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1 **VASODILATORS AND LOW DOSE ACETYLSALICYLIC ACID ARE ASSOCIATED**
2 **WITH A LOWER INCIDENCE OF DISTINCT PRIMARY MYOCARDIAL DISEASE**
3 **MANIFESTATIONS IN SYSTEMIC SCLEROSIS: Results of the DeSSciper inception**
4 **cohort study**

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1 **ABSTRACT**

2 **Objectives**

3 To investigate the influence of vasodilator drugs on the occurrence of features depending
4 on myocardial ischemia/fibrosis

5 (ventricular arrhythmias, Q waves, cardiac blocks, pacemaker implantation, left ventricular
6 ejection fraction -LVEF-<55% and/or congestive heart failure and sudden cardiac death) in
7 Systemic Sclerosis (SSc).

8 **Methods**

9 Six hundred and 1 SSc patients were enrolled from December 1st, 2012 to November 30th,
10 2015 and had a second visit 0.5-4 years apart. 153 received no vasodilators; 448 received
11 vasodilator therapy, (i.e. Calcium Channel Blockers and/or Angiotensin Converting
12 Enzyme inhibitors or Angiotensin II receptor blockers or combinations of them), 89 of them
13 being also treated with either endothelin receptor antagonists or PDE5 inhibitors or
14 prostanoids. Associations between the occurrence of myocardial disease manifestations
15 and any demographic, disease and therapeutic aspect were investigated by Cox
16 regression analysis. A Cox frailty survival model with centre of enrollment as a random
17 effect was performed.

18 **Results**

19 During 914 patient/follow-up years, 12 ventricular arrhythmias, 5 Q waves, 40 cardiac
20 blocks, 6 pacemaker implantations, 19 reduced LVEF and/or CHF occurred. In multivariate
21 Cox regression analysis, vasodilator therapy was associated with a lower incidence of
22 ventricular arrhythmias ($p=0.03$); low dose acetylsalicylic acid (ASA) with a lower
23 incidence of cardiac blocks and/or Q waves and/or pacemaker implantation ($p=0.02$),
24 active disease with a higher incidence of LVEF<55% and/or CHF and cardiac blocks
25 and/or Q waves and/or pacemaker implantation ($p=0.05$).

26 **Conclusions**

27 The present study might suggest a preventative effect on the occurrence of distinct
28 myocardial manifestations by vasodilator therapy and low dose ASA.

29

30 **Keywords:** primary myocardial disease in scleroderma, preventative role of vasodilator
31 therapy.

1 INTRODUCTION

2 Myocardial disease occurring in patients with Systemic Sclerosis (SSc) is classically
3 subdivided into primary and secondary, depending the absence or, respectively,
4 coexistence of pulmonary and/or renal involvement.[1-3]

5 Primary myocardial disease is morphologically characterized by vasculopathy of small
6 arteries and biventricular patchy myocardial fibrosis which presents a strong association
7 with contraction band necrosis, suggesting the implication of ischemia-reperfusion events
8 i.e. a myocardial Raynaud's phenomenon (RP).[4] In this regard, short term trials and
9 retrospective observational studies have underlined a beneficial effect of calcium channel
10 blockers (CCB), angiotensin converting enzyme inhibitors (ACEinh) on cardiac
11 vascularization and function.[5-11]

12 By now, the role of vasodilator agents in the prevention of primary myocardial disease in
13 SSc has not yet been clarified. In order to define the management of SSc, a project named
14 DeSScIPHER (To decipher the optimal treatment of SSc) was submitted to and funded by
15 the European Community (FP7- HEALTH n°305495). Here, we report the results of the
16 subproject devoted to investigate the influence of vasodilator drugs on the occurrence of
17 primary myocardial complications, specifically those associated with a poor prognosis i.e.
18 ventricular arrhythmias, Q waves , cardiac blocks , pacemaker implantation , reduced left
19 ventricular ejection fraction (LVEF), congestive heart failure (CHF) and sudden cardiac
20 death.[1-3,12-14]

21

22 METHODS

23 Patients and study design

24 Patients fulfilling the ACR/EULAR criteria for SSc,[15] consecutively admitted to 20
25 DeSScIPHER-EUSTAR centres from December 1st, 2012 to November 30th, 2015, were
26 enrolled, according to local ethical requirements.

27 Patients with the following characteristics were excluded: significant pulmonary
28 parenchymal (forced vital capacity and/or diffusing lung capacity for CO < 70%) or
29 vascular involvement (estimated systolic pulmonary arterial pressure > 40 mmHg),
30 intestinal involvement (malabsorption syndrome or paralytic ileus or renal involvement
31 (serum creatinine level >1.2 mg/dl and/or dialysis or previous scleroderma renal crisis) or

1 any sign/symptom/ electrocardiographic (ECG) finding of myocardial disease, basal
2 pulmonary rales and/or leg edema indicative of congestive heart failure.

3 Patients enrolled in the study were investigated according to the DeSSciper protocol,
4 shared by all participating centres. In particular, they were assessed for the items listed in
5 the European Scleroderma Trials and Research group (EUSTAR) protocol,[16] including
6 European Scleroderma Study Group (EScSG) activity criteria.[17] Moreover, as far as
7 myocardial disease is concerned, each patient was examined at baseline by means of
8 medical history, clinical examination, ECG, Holter ECG and B-mode echocardiography at
9 baseline, and was reassessed every 3 months with respect to medical history, clinical
10 examination, and ECG, and every 6 months by Holter ECG and B-mode echocardiography
11 until the end of each follow-up-year. According to local policies, patients had to undergo
12 either standard vasodilator therapy i.e. CCB such as nifedipine up to 60 mg/qd or
13 comparable doses of other drugs of the same class and/or ACEinh such as captopril up to
14 100 mg/qd, or no vasodilator therapy. Two hundred and 50 patients per arm had to be
15 enrolled. Despite the strictly defined entry criteria, 2 major protocol deviations occurred. As
16 far as treatment is concerned, some patients with baseline myocardial disease were
17 enrolled. As far as treatment is concerned, 63 patients undergoing AgIIrb±CCB treatment
18 were enrolled. Because of the influence on the same pathophysiologic pathway, they were
19 considered in the same class of ACEinh and included in the arm of those treated with CCB
20 and/or ACEinh, with the whole group being referred to as standard vasodilator therapy.
21 Moreover, some patients treated with targeted vasodilator drugs (i.e. prostanoids or
22 endothelin receptor antagonists or phosphodiesterase type 5 inhibitors), were enrolled.
23 Out of them, those undergoing standard vasodilator therapy were included in the same
24 arm which was referred to as vasodilator therapy; those treated with targeted vasodilator
25 drugs only were excluded because of the intermittent drug regimen in most of them. The
26 role of other features potentially influencing the occurrence of cardiac disease during
27 follow-up was also investigated i.e. diffuse subset, disease activity, digital ulcers,
28 traditional risk factors such as sex, cigarette smoking, systemic arterial hypertension,
29 hypercholesterolemia and drugs including ongoing corticosteroids ± immunosuppressive
30 therapy and low dose acetylsalicylic acid (ASA) (≤ 325 mg daily).[1-3,18-21]

31 **Follow-up and outcome measures**

32 The new occurrence of ventricular arrhythmias as manifestations indicative of myocardial
33 ischemia, that of Q waves and/or cardiac blocks and/or pacemaker implantation as

1 manifestations indicative of myocardial fibrosis or a therapeutic intervention promoted by it,
2 and that of LVEF<55% and/or CHF, as manifestations of evolved disease, were
3 investigated.[1-4]

4 Finally, the incidence of withdrawal from treatment was used as safety endpoint.

5 **Statistical analysis**

6 StataMP 13, IBM SPSS 24.0 and MedCalc 11.3 for Windows software were used for
7 statistical analyses. Continuous data were expressed as means and standard deviations
8 (SD) and compared by t student test. The predictivity of myocardial disease occurrence by
9 each distinct feature was assessed by Cox proportional hazard regression models. The
10 number of covariates to be included in the multivariate model was defined by using a ratio
11 of cases per covariate in the size of 10.[24] Moreover, in order to address the potential
12 influence of different therapeutic strategies by clinician from different centres, we carried
13 out a Cox frailty survival model with centre of enrollment as random effect.[25] Statistical
14 significance was set at $P < 0.05$.

15

16 **RESULTS**

17 **Patients**

18 From December 1st, 2012 to November 30th, 2015, a total of 654 SSc patients, with a
19 mean age of 56 ± 13 years a disease duration from the first non-RP manifestation ranging
20 from 0.5 to 61 years (mean 10 ± 9 SD), were enrolled in the study and followed-up for at
21 least six months.

22 One hundred and 53 patients did not undergo any vasodilator; 448 were prescribed
23 vasodilators including 89 treated with either prostanoids and/or endothelin receptor
24 antagonists and/or phosphodiesterase inhibitors. The 43 patients treated only with
25 targeted vasodilators were excluded.

26 Table 1 shows the demographic, clinical, serological and therapeutic features as assessed
27 at enrollment and during follow-up as far as the drug regimen is concerned, in the
28 remaining 601 patients subdivided according to the therapeutic subgroup. Given the
29 presence of missed items, the prevalence of each feature has been calculated among
30 patients in whom it had been underlined. Hypercholesterolemia was noticed in few
31 patients; no data were available for statin use.

1 With respect to patients undergoing no vasodilators, those treated with vasodilator therapy
 2 resulted to be more frequently aged ≥ 50 years ($p=0.005$), affected by systemic arterial
 3 hypertension ($p<0.001$) and to be undergoing in a greater percentage corticosteroids
 4 \pm immunosuppressors ($p<0.001$) and low dose ASA ($p<0.001$) i.e. they presented a
 5 greater prevalence of disease features potentially associated with a worse cardiovascular
 6 outcome.

7

8

9 **Table 1. Demographic, clinical, serological and therapeutic features of the 601**
 10 **SSc patients subdivided according to the treatment subgroup**

FEATURES	No vasodilators (n=153)	Vasodilator therapy (n=448)	P
Female Sex	134/153 (87%)	395/448 (88%)	0.88
Age (mean \pm SD) years	55 \pm 14	57 \pm 13	0.21
Age ≥ 50 years	95/153 (62%)	332/448 (74%)	0.005
Early disease	53/145 (36%)	148/428 (35%)	0.69
<u>Clinical subset</u>			
Limited cutaneous	124 (81%)	348 (78%)	0.42
Diffuse cutaneous	29 (19%)	100 (22%)	0.42
<u>Serological subset</u>			
Antinuclear antibodies (ANA) positive	134/137 (98%)	400/410 (98%)	0.99
Anti-centromere (ACA) positive	64/137 (47%)	163/410 (42%)	0.16
Anti-Scl-70 positive	39/130 (30%)	136/388 (35%)	0.33
<u>Further aspects</u>			
Baseline Myocardial Disease	18/123 (15%)	56/353 (16%)	0.27
Digital ulcers (ever)	50/149 (33%)	168/437 (38%)	0.33
Tendon friction rubs	7/148 (5%)	20/432 (5%)	0.99
Arthritis	18/153 (12%)	52/442 (12%)	0.99
EScSG activity index ≥ 3	13/153 (8%)	41/448 (9%)	0.87
Systemic arterial	0/153	139/448 (31%)	<0.001

Hypertension			
Cigarette smoking ever	39/127 (31%)	88/350 (25%)	0.24
Hypercholesterolemia	0/7	0/23	-
Ongoing corticosteroids ± immunosuppressors	44/145 (30%)	215/408 (53%)	<0.001
Ongoing low dose acetylsalicylic acid	28/146 (19%)	205/377 (54%)	<0.001

1

2 Occurrence of myocardial disease features during follow-up

3 During 914 follow-up patient/years, ventricular arrhythmias developed in 12 patients; Q
4 waves developed in 5, cardiac blocks in 40, a Pacemaker was implanted in 6; 15
5 developed a LVEF<55% and/or a CHF. No patient underwent a sudden cardiac death.
6 In univariate analysis, vasodilator therapy resulted to be associated with a nearly
7 significant occurrence of ventricular arrhythmias (7/285 events (2%) occurring during 709
8 patient/years as compared to 5/97 (5%) during 206 patient/years in those not treated with
9 any vasodilator) (HR 0.33 95%CI 0.10-104; p=0.060); low dose ASA with a reduced
10 incidence of Q waves and/or cardiac blocks and/or pacemaker implantation (17/161 events
11 (10%) occurring during 434 patient/years as compared to 29/182 (16%) during 383
12 patient/years in those not treated with ASA) (HR 0.41 95%CI 1.98-16.56; p=0.004). On the
13 contrary, male sex (HR 5.73; 95%CI 1.98-16.56; p=0.002) and a EScSG activity index ≥ 3
14 at the enrollment into the study (HR=4.83; 95%CI 1.52-15.34;p=0.008) were found to
15 predict the development of a LVEF<55% and/or CHF.

16 In order to perform the multivariate Cox regression analysis, five covariates were selected
17 because of their potential value in influencing the occurrence of cardiac events over time.
18 Several tentatives were performed by selecting, according to the number of the events
19 occurred, all the 5 covariates were considered for cardiac blocks and/or Q waves and/or
20 pacemaker implantation; 2 covariates for ventricular arrhythmias; 2 covariates for
21 LVEF<55% and or CHF. Table 2 shows the results of this approach: vasodilator therapy
22 resulted to be associated with a lower incidence of ventricular arrhythmias (HR 0.28; 95%
23 CI 0.09-0.90; p=0.03); low dose ASA with a lower incidence of cardiac blocks and/or Q
24 waves and/or pacemaker implantation (HR 0.46; 95% CI 0.24-0.87; p=0.02) ; a EScSG
25 activity index≥3 with a higher occurrence of a LVEF<55% and/or CHF (HR 3.71; 95% CI
26 1.02-13.42;p= 0.05) and cardiac blocks and/or Q waves and/or pacemaker implantation

1 (HR 2.15; 95% CI 1.00-4.63; p=0.05). Moreover, an unfavourable role of male sex
 2 emerged.

3 Finally, since therapeutic strategies can differ among distinct centres, a Cox frailty survival
 4 model with center of enrollment as random effect, was performed (Table 3). The
 5 associations of vasodilators, low dose ASA and an EScSG activity index \geq 3 were
 6 confirmed.

7

8 **Table 2. Associations detected for each outcome measure by multivariate Cox**
 9 **regression analysis**

COVARIATES	Cardiac Blocks and/or Q waves and/or Pacemaker Implantation n.events=49*	Ventricular Arrhythmias n. events=12	LVEF\leq 55% and/or CHF n.events=19
	HR; 95%CI; p	HR: 95%CI; p	HR: 95%CI; p
Male sex		-	5.70; 2.20-18.9; <0.001
Age\geq50			-
EScSG activity index \geq3	2.15; 1.00-4.63; 0.05	-	3.71; 1.02-13.42; 0.05
Low dose ASA	0.46; 0.24-0.87; 0.02	-	
Vasodilators		0.28; 0.09-0.90; 0.03	-

10 *Two patients developed 2 events (1 Cardiac Block and Pacemaker Implantation; 1
 11 Cardiac Block and/or Q wave)
 12 -----

13

14 **Table 3. Associations detected for each outcome measure by Cox frailty**
 15 **analysis**

COVARIATES	Cardiac Blocks and/or Q waves and/or Pacemaker Implantation n.events=49*	Ventricular Arrhythmias n. events=12	LVEF\leq 50% and/or CHF n.events=19
	HR; 95%CI; p	HR; 95%CI; p	HR; 95%CI; p

EScSG activity index ≥ 3	2.12; 0.98-4.57; 0.06	-	3.79; 1.04-13.82; 0.04
Low dose ASA	0.53; 0.26-1.08; 0.08	-	-
Vasodilators	-	0.32; 0.10-1.02; 0.05	-

* **Two patients developed 2 events (1 Cardiac Block and Pacemaker Implantation; 1 Cardiac Block and/or Q wave)**

Withdrawal from vasodilator therapy and low dose ASA

Ninety-three out of the 448 patients undergoing vasodilator therapy withdrew from treatment: 15 treated with CCB alone, 3 treated with ACEi or AngIIrb alone, none with CCB + ACEi or AngIIrb reaching an incidence of 2.1/100 patient-years; 31 treated with endothelin receptor antagonists, 19 treated with phosphodiesterase type 5 inhibitors and 25 treated with prostanoids reaching an incidence of 32/100 patient-years. Moreover, 16 of the 230 patients undergoing ASA withdrew from treatment reaching an incidence rate of 3/100 patient-years.

DISCUSSION

To the best of our knowledge, this is the first observational, prospective, long term study to investigate the association between vasodilator therapy and the occurrence of disease manifestations probably or potentially related to myocardial ischemia (ventricular arrhythmias), fibrosis (Q waves and/or cardiac blocks and/or pacemaker implantation) or both (reduced LVEF, congestive heart failure and sudden cardiac death). Actually, as far as the influence of vasodilator therapy on myocardial disease is concerned, Kazzam et al.[27] only investigated diastolic and systolic function in 22 SSc patients receiving captopril treatment (1.3 mg/ kg/ daily) for 11-15 months. These authors found an increase in LVEF and a decrease in isovolumic relaxation time, indicating an improved left ventricular filling, but did not consider any of the features assessed in our study.

In order to address the aim of the study, we also investigated the association between the occurrence of the investigated manifestations and demographic, disease and different therapeutic aspects potentially involved in SSc cardiac disease.[1-3,18-23] After excluding any bias deriving from potential differences in the treatment policies among the distinct centres involved in the study, vasodilators were found to be associated with a lower

1 incidence of ventricular arrhythmias, low dose ASA with a nearly significant, lower
2 incidence of cardiac blocks and/or Q waves and/or pacemaker implantation; active
3 disease, as defined by a EScSG activity index ≥ 3 at enrollment with a higher incidence of
4 a reduced LVEF and/or CHF.

5 We underwent our prospective study because of the commonly shared opinion on the
6 implication of ischemia/reperfusion events in the induction of myocardial fibrosis in SSc,[1-
7 4] as well as the evidence emerged by short term trials and retrospective observational
8 studies suggesting a beneficial effect of vasodilators on cardiac vascularization and
9 function in the disease.[5-11] We could not confirm the retrospectively detected
10 association between vasodilators use and a preserved LVEF,[10] neither we detected any
11 association between vasodilators and a reduced incidence of cardiac blocks and/or Q
12 waves and/or pacemaker implantation, which are distinct manifestations of myocardial
13 fibrosis or of a therapeutic intervention promoted by its consequences.[12] Nevertheless,
14 we pointed out an association between vasodilators and a lower incidence of ventricular
15 arrhythmias, which likely depend on ischemic processes.[13,14] This result deserves to be
16 underlined since ventricular arrhythmias have long been known to be associated with a
17 poor prognosis in SSc.[13-14,21]

18 Investigating different aspects potentially associated with the incidence of cardiac events,
19 we happened to point out an unexpected protective role of low dose ASA and an
20 unfavourable prognostic role of the EScSG activity index.

21 Low dose ASA is currently prescribed to patients with a high risk of coronary artery
22 disease.[23] Moreover, it has been recently reported to be associated with a decrease in
23 the occurrence of major cardiovascular events (i.e. myocardial infarction and stroke) in
24 patients with systemic lupus erythematosus[27-28] and rheumatoid arthritis.[29] It might,
25 therefore, be hypothesized that the associations detected between the reduction in the
26 occurrence of distinct cardiac events and low dose ASA do not depend on a potential
27 protective effect on small intramyocardial coronary artery disease. Nevertheless, platelet
28 activation has been reported to play a role of both vascular and fibrotic manifestations of
29 SSc.[30] Moreover, markers of platelet activation have long been known to be responsive
30 to antiplatelet therapy.[31]

31 As far as EScSG activity index, Nevskaya et al.[19] have recently reported a predictive role
32 of the severity heart disease accrual by its adjusted mean over 3 years. Our results seem
33 to indicate that even a single evaluation might have a prognostic meaning. This result

1 prospects that achieving a EScSG activity index \geq 3 might be a target at least in clinical
2 practice.

3 In the original design of our study, we had envisaged 3 treatment arms i.e. CCB, ACEinh,
4 CCB +ACEinh. Actually, we had not considered the possibility of a SSc patient who is not
5 prescribed any vasodilator drug. This does not appear to be the case, our data on
6 prospectively enrolled patients from 20 EUSTAR centres confirming those reported by the
7 German SSc network highlighting the high percentage of SSc patients who do not receive
8 any vasoactive therapy.[32]

9 The observational nature of the study does not allow to prospect any cause/effect
10 relationship. Well designed Randomised Controlled Trials (RCTs) are needed to either
11 support or refuse any therapeutic role of vasodilators and low dose ASA in the prevention
12 of myocardial disease in SSc patients. In addition, the variable, non-standardised length of
13 follow-up represents a limitation, that, however, appears to be balanced by the long
14 cumulative duration of follow-up (914 patient/years) and its median time (2.4 years).

15 Vascular disease has long been considered a pathological hallmark of SSc.[33] The low
16 incidence of withdrawals from vasodilator therapy and low dose ASA in our study, even if
17 waiting for the results of properly designed RCTs, might suggest to consider adding low
18 dose ASA and a vasodilator agent to the therapeutic strategy of any SSc patients. In that
19 regard, given the apparent protective role of CCB for SRC on one side,[34] and the
20 increased risk of death associated with previous exposure to ACEinh in patients
21 developing a SRC,[35] it appears advisable to start with a CCB and to add an ACEinh in
22 patients with diastolic dysfunction for the known effect of the latter on ventricular filling.[26]

23 In conclusion, our prospective, observational study suggests a protective role of
24 vasodilators and low dose ASA on distinct manifestations of SSc myocardial disease and
25 prospects the opportunity to conduct well designed RCTs on both therapeutic strategies.

26

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1 **Competing interests:** none

2 **Ethics approval:** All contributing EUSTAR centres have obtained approval from their
3 respective local ethics committee for including patients data in the EUSTAR database and
4 patients have provided an informed consent according to local ethical requirements.

5

6 **Key messages:**

7 **What is already known about this subject?**

- 8 - Short term studies have underlined a beneficial effect of calcium channel blockers (CCB)
9 and other vasodilators including angiotensin converting enzyme inhibitors (ACEinh) on
10 cardiac vascularization and function in Systemic Sclerosis (SSc).
11 - However, the role of vasodilative agents in the prevention of primary myocardial disease
12 has not yet been defined.

13 **What does this study add?**

- 14 -This is the first observational, long term study to investigate the association between
15 vasodilators use and the occurrence of disease manifestations probably or potentially
16 related to myocardial fibrosis.
17 - Associations between vasodilators and low dose ASA use and a decrease in the
18 incidence of distinct manifestations have emerged.

19 **How might this impact on clinical practice?**

- 20 -Our study could prompt clinicians to consider adding a vasodilator agent and low dose
21 ASA to the therapeutic strategy of any SSc patient.

22

23 **References**

24 1. Kahan A, Allanore Y. Primary myocardial involvement in systemic sclerosis.
25 *Rheumatology (Oxford)* 2006;45(Suppl.4):14-7

26 2 Kahan A, Coghlan G, McLaughlin V. Cardiac Complications of Systemic
27 sclerosis. *Rheumatology* 2009;48:iii45-iii48

28 3 Parks JL, Taylor MH, Parks LP et al. Systemic Sclerosis and the Heart. *Rheum*
29 *Dis Clin North Am* 2014;40:87-102

30 4 Follansbee WP, Miller TR, Curtiss EI et al. A controlled clinicopathologic study of
31 myocardial fibrosis in systemic sclerosis (scleroderma). *J Rheumatol* 1990;17:656-
32 62

33 5 Kahan A, Devaux JY, Amor B et al. Nifedipine and thallium-201 myocardial
34 perfusion in progressive systemic sclerosis. *N Engl J Med* 1986;314:1397-402

- 1 6 Kahan A, Devaux JY, Amor B et al. Nicardipine improves myocardial perfusion in
2 systemic sclerosis. *J Rheumatol* 1988;15:1395-400
- 3 7 Kahan A, Devaux JY, Amor B, et al. Pharmacodynamic effect of nicardipine on left
4 ventricular function in systemic sclerosis. *J Cardiovasc Pharmacol* 1990;15:249-53
- 5 8 Kahan A, Devaux JY, Amor B, et al. The effect of captopril on thallium 201
6 myocardial perfusion in systemic sclerosis. *Clin Pharmacol Ther* 1990;47:483-9
- 7 9 Duboc D, Kahan A, Maziere B, et al. The effect of nifedipine on myocardial
8 perfusion and metabolism in systemic sclerosis. A positron emission tomographic
9 study. *Arthritis Rheum* 1991;34:198-203
- 10 10 Allanore Y, Meune C, Vonk MC et al. Prevalence and factors associated with left
11 ventricular dysfunction in the EULAR Scleroderma Trial and Research group
12 (EUSTAR) database of patients with systemic sclerosis. *Ann Rheum Dis*
13 2010;69:218-21
- 14 11 Lee SW, Choi EY, Jung SY et al. E/E' ratio is more sensitive than E/A ratio for
15 detection of left ventricular diastolic dysfunction in patients with systemic sclerosis.
16 *Clin Exp Rheumatol* 2010;28(Suppl58):S12-7
- 17 12 Follansbee WP, Curtiss EI, Rahko PS, et al. The electrocardiogram in systemic
18 sclerosis (scleroderma). Study of 102 consecutive cases with functional correlations
19 and review of the literature. *Am J Med* 1985;79:183-9
- 20 13 Kostis JB, Seibold JR, Turkevich D et al. Prognostic importance of cardiac
21 arrhythmias in systemic sclerosis. *Am J Med* 1988;84:1007-15
- 22 14 Vacca A, Meune C, Gordon J et al. Scleroderma Clinical Trial Consortium
23 Cardiac Subcommittee. Cardiac arrhythmias and conduction defects in systemic
24 sclerosis. *Rheumatology (Oxford)* 2014; 53:1172-7
- 25 15 Van den Hoogen F, Khanna D, Fransen J et al. 2013 classification criteria for
26 systemic sclerosis: an American College of Rheumatology/ European League
27 Against Rheumatism collaborative initiative. *Arthritis Rheum* 2013;65:2737-47.
- 28 16 Walker UA, Tyndall A, Czirják L et al. Clinical risk assessment of organ
29 manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials
30 and Research group database. *Ann Rheum Dis* 2007;66:754-63

- 1 17 Valentini G, Bencivelli W, Bombardieri S et al. European Scleroderma Study
2 Group to define disease activity criteria for systemic sclerosis. III. Assessment of the
3 construct validity of the preliminary activity criteria. *Ann Rheum Dis* 2003;62:901–
4 903
- 5 18 Steen VD, Medsger TA Jr. Severe organ involvement in systemic sclerosis with
6 diffuse scleroderma. *Arthritis Rheum* 2000;43:2437-44
- 7 19 Nevskaya T, Baron M, Pope JE; Canadian Scleroderma Research Group.
8 Predictive value of European Scleroderma Group Activity Index in an early
9 scleroderma cohort. *Rheumatology (Oxford)* 2017;56:1111-1122
- 10 20 Mihai C, Landewé R, van der Heijde D et al. Digital ulcers predict a worse
11 disease course in patients with systemic sclerosis. *Ann Rheum Dis* 2016;75: 681-
12 686
- 13 21 Tyndall AJ1, Bannert B, Vonk M et al. Causes and risk factors for death in
14 systemic sclerosis: a study from the EULAR Scleroderma Trials and Research
15 (EUSTAR) database. *Ann Rheum Dis* 2010;69:1809-15
- 16 22 Elhai M, Meune C, Boubaya M et al. Mapping and predicting mortality from
17 systemic sclerosis. *Ann Rheum Dis* 2017;76:1897-1905
- 18 23 Piepoli MF, Hoes AW, Agewall S, et al. 2016 European guidelines on
19 cardiovascular disease prevention in clinical practice: The sixth joint task force of
20 the European Society of Cardiology and other societies on cardiovascular disease
21 prevention in clinical practice (constituted by representatives of 10 societies and by
22 invited experts): Developed with the special contribution of the European
23 association for cardiovascular prevention & rehabilitation (EACPR). *Eur Heart J*.
24 2016;37:2315–2381
- 25 24 Lydersen S. Statistical review: frequently given comments. . *Ann Rheum Dis*
26 2015;74: 323–325
- 27 25 Karagrigoriou A. Frailty Models in Survival Analysis. *Journal of Applied Statistics*
28 2011;38:2988-2989
- 29 26 Kazzam E, Caidhal K, Hilgren R, et al. Non-invasive evaluation of long-term
30 effects of captopril in systemic sclerosis. *J Intern Med* 1991;230: 203-12

- 1 27 Iudici M, Fasano S, Gabriele Falcone L et al. Low-dose aspirin as primary
2 prophylaxis for cardiovascular events in systemic lupus erythematosus: a long-term
3 retrospective cohort study. *Rheumatology (Oxford)* 2016; 55:1623-30
- 4 28 Fasano S, Pierro L, Pantano I et al. Longterm Hydroxychloroquine Therapy and
5 Low-dose Aspirin May Have an Additive Effectiveness in the Primary Prevention of
6 Cardiovascular Events in Patients with Systemic Lupus Erythematosus. *J*
7 *Rheumatol* 2017; 44: 1032-1038
- 8 29 Iacono D, Fasano S, Pantano I et al. Low-Dose Aspirin as Primary Prophylaxis
9 for Cardiovascular Events in Rheumatoid Arthritis: An Italian Multicentre
10 Retrospective Study. *Cardiol Res Pract* 2019: 2748035
- 11 30 Ntelis K, Solomou EE, Sakkas L et al. The role of platelets in autoimmunity,
12 vasculopathy, and fibrosis: Implications for systemic sclerosis. *Semin Arthritis*
13 *Rheum* 2017;47:409-417
- 14 31 Kahaleh MB, Osborn I, LeRoy EC. Elevated Levels of Circulating Platelet
15 Aggregates and Beta-Thromboglobulin in Scleroderma. *Ann Intern Med.*
16 1982;96:610–613.
- 17 32 Moinzadeh P, Riemekasten G, Siegert E et al. German Network for Systemic
18 Scleroderma. Vasoactive Therapy in Systemic Sclerosis: Real-life Therapeutic
19 Practice in More Than 3000 Patients. *J Rheumatol* 2016; 43:66-74
- 20 33 Matucci-Cerinic, M, Kahaleh, B, Wigley, FM. Evidence that systemic sclerosis is
21 a vascular disease [review]. *Arthritis Rheum* 2013; 65: 1953– 62
- 22 34 Montanelli G, Beretta L, Santaniello A et al. Effect of dihydropyridine calcium
23 channel blockers and glucocorticoids on the prevention and development of
24 scleroderma renal crisis in an Italian case series. *Clin Exp Rheumatol*
25 2013;31(Suppl 76):135-9
- 26 35 Hudson M, Baron M, Tatibouet S, et al. Exposure to ACE inhibitors prior to the
27 onset of scleroderma renal crisis-Results from the International Scleroderma Renal
28 Crisis Survey. *Semin Arthritis Rheum* 2014;43:666-72