friedman's Test	ILO+ BOSE	34.6 ±9	36 ±4	34.8 ±6.4	34.6 ±6.7	34.5 ±7.1	0.8
		ILO	29.3 ±3.4 p=0.01	33 ±7	33.7 ±5.4	32.5 ±5.6	33.7 ±6.6	0.04

sPAP mmHg	Correlation	ILO+ BOSE						0.42 0.22 -0.47 -0.9563 to 0.7021
		ILO						
RI	Friedman's Test	ILO+ BOSE	0.66 ±0.06	0.68 ±0.04	0.7 ±0.05	0.67 ±0.1	0.67±0.1	0.6
		ILO	0.69 ±0.06 p=0.22	0.68 ±0.05	0.69 ±0.05	0.69 ±0.1	0.68 ±0.1	0.9
	Correlation	ILO+ BOSE						0.92 0.003 0.05 -0.8688 to 0.8946
		ILO						0.29 0.35 -0.5 -0.9685 to 0.6073
ESR mm	Friedman's Test	ILO+ BOSE	34.8 ±27.4	34.6 ± 26.3	42.6 ±25	47.1 ±30	43.9±27	0.07
		ILO	39 ±25.3 p=0.47	32.7 ±17.7	28 ±9.3	29.9 ±17	31.7 ±21	0.28
	Correlation	ILO+ BOSE						0.06 0.7 0.8 -0.08880 to 0.9907
		ILO						0.2 0.43 -0.6 -0.9750 to 0.5284

CRP mg/dl	Friedman's Test	ILO+ BOSE	5 ±2.7	5.4 ±3.5	6.3 ±3.9	14 ±22	8.4 ±8.8	0.17
		ILO	5.9 ±7.2 p=0.05	4.5 ±4.4	3 ±0.2	3 ±0.1	4.2 ±4.7	0.2
	Correlation	ILO+ BOSE						0.006
		ILO						0.9 0.9 0.2 0.4 -06

DUs= Digital Ulcers, DLCO= diffusing capacity of the lungs for carbon monoxide; sPAP= systolic pulmonary arterial pressure; RI= renal artery resistive index; ESR= erythrocyte sedimentation rate; CRP= C-reactive protein.

Supplementary Table 2. Instrumental variables values, in the two patients groups (ILO and ILO+BOSE), for each follow up year, with baseline and overall significant differences reported.

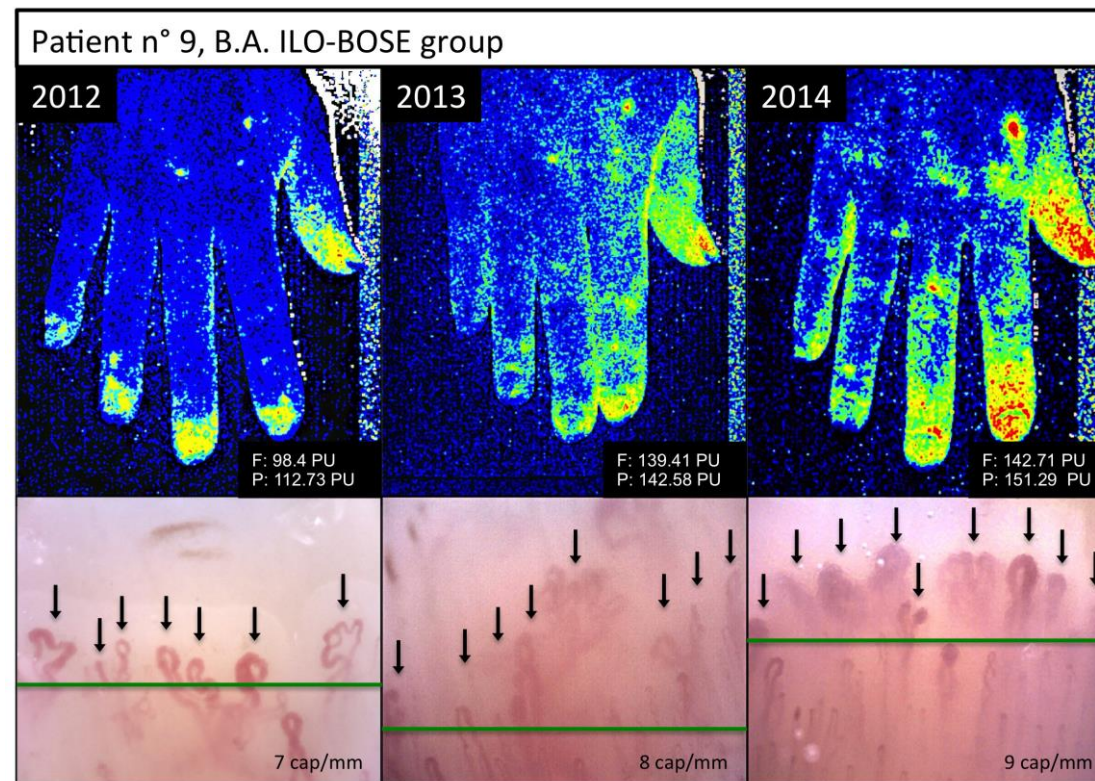
INSTRUMENTAL VARIABLES	STATISTICAL TEST	PATIENTS GROUP	T0	T1	T2	T3	T4	OVERALL FU p R ² SLOPE
CAPILLARIES ABSOLUTE NUMBER/mm	Friedman's Test	ILO+ BOSE	6.8 ±1.3	7.3 ±1.6	7.6 ±1.8	7.7 ±1.5	7.8 ±1.5	0.018
		ILO	7.18 ±0.5 p=0.42	6.8 ±0.9	6.7 ±0.9	6.6 ±1.1	6.5 ±1.1	0.29
	Correlation	ILO+ BOSE ILO						0.02 0.86 0.06686 to 0.4014 0.089 0.92 -0.2211 to -0.06916
CAPILLARY NUMBER SCORE	χ^2	ILO+ BOSE	1= 4 2= 8 3= 3	1= 2 2= 11 3= 2	1= 2 2= 11 3= 2	1= 4 2= 9 3= 2	1= 6 2= 7 3= 2	0.77
		ILO	1= 6 2= 8 3= 1 p=0.49	1= 2 2= 12 3= 1	1= 4 2= 10 3= 1	1= 2 2= 12 3= 1	1= 3 2= 11 3= 1	0.82
	Friedman's Test	ILO+ BOSE	67.3 ±31.7 91 ±47.4	83.8 ±33 85.7 ±43	99 ±34 76.7 ±43	103 ±32 72.3 ±43	104 ±31 71 ±37	< 0.0001
		ILO	p=0.08					0.079

FBP (PU):	Correlation	ILO+ BOSE ILO						0.03 0.83 1.599 to 16.62 0.02 0.86 -7.927 to -1.325
FBP 36°C (PU):	Friedman's Test	ILO+ BOSE ILO	96.47 ±51 138.9 ±50 p=0.05	116.9 ±51 122.4 ±51	141 ±65 109 ±52	137 ±64 101 ±52	141 ±57 104 ±50	0.0001 0.0009
	Correlation	ILO+ BOSE ILO						0.05 0.76 -0.2781 to 24.58 0.04 0.78 -13.70 to -0.1787
Δ FBP:	Friedman's Test	ILO+ BOSE ILO	37 ±31 45.8 ±3 p=0.16	40 ±32 38.4 ±28	51 ±40 36.5 ±26	43.7 ±43 32.6 ±24	47 ±38 28 ±24	0.47 0.08
	Correlation	ILO+ BOSE ILO						0.63 0.08 -6.994 to 9.768 0.03 0.83 -7.859 to -0.7637

LASCA F (PU):	Friedman's Test	ILO+ BOSE	/	/	103 ±22	120 ±24	132 ±27	0.045
		ILO	/	/	107 ±28	99 ±28	99 ±18	0.3
	Correlation	ILO+ BOSE						0.07 0.99 0.98
LASCA P (PU):		ILO						0.32 -0.8 0.7
	Friedman's Test	ILO+ BOSE	/	/	106 ±31	124 ±27	143 ±18	0.05
		ILO	/	/	115 ±30	107 ±30	100 ±33	0.27
LASCA P (PU):	Correlation	ILO+ BOSE						0.0018 1 1
		ILO						0.045 -0.99 0.99

FBP= Fingertip blood perfusion at basal skin temperature; PU= Perfusion units; FBP 36°= Fingertip blood perfusion after probe heating; ΔFBP: Perfusion gradient= FBP 36°- FBP; LASCA F= laser speckle contrast analysis of the fingertip region; LASCA P= laser speckle contrast analysis of the periungueal region.

Supplementary Figure 1. Scleroderma patient (66 years old) belonging to the group on therapy with iloprost and bosentan. In the upper part LASCA images for three follow-up years with relative perfusion measurements are displayed. A gradual improvement in both Fingertip and Periungueal region of interest is reported. In the lower part of the image, the capillaroscopic pictures of the same follow up years with the number of capillaries per mm, indicated by the arrows. A gradual rise in absolute capillary number/mm is observed from 2012 to 2014 (overall average rise in absolute capillary number from T0 to T4: 6.8 - 7.8/mm, $p=0.018$). The NVC images of present patient were always taken at the level of the third finger/right hand, according to the optimized methods reported in Reference 1. It is evident the increased density of capillaries in all the field behind the first row, as consequence of the intensive remodelling over the years (green bar placed by the software according to the validated methods Reference 1).



ILO-BOSE: Iloprost and bosentan therapy; F= Fingertip; P= Periungueal; PU= Perfusion Unit; NVC= Nailfold videocapillaroscopy.

References

1. Cutolo M, Herrick AL, Distler O, Becker M, Beltran E, Carpentier P, et al. Nailfold videocapillaroscopic and other clinical risk factors for digital ulcers in systemic sclerosis: a multicenter, prospective cohort study. *Arthritis Rheumatol* 2016 Apr 25 (E-pub ahead of print).