Sklerodermiyalı pasientdə pulmonar hipertenziya

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Modern Rheumatology, **00**, 2024, 1–6
DOI: https://doi.org/10.1093/mr/roae095
Advance Access Publication Date: 17 October 2024
Original Article

Mortality and associated factors in patients with systemic sclerosis-associated pulmonary hypertension with and without interstitial lung disease: A long-term follow-up study

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ABSTRACT

Objectives: We aimed to investigate mortality and prognostic factors in systemic sclerosis (SSc) patients with pulmonary hypertension (PH) with or without interstitial lung disease (ILD).

Methods: The associations between mortality and demographics, transthoracic echocardiography, right heart catheterization (RHC), pulmonary functional parameters at baseline, and treatment modalities were evaluated.

Results: Survival rates for PH-SSc patients (42 female, mean age 56.6 ± 13.5, median follow-up 45 months) were 91% at the first year, 75% at 2 years, and 43.1% at 5 years. The majority of the deceased patients had PH + ILD (P = .007). The PH + ILD group had more diffuse skin involvement, anti-Scl-70, high C-reactive protein, low FVC, and lower DLCO. The deceased patients had higher estimated pulmonary arterial systolic pressure (PASP), low cardiac output, and FVC values. Median survival time was significantly better in patients on combined therapy. Mortality-related factors in the PH + ILD group were decreased initial FVC, high estimated PASP, low cardiac output, deteriorated functional class, and monotherapy.

Conclusion: This is the first reported SSc-PH cohort from Turkey by a multidisciplinary team. PH is a severe complication of SSc with high mortality especially in patients with accompanying severe ILD.

KEYWORDS: Systemic sclerosis; pulmonary hypertension; interstitial lung disease; pulmonary function tests; PAH-specific therapy

PULMONARY HYPERTENSION

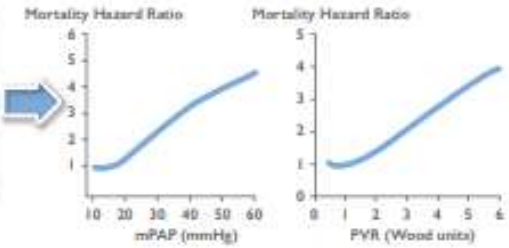
Prevalence

1%

Global population

Pulmonary congestion in post-capillary PH

Pulmonary vascular disease / obstruction in pre-capillary PH



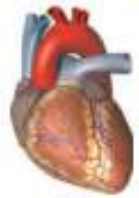
Right heart failure

CLINICAL CLASSIFICATION

Pulmonary arterial hypertension (PAH)

- Idiopathic/heritable
- Associated conditions

PH associated with left heart disease



- IpcPH
- CpcPH

PH associated with lung disease

- Non-severe PH
- Severe PH

PH associated with pulmonary artery obstructions

- CTEPH
- Other pulmonary obstructions

PH with unclear and/or multifactorial mechanisms

?

- Haematological disorders
- Systemic disorders

PREVALENCE

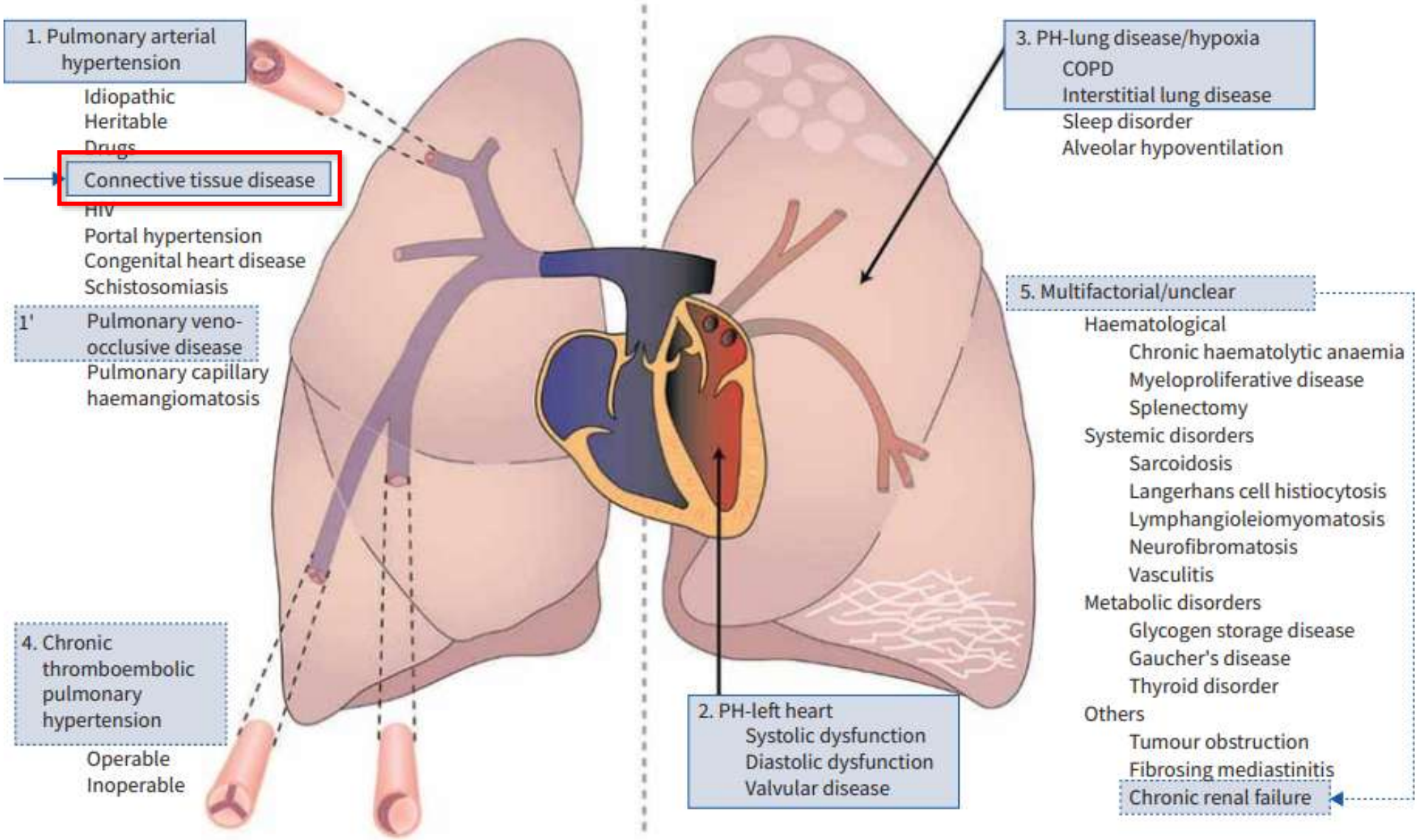
Rare	Very common	Common	Rare	Rare
				

Definition	Haemodynamic characteristics
PH	mPAP >20 mmHg
Pre-capillary PH	mPAP >20 mmHg PAWP ≤15 mmHg PVR >2 WU
IpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR ≤2 WU
CpcPH	mPAP >20 mmHg PAWP >15 mmHg PVR >2 WU
Exercise PH	mPAP/CO slope between rest and exercise >3 mmHg/L/min

TABLE 1 Haemodynamic diagnostic criteria of the six World Symposia on Pulmonary Hypertension (WSPH)

	First WSPH [14]	Second WSPH [15]	Third WSPH [16]	Fourth WSPH [17, 18]	Fifth WSPH [19, 20]	Sixth WSPH [5, 21]
Year	1973	1998	2003	2008	2013	2018
Location	Geneva, Switzerland	Evian, France	Venice, Italy	Dana Point, CA, USA	Nice, France	Nice, France
mPAP PH diagnostic threshold	>25 mmHg	Not defined	>25 mmHg	⩾25 mmHg	⩾25 mmHg	>20 mmHg
PVR included in PAH definition	No	No	>3 WU	No	>3 WU	⩾3 WU
PAWP post-capillary threshold	Discussed but not defined	Not discussed	>15 mmHg	⩾15 mmHg	>15 mmHg	>15 mmHg
Isolated post-capillary PH	Not discussed	Not discussed	Not discussed	PVR <3 WU[#] TPG ⩽12 mmHg	DPG <7 mmHg	PVR <3 WU
Combined pre- and post-capillary PH	Not discussed	Not discussed	Not discussed	PVR ⩾3 WU[¶] TPG >12 mmHg	DPG ⩾7 mmHg	PVR >3 WU
PH-exercise	Discussed but not defined	Not discussed	>30 mmHg	No	No	No
mPAP 21–24 mmHg	20 mmHg as upper limit of normal recognised	Not discussed	Not discussed	Uncertainty in patients with mPAP 21–24 mmHg	At-risk patients (*e.g.* CTD) should be followed closely	Most now defined as PH; however, mPAP >20 mmHg, PAWP ⩽15 mmHg but PVR <3 WU not classified

Pulmonary hypertension phenotypes in patients with systemic sclerosis Eur Respir Rev 2021 A. Haque et al.



Qrup 1: pulmonar vaskulyar yatağın remodelinqi

Qrup 2: Miokardial fibroz və sürətlənmiş aterosklerotik xəstəliyə bağlı sistolik, diastolik disfunksiya

Qrup 3: İnterstisial ağciyər xəstəliyi

Qrup 4: tromboembolizm sıxlığında artış

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TABLE 2 Systemic sclerosis (SSc)-pulmonary hypertension (PH) phenotypes

SSc-PAH: post-6th WSPH	mPAP ⩾20 mmHg, PAWP ⩽15 mmHg, PVR ⩾3 WU
SSc-PAH: pre-6th WSPH	mPAP ⩾25 mmHg, PAWP ⩽15 mmHg, PVR >3 WU
SSc: mPAP >20 mmHg, PVR <3 WU	A group of patients with elevated mPAP who do not fulfil current PH diagnostic criteria of pre- or post-capillary PH
SSc-BoPH	Term used in the literature to describe patients with borderline haemodynamics (mPAP 21–24 mmHg) prior to the current 6th WSPH PH definition
SSc-PH-exercise	Previously, resting mPAP <25 mmHg but mPAP >30 mmHg on exercise; more recent definition (not included in 6th WSPH) suggested as resting mPAP <25 mmHg but mPAP >30 mmHg and TPR >3 WU on exercise
SSc-PVOD	Meets haemodynamic criteria for PAH but radiological and clinical features of PVOD
SSc-PH-LHD	mPAP ⩾20 mmHg, PAWP >15 mmHg
SSc-IpcPH	mPAP ⩾20 mmHg, PAWP >15 mmHg, PVR <3 WU
SSc-CpcPH	mPAP ⩾20 mmHg, PAWP >15 mmHg, PVR ⩾3 WU
SSc-PH-HFpEF	SSc-PH-LHD due to heart failure with preserved ejection fraction
SSc-PH-HFrEF	SSc-PH-LHD due to heart failure with reduced ejection fraction
SSc-PH-ILD	mPAP ⩾20 mmHg, PAWP ⩽15 mmHg, PVR ⩾3 WU in the presence of significant ILD (often defined as HRCT showing >20% fibrotic lung involvement and/or FVC <70% predicted)

Pulmonary hypertension phenotypes in patients with systemic sclerosis Eur Respir Rev 2021 A. Haque et al.

- SSk-PAH ilə İPAH ortaq əlamətləri:
- İntimal hiperplaziya
- Medial hipertrofiya
- Angioproliferativ lezyonlar

- İPAH üçün xarakterik olan pleksiform lezyonlar SSk-PAH'da daha az rast gəlinir

- İntimal fibroz və venookluzif xəstəlik SSk-PAH'da İPAH ilə müqayisədə daha çox rast gəlinir

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- **Sistem skleroz (SSk)** nadir autoimmun multisistem birləşdirici toxuma xəstəliyidir.

- Prevalansı 30-120 klinik hal/milyon

- Anormal kollagen depolanması, dəri və daxili orqanların fibrozu
- Endotel disfunksiyası, vaskulopatiya
- Autoantitellərin varlığı

State-of-the-art evidence in the treatment of systemic sclerosis Pope et al Nature Reviews Rheumatology | Volume 19 | April 2023 | 212–226
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Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: A systematic review and meta-analysis of long-term outcomes Brown et al Seminars in Arthritis and Rheumatism 51 (2021) 495-512

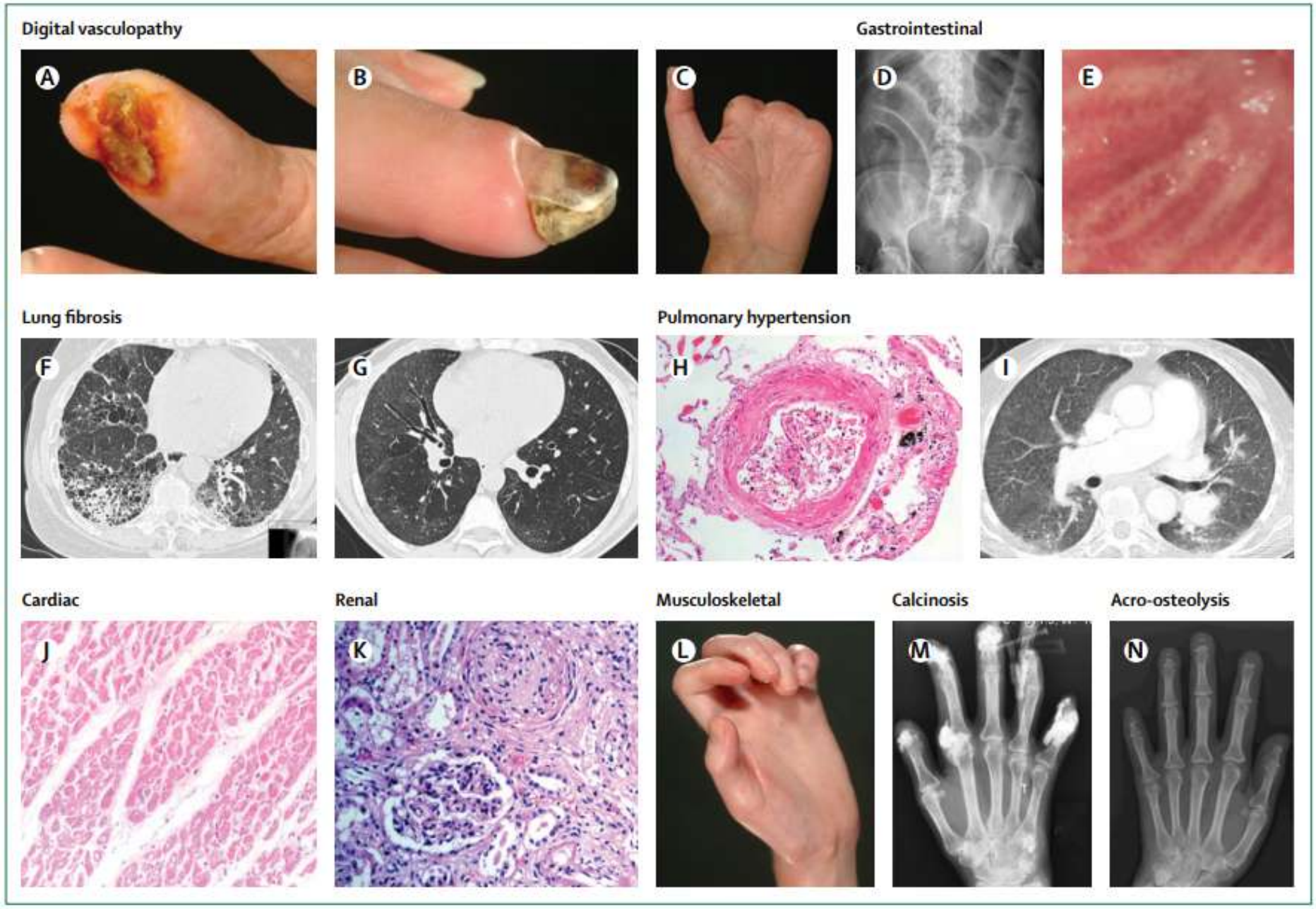
- Mortalitesi ən yüksək autoimmun xəstəlikdir
- Xəstələrin yarısı xəstəliyin özü və ya ona bağlı ağırlaşmadan vəfat edir

Pulmonar xəstəlik
Ağciyər xəstəliyi
Kanser
Renal xəstəlik
İnfeksiya

- Xəstəliyin diaqnostikası gecikir
- Raynaud fenomeni (RF) başlanğıcından > 10 il sonra
- İlk non-RF əlamətdən 12 ay sonra

- Erkən simptomların çoxu qeyri-spesifikdir
- Nadir rast gəlinir
- Autoimmun testlər və kapillaroskopiya hər zaman əlçatan deyil

The 2024 British Society for Rheumatology guideline for management of systemic sclerosis—executive summary Rheumatology, 2024, 63, 2948–2955



Systemic sclerosis Christopher P Denton, Dinesh Khanna Lancet 2017 Oct 7;390(10103):1685-169

Panel 1: Summary items from the 2013 American College of Rheumatology and European League Against Rheumatism criteria for the classification of systemic sclerosis*

Proximal skin involvement

- Skin thickening of the fingers of both hands, extending proximal to the metacarpophalangeal joints (sufficient criterion; score 9)

Skin thickening of the fingers (only count the higher score)

- Puffy fingers (score 2)
- Sclerodactyly of the fingers (distal to the metacarpophalangeal joints but proximal to the proximal interphalangeal joints; score 4)

Fingertip lesions (only count the higher score)

- Digital tip ulcers (score 2)
- Fingertip pitting scars (score 3)

Telangiectasia (score 2)

Abnormal nailfold capillaries (score 2)

Pulmonary arterial hypertension or interstitial lung disease (maximum score of 2)

- Pulmonary arterial hypertension (score 2)
- Interstitial lung disease (score 2)

Raynaud's phenomenon (score 3)

Systemic sclerosis-related autoantibodies (maximum score of 3)

- Anti-centromere (score 3)
- Anti-topoisomerase I (score 3)
- Anti-RNA polymerase III (score 3)

*A total score of 9 is needed for a definite classification.

Panel 2: Typical features of the major subsets of systemic sclerosis

Limited cutaneous systemic sclerosis

- Distal skin sclerosis
- Long history of Raynaud's phenomenon
- Late-stage complications frequent
- Pulmonary arterial hypertension and severe gut disease frequent and serious

Diffuse cutaneous systemic sclerosis

- Proximal limb or trunk involvement, with skin sclerosis
- Short history of Raynaud's phenomenon
- Increased risk of renal crisis and cardiac involvement
- High frequency of severe lung fibrosis

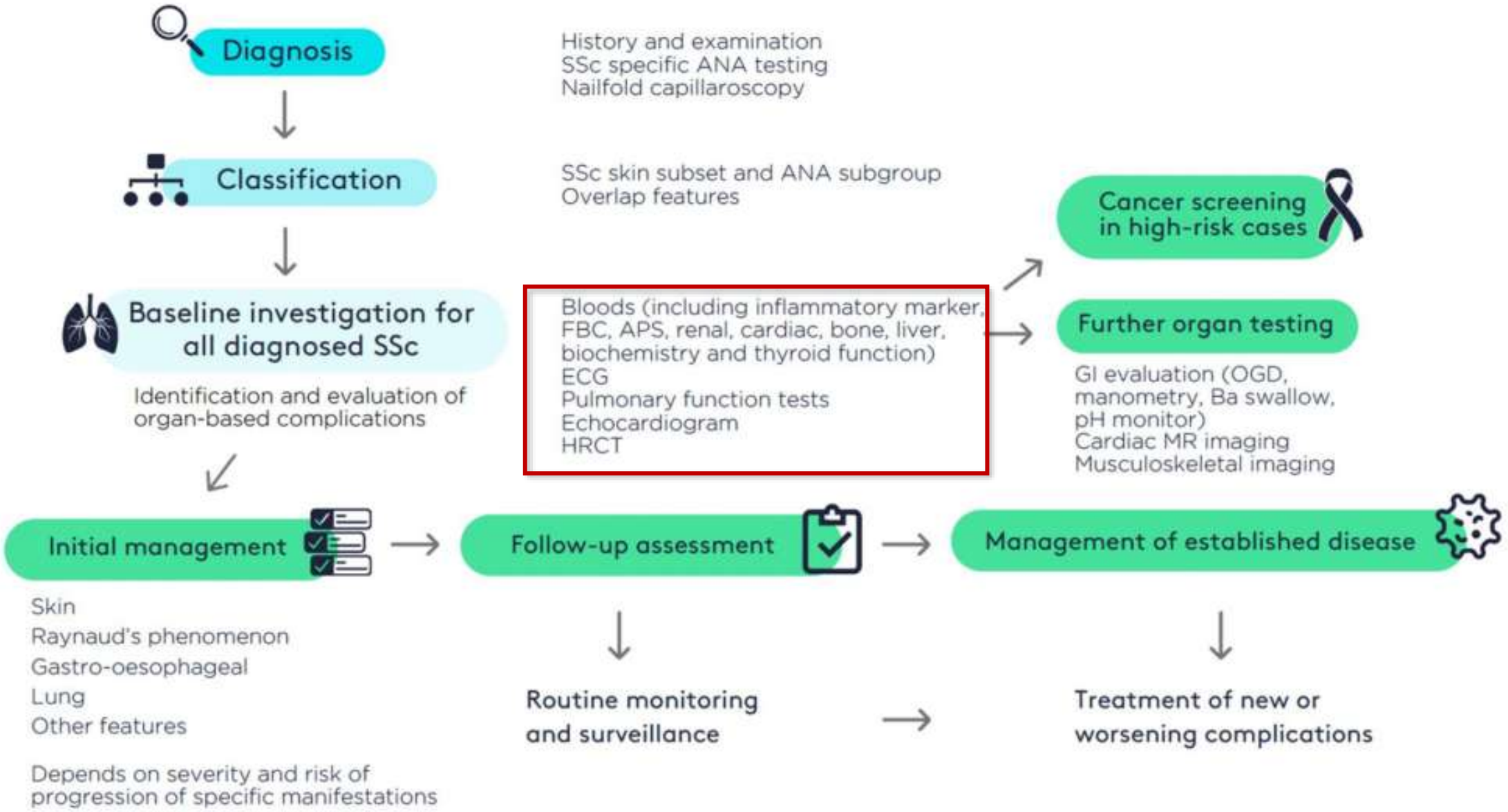
Sine scleroderma

- Raynaud's phenomenon
- Typical systemic sclerosis serology or capillaroscopic features
- No skin thickening
- Organ-based or other vascular manifestations

Systemic sclerosis overlap syndrome

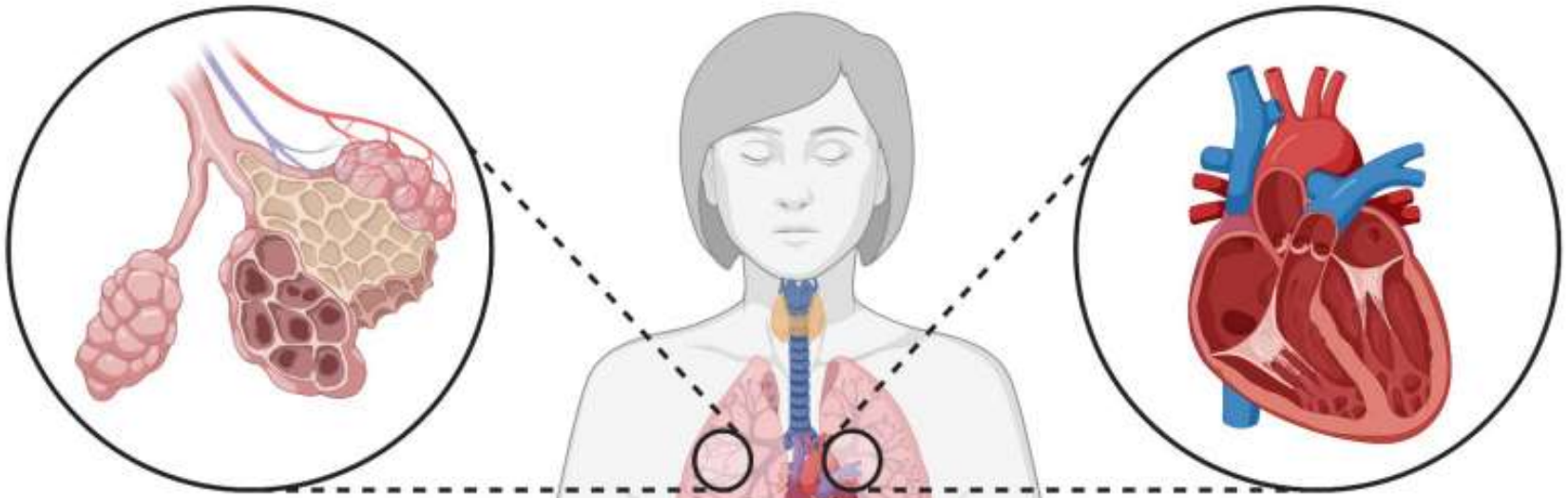
- One of the three subsets together with clinical and investigational features of another autoimmune rheumatic disease

Systemic sclerosis Christopher P Denton, Dinesh Khanna Lancet 2017 Oct 7;390(10103):1685-169



The 2024 British Society for Rheumatology guideline for management of systemic sclerosis—executive summary Rheumatology, 2024, 63, 2948–2955

Pulmonary Complications of SSc



Antibodies Associated with Risk of ILD

Anti-topoisomerase 1
Anti-U11/U12 RNP
Anti-Th/To
Anti- EIF2B

Antibodies Associated with Risk of PAH

Anti-U3 RNP
Anti-centromere
Anti-Th/To
Anti-nuclear
Anti-phospholipid

A

B

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- SSk-PAH kimlərdə daha çoxdur?
- Yaşlı xəstə
- Uzun xəstəlik müddəti
- Anti sentromer AT
- Anti-topoisomerase I AT
- Anti-U3-RNP AT
- Yüksək eritrosit çökmə sürəti
- Digital xora və pittinq skar

- Limitli dəri zədələnməsi olanlarda PAH daha çox rast gəlinir
- Xəstəlik daha gec yaşda başlayır
- Bu xəstələr daha uzun yaşayır

- Afrika mənşəyi PAH riskini artırır

- Ağciyər parenximası və qan dövranı pozğunluqları xəstəliyin hərhansı mərhələsində inkişaf edə bilər.

- SSk’da 8-12% halda PH inkişaf edir
- LdSSk və DdSSk arasında PAH insidansı hər 100 xəstə/il üçün 1.25 ve 0.4’dir

- Mortalitesi yüksəkdir (3 illik sürvi 52%)

- Mortalite və hospitalizasiyanı əsas müəyyən edən faktor pulmonar hipertenziyadır

Pulmonary hypertension phenotypes in patients with systemic sclerosis Eur Respir Rev 2021 A. Haque et al.
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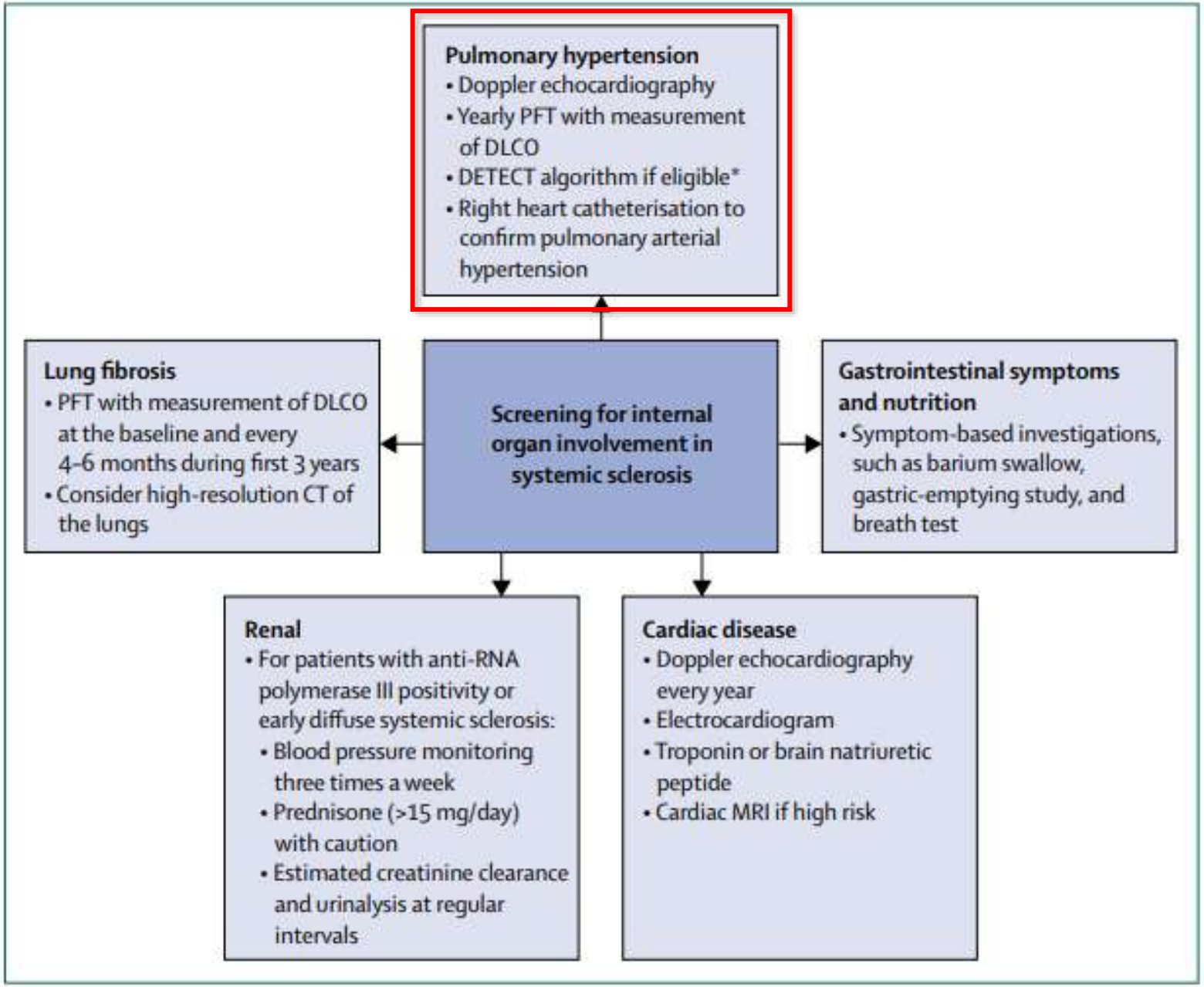

Systemic sclerosis Christopher P Denton, Dinesh Khanna Lancet 2017 Oct 7;390(10103):1685-169

- Qadın>Kişi

- Kişilərdə gec diaqnostika, daha ağır xəstəlik, daha pis proqnoz

- SSk-PAH'n proqnozu digər qrup 1 PAH'dan daha pisdir
- SSk-PAH'n müalicəyə cavabı İPAH ilə müqayisədə daha az və sürvisi daha qısadır

- Gec yaşda diaqnoz, NYHA funksional təsnifatda pis funksional sinif, hiponatremiya pis proqnostik faktorlardır

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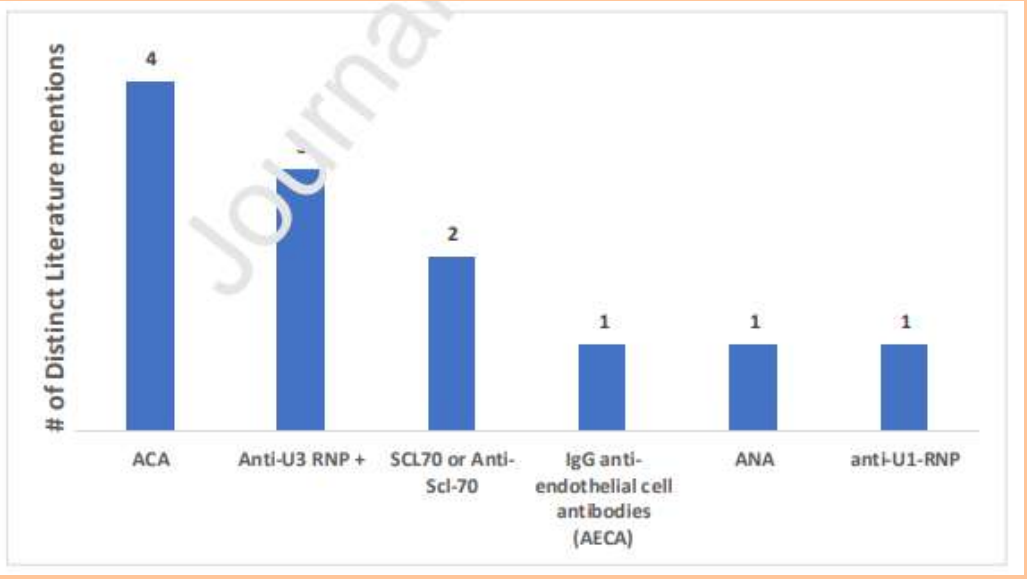
Autoimmunity Reviews
Volume 19, Issue 9, September 2020, 102602

Factors associated with pulmonary arterial hypertension (PAH) in systemic sclerosis (SSc)

Yuxuan Jiang [a], Matthew A. Turk [b], Janet E. Pope [c d]



Results

Among 2654 articles, 984 duplicates and 1578 irrelevant articles were removed, leaving 92 articles for manual screening. After excluding 55 papers with small sample sizes, publications from identical cohorts, not English language, or PAH n ascertained by RHC, 37 articles were eligible. A total of 43 factors for SSc-PAH we identified within seven categories. Several associations were due to PAH and risk factors such as dynpnea, right heart failure, and short 6-minute walk distance. Patient characteristics (14), pulmonary physiology (6), antibody profiles (6) and genetics/epigenetics (6) had the most numerous and diverse factors, while biomarkers (4) and other labs (2) features were infrequent. Low carbon monoxid (DLCO) (6), older age (4), longer disease duration (4), positive anticentromere antibodies (ACA) (4), telangiectasias (4), high brain natriuretic peptide (4) were frequent associations.

Conclusions

Risk factors for SSc-PAH such as ACA, older age, longer disease duration limited cutaneous SSc subset and presence of ILD may enrich screening programs. Genes and other antibody profiles are inconsistent and requires further validation.

Seminars in Arthritis and Rheumatism 51 (2021) 495–512

Contents lists available at ScienceDirect

Seminars in Arthritis and Rheumatism

journal homepage: www.elsevier.com/locate/semarthrit

Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: A systematic review and meta-analysis of long-term outcomes

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ARTICLE INFO

Keywords:
Pulmonary arterial hypertension
Screening
Outcomes
Survival
Systemic sclerosis
Scleroderma
Screening algorithms

ABSTRACT

Background: Systemic sclerosis (scleroderma, SSc) is a chronic multisystem autoimmune disease characterised by fibrosis of the skin and internal organs and vasculopathy. One of the major contributors to mortality in patients with SSc is pulmonary arterial hypertension (PAH). International recommendations advise annual screening for the early detection of PAH in asymptomatic patients with SSc.
Objectives: To evaluate by systematic review current measures employed for screening for PAH. To summarise by meta-analysis the current evidence for long-term outcomes of screening for PAH in SSc.
Methods: Manuscripts published until 12th March 2019 were identified through searching Medline, Embase and Cochrane Central Register of Controlled Trials and Database of Systematic Reviews. Eligible studies included abstracts or full reports investigating patients with SSc undergoing screening by any protocol to detect PAH. Risk of bias was assessed with reference to the QUADAS-2 tool.
Results: The review resulted in 580 unique citations with 15 manuscripts included for final systematic review of screening methods, and six for meta-analysis. The systematic review demonstrated that there are varying protocols for screening for PAH. Screened populations were reported to have better risk stratification parameters at PAH diagnosis. Meta-analysis showed improved survival in patients with SSc-PAH diagnosed as a result of screening. There were trends towards having better risk stratification parameters at PAH diagnosis in those screened, although not all of these were statistically significant.
Limitations: There are no randomised controlled trials of screening for PAH in patients with SSc and the evidence presented in this review is derived from publications of registry data, cross-sectional and cohort studies.
Conclusions: This review demonstrates long-term benefit through the systematic screening of patients with SSc of varying disease duration for the early detection of PAH. Screened cohorts had improved survival, and were more likely to have better prognostic factors at the time of diagnosis with PAH.

- Proqnozu yaxşılaşdırmağın əsas yolu erkən aşkarlamaqdır

Sağqalım	Simptomatik olmadan skrininq olanlar	PAH diaqnozu qoyulanda simptomatik olanlar
1 illik	100%	75%
3 illik	81%	31%
5 illik	73%	25%
8 illik	64%	17%

Diagnostic and prognostic markers and treatment of connective tissue disease-associated pulmonary arterial hypertension: current recommendations and recent advances Masaru Kato et al Expert Review of Clinical Immunology 2021

- 2015 ESC/ERS international guidelines
- DETECT algorithm
- Australian Scleroderma Interest Group (ASIG) algorithm

Screening for the early detection of pulmonary arterial hypertension in patients with systemic sclerosis: A systematic review and meta-analysis of long-term outcomes Brown et al Seminars in Arthritis and Rheumatism 51 (2021) 495-512

Screening and improved detection of pulmonary arterial hypertension and chronic thrombo-embolic pulmonary hypertension – Recommendation Table 3				
N			In patients with SSc, an annual evaluation of the risk of having PAH is recommended	I
R	Resting echocardiography is recommended as a screening test in asymptomatic patients with SSc, followed by annual screening with echocardiography, DLCO, and biomarkers	I	In adult patients with SSc of >3 years' disease duration, an FVC ≥40%, and a DLCO <60%, the DETECT algorithm is recommended to identify asymptomatic patients with PAH	I
N			In patients with SSc, where breathlessness remains unexplained following non-invasive assessment, RHC is recommended to exclude PAH	I
N			Assessing the risk of having PAH, based on an evaluation of breathlessness, in combination with echocardiogram or PFTs and BNP/NT-proBNP, should be considered in patients with SSc	IIa
N			Policies to evaluate the risk of having PAH should be considered in hospitals managing patients with SSc	IIa
R	RHC is recommended in all cases of suspected PAH associated with CTD	I	In symptomatic patients with SSc, exercise echocardiography or CPET, or CMR may be considered to aid decisions to perform RHC	IIb
N			In patients with CTD with overlap features of SSc, an annual evaluation of the risk of PAH may be considered	IIb

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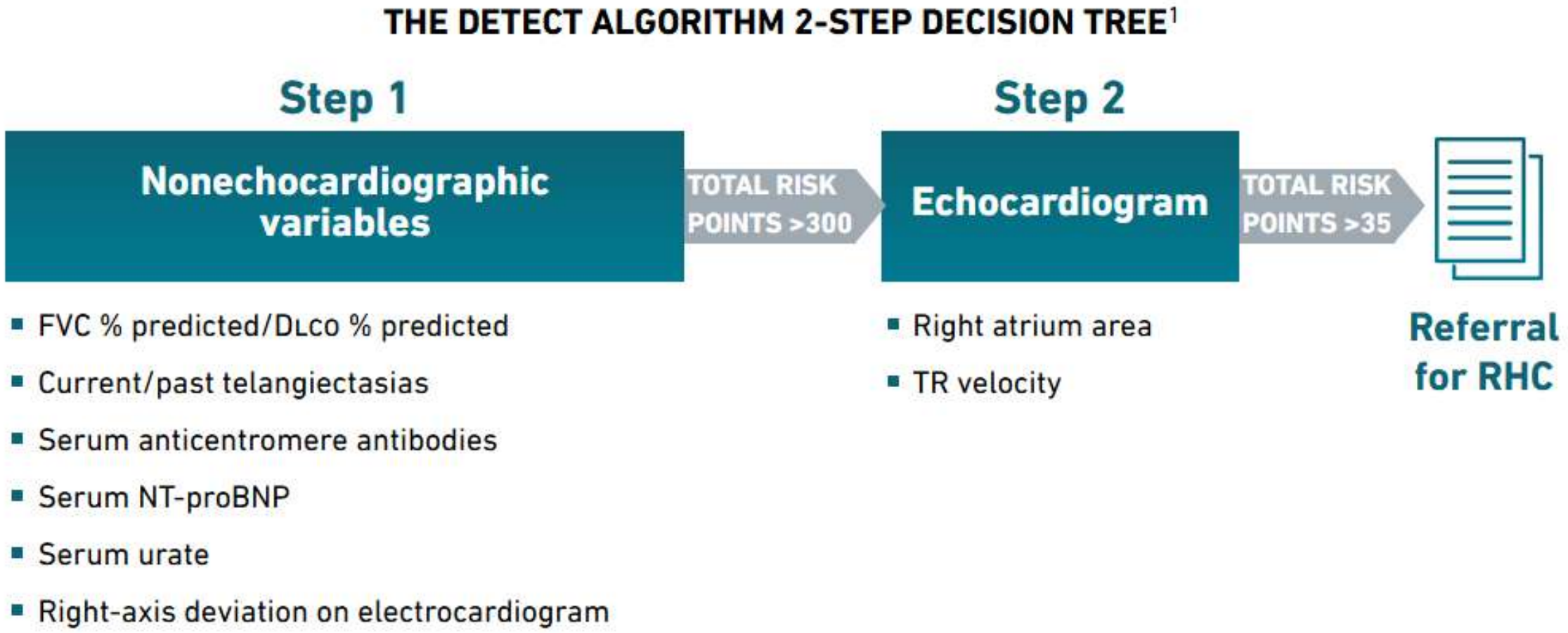
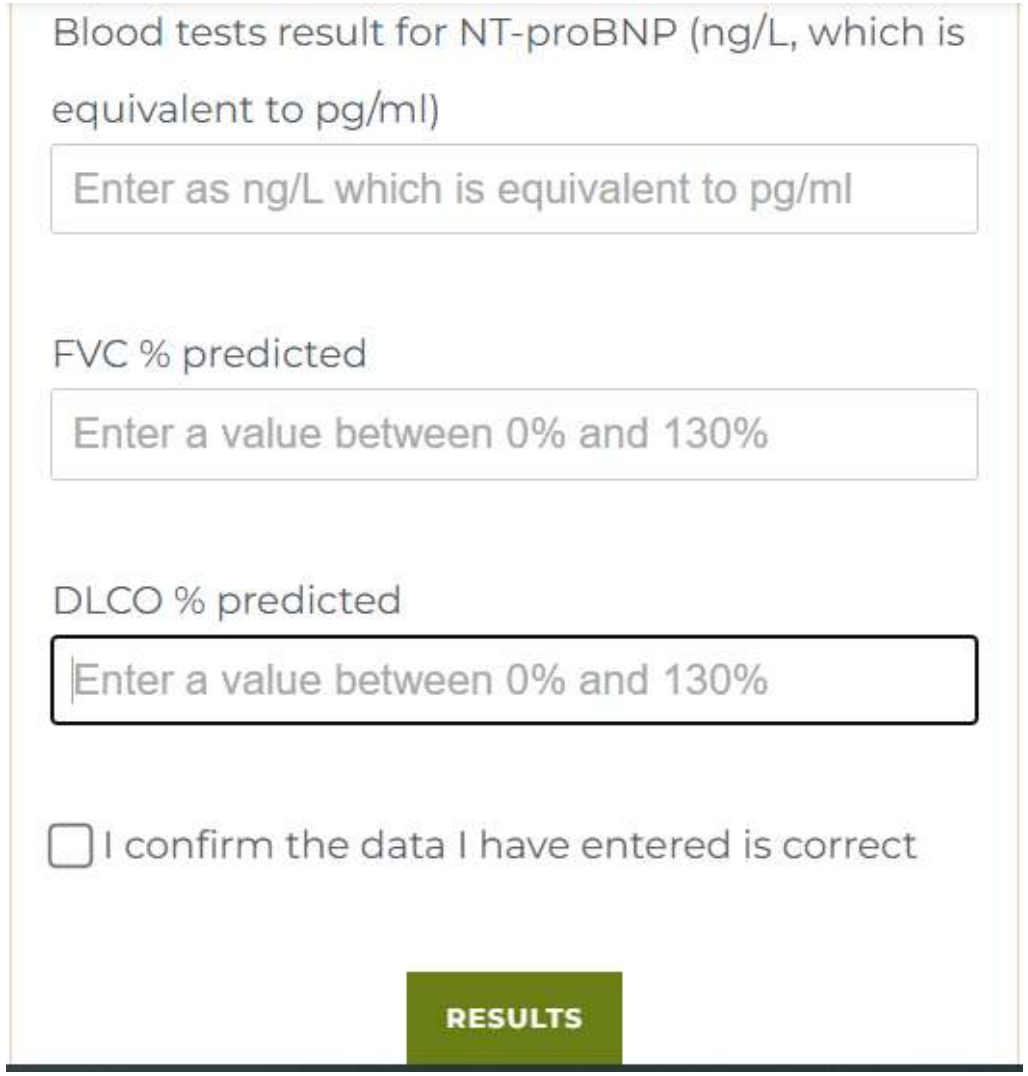
DETECT alqoritmi



Diagnostic and prognostic markers and treatment of connective tissue disease-associated pulmonary arterial hypertension: current recommendations and recent advances Masaru Kato et al Expert Review of Clinical Immunology 2021

Australian Scleroderma Interest Group (ASIG) alqoritmi



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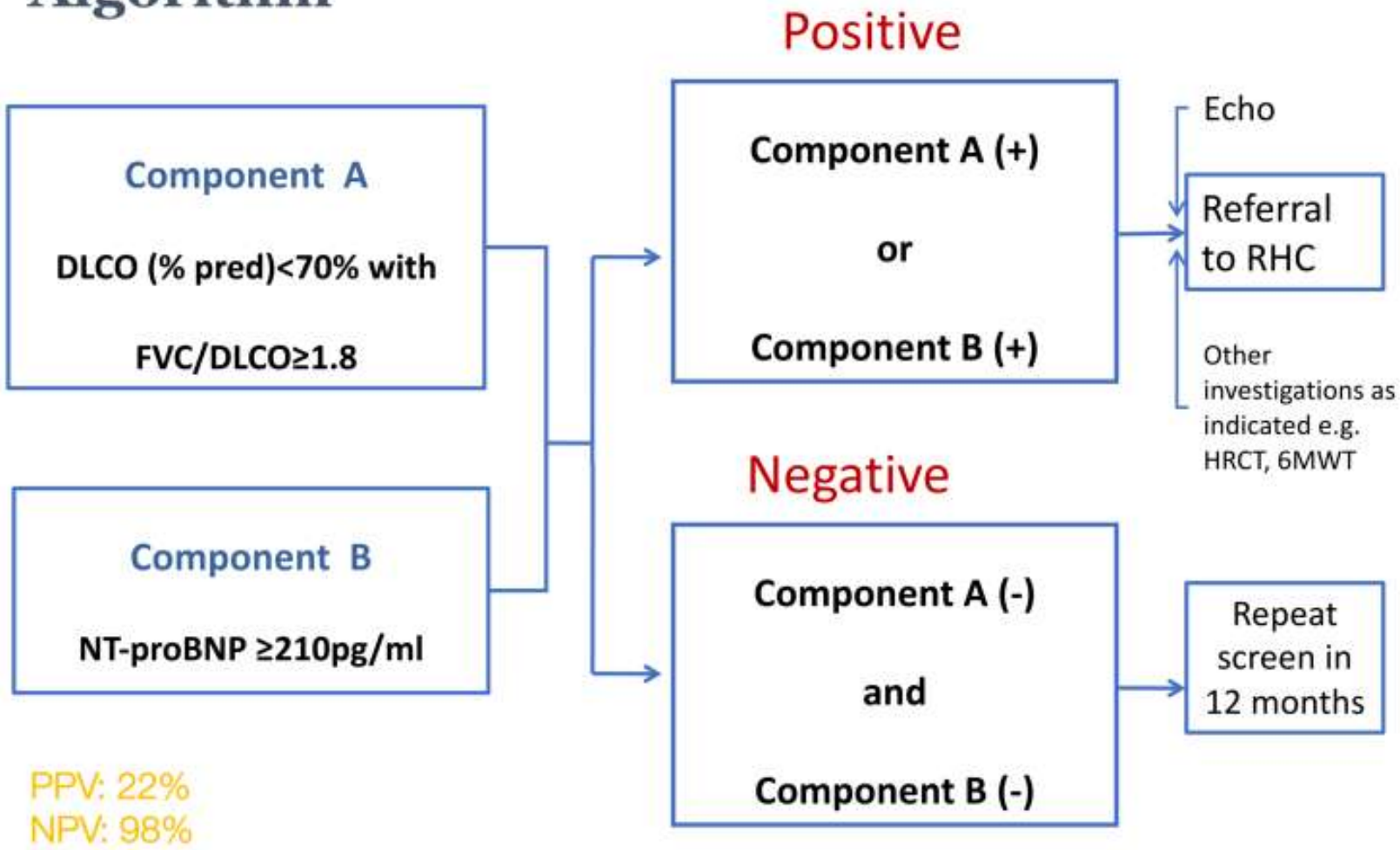
ASIG Pulmonary Arterial Hypertension Screening Algorithm



Footnotes:
DLCO (%pred) – diffusion capacity for carbon monoxide (Corrected) % of predicted value; FVC – Forced Vital Capacity; FVC/DLCO – FVC/DLCO ratio; NT-proBNP – serum N-terminal pro-brain type natriuretic peptide; Echo – transthoracic echocardiography; HRCT – High resolution computed tomography; 6MWT – 6 minute walk test; PPV – positive predictive value; NPV – negative predictive value

https://asigresearch.com.au/screening-for-pah/

Evaluating the disease severity and risk of death in patients with pulmonary arterial hypertension – Recommendation Table 4				
N			For risk stratification at the time of diagnosis, the use of a three-strata model (low, intermediate, and high risk) is recommended, taking into account all available data including haemodynamics	I
N			For risk stratification during follow-up, the use of a four-strata model (low, intermediate–low, intermediate–high, and high risk) based on WHO-FC, 6MWD, and BNP/NT-proBNP is recommended, with additional variables taken into account as necessary	I
R	Achievement/maintenance of an intermediate-risk profile should be considered an inadequate treatment response for most patients with PAH	IIa	In some PAH aetiologies and in patients with comorbidities, optimization of therapy should be considered on an individual basis while acknowledging that a low-risk profile is not always achievable	IIa

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ESC/ERS three-strata model

Determinants of prognosis (estimated 1-year mortality)	Low risk (<5%)	Intermediate risk (5–20%)	High risk (>20%)
Clinical observations and modifiable variables			
Signs of right HF	Absent	Absent	Present
Progression of symptoms and clinical manifestations	No	Slow	Rapid
Syncope	No	Occasional syncope[a]	Repeated syncope[b]
WHO-FC	I, II	III	IV
6MWD[c]	>440 m	165–440 m	<165 m
CPET	Peak VO_2 >15 mL/min/kg (>65% pred.) VE/VCO_2 slope <36	Peak VO_2 11–15 mL/min/kg (35–65% pred.) VE/VCO_2 slope 36–44	Peak VO_2 <11 mL/min/kg (<35% pred.) VE/VCO_2 slope >44
Biomarkers: BNP or NT-proBNP[d]	BNP <50 ng/L NT-proBNP <300 ng/L	BNP 50–800 ng/L NT-proBNP 300–1100 ng/L	BNP >800 ng/L NT-proBNP >1100 ng/L
Echocardiography	RA area <18 cm^2 TAPSE/sPAP >0.32 mm/mmHg No pericardial effusion	RA area 18–26 cm^2 TAPSE/sPAP 0.19–0.32 mm/mmHg Minimal pericardial effusion	RA area >26 cm^2 TAPSE/sPAP <0.19 mm/mmHg Moderate or large pericardial effusion
cMRI[e]	RVEF >54% SVI >40 mL/m^2 RVESVI <42 mL/m^2	RVEF 37–54% SVI 26–40 mL/m^2 RVESVI 42–54 mL/m^2	RVEF <37% SVI <26 mL/m^2 RVESVI >54 mL/m^2
Haemodynamics	RAP <8 mmHg CI ≥2.5 $L/min/m^2$ SVI >38 mL/m^2 SvO_2 >65%	RAP 8–14 mmHg CI 2.0–2.4 $L/min/m^2$ SVI 31–38 mL/m^2 SvO_2 60–65%	RAP >14 mmHg CI <2.0 $L/min/m^2$ SVI <31 mL/m^2 SvO_2 <60%

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

ESC/ERS four-strata model

Determinants of prognosis	Low risk	Intermediate–low risk	Intermediate–high risk	High risk
Points assigned	1	2	3	4
WHO-FC	I or II[a]	-	III	IV
6MWD, m	>440	320–440	165–319	<165
BNP or NT-proBNP,[a] ng/L	<50 <300	50–199 300–649	200–800 650–1100	>800 >1100
1 illik mortalite	0– 3%	2–7%	9–19%	20%

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- SSk-PAN’n sağqalımı İPAH və non-BTX-PAH ilə müqayisədə daha azdır
- *SSk-PAN’n 1 və 3 illik sağqalımı 80% və 50%dir*

- SSk-PAH’da mortalite artışını göstərən faktorlar:
- Kişi cinsiyyət
- Yüksək WHO funksional sinifi
- Kiçik 6 dq yerimə testi məsafəsi
- Ağır hemodinamik pozğunluq
- Yüksək sağ qulaqcıq təzyiqi
- Aşağı DLCO
- Yüksək NT-proBNP səviyyəsi
- Yüksək serum sidik turşusu səviyyəsi
- Perikardial effuziya

Diagnostic and prognostic markers and treatment of connective tissue disease-associated pulmonary arterial hypertension: current recommendations and recent advances Masaru Kato et al Expert Review of Clinical Immunology 2021

SSk-PVOX

- Pulmonar venookluzif xəstəlik (SSk-PVOX) : pulmonar vena və venulların zədələnməsi ilə seyr edən nadir PH formasıdır

- BMPR2, EIF2AK4 genində mutasiya
- Alkilləşdirici kimyəvi terapiya

- İnsidansı 0.5/milion/il

- Venoz intimal fibroz
- Alveolyar kapilyarlarda genişləmə
- Angioproliferativ lezyonlar
- Pulmonar arteriyada intimal fibroz və medial hipertrofiya
- Pleksiform lezyonlar olmaz

- DLCO'da ciddi azalma (35%)
- Mediastinal limfa düyünlərində böyümə
- Sentrilobulyar buzlu şüşə opasiteləri/nodulları
- Septal cizgilənmələr
- PAH spesifik müalicəyə məhdud cavab və müalicə altında pulmonar ödem riski

Pulmonary hypertension phenotypes in patients with systemic sclerosis Eur Respir Rev 2021 A. Haque et al.

- İstirahətdə hipoksik və SpO2 < 92%’də ≥ 15 saat oksigen dəstəyi
- 6 dəq yerimə testində SpO2 ≤88% ’də ambulator oksigen dəstəyi

- Dəmir çatışmazlığı anemiyasında dəmir çatışmazlığının bərpası

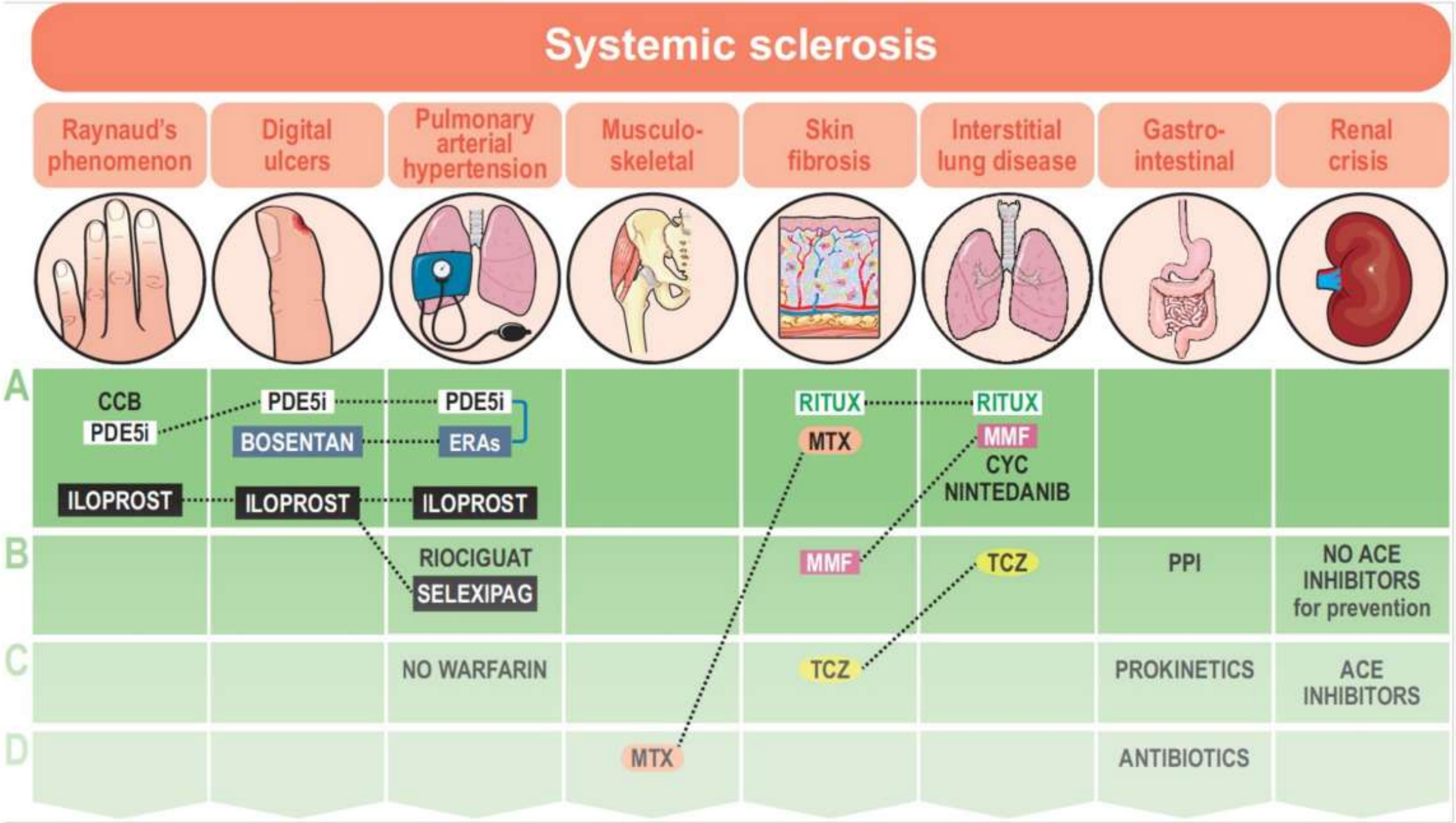
- SARS-CoV-2, influenza və Streptococcus pneumoniae peyvəndi

- Kontrasepsiya və hamiləlik planlaması

- Psixososyal dəstək

- Diuretiklər (volum yüklənməsinin qarşısını almaq üçün)
- Atrial aritmiya ilə ağırlaşan sağ ürək çatışmazlığında diqoksin
- SÜK’da vazoreaktivite test (+) olanlarda kalsiyum kanal blokatorları (KKB)

Clinical features of pulmonary arterial hypertension associated with systemic sclerosis Tuhy et al Frontiers in Medicine 2023
The 2024 British Society for Rheumatology guideline for management of systemic sclerosis—executive summary Rheumatology, 2024, 63, 2948–2955

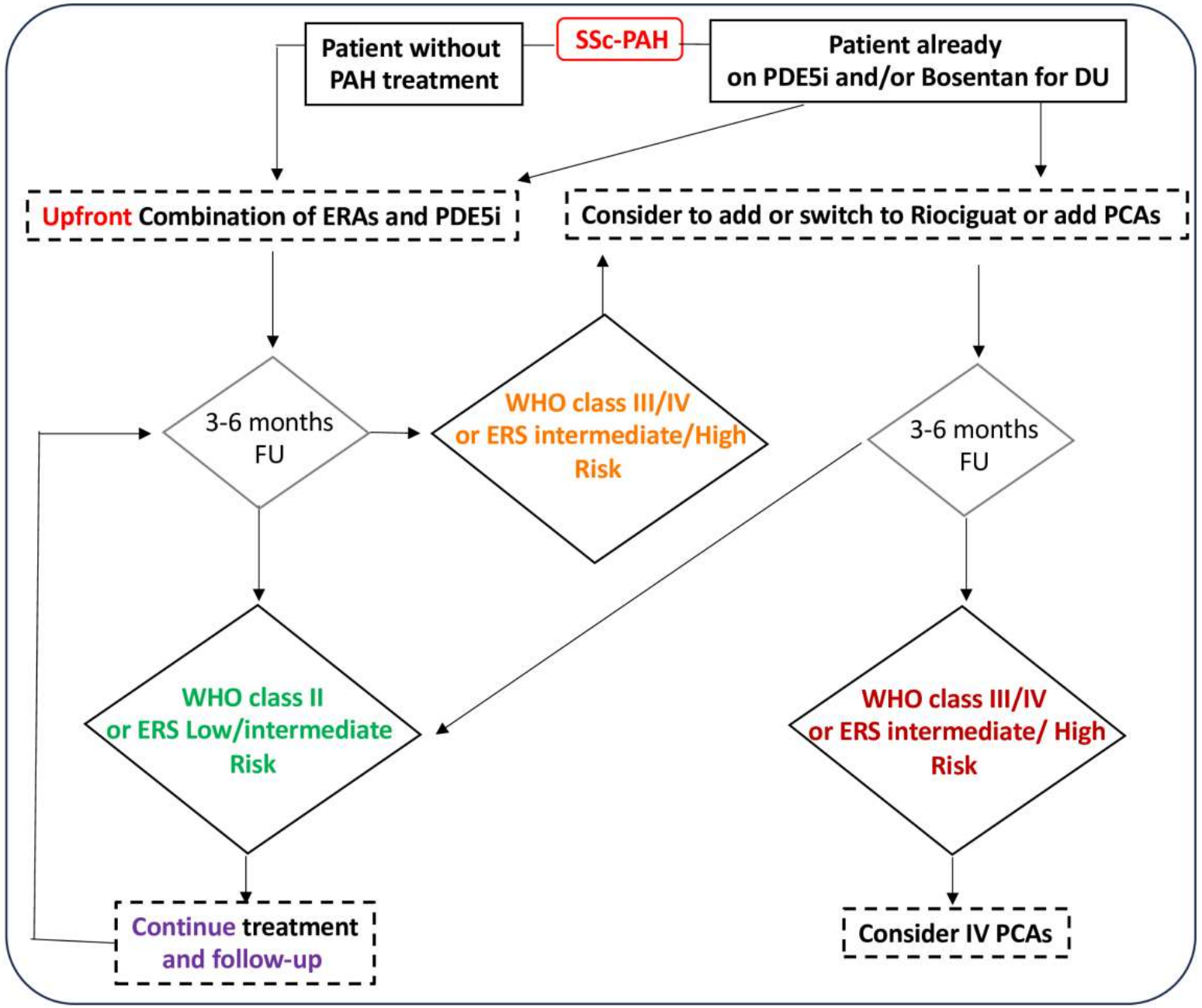


Del Galdo F, et al. Ann Rheum Dis 2024;0:1–12. doi:10.1136/ard-2024-226430

Table 1 Updates of EULAR recommendations for the treatment of systemic sclerosis

Organ involvement	Recommendation	LoE	SoR	LoA (SD)	% LoA>8
SSc-RP	Dihydropyridine-type calcium antagonists, usually oral nifedipine, should be used as first-line therapy for SSc-RP.	1a	A	8.6 (2.4)	88
	PDE5 inhibitors should also be considered for treatment of SSc-RP.	1a	A	8.6 (2.4)	88
	Intravenous iloprost should be considered for severe SSc-RP following failure of oral therapy.	1a	A	9.0 (1.4)	80
Digital ulcers	PDE5 inhibitors and/or intravenous iloprost should be considered for the treatment of digital ulcers in patients with SSc.	1a	A	8.8 (1.9)	92
	Bosentan should be considered for reduction of number of new digital ulcers in SSc.	1a	A	8.0 (2.5)	84
SSc-PAH	Combination of PDE5i and endothelin receptor antagonists should be considered as first-line treatment of SSc PAH.*	1a	A	8.1 (2.9)	80
	Intravenous epoprostenol should be considered for the treatment of SSc patients with advanced PAH (class III and IV)	1a	A	7.7 (3.1)	76
	Other prostacyclin analogues or agonists should be considered for the treatment of SSc PAH	1b	B	7.7 (3.1)	76
	Riociguat can be considered for treatment of SSc PAH	1b	B	8.0 (2.4)	76
	The use of anticoagulants (warfarin) for the treatment of SSc-PAH is not recommended*	2a	C	8.2 (2.1)	68
Renal crisis	ACE inhibitors should be used immediately at diagnosis of scleroderma renal crisis	4	C	8.4 (2.6)	84
	SSc patients treated with glucocorticoids should have regular monitoring of blood pressure to detect scleroderma renal crisis	3	C	7.9 (3.1)	84
Gastrointestinal involvement	PPI should be considered for the treatment of SSc-GERD and prevention of oesophageal ulcers and strictures	3	B	8.3 (2.5)	84
	The use of prokinetic drugs should be considered for the treatment of symptomatic motility disturbances related to SSc	1b	C	8.0 (2.3)	72
	The use of rotating antibiotics should be considered for the treatment of small intestinal bacterial overgrowth	2b	D	7.3 (2.7)	60
Skin	Methotrexate (1B), mycophenolate mofetil (MMF) (1B) and/or rituximab (1A) should be considered for treatment of SSc skin fibrosis*	1a-b	A/B	7.6 (3.2)	72
	Tocilizumab may be considered for the treatment of skin fibrosis in patients with early, inflammatory dcSSc*	1b	C	7.2 (2.1)	60
ILD	MMF (1A), cyclophosphamide (1A) or rituximab (1A) should be considered for the treatment of SSc-ILD*	1a	A	8.1 (2.8)	88
	Nintedanib should be considered alone or in combination with MMF for the treatment of SSc-ILD*	1a	A	8.5 (2.5)	84
	Tocilizumab should be considered for the treatment of SSc-ILD*	1b	B	7.8 (2.8)	76
Poor prognosis	High-intensity immunosuppression (usually including cyclophosphamide) followed by autologous HSCT may be considered for the treatment of selected patients with early dcSSc and poor prognosis, in the absence of advanced cardiorespiratory involvement	1a	A	7.8 (2.5)	68
Musculoskeletal	Methotrexate should be considered for the treatment of musculoskeletal involvement in SSc.	2b	D	7.8 (2.7)	80

Del Galdo F, et al. Ann Rheum Dis 2024;0:1–12. doi:10.1136/ard-2024-226430



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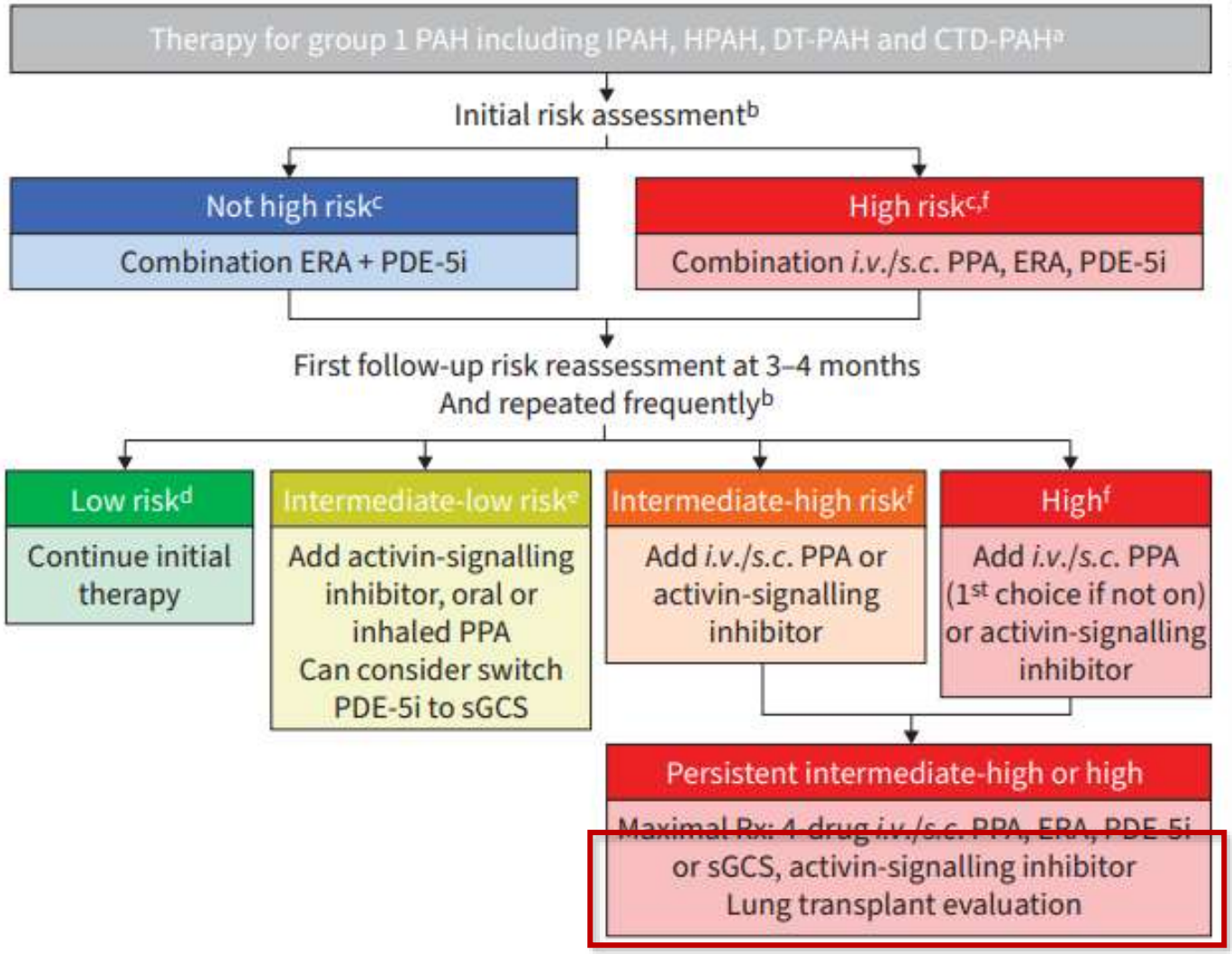


Treatment algorithm key points

a. The treatment algorithm is intended for patients with confirmed group 1 PAH (phenotypically clear-cut, including **mPAP ≥25 mmHg and PVR >3 Wood Units** and no significant response on acute vasoreactivity testing). See text for treatment in PAH with complex phenotypes.

b. ***Risk assessment*** should be performed at baseline, within 3–4 months and periodically thereafter, and using FC, 6MWD and natriuretic peptides as a part of a validated risk calculator. Haemodynamics, RV imaging and other measures should be used to supplement risk assessment.

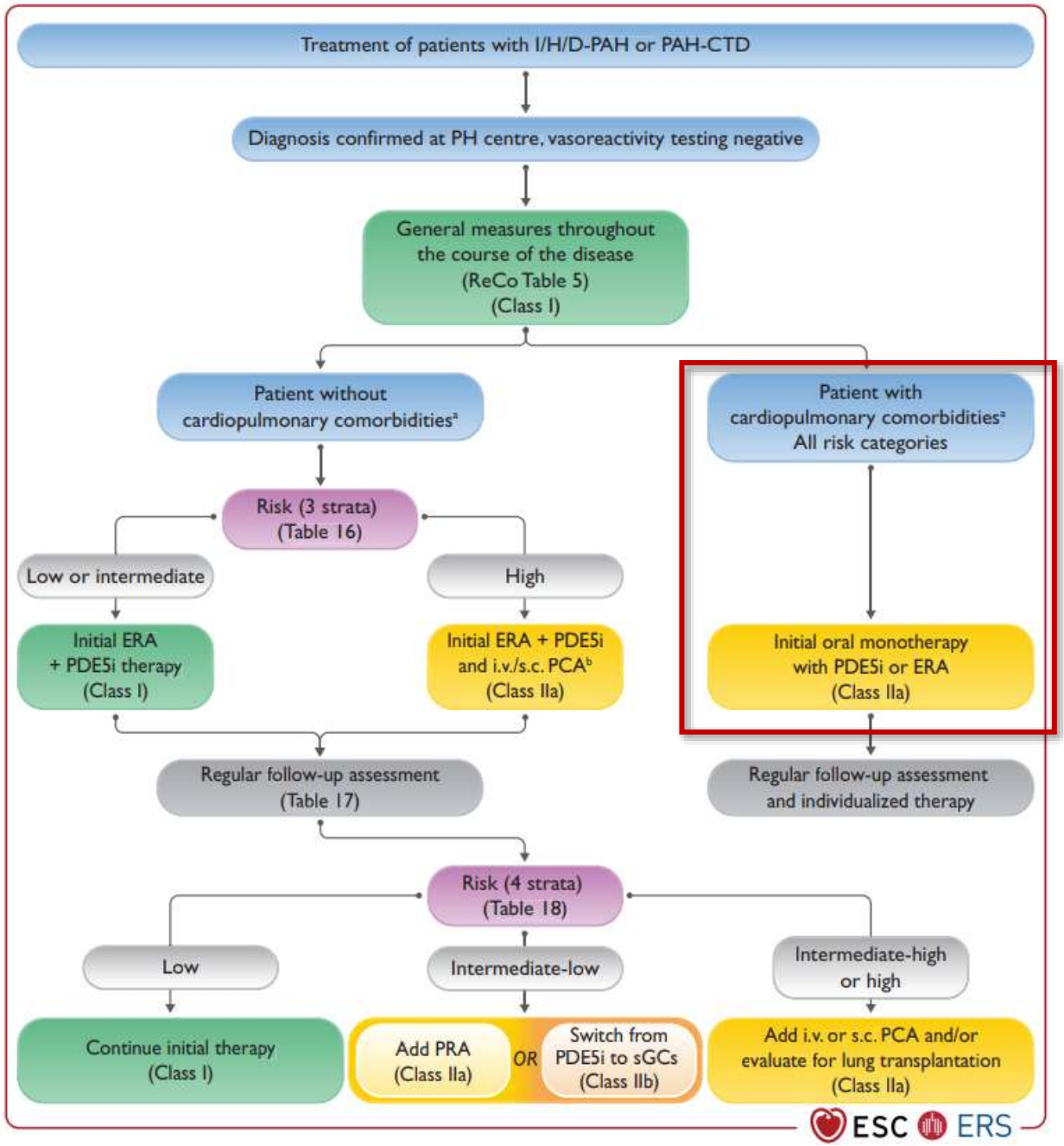
c. ***Initial triple therapy*** with an *i.v./s.c.* PPA is recommended in high-risk patients and may be considered in non-high risk with severe haemodynamics and/or poor RV function.

d. Most ***low-risk patients*** at follow-up should continue initial therapy.

e. Clinical trials with oral and inhaled treprostinil included ***only patients on monotherapy***, while studies of selexipag and sotarcept included patients on combination therapy.

f. ***Transplant referral*** should be considered for select high-risk patients at diagnosis, and for intermediate-high and high-risk patients at first or subsequent follow-up.

Treatment algorithm for pulmonary arterial hypertension EUROPEAN RESPIRATORY JOURNAL 2024 7TH WORLD SYMPOSIUM ON PULMONARY HYPERTENSION | K.M. CHIN ET AL



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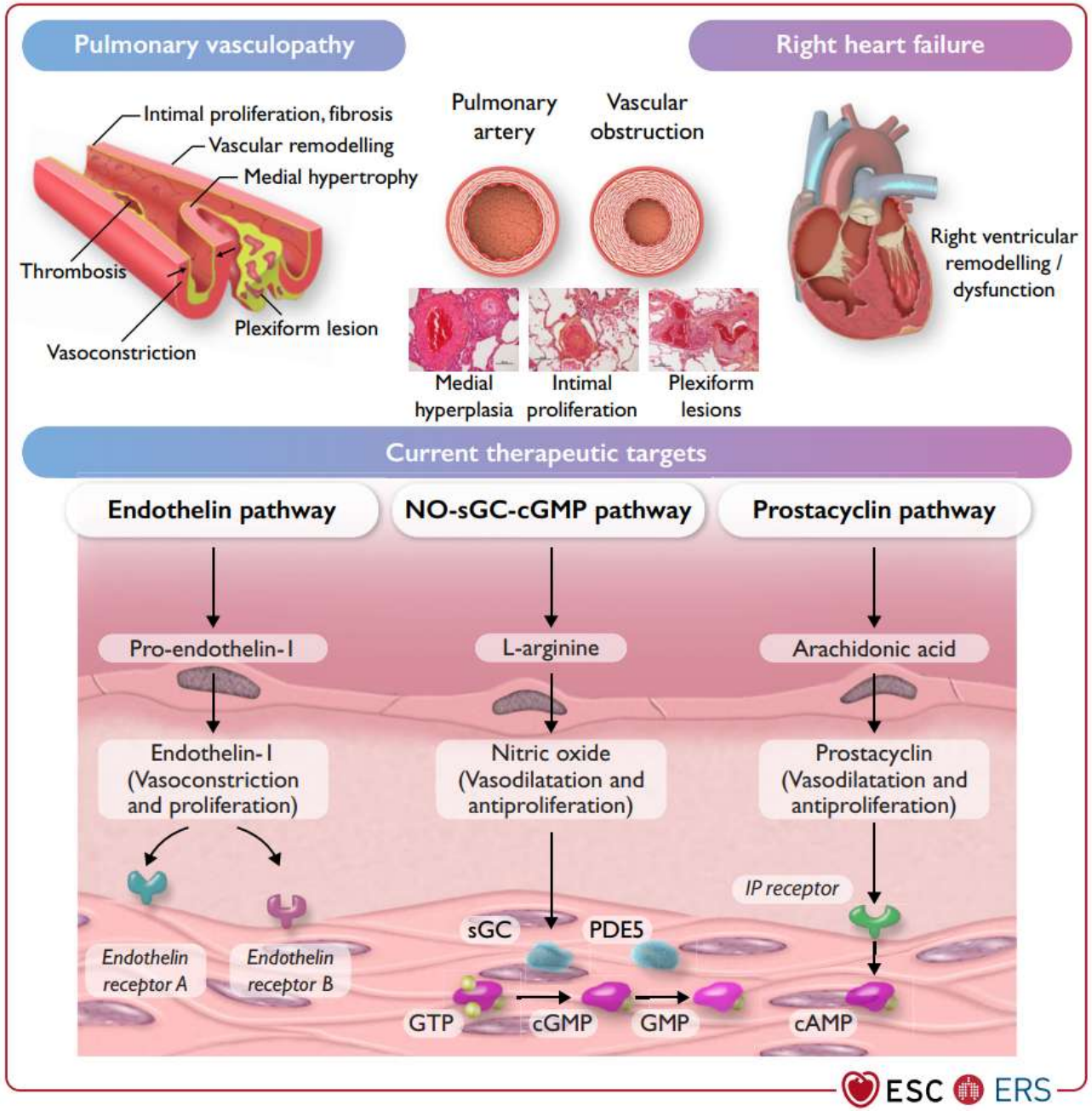

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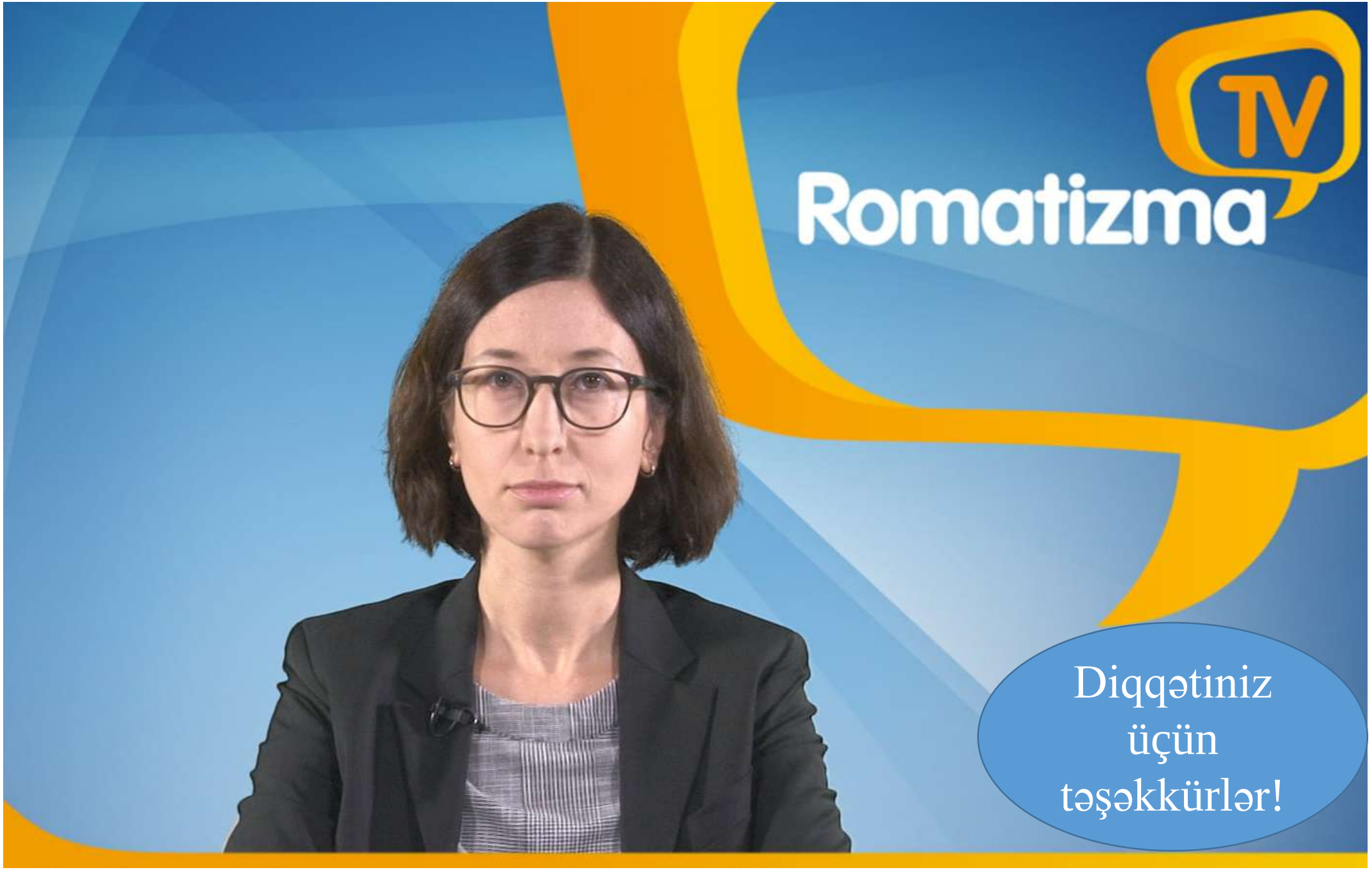
Therapy	Dosing
Endothelin receptor antagonists	
Ambrisentan	5–10 mg daily orally
Bosentan	62.5–125 mg, twice per day orally
Macitentan	10 mg daily orally
Phosphodiesterase 5 inhibitors	
Sildenafil	20 mg three times per day orally
Tadalafil	40 mg daily orally
Prostacyclin analogues	
Epoprostenol	1–12 ng/kg/min continuous intravenous infusion via central venous catheter Dose titrated up every 1–2 weeks
Iloprost, inhaled	Initial dose: 2.5 µg inhaled; if well-tolerated, then 5 µg subsequent doses 6–9 times per day as needed; not more than once every 2 h while awake Maintenance: 2.5–5 µg per dose; not to exceed 45 µg per day
Iloprost, intravenous[a]	Intravenous infusion over 6 h daily at 0.5–2.0 ng/kg /min
Selexipag	200 to 1600 µg twice per day orally
Treprostinil, subcutaneous	0.625 to 1.25 ng/kg/min continuous intravenous infusion via central venous catheter or continuous subcutaneous infusion
Trepostinil, inhaled	18 µg inhaled four times per day
Soluble guanylate cyclase stimulator	
Riociguat	Initial dose: 0.5–1 mg three times per day orally, titrated up by 0.5 mg three times per day every 2 weeks to a maximum dose of 2.5 mg three times per day orally

	Starting dose	Target dose
Calcium channel blockers		
Amlodipine	5 mg o.d.	15–30 mg o.d.[a]
Diltiazem	60 mg b.i.d.[b]	120–360 mg b.i.d.[b]
Felodipine	5 mg o.d.	15–30 mg o.d.[a]
Nifedipine	10 mg t.i.d.	20–60 mg b.i.d. or t.i.d.
Endothelin receptor antagonists (oral administration)		
Ambrisentan	5 mg o.d.	10 mg o.d.
Bosentan	62.5 mg b.i.d.	125 mg b.i.d.
Macitentan	10 mg o.d.	10 mg o.d.
Phosphodiesterase 5 inhibitors (oral administration)		
Sildenafil	20 mg t.i.d.	20 mg t.i.d.[c]
Tadalafil	20 or 40 mg o.d.	40 mg o.d.
Prostacyclin analogues (oral administration)		
Beraprost sodium	20 µg t.i.d.	Maximum tolerated dose up to 40 µg t.i.d.
Beraprost extended release	60 µg b.i.d.	Maximum tolerated dose up to 180 µg b.i.d.
Treprostinil	0.25 mg b.i.d. or 0.125 mg t.i.d.	Maximum tolerated dose
Prostacyclin receptor agonist (oral administration)		
Selexipag	200 µg b.i.d.	Maximum tolerated dose up to 1600 µg b.i.d.
Soluble guanylate cyclase stimulator (oral administration)		
Riociguat[d]	1 mg t.i.d.	2.5 mg t.i.d.
Prostacyclin analogues (inhaled administration)		
Iloprost[e]	2.5 µg 6–9 times per day	5.0 µg 6–9 times per day
Treprostinil[e]	18 µg 4 times per day	54–72 µg 4 times per day
Prostacyclin analogues (i.v. or s.c. administration)		
Epoprostenol i.v.	2 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 16–30 ng/kg/min, with wide individual variability
Treprostinil s.c. or i.v.	1.25 ng/kg/min	Determined by tolerability and effectiveness; typical dose range at 1 year is 25–60 ng/kg/min, with wide individual variability

2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension

	Medications	Common adverse reactions	Other important information
Oral medications			
PDE-5i [18–21]	Sildenafil, tadalafil	Headache Flushing Dyspepsia Epistaxis	Rare loss of vision or hearing Avoid with nitrates, riociguat
Guanylyl cyclase stimulators [22]	Riociguat	Headache Dyspepsia Dizziness Hypotension	Avoid in pregnancy[#], avoid with nitrates, PDE-5i Monitor for hypotension; may require dose adjustment based on systemic SBP
Endothelin-1 receptor antagonists [21, 23–27]	Ambrisentan, bosentan, macitentan	Peripheral oedema Nasal congestion Anaemia[¶]	Avoid in pregnancy[#], monitor haemoglobin (all), liver function (monthly for bosentan, as clinically indicated for others)
Prostacyclin receptor agonists [28]	Selexipag	Prostanoid-type AEs[+]	Data on selexipag in pregnancy are not available
Prostanoids, *p.o.* [11, 29–32]	Treprostinil, beraprost	Prostanoid-type AEs[+]	
Inhaled medications			
Prostanoids, inhaled [33, 34]	Iloprost, treprostinil	Cough Prostanoid-type AEs[+]	
Parenteral medications			
Prostanoids, parenteral [35, 36]	Epoprostenol (*i.v.*), treprostinil (*i.v.*, *s.c.*)	Prostanoid-type AEs[+]	Sudden discontinuation of parenteral prostanoids can be life-threatening
Activin-signalling inhibitor [7, 8]	Sotatercept (*s.c.*)	Headache Diarrhoea Nosebleed Bleeding events Telangiectasia	Avoid in pregnancy[#]; potential risk of reduced future fertility based on animal studies; monitor for thrombocytopenia and increased haemoglobin for first five doses and periodically

PDE-5i: phosphodiesterase-5 inhibitor; SBP: systolic blood pressure; AE: adverse events; *i.v.*: intravenous; *s.c.*: subcutaneous. [#]: highly reliable contraception and monthly pregnancy testing required for all individuals of childbearing potential due to risk of teratogenicity; [¶]: while adverse reactions to endothelin-1 receptor antagonists tend to be class effects, there is some variability and switching within the same class can be considered; [+]: prostanoid-type AEs include flushing, headache, jaw pain, nausea/vomiting, diarrhoea.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