Bosentan effect on echocardiographic systolic pulmonary arterial pressure in systemic sclerosis-related pulmonary hypertension: a systematic review and metanalysis

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Abstract

Objective

Bosentan is a dual endothelin receptor antagonist approved for the treatment of SSc digital ulcers (DU) and pulmonary arterial hypertension (PAH). Systolic pulmonary arterial pressure (sPAP) is a relevant parameter for the follow-up and prognosis of SSc-PAH. The therapeutic magnitude of bosentan in SSc-PAH is not fully understood, thus we aim to establish the degree of sPAP reduction in bosentan treated SSc-PAH patients.

Methods

We performed a systematic literature review in three databases from January 2000 to June 2023, involving sPAP measurement at transthoracic echocardiography of SSc patients before and after starting bosentan. Following the study quality assessment and data extraction, we performed random-effects meta-analysis and Egger's test for publication bias. Stratified analysis was performed for mono-/combination therapy, follow up duration (≤1 year), indication for bosentan therapy (PAH or DU/mixed).

Results

In the 11 selected manuscripts, sPAP mean difference before and after bosentan therapy was -5.63mmHg (CI95% -9.79 to -1.48, p=0.0078). In stratified analysis, sPAP mean was significantly different before and after bosentan therapy only for studies considering <1 year of follow-up (p=0.0020), monotherapy (p=0.0140) and the strict indication for PAH (p=0.0002).

Conclusion

Bosentan significantly decreases sPAP, a relevant prognostic marker, especially in overt SSc-PAH. However, bosentan did not decrease sPAP when started for DU/mixed indication nor for follow-up>1 year. The burden of publication bias was significant. Therefore, further studies are required to assess bosentan's haemodynamic effect in high-risk patients for SSc-PAH.

Key words

bosentan, endothelin receptor antagonist, systemic sclerosis, pulmonary arterial hypertension, echocardiography

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Introduction

Systemic sclerosis (SSc) is a rare systemic autoimmune disease characterised by vasculopathy and fibrosis of different organs; in particular, 6.4 to 21% of SSc patients are affected by pulmonary arterial hypertension (PAH) (1, 2). According to recent data, PAH is a rare manifestation of SSc, with an estimated incidence of 18.2 cases per 1000 person-years, but it accounts significantly on the morbidity of SSc patients, together with interstitial lung disease (ILD) (2, 3). Recent studies, including EUSTAR data, have shown the strong effect of PAH in SSc-related mortality: ILD and PAH were the most common cause of death, accounting for about 16.8% and 14.7% of SSc-related deaths, respectively (3, 4). Furthermore, among deaths due to cardiovascular diseases in SSc patients, only 5-8% were related to atherosclerosis, suggesting that PAH-related severity and deaths could be underestimated, especially by non-SSc experts (3). PAH is often characterised by late onset non-specific symptoms, such as exertional dyspnoea, palpitations, and arrhythmias, and may be complicated by pulmonary embolism (4, 5). For these reasons, recent ESC/ERS guidelines and ACR/EULAR recommendations suggest yearly transthoracic echocardiography (TTE) screening for PAH in SSc patients to monitor the right heart function, including pulmonary arterial pressure (PAP) and tricuspid regurgitation velocity (TRV) (5, 6).

The new ESC/ERS guidelines suggest peak TRV as the best TTE parameter to assess the PAH risk, while for many years, systolic PAP (sPAP) was considered the key parameter for TTE PAH screening. For this reason, the majority of studies investigating PAH screening used sPAP as suitable parameter for this goal, including studies in SSc-PAH (5, 7, 8). Specifically, a recent study on a EUSTAR cohort showed that the tricuspid annular plane excursion (TAPSE)/sPAP ratio ≤0.32 mm/mmHg was a predictive risk factor for all-cause mortality in SSc at multivariate analysis (9). Finally, TAPSE/sPAP ratio <0.55 mm/mmHg is significantly and independently associated with PAH and is a potential predictive risk factor for PAH (10).

The gold standard for PAH diagnosis is mean PAP (mPAP) ≥20mmHg at right heart catheterisation (RHC), which is an invasive, time consuming and expensive technique (5). For this reason, both the DETECT-PAH and ASIG multiparametric algorithms have been developed to discriminate the best candidates for RHC in SSc patients at high risk of PAH (11-14). To improve the sensibility of both algorithms, some Authors recently suggested to add the TAPSE/sPAP ratio <0.55 mm/mmHg in the core set of both algorithms in order to better define the eligibility for RHC, thus underlying the clinical importance of sPAP in this context (9, 10).

According to the latest ACR/EULAR and ESC guidelines, dual endothelin receptor antagonists (ERA) are recommended as first-line treatment in SSc-PAH, in monotherapy or in combination with PhosphoDiEsterase 5 inhibitors (PDE5i), soluble guanylate cyclase stimulator(sGCS) riociguat, and/or prostanoids (6). This indication results from high-quality RCTs, including patients affected by different forms of connective tissue disease-related PAH (15). Furthermore, bosentan, a dual ERA, has been also approved for the healing and prevention of digital ulcers(DU) in SSc (6). At present, it is not still clear the potential role of ERA in preventing the progression of SSc-PAH and recent data, including different PAH forms, seems to confirm that bosentan may ameliorate exercise capacity, but no significant effect was reported in haemodynamic parameters, including sPAP (6, 16).

Since sPAP widely used in SSc-PAH clinical studies, our metanalysis was aimed at identifing the therapeutic magnitude on resting sPAP of bosentan, administered for any approved indications (DU and/or SSc-PAH), in SSc patients, to evaluate the possible haemodynamic effect of this drug in this specific setting.

Material and methods

Following the PICO strategy, we identified scientific manuscripts from January 2000 to June 2023, excluding congress abstracts and non-English written manuscripts, involving (Population) patients with SSc (ACR/EULAR 2013 criteria or ARA 1980 criteria); (Inter-

vention) treated with bosentan (mono- or combination therapy with SSc-PAH drugs). The Outcome of interest was mean sPAP reduction at TTE before and after bosentan treatment (Comparison). Studies comprising mixed connective tissue disorder (MCTD) and/or SSc-overlap syndrome-PAH were considered if at least >75% of involved participants in the study were SSc-PAH.

Three independent investigators performed systematic literature review (SLR) from three scientific databases (PubMed and EMBASE and Medline) for the following terms "Systemic Sclerosis" AND "Pulmonary Hypertension" AND "Bosentan". Following duplicate removal, the SLR yielded 31 records, of which 4 were excluded as written in non-English language, 4 were excluded as congress abstracts (Fig. 1). After a full assessment of 23 manuscripts, 11 manuscripts responded to the PICO strategy, and 12 manuscripts were excluded: 7 included patient population in which SSc-PAH was low represented (5 with CTD-PAH, 1 with SSc related-ILD and 1 with borderline SSc-PAH), 4 did not assess the primary outcome (3 studies measured mPAP at RHC and 1 study measured exercise sPAP) and 1 for missing data on the target population. Resting TTE measured sPAP mean values with standard deviation were collected from the 11 manuscripts (17-27). No study used contrast medium to enhance tricuspid regurgitation at TTE. Within the included studies, Funauchi *et al*. reported right ventricular pressure, which, in the lack of right ventricle outflow tract obstruction, is equal to sPAP; thus, this study was included in this metanalysis (28).

Manuscripts were qualitatively analysed (Table I) to perform subgroup analysis according to: i. bosentan monotherapy *vs*. combo therapy with other PAH drugs; ii. follow-up duration ≤ 1 year *vs*. >1 year; and iii. indication for treatment (PAH *vs*. DU/mixed). The heterogeneity, variability, influence analyses were performed for each metanalysis (Supplementary file). In all metanalysis involving 10 or more studies, publication bias has been evaluated by funnel plot and Egger's test for funnel plot asymmetry (Fig. 2).

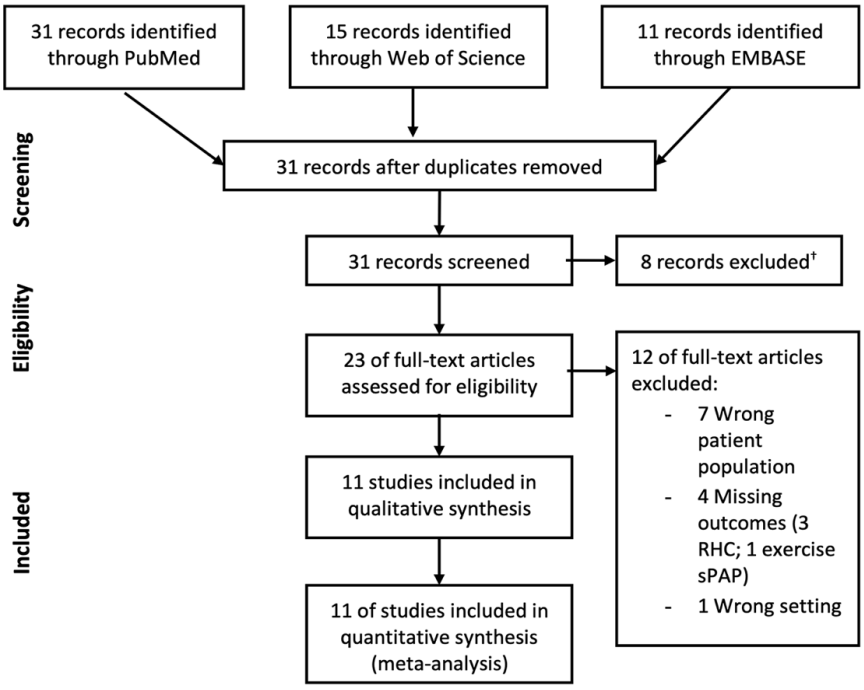

Fig. 1. Flow diagram for the systematic literature review.
†4 records excluded as congress abstracts and 4 records excluded as written in non-English language.

Quality assessment has been performed for all the studies included in the metanalysis. For observational studies (10/11), the Agency for Healthcare Research and Quality (AHRQ) checklist has been performed (Supplementary Table S1). For Phat *et al*. the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2) has been performed (Suppl. Table S2).

Results

Bosentan effect on resting sPAP at TTE

In the 11 analysed manuscripts (Table I), bosentan treatment in SSc-PAH reduced significantly resting sPAP: -5.63mmHg (CI95% -9.79 to -1.48, p=0.0078; I^2 = 93.0 %, tau^2 = 35.2858, SE = 21.0939, Q test p<0.0001) (Fig. 2). These results showed substantial heterogeneity. Testing funnel plot asymmetry via Egger's test showed significant publication bias: t = 0.3345, p=0.7457 (Fig. 2). In the influence analysis, the effect of bosentan on sPAP was significant, independently from the excluded study (Suppl. Table S3).

Subgroup analysis: follow up ≤1 year and >1 year

Five studies had a follow up ≤1 year, showing mean sPAP reduction –9.19mmHg (CI95% -15.01 to -3.36, Fig. 3). Besides being significant (p=0.0020), this patient subgroup showed a larger mean sPAP reduction when compared with the whole group of patients, regardless of length of follow up. Substantial heterogeneity has been demonstrated according to I^2 = 89.2 %, tau^2 = 28.6105 (SE = 30.0496), Q test p<0.0001.

In the six studies with a follow up >1 year, sPAP reduction was not significant: -2.74 mmHg (CI95% -7.65 to 2.17, p=0.2743; Fig. 3). As for studies with short-term follow-up, significant heterogeneity was present: I^2= 87.7%, tau^2 = 26.5406 (SE = 23.1517), Q test p<0.0001.

Subgroup analysis: bosentan monotherapy vs. combo therapy for PAH

Studies were divided according to the concomitant use of other anti-PAH drugs. 6 out of 11 studies evaluated the mean sPAP reduction in patients on bosentan monotherapy, showing a significant effect: -4.34 mmHg (CI95% -7.81 to -0.88, p=0.0140). In patients on combination therapy with other PAH drugs (either prostanoids, calcium channel blockers, sGCS, or PDE5i), the

Table I. Main characteristics of the studies resulting from SLR and included in the metanalysis.

Author, year	Journal	Country	Type of study	Quality assessment	Indication for bosentan therapy	Bosentan Therapy for PH	PAH diagnosis	Interval of observation (months)	n. of patients on bosentan therapy	Limited cutaneous SSc	mean sPAP before treatment mmHg (SD)	mean sPAP after treatment mmHg (SD)
Castellvì *et al*. 2020	PLoS One	Spain	Case-control study (R)		SSc-digital ulcers	Combination therapy	sPAP> 40 mmHg	34	59	138 (62%)	30.5 (5.3)	34.4 (18.8)
Phat *et al*. 2022	Asian Pac J Allergy Immunol	Vietnam	RCT (P)		SSc-PH	Mono-therapy	sPAP >35mmHg	4	45	15 (33%)	40.8 (39,0; 42,5)	Mean difference: 4.1 (3.8)
Trombetta e*t al*. 2016	J Rheumatol	Italy	Open label observational study (P)		Both SSc-PAH and SSc-digital ulcers	Combination therapy	RHC	48	15	7 (47%)	34.6 (9)	34.5 (7.1)
Murdaca *et al*. 2016	J Int Med Res	Italy	Longitudinal observational study (P)	5	SSc- digital ulcers	Monotherapy	RHC	144	25	18 (72%)	33.6 (2.9)	26.2 (1.78)
Ahmadi Simab et al, 2006	Eur J Clin Invest	Germany	Open label observational study (P)	5	SSc-PAH	Monotherapy	RHC	6	7	1 (12.5%)	56.4 (24.7)	Mean difference: –15.0 (20.3)
Rotondo *et al*. 2017	Int J Rheum Dis	Italy	Observational Study (P)		SSc-PAH	Monotherapy	RHC	24	16	21 (100%)	53 (19)	47 (16)
Hamaguchi *et al*. 2009	J Dermatol Sci	Japan	Observational Study (P)		SSc-PAH	Combination therapy	sPAP >35mmHg	6	10	7 (10%)	49 (18)	37 (15)
Giordano *et al*. 2010	Int J Immunopathol Pharmacol	Italy	Open label observational study (R)		SSc-PAH	Combination therapy	sPAP >35mmHg	11	14	10 (71%)	50.07 (3.5)	34.92 (2.3)
Romaniello *et al*. 2014	Rheumatology (Oxford)	Italy	Observational Study (R)	SSc-DU	Monotherapy	RHC	41	54	26 (48%)	29 (6.3)	30 (7.9)	
Giannelli *et al*. 2006	Eur J Clin Invest	Italy	Observational Study (P)		Both SSc-PAH and SSc-ulcers	Monotherapy	sPAP >30 mmHg	12	8	32 (91%)	40.0 (8.0)	35.0 (4.9)
Funauchi *et al*. 2 009	Rheumatol Int	Japan	Observational study (P)		13/15 SSc-PAH + 2/15 MCTD-PH	Combination therapy	sPAP >35mmHg	24	12	6 (40%)	RVP = 51.3(22.9)	RVP = 34.7 (8.1)

SLR: systematic literature review; PAH: pulmonary arterial hypertension; sPAP: systolic pulmonary artery pressure; P: prospective; R: retrospective; DU: digital ulcers; RVP: right ventricle pressure.
RVP can be considered equal to sPAP in the absence of right ventricle outflow tract obstruction (28).

sPAP reduction was surprisingly not significant: -7.15mmHg (CI95% -15.80 to 1.51, p=0.1058). Heterogeneity was reported: I^2 =84.68%, tau^2 11.2303 (SE=10.9635), and Q test p<0.0001 for monotherapy; and I^2 =90.6%, tau^2 =78.2148 (SE = 68.5469) and Q test p<0.0001 for combination therapy. Finally, a significant sPAP decrease with combination therapy was detected at influence analysis by excluding the manuscript from Castellví *et al*. (-10.33 mmHg CI95% -18,81 to -1,85; p=0.017, Suppl. Table S4).

Subgroup analysis: indication for bosentan treatment

Studies were divided according to the indication for bosentan therapy: only PAH and mixed indication (DU with/without PAH). When assessing studies with only PAH indication for bosentan therapy, the six identified studies showed the largest significant mean sPAP reduction: -10.52mmHg (CI95% -16.14 to -4.91, p=0.0002) (Fig. 4). This positive effect was also confirmed at the influence analysis, with sPAP reduction being significant in all cases (Suppl. Table S5). At the same time, when assessing studies with mixed indication, the reduction sPAP was not significant (-1.66 mmHg, CI95% -15.80 to 1.51, p=0.4510; Fig. 4). For this subgroup metanalyses, heterogeneity was significant as evidenced by I^2 = 85.3%, tau^2 = 26.6954 (SE = 29.7111) and Q test p=<0.0001 for indication PAH and I2=87.1%, tau2 19.1253 (SE = 17.0453) and Q test p=<0.0001 for mixed indication.

Discussion

In this paper we analysed the possible efficacy of bosentan in decreasing resting sPAP at TTE in SSc patients, who started therapy for DU and/or concomitant PAH. Although bosentan is considered a mainstay treatment in SSc-related DU, as documented by RCTs, its effect on sPAP is still largely unknown (29). This is an understudied argument as evidenced by the significant publication bias and chronological gap of the SLR selected studies, which are mostly published more than 7 years ago. So far, sPAP has been considered a relevant parameter for PAH follow-up and thus included in different composite scores (*e.g*. TAPSE/sPAP) aimed to predict mortality in PAH patients, including SSc-PAH and SSc-ILD (30-

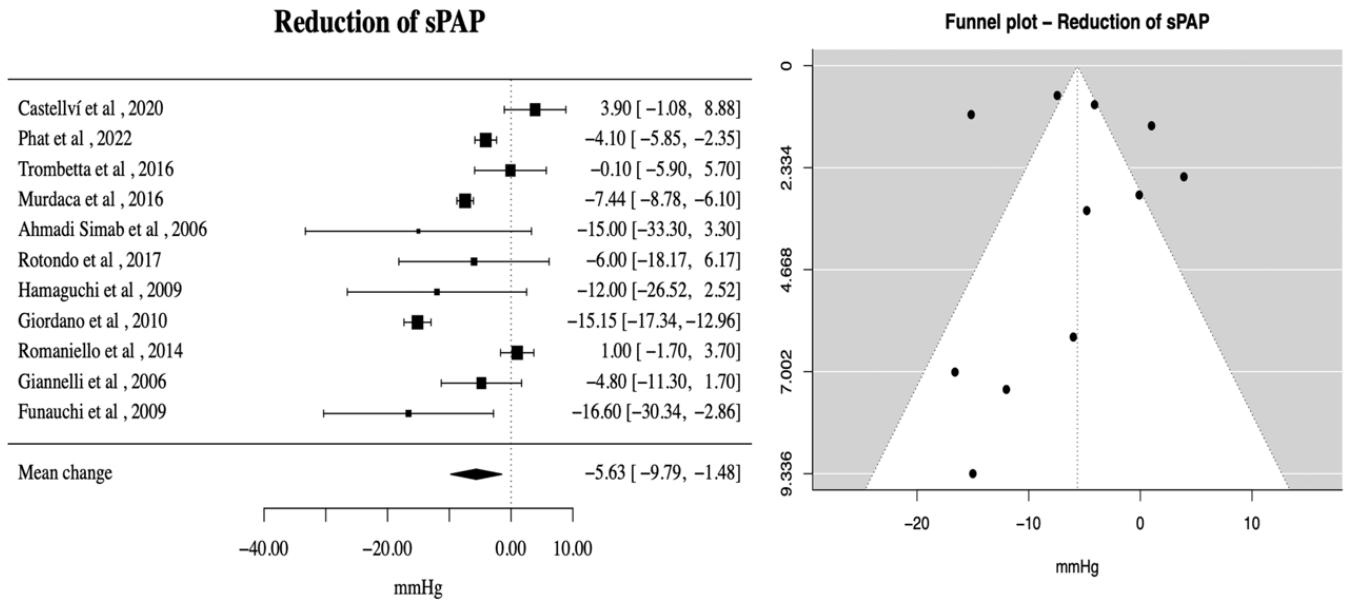

Fig. 2. Forrest Plot for sPAP mean change at TTE. Funnel plot for publication bias (Egger's test for funnel plot asymmetry has been performed - Supplementary material 1).

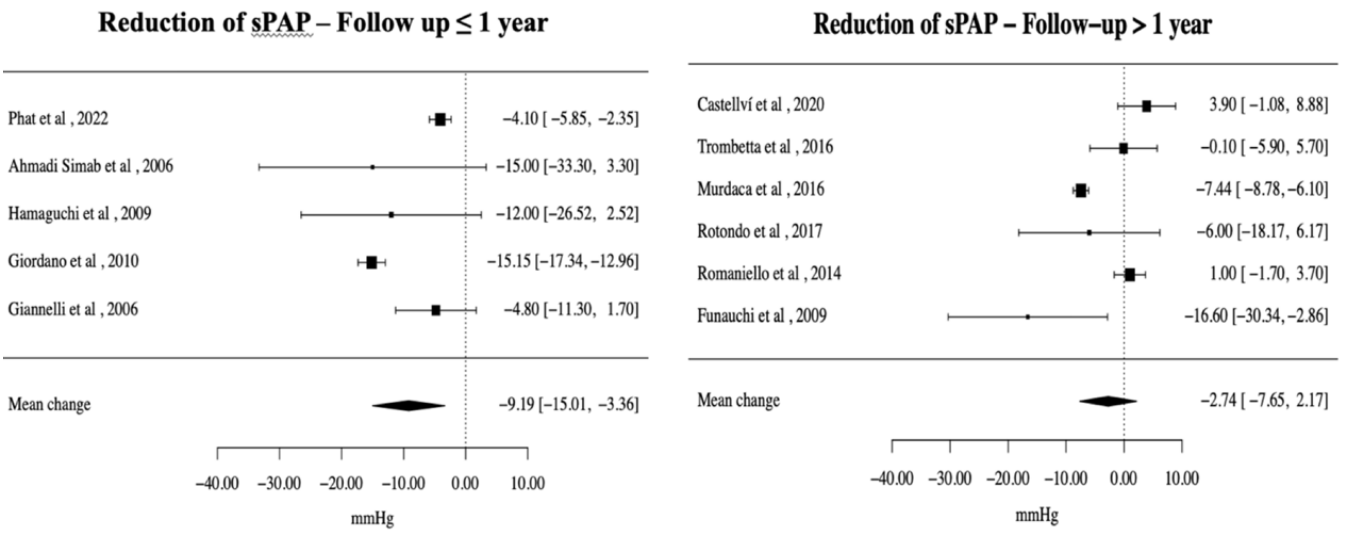

Fig. 3. Forrest plot for sPAP mean change for follow up ≤1 year and follow up >1 year.

33). More recently, peak TRV has been suggested as a better TTE parameter for the screening of patients at risk for PAH, but the majority of available results derive from previous studies designed using sPAP and, therefore, sPAP was selected for our SLR (5).

PAH RCTs showed the inefficacy of bosentan, given as monotherapy and in combination with intravenous epoprostenol, in significantly reducing mPAP (15, 34, 35). In this context, a metanalysis, collecting data from different PAH studies, showed the improvement of both WHO functional class and exercise capacity following an intraclass switch, from bosentan to macitentan, but these effects were not associated with a modification of haemodynamic and/or echocardiographic parameters (36). Although belonging to the same family, bosentan seems to have a worse pharmacodynamics and pharmacokinetics when compared to macitentan, the latter showing higher receptor affinity, higher inhibitory potency on the endothelin receptors as well as a better tissue penetration (37, 38). Additionally, bosentan has a shorter half-life, requiring a b.i.d. administration, and it has been shown to alter the blood concentration of PDE5i, thus affecting the efficacy of PAH combination therapy (39, 40). Regarding the efficacy of macitentan, on the one hand it was not able to prevent SSc-DU formation as evidenced by the DUAL-1 and DUAL-2 RCTs; on the other hand macitentan showed *in vitro* the capacity to interfere with different key pathogenic mechanisms of SSc, including fibroblast-mediated fibrosis and endothelial-to-mesenchymal transition (41-44). Further studies comparing the efficacy of bosentan versus macitentan are needed to determine the best therapeutic strategy in SSc-PAH, as macitentan seems to be more effective in PAH treatment (41, 45, 46).

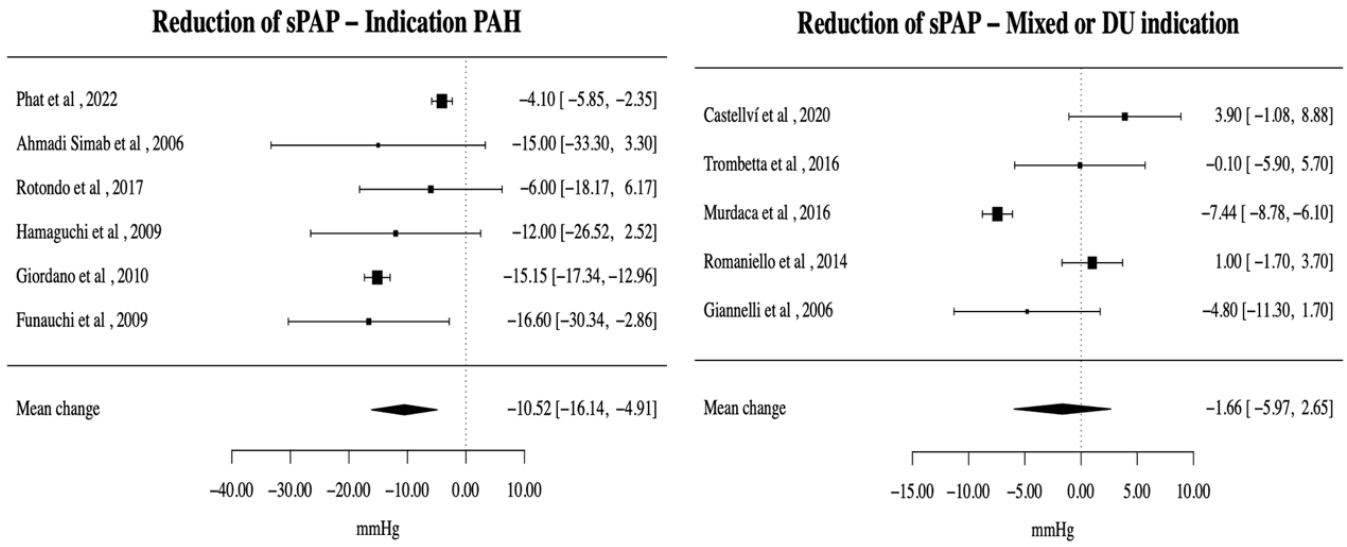

Fig. 4. Digital ulcers (DU) indication for bosentan treatment.

It must be pointed out that in PAH RCTs involving bosentan, the SSc-PAH cohort represented the minority of the enrolled patients; thus, making it difficult to derive robust data from the SSc-PAH population. The data obtained from our metanalysis suggest that bosentan may be able to decrease sPAP in patients with SSc-PAH; on the contrary, the metanalytic data did not show any effect on sPAP when bosentan was started for DU in patients without associated PAH. In this setting we may speculate that the lack of haemodynamic modification observed in these patients may be due to the absence of a specific endothelin-1 hyperactivation in the lung vessels of these patient (47). We are aware that our results partially conflict with the recent PAH therapy guidelines, recommending the combination of ERA plus PDE5i and/or endovenous prostanoids for the treatment of these patients (5, 6, 48). Several reasons may explain these data: firstly, by influence analysis, when excluding the study by Castellví *et al*. enrolling SSc patients with DU and no PAH, combination therapy reached significant sPAP decrease (p=0.0170) (17); secondly, the limited number of papers, responding to our PICO strategy, associated with the low number of enrolled SSc-PAH patients and limited time of follow up, may underestimate the efficacy of combination therapy.

Although the data obtained in our work derive from the analysis of the literature and not from a prospective study, bosentan seems to be effective in decreasing sPAP in SSc-PAH and this pulmonary pressure reduction might be associated with an improvement of patients' prognosis, as suggested in available literature (9). Specifically, our data show that bosentan was able to give a significant decrease sPAP in those studies in which the patient follow up was less than one year, but this decrease was not observed in studies with a longer follow up. This finding may be related to: i. most studies with follow up >1 year included SSc-DUs patients without SSc-PAH; ii. the significant paucity of data and chronologic gap between our recent analysis and most studies in this SLR, which were published several years ago without any further data on follow up.

Conflicting results are reported in the available literature and a recent metanalysis did not show any improvement in the haemodynamic parameters, including PAP, in SSc-PAH patients treated with bosentan (16). It must be pointed out that the PICO strategy of the aforementioned study combined different forms of PAH and different methods of PAP measurement (16). On the contrary, we strictly selected studies only including SSc patients, whose TTE resting sPAP was reported, thus allowing us to obtain more homogeneous data, despite the limited number of studies.

A limit of our study is the selection of TTE resting sPAP and not the gold standard RHC mPAP as parameter of study, although TTE sPAP was the most applied method of follow up in our SLR (11 *vs*. 3 studies). A recent study showed that sPAP is an efficient tool for PAH screening, comparable to other parameters such as TRV (49). Accordingly, different authors have recently proposed multiparametric algorithms derived from resting and exercise TTE to evaluate cardiopulmonary haemodynamic with comparable results with RHC (50, 51). In detail, a recently proposed TTE diagnostic algorithm, including TTE sPAP and diastolic PAP (dPAP), resulted accurate in PAH diagnosis (51). In fact, sPAP has been successfully used to assess treatment efficacy in PAH patients treated with tadalafil (52). Finally, it must be taken into account that sPAP values are estimated values, thus operator dependent, and may be affected by age and body mass index; in our analysis this factors could not be taken into consideration due to the lack of specific data (53, 54). No robust data support the role of bosentan as preventive strategy against the development of SSc-PAH. In our metanalysis, bosentan used for DU did not significantly modify sPAP in patient without SSc-PAH. In this context, large clinical trials to explore a possible preventive role of bosentan on the development of SSc-PAH in patients enriched for risk factors, defined by clinical biomarkers (*e.g*. presence of DU, ACA +ive, U1-RNP +ive, U3RNP +ive

autoantibodies), are still lacking (18, 25). Furthermore, the AMBITION and TRITON trials, establishing the efficacy of macitentan + tadalafil, enrolled PAH patients (including CTD-PAH) responding to the previous classification of PAH, reporting mPAP ³25mmHg and Pulmonary Vascular Resistance (PVR) >3 WU (45, 46). The 2022 modification of RHC cut-off values for PAH diagnosis, now defined as mPAP >20 mmHg and PVR >2 WU, has generated a grey zone of PAH patients with mPAP ranging from 20 mmHg to 25 mmHg, on which limited evidence of any pharmaceutical intervention is available (5).

Although our metanalysis may be affected by some well-known biases, including low number of articles and strong heterogeneity, it underlines the need for more extensive real-life TTE data of SSc-PAH treated with bosentan. Furthermore, specific patient populations, as those having an mPAP ranging between 20 and 25mmHg, which were not included in previous PAH-RCTs, should be considered in the future as one of the most important target populations for future studies designed to define the effective role and best timing of bosentan therapy in preventing PAH progression.

Despite the low number of papers included in this metanalysis, our findings parallel the recommendation from ESC/ERS and ACR/EULAR regarding the use of ERA as first-line agent in SSc-PAH. As evidenced by epidemiological studies, SSc-PAH is a significant cause of morbidity and mortality in SSc patients, and efforts must be oriented to define the best timing to start an effective treatment and ameliorate the patients' outcome.

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