Sexuality in systemic sclerosis for Men & Women

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Problems specific to women in SSc

- Sexuality
- Fertility
- Pregnancy outcomes
- Effects of pregnancy on SSc
- Pregnancy management
- Management of delivery

Sexuality in women who have SSc

- Changes in appearance
- Emotional effects of the disease
- 60% of women nevertheless sexually active
- Only 17% attributed sexual inactivity to SSc

Parameter	*Systemic sclerosis (%)*			*Controls (%)*			*Significance†*
	Decreased	*Same*	*Increased*	*Decreased*	*Same*	*Increased*	
Desire for sexual intercourse							
+1 yr	57	41	2	53	40	7	NS
Present	66	32	2	60	40	0	NS
Frequency of sexual intercourse							
+1 yr	52	43	5	40	60	0	NS
Present	73	24	3	73	27	0	NS

Impens AJ, Clin Exp Rheum 2009

Steen VD, *Rheum Dis Clin North Am* 2007 ; Bhadauria S, *Am J Obstet Gynecol 1995*

Primary reasons for sexual dysfunction

Symptom	*Systemic sclerosis (No.)*	*Controls (No.)*	*Significance†*
Skin tightness on hips, thighs, or buttocks	16 (n = 48)	0 (n = 23)	p = 0.0007
Heartburn, reflux, vomiting	18 (n = 48)	1 (n = 17)	p = 0.011
Muscle weakness	13 (n = 47)	1 (n = 17)	p = 0.057
Contractures (knees, elbows, hands)	20 (n = 48)	3 (n = 17)	p = 0.066
Fatigue	30 (n = 48)	11 (n = 18)	p = 0.570
Joint pains (hips, knees, back)	26 (n = 48)	10 (n = 18)	p = 0.570
Other‡	10 (n = 25)	1 (n = 10)	p = 0.089
Side effects of medications causing sexual problems§	11 (n = 47)	4 (n = 17)	–

- Vaginal dryness (42-71%)
- Vaginal tightness, constricted introitus (8%)

Wilson D, *J Rheumatol* 1993 ; Bhadauria S, *Am J Obstet Gynecol 1995*

Dyspareunia in a healthy population

Dyspareunia in SSc 37% - 56%

Dysparenunia in two healthy populations

Glatt:

- 428 women ‘in early thirties’
- 105 (33.5%) persistent dyspareunia
- 35 (33.7%) important adverse effect on their relationship
- 43 (41.3%) ever discussed this with HP

Valadares:

- 200 Brazilian-born women, 40 to 65 years of age
- dyspareunia 39.5%

Glatt AE *Obstet Gynecol* 1990; Valadares AL *Menopause* 2008

Sexual functioning

Female Sexual Function Index (FSFI, higher scores better)

	SSc n=37	Controls n=37	P value
FSFI total	**20.6 (9.4)**	**27.6 (6.2)**	***0.000****
- desire	**3.1 (1.2)**	**3.4 (0.9)**	**0.119**
- arousal	**3.5 (1.9)**	**4.5 (1.2)**	***0.005****
- lubrication	**3.4 (2.1)**	**5.3 (1.1)**	***0.000****
- orgasm	**3.7 (2.2)**	**4.7 (1.4)**	***0.018****
- satisfaction	**4.0 (1.5)**	**4.6 (1.4)**	**0.062**
- pain	**3.0 (2.5)**	**5.0 (1.8)**	***0.000****
FSDS (Depression)	**16.8 (12.4)**	**10.3 (10.9)**	***0.016****

Schouffour A, *Arthritis Care Res* 2009

Sexuality in women who have SSc

Longer SSc duration associated with low sexual function and distress
No difference between diffuse and limited SSc.

Multivariate analysis
- *marital distress* as the only variable associated with sexual dysfunction
- *depression* as the only variable associated with sexual distress

Counseling
16% of women with SSc wanted to talk to someone about sex problems
None mentioned her rheumatologist
1 mentioned her general practitioner

Schouffour A, *Arthritis Rheum* 2009

Abnormal PAP-smears

Reports of abnormal cervical cancer screening tests in SSc

320 women with SSc onset before the age of 50 yrs

Life time prevalence 25.4% (compared to 13.8% in general population)

Associated with
- diffuse disease, odds ratio 1.87
- younger age at disease onset

Bernatsky S, *Rheumatology* 2009

Fertility in women with SSc

- No differences in menopause and menstruation

- EUSTAR:
  - Mean age at onset of Raynaud´s: 43 years
  - Mean age at onset of Non-Raynaud´s: 45-48 years

→ Most women have completed their pregnancy prior to SSc onset

Bhadauria S, *Am J Obstet Gynecol 1995 ;* Walker UA *Ann Rheum Dis* 2007

Fertility

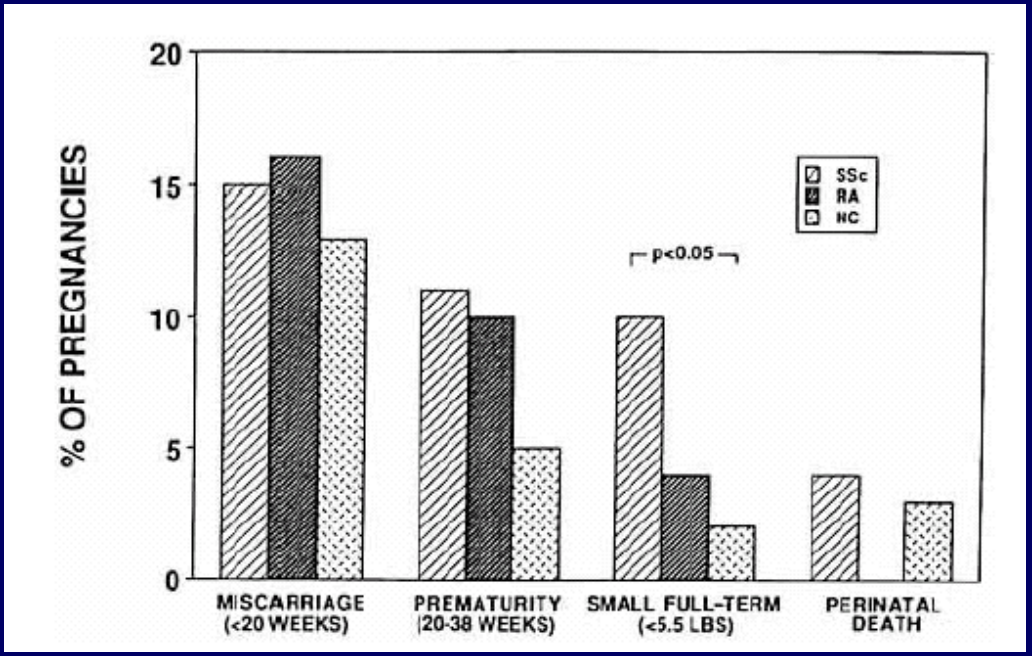
- No overall compromise in fertility after adjusting for confounders
  - marital status
  - sexual activity
  - choice not to have children
- No delay in conception

Englert H, *J Rheumatol* 1992 ; Silman AJ, Ann Rheum Dis 1988 ; Steen VD, *Arthritis Rheum* 1999

Pregnancy in SSc

Miscarriage / prematurity / small full term babies

SSc: n=133
RA: n=134
NC: n=158



Another controlled study: RR for miscarriage: 2.1 (compared to healthy contr.)

- Premature delivery
  - Frequency increased in early diffuse SSc (65%)
  - Prematurity more common after SSc onset, compared with before

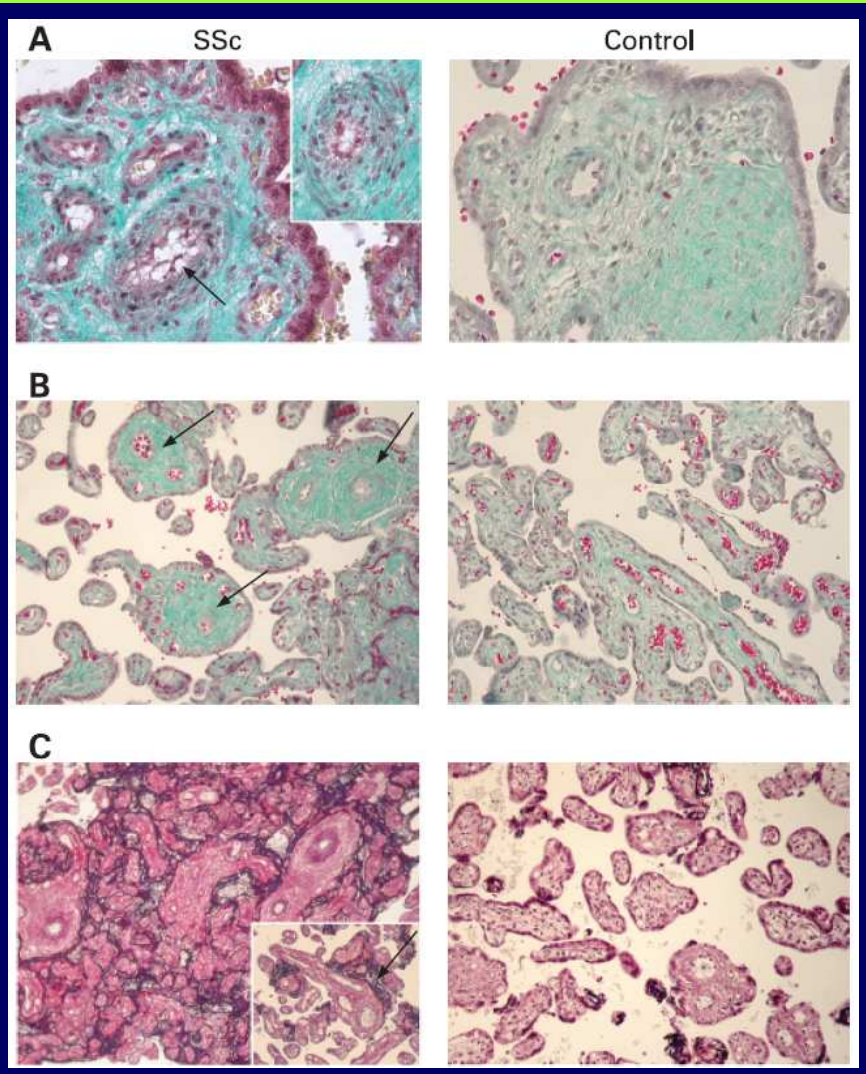
Silman AJ, *ARD* 1988 ; Steen VD, *Arthritis Rheum* 1989 ; Steen VD, *Arthritis Rheum* 1999
Chakravarty EF, *Obstetr Gynecol* 2008

Placental changes in SSc

Foamy degeneration of endothelial cells in decidua
Thickening and delamination of vessel wall

Perivascular and stromal fibrosis of maternal decidua (A) and chorionic villi (B)

Fibrinoid material in infarcted areas around decidual vessels and in intervillous spaces



Ibba-Manneschi L *Ann Rheum Dis* 2010

Summary: Pregnancy outcomes in SSc

- Fertility
  No adverse effect of SSc
- Miscarriage
  Ambiguous data
- Premature delivery
  More frequent in SSc
  In early dcSSc ?
- Small for gestational age infants
  More frequent in SSc

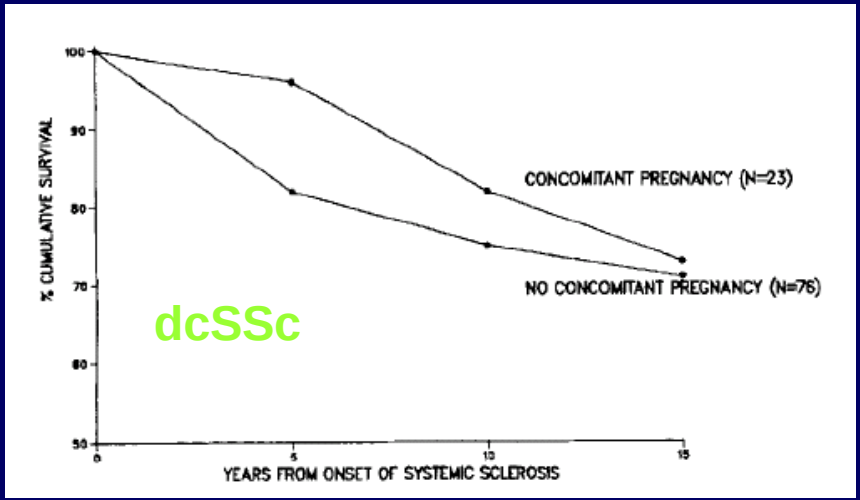
Silman AJ, *ARD* 1988 ; Steen VD, *Arthritis Rheum* 1989 ; Steen VD, *Arthritis Rheum* 1999
Chakravarty EF, *Obstetr Gynecol* 2008

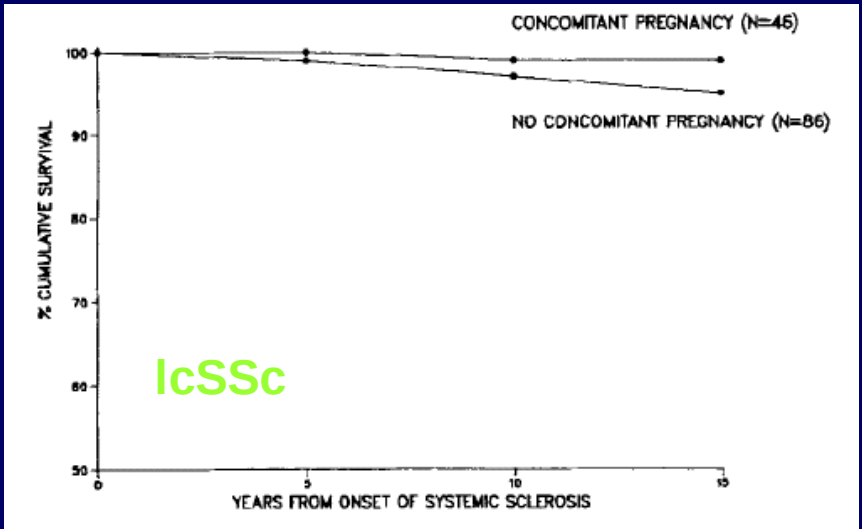
No adverse effects of pregnancy on SSc

- Many pregnancy symptoms are similar to SSc
  - Oedema
  - Arthralgias
  - Gastrointestinal reflux
  - Dyspnea
  - Hypertension/ eclampsia (frequency in SSc probably not elevated)
- No significant changes in the SSc status during pregnancy
- Raynauds may get better

Steen VD, *Arthritis Rheum* 1989 ; Steen VD, *Rheum Dis Clin N Am* 2007
Chakravarty EF, *Obstetr Gynecol* 2008

No effects of pregnancy on SSc mortality





- Similar 10-year cumulative survival for women who had SSc with and without a pregnancy

Steen VD, *Arthritis Rheum* 1989

Preeclampsia / renal crisis

- No increased risk of preeclampsia in tertiary care centres
- Renal crisis has been described (high mortality)

→ BP, creatinine, proteinuria must be checked regularly

- ACE inhibitors cause fetal abnormalities
  (anhydramnions, renal atresia, pulmonary hypoplasia, fetal death)
- Frequency of ACE fetopathy is unknown

→ ACE inhibitors in suspected renal crisis

Black CM, *Rheum Dis Clin North Am* 1989 ; Mehta N, *Lancet* 1989; Pryde PG, *Obstet Gynecol* 2001
Steen VD, *Rheum Dis Clin North Am* 2007 ; Chakravarty EF, *Obstetr Gynecol* 2008

Management of delivery

- Epidural anaesthesia to be preferred
  → Peripheral vasodilatation
  → Enhanced skin perfusion of lower extremities
- General anaesthesia to be avoided
  → Difficulty in intubation (small mouth)
  → Aspiration
- Raynaud's phenomenon
  → Warming the delivery room, warm intravenous fluids, thermal socks, and blankets
- Cervical scleroderma with soft tissue dystocia
  → Caesarean section (abdominal skin usually heals well)

Thompson J, Anesthesiology 1983 ; Eisele JH, *Anesthesiology* 1971
Stenchever MA, *Am J Obstet Gynecol* 1970 ;Bellucci MJ, *Am J Obstet Gynecol* 1984

Pregnancy outcome

Life births 82%

Steen VD, *Obstet Gynecol* 1999

Erektile dysfunction (ED)

Definition of ED

The consistent or constant inability to achieve or maintain an erection sufficient for satisfactory intercourse.

Prevalence of ED in the general population:

	Moderate	Severe/ complete
Age 40-49	5%	17%
Age 70-79	15%	34%

Feldman HA, *J Urol* 1994

International Index of Erectile Function ($IIEF_5$)

1. How do you rate your confidence that you could keep an erection?

1	2	3	4	5
Very low	Low	Moderate	High	Very High

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner?)

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most of the time (much more than half the time)	Almost always or always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most of the time (much more than half the time)	Almost always or always

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?

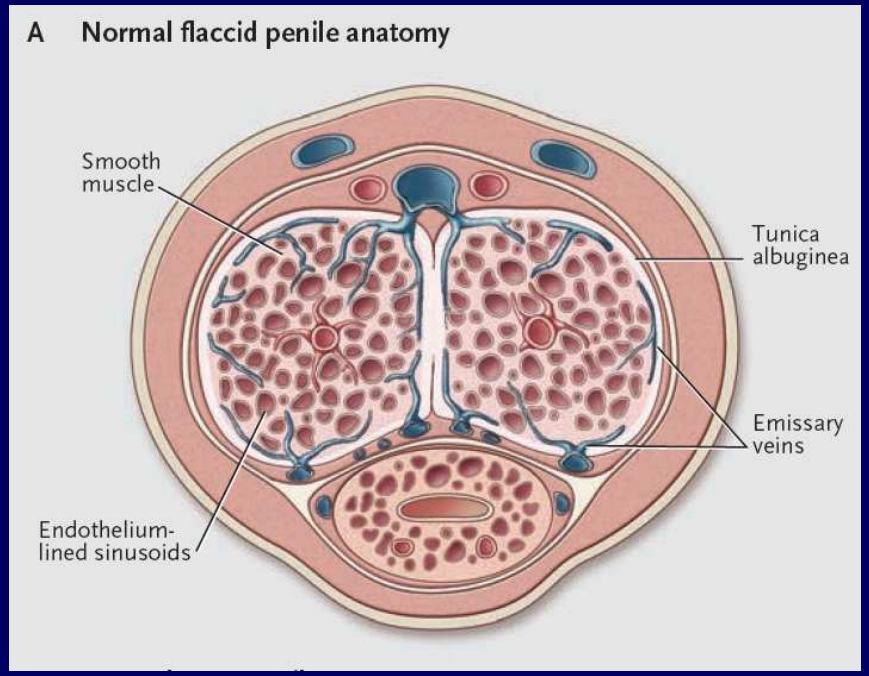
1	2	3	4	5
Extremely difficult	Very difficult	Difficult	Slightly difficult	Not difficult

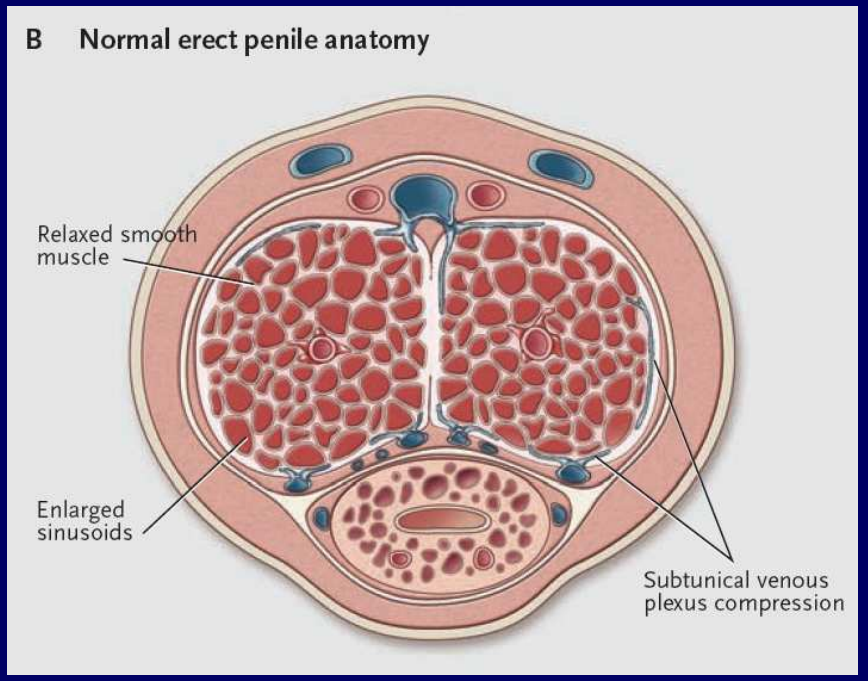
5. When you attempted sexual intercourse, how often was it satisfactory for you?

1	2	3	4	5
Almost never or never	A few times (much less than half the time)	Sometimes (about half the time)	Most of the time (much more than half the time)	Almost always or always

Mild 17-21, Mild to moderate 12-16, Moderate 8-11, Severe 5-7

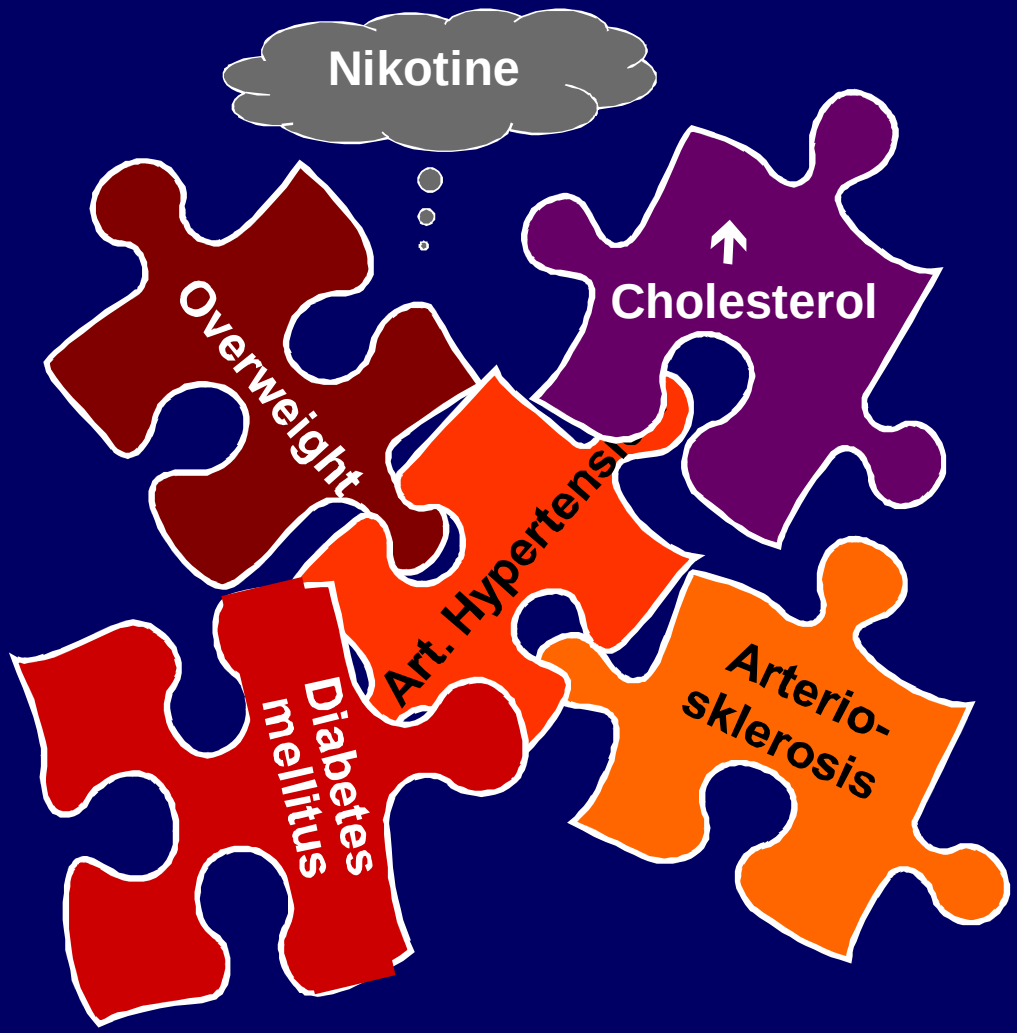
Penile anatomy



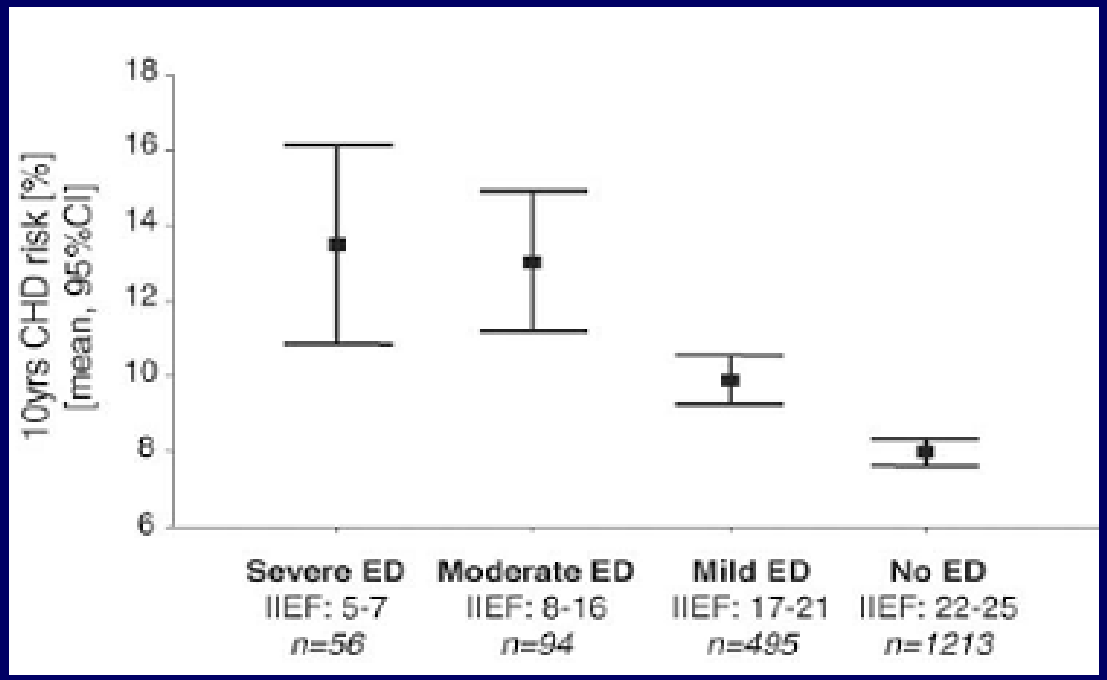


McVary, *N Engl J Med* 2007

Erektile dysfunction = Endothelial dysfunction



ED → increased risk of coronary heart disease

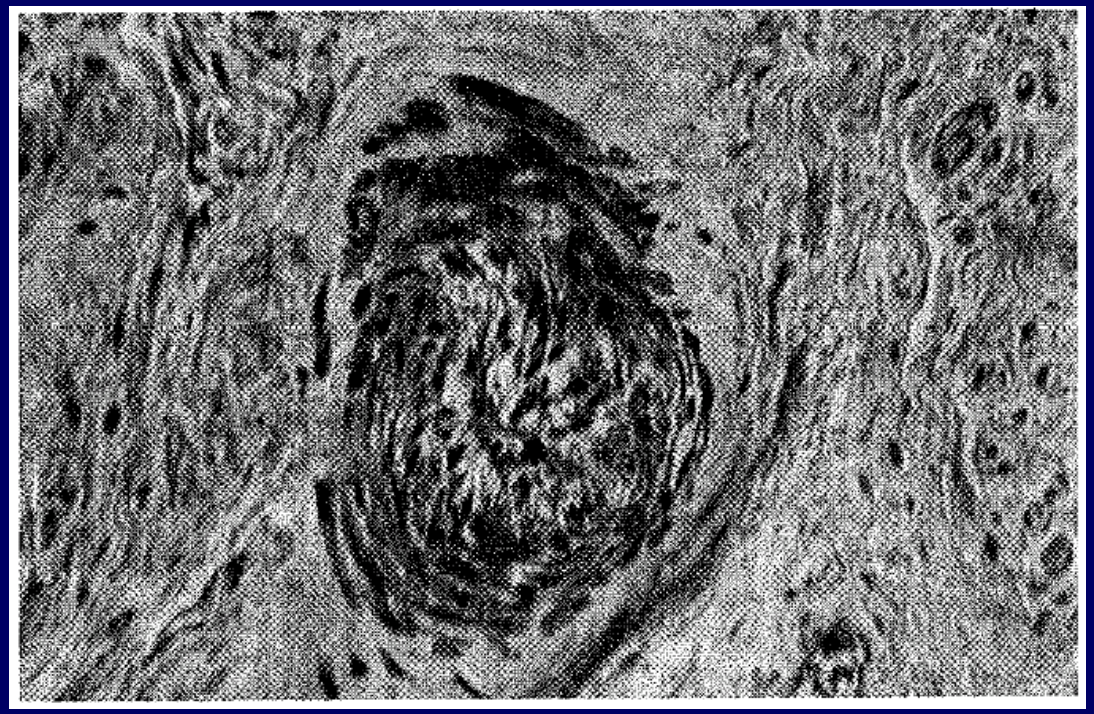


ED prevalence in patients with symptomatic CHD: 49%
ED manifests 39 months prior to CHD
ED predicts cardiovascular event

Kendirci M, *J Urol* 2007 ; Thompson I, *JAMA* 2005 ; Montorsi F, *Eur Urol* 2003 ; Ponholzer A, *Eur Urol* 2005

Penile vasculature in SSc

Medium-sized penile artery



Adventitial fibrosis, myointimal proliferation, stenosis

Nehra A, *J Urol* 1995

Penile vasculature in SSc

- No endocrine dysfunction
- Severely impaired peak systolic velocities 15/15
- Low baseline temperature, slow recovery from cooling
- Normal intimal medial thickness
- Biopsy: corporeal fibrosis

  - Increased collagen synthesis by smooth muscle cells

  - Excessive ECM accumulation

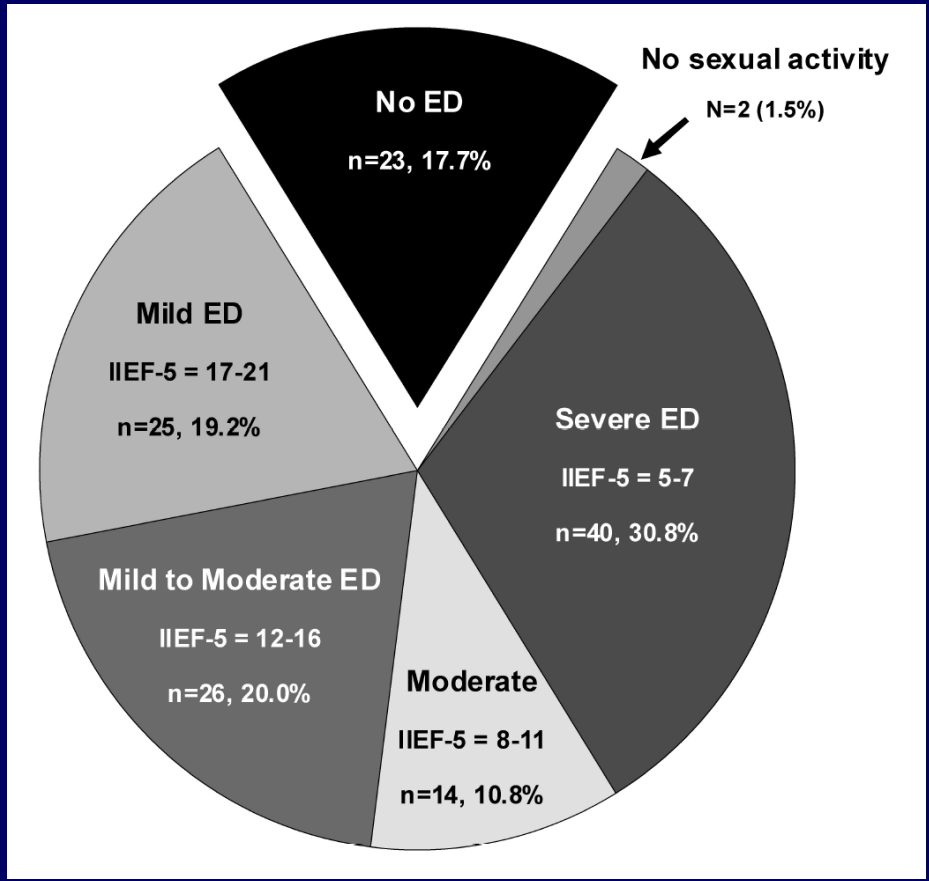
Lally EV, *NEJM* 1990 ; Nowlin NS, *Ann Int Med* 1986 ; Aversa A, *J Sex Med* 2006 ; Nehra A, *J Urol* 1995
Merla A, *Int J Immunopathol Pharmacol* 2006

Prevalence and severity of ED in SSc (EUSTAR)

N= 130
Median IIEF-5 score 13

ED in 77% after SSc diagnosis

ED onset 2.7 yrs after SSc onset



Hong P, *J Rheumatol* 2004 ; Aversa A, *J Sex Med* 2006 ; Foocharoen C *Arthritis Res Ther in press*

Basic ED evaluation

History

Drugs

Drug Class	Examples
Diuretics	Thiazides, spironolactone
Antihypertensive drugs	Calcium-channel blockers, beta-blockers, methyldopa, clonidine, reserpine, guanethidine
Cardiac or cholesterol drugs	Digoxin, gemfibrozil, clofibrate
Antidepressants	Selective serotonin-reuptake inhibitors, tricyclic antidepressants, lithium, monoamine oxidase inhibitors
Tranquilizers	Butyrophenones, phenothiazines
H_2 antagonists	Ranitidine, cimetidine
Hormones	Progesterone, estrogens, corticosteroids, luteinizing hormone–releasing hormone agonists, 5α-reductase inhibitors, cyproterone acetate
Cytotoxic agents	Methotrexate
Immunomodulators	Interferon-α
Anticholinergic agents	Disopyramide, anticonvulsants
Recreational drugs	Alcohol, cocaine

McVary KT, *NEJM* 2007 ; eau Guidelines

Basic ED evaluation

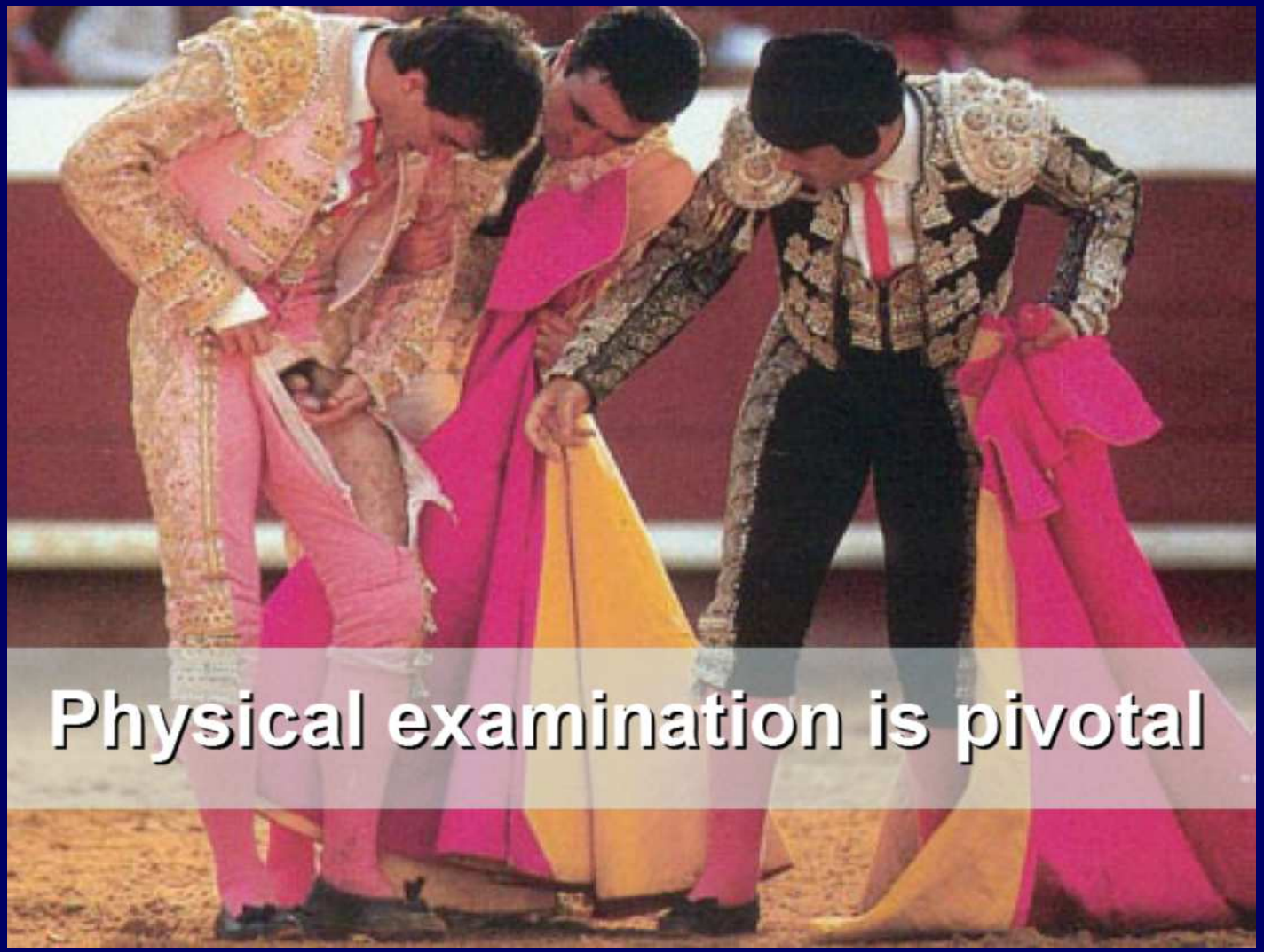
History

Drugs, hypertension, diabetes, other comorbidities

Focused physical examination

Secondary sexual characteristics (hypogonadism)
Penile abnormalities
Prostatic disease
Groin and peripheral pulses
Neurologic status

Basic ED evaluation



Basic ED evaluation

History

Drugs, hypertension, diabetes, other comorbidities

Focused physical examination

Secondary sexual characteristics (Hypogonadism)
Penile abnormalities
Prostatic disease
Groin and peripheral pulses
Neurologic status

Lab studies

Fasting glucose, lipids, testosterone

Wespes E, Eur Urol 2006 ; eau Guidelines

Comorbidities in SSc (EUSTAR data)

	No ED N = 23	ED N = 105	OR (95%CI)
Cardiovascular risk factors			
Systemic arterial hypertension	14.3%	24.1%	(0.92-1.34)
Diabetes mellitus	4.4%	6.9%	(0.82-1.42)
Coronary heart disease	4.4%	13.3%	(0.98-1.39)
Hypercholesterolemia	19.1%	13.3%	0.92 (0.70-1.21)
History of smoking	31.8%	42.6%	(0.92-1.29)
Cigarette smoking (median pack-years, IQR)	15 (10-21)	20 (9-30)	p=0.69
Medication			
Antidepressant, sedative, neuroleptic or antiepileptic	4.4%	9.1%	(0.89-1.40)
Thiazides or spironolactone	4.4%	7.0%	(0.82-1.43)
Alcohol consumption (>2 units/d)	0%	13.7%	(1.15-1.40)*
Other			
Depression	4.6%	9.0%	(0.88-1.39)
Central nervous system problems	0%	3.9%	(1.13-1.35)*
Prostatic disease	0%	8.4%	(1.13-1.36)*
Hormonal (hypogonadism, hyperprolactinemia)	0%	2.8%	(1.11-1.36)

Comorbidities more frequent in ED (EUSTAR data)

	No ED N = 23	**ED** N = 105	**OR (95%CI)**
At least 1 comorbidity	52.2%	61.5%	(0.90-1.28)
At least 2 comorbidities	13.0%	36.5%	(1.05-1.40)*
At least 3 comorbidities	4.4%	14.4%	(1.00-1.34)*
At least 4 comorbidities	0%	5.8%	(1.13-1.35)*
At least 5 comorbidities	0%	1%	(1.13-1.33)*

Hypertension, diabetes, coronary heart disease, hypercholesterolemia, smoking, alcohol consumption

Foocharoen C *Arthritis Res Ther in press*

Treatment options

First line

- Oral PDE5-Inhibitor (Sildenafil, Tadalafil, Vardenafil)

Side effects of PDE 5-Inhibitors

	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%	–	<2%
Back pain	–	6.5%	–
Myalgia	–	5.7%	–

Contraindications

- Retinitis pigmentosa
- High or intermediate risk of coronary artery disease
- Nitrate use

Wespes E, Eur Urol 2006 ; EAU Guidelines

Cardiac risk stratification

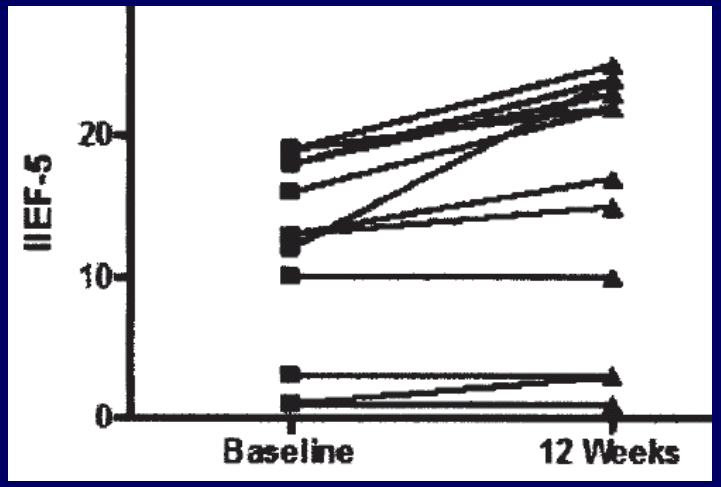
Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated past MI	Recent MI (>2, <6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

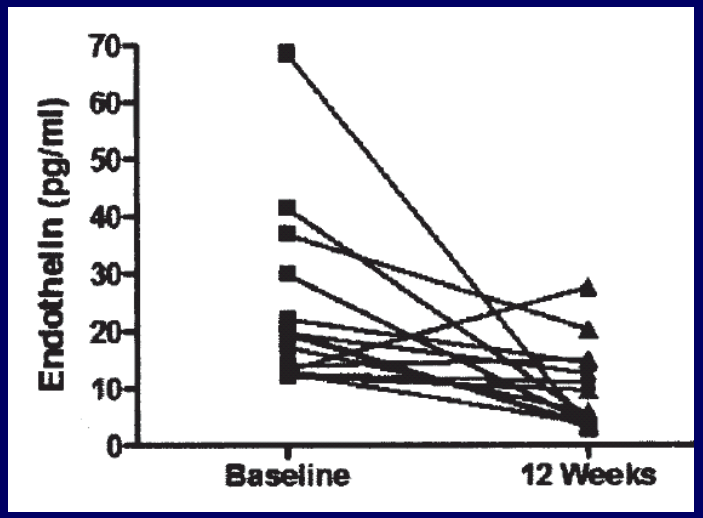
CAD, coronary artery disease; CHF, congestive heart failure; LV, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association.

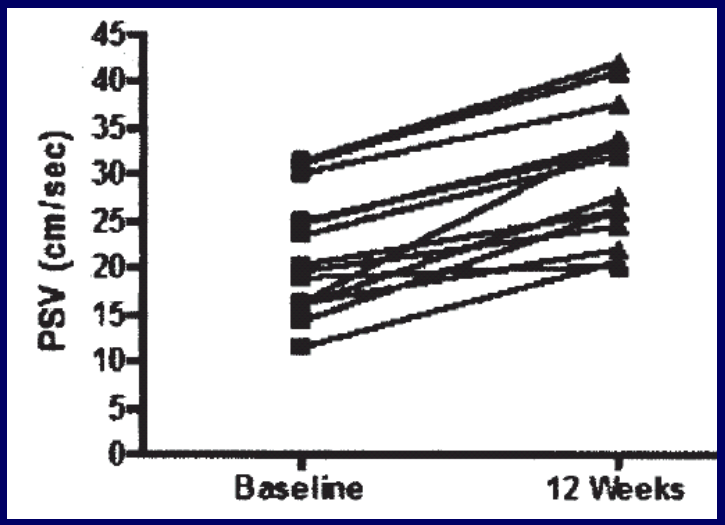
Wespes E, Eur Urol 2006 ; EAU Guidelines

Tadalafil in SSc

Tadalafil fixed dose (10 mg OD)







Aversa A, *J Impot Res 2007* ; Proietti M, *J Rheumatol* 2007

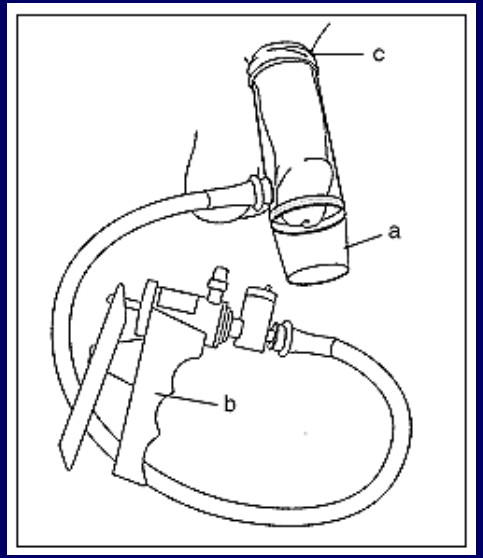
Impact of PDE-5 inhibitors on arterial function

Study	Drug used	Target group	Method of assessment	Result in endothelial function
Katz [6]	Single dose of sildenafil 12.5, 25, or 50 mg taken 1 h before assessment (double-blind, randomised, placebo-controlled study)	Patients with chronic heart failure	Flow-mediated dilation (FMD) 1, 3, and 5 min after release of transient brachial artery occlusion	Improvement (after 25 and 50 mg sildenafil)
Halcox [7]	Single dose of sildenafil 100 mg vs 10 mg isosorbide dinitrate (ISDN) or placebo taken 45 min before assessment (double-blind, randomised, placebo-controlled study)	CAD patients vs control group (healthy volunteers)	FMD of the brachial artery	Improvement
Desouza [8]	Sildenafil 25 mg daily for 2 wk (double-blind, placebo-controlled, crossover study)	Patients with type 2 diabetes and ED	FMD of the brachial artery	Improvement (sustained at least 24 h after last dose)
Kimura [9]	Single dose of sildenafil 100 mg taken 1 h before assessment	Chronic smokers vs nonsmokers	Forearm blood flow (FBF) responses to acetylcholine and to sodium nitroprusside	Improvement (similar to smokers and nonsmokers)
Vlachopoulos [16]	Single dose of sildenafil 50 mg (double-blind, placebo-controlled, crossover study) measurements for 3 h	Patients with CAD	Aortic stiffness, wave reflections from peripheral sites	Improvement
Vlachopoulos [10]	Single dose of sildenafil 50 mg taken 50 min before smoking (randomised, placebo controlled, crossover study)	Smokers	FMD of the brachial artery	Improvement
Dishy [98]	Single dose of sildenafil 25 mg taken 1 h before assessment (double-blind, placebo-controlled, crossover study)	Chronic smokers	FMD of the brachial artery and forearm postischemic reactive hyperemia	No improvement
Hirata [17]	Single dose of sildenafil 50 mg (double-blind, placebo-controlled, crossover study) measurements for 3 h	Patients with controlled left ventricular failure and ejection fractions <35%	Total systemic resistance, aortic stiffness, wave reflections from peripheral sites	Improvement
Caretta [12]	Tadalafil 20 mg/48 h vs controls for 3 mo	ED patients (60–70 yr old) vs control patients (aged 18–40 yr affected by psychogenic ED)	Ultrasound evaluation of common carotid artery intima-media thickness (IMT)	Improvement with spontaneous resumption of erections
Foresta [14]	Single dose of vardenafil	Healthy young men	Endothelial progenitor cells (EPCs), which add to the process of continuous repair of the endothelium	Significant increase in EPCs. The effect occurred early (~4 h)

Treatment options

First line

- Oral PDE5-Inhibitor
- Vacuum device
- Non-intercourse options



Treatment options

First line
- Oral PDE5-Inhibitor
- Vacuum device
- Non-intercourse options

Second line
- Penile injection
- Topical urethral applications (alprostadil)

Third line
- Penile implants
- Vascular surgery