The heart and pulmonary arterial hypertension in systemic sclerosis

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Systemic sclerosis (SSc) is an autoimmune connective tissue disease characterized by vasculopathy and progressive fibrosis of the skin and visceral organs (gastrointestinal tract, heart, kidneys and lungs). Although the prevalence is low, SSc is a disease with high morbidity and mortality. Since pulmonary arterial hypertension (PAH) associated with SSc (SSc-PAH) and clinically evident cardiac involvement is associated with increased mortality, the cardiac complications and PAH in SSc are reviewed. Both diffuse cutaneous (DcSSc) and limited cutaneous (LcSSc) subgroups are at risk for cardiac involvement and SSc-PAH. Cardiac involvement can be divided in pericardial involvement, myocardial involvement and rhythm disturbances and mostly occurs asymptotically. However, when symptomatic, it is associated with a poor prognosis. Screening for asymptomatic cardiac involvement should be considered in SSc in order to initiate treatment in an early stage. However, there are no randomized controlled trials on treatment options for cardiac involvement in SSc. SSc-PAH is a devastating complication of SSc, which can develop early in DcSSc and LcSSc. Screening for PAH should be performed since screening leads to earlier diagnosis and earlier treatment is associated with a better prognosis. Today, screening is performed by clinical judgement and echocardiography. Recently the DETECT algorithm, a 2-step screening algorithm is proposed in a SSc-subgroup at increased risk for PAH, but further validation is needed. Despite current treatment options with prostacyclins, endothelin-1 receptor antagonists and phosphodiesterase type-5 inhibitors, mortality remains high. Several promising new treatment options for PAH are evaluated in phase II and III clinical trials.

**Keywords:** Systemic sclerosis, Heart, Pulmonary arterial hypertension

**Introduction**

Systemic sclerosis (SSc) is an orphan autoimmune connective tissue disease characterized by vasculopathy and fibrosis of the skin and visceral organs. Progressive fibrosis of the skin and internal organs (gastrointestinal tract, heart, kidneys and lungs) results in major organ damage and high morbidity and mortality. Two clinical subgroups of SSc are defined based on the extent of skin involvement. Skin thickening restricted to the skin of the face and distal of elbows and knees is found in limited cutaneous disease (LcSSc), whereas more extensive skin thickening is seen in diffuse cutaneous disease (DcSSc). Patients with LcSSc and DcSSc differ in prevalence of organ manifestations and in the natural history of the disease. LcSSc patients often have Raynaud’s phenomenon (RP) years before other clinical manifestations (skin thickening and internal organ involvement) appear, whereas in DcSSc, the time between RP and other clinical manifestations may be shorter. Compared to the LcSSc subgroup, the DcSSc subgroup shows the highest frequencies of organ involvement (musculoskeletal manifestations, gastrointestinal involvement, pulmonary fibrosis and renal complications) with higher mortality risk.

Prevalence of SSc is around 5 per 100,000. The 10-year survival rate for SSc has improved from 54% in the 1970s to 66% in the 2000s. During this period, the frequency of SSc-related mortality due to renal crisis decreased from 42 to 6%, while SSc-related mortality due to pulmonary fibrosis increased from 6 to 33% and SSc-related mortality due to pulmonary arterial hypertension (PAH) increased from slightly more than 20% to close to 30%. Over the same period, SSc-related mortality due to cardiac involvement (±10%) and to gastrointestinal involvement (±10%) did not change significantly. In 2010, similar SSc-related mortality rates were found for pulmonary fibrosis (35%)
and PAH (26%), but in 26% of the SSc-related deaths a cardiac cause was found (arrhythmias, heart failure or pericarditis).\textsuperscript{4} Today pulmonary fibrosis, PAH and cardiac involvement are the leading causes of disease related mortality in SSc and both the \textit{DcSSc} and \textit{LcSSc} subgroups are at risk for cardiac and pulmonary complications.\textsuperscript{1,3} The suspicion for cardiac involvement or PAH on pure clinical grounds is difficult, since symptoms of dyspnoea on exertion or limited exercise capacity are frequently present in SSc.\textsuperscript{1} Additionally, SSc patients often have an impaired level of activity due to locomotoric disturbance.\textsuperscript{2}

In 2006, the Ghent University Scleroderma Unit was created in order to build up a cohort of well-defined SSc patients.\textsuperscript{2} The goals were to better identify and describe the disease through standardized follow-up, to provide optimal care to patients with SSc and to ameliorate their condition.\textsuperscript{7} To achieve these goals, multidisciplinary and multicentre cooperation was promoted, both national -through the Belgian Systemic Sclerosis Cohort- and international -through collaboration with centres of the EUSTAR group (European League Against Rheumatism [EULAR] Scleroderma Trial and Research).\textsuperscript{2,3,6,7}

Since PAH and clinically evident cardiac involvement are associated with an increased risk of death, we will review the present knowledge concerning screening and treatment of cardiac complications and PAH in SSc.\textsuperscript{5,8}

\section*{Cardiac Involvement}
Cardiac involvement can be divided in pericardial involvement, myocardial involvement and rhythm disturbances. Both \textit{LcSSc} and \textit{DcSSc} patients are at risk.\textsuperscript{1,8} Although cardiac deaths only count for 10–25% of SSc-related deaths, cardiac involvement is found in the majority of patients on autopsy.\textsuperscript{4,5,8} Most patients are asymptomatic, but symptomatic cardiac involvement has a poor prognosis with two - and five-year mortality rates of approximately 60 and 75%.\textsuperscript{8} Cardiac complications can be a primary cardiac involvement or secondary to involvement of other organ systems (pulmonary hypertension [PH], interstitial lung disease [ILD] or kidney disease).\textsuperscript{8}

\section*{Screening}
Given the poor prognosis of clinically evident cardiac involvement, screening for subclinical cardiac disease in SSc patients should be considered. Nevertheless, data on optimal screening methods or timing of screening for cardiac involvement are lacking. The essential initial investigations used for diagnosis of heart failure (electrocardiogram [ECG], echocardiography, cardiac biomarkers) can be used for screening purposes complemented with cardiac imaging techniques (cardiac magnetic resonance [CMR], single-photon emission computed tomography, computed tomography [CT]).\textsuperscript{9}

An ECG gives information about the heart rhythm and electrical conduction. Although ECG changes are often non-specific, a normal ECG has a high negative predictive value.\textsuperscript{9} Since echocardiography is routinely performed in SSc patients for PH screening, simultaneous screening for cardiac involvement should be performed. The cardiac biomarkers B-type natriuretic peptide and N-terminal proB-type natriuretic peptide (NT-proBNP) are secreted in increased amounts in many different types of heart disease or when loading conditions are increased. Unfortunately, these markers are non-specific and can be elevated in right ventricular dysfunction, left ventricular systolic and diastolic dysfunction, myocardial ischaemia, atrial fibrillation and non-cardiovascular conditions (including renal failure).\textsuperscript{9}

CMR is the golden standard for the evaluation of volume, mass and wall motion. It is also an optimal tool to identify inflammatory and infiltrative conditions.\textsuperscript{9} CT is often routinely performed for the evaluation of ILD and may provide additional information on pericardial thickness or pericardial effusion.

\section*{Pericardial disease}
Symptomatic pericarditis occurs in 7 to 20% of the SSc patients, although autopsy reports describe up to 72% pericardial involvement (pericarditis, pericardial effusion or pericardial adhesions).\textsuperscript{8} Six per cent of the \textit{LcSSc} and 12% of the \textit{DcSSc} patients have pericardial effusion on echocardiography.\textsuperscript{1} Most of the patients have asymptomatic small amounts of pericardial fluid, which do not affect prognosis, whereas large and/or symptomatic pericardial effusions are associated with poor prognosis.\textsuperscript{8}

Therapeutic options are the conventional treatment options for pericarditis (namely high doses of aspirin, non-steroidal anti-inflammatory drugs, colchicine or corticosteroids). In only a few cases pericardiocentesis is needed.\textsuperscript{8}

\section*{Myocardial disease}
Myocardial fibrosis is reported in 50–89% of post-mortem reports and in two-thirds of patients investigated with CMR.\textsuperscript{8,10} Again, there is a high incidence of asymptomatic, subclinical disease.\textsuperscript{8} Myocardial fibrosis is probably due to microvasculopathy in the arteries of the heart muscle and is associated with an impairment in coronary vascular flow reserve.\textsuperscript{8}

Microvasculopathy can be caused by structural small vessel disease (inflammation and/or focal ischaemia), recurrent vasospasm (the so-called myocardial RP) or a combination of both (recurrent ischaemia–reperfusion injury).\textsuperscript{8,11,12} Several arguments suggest that vasospasm superimposed on structural vessel alterations are responsible for the fibrosis. First, microscopic characteristics are myocardial fibrosis and contraction band necrosis, an anatomo-pathological phenomenon typical seen after transient coronary occlusion followed by reperfusion.\textsuperscript{8,12} Second, in SSc patients, exercise and cold exposure can give transient myocardial perfusion defects and cold exposure can cause long-term left ventricular dysfunction and remodelling.\textsuperscript{8,11} Furthermore, in the majority of post-mortem studies, there was no significant atherosclerotic disease
of the epicardial coronary arteries, fibrosis was seen in both the left and right ventricle and the areas of fibrosis did not correspond to the regional distribution of one specific coronary artery. Microvasculopathy definitely causes cardiac disease in SSc patients.

The question remains whether SSc patients are at increased risk for atherosclerotic disease. A systematic review and meta-analysis on atherosclerosis concluded that SSc patients have an increased risk of coronary atherosclerosis compared to age- and gender-matched controls. However, this systematic review and meta-analysis made no difference between micro- and macrovascular disease. Of the three studies included in this systematic review, one (a retrospective study using a flow chart [clinical evaluation, ECG, echocardiography, scintigraphy, cardiac enzymes or coronarography to diagnose coronary artery disease]) revealed no significant difference in coronary atherosclerosis between SSc and age- and gender-matched controls, while another (a coronary CT study) found an elevated coronary calcium score – which is a marker for coronary atherosclerosis – in SSc patients as compared to age-, gender- and race-matched controls. For clinically relevant coronary artery disease, a recent systematic review and meta-analysis of four studies showed an increased risk for coronary artery disease in SSc patients as compared to controls. As control population, 3 of the 4 studies used age- and sex-matched subjects of databases provided by health care providers or general practitioners and one used data from a national health survey. However, these results should be interpreted with some caution, as in 2 of the 4 included studies, the diagnosis of coronary artery disease was made on either the presence of angina pectoris, myocardial infarction or a history of percutaneous coronary intervention (PCI) or coronary arterial bypass grafting (CABG), while it is known that recurrent vasospasm in SSc patients can cause angina pectoris. One can conclude that SSc patients are at an increased risk for microvascular coronary disease, but whether this is superimposed by macrovascular atherosclerotic disease still remains unclear.

Myocardial disease can result in systolic and diastolic heart failure. The systolic left ventricular ejection fraction mostly is preserved, but diastolic heart failure is seen in 17% of the SSc patients (17% in LcSSc and 18% in DcSSc). Until today, there are no randomized controlled trials (RCTs) on treatment options for heart failure in SSc patients. Traditional drugs and treatment options for heart failure are being used: angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers when ACE-I is not tolerated, aldosterone receptor antagonists, diuretics, ivabradine, digoxin, implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT). Beta-blocking agents are generally accepted for treatment of heart failure, but in SSc patients, beta-blocking agents can worsen the RP. Metoprolol, a cardioselective beta-blocker, seems to reduce RP when co-administrated with a calcium-channel blocker in patients with primary RP, but there are no data available in RP secondary to SSc. Calcium-channel blockers may be useful for treatment of systemic hypertension, myocardial ischaemia, coronary vasospasm, diastolic heart failure and ventricular rate control in atrial fibrillation. However, caution is needed in patients with systolic heart failure, since calcium-channel blockers may be dangerous in this population as their negative inotropic effect can further depress systolic function. When significant macrovascular atherosclerotic coronary disease is present in SSc patients, we are convinced that the choice between performing PCI or CABG should be discussed in a multidisciplinary team, since wound healing problems of the sternotomy and lower limbs may be expected after CABG in some SSc patients due to skin fibrosis. Neither PCI nor CABG will resolve the microvascular disease.

In a prospective non RCT, short-term treatment (4 weeks) with bosentan, an endothelin receptor antagonist (ERA) improved myocardial perfusion and function.

To prevent secondary cardiac damage due to kidney disease or PAH, systemic arterial hypertension and PAH should be treated immediately when diagnosed.

**Rhythm disturbances**

Rhythm disturbances are common in SSc with 21% of the LcSSc and 26% of the DcSSc experiencing palpitations. Both arrhythmias (ventricular and supraventricular) and conduction abnormalities can occur. Most likely, they are the result of fibrosis of the myocardium and conduction system.

An abnormal ECG (conduction defects, ST segment changes, ventricular or supraventricular arrhythmias) is present in 25–75% of the SSc patients. The most common conduction abnormalities on the ECG are a left bundle branch block, a first-degree atrioventricular (AV) block, a left anterior fascicular block and a right bundle branch block, while a second- or third-degree AV block and non-specific intraventricular conduction delay are infrequent. Arrhythmias, supraventricular or ventricular, are described in 4–6% of the SSc patients on the ECG. Using 24-h holter ECG monitoring, conduction abnormalities were found in 8–14% of the SSc patients, supraventricular arrhythmias in 66% (premature atrial contractions in 61% and supraventricular tachycardia in 21–32%) and ventricular arrhythmias in up to 90% (premature ventricular contractions in 40–67%, pairs of premature ventricular contractions in 20–28% and ventricular tachycardia in 7–13%).
tachyarrhythmia and ventricular arrhythmias (both isolated premature ventricular contractions, pairs of premature ventricular contractions and ventricular tachycardia) on holter monitoring are correlated with mortality. 17 Since only 24% of the patients experience palpitations, most of the arrhythmias are asymptomatic. 1,15 Given the high asymptomatic prevalence and the prognostic significance of rhythm disturbances in SSc patients, further investigation is needed to evaluate whether holter monitoring should be part of the routine screening evaluation of SSc patients and if so, on what time base holter monitoring should be performed. Meanwhile, we are convinced that holter monitoring is necessary in every symptomatic SSc patient. Patients with rhythm disturbances are being treated with the conventional treatment options for rhythm disturbances (antiarrhythmic drugs, pacemaker, catheter ablation therapy, ICD or CRT).

Pulmonary Arterial Hypertension
Diagnosis of PAH and classification of PH
PAH is a subgroup of PH. PH is defined as a resting mean pulmonary artery pressure (mPAP) ≥25 mm of mercury (mmHg) measured during right heart catheterization (RHC) and can be precapillary (pulmonary capillary wedge pressure [PCWP] ≤15 mmHg) or postcapillary (PCWP > 15 mmHg). 18 Recently, the Dana Point classification was updated in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) revised guidelines for PH. 18 Patients with PH are classified into five groups based upon the aetiology: PAH (group 1), PH associated with left heart disease (group 2), PH associated with lung disease/hypoxia (group 3), chronic thromboembolic PH (CTEPH) and other pulmonary artery obstructions (group 4) and PH with unclear and/or multifactorial mechanisms (group 5). Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis and persistent PH of the newborn are designated as group 1’ and group 1”, respectively, since they share some characteristics with group 1 (PAH), but also demonstrate a number of differences (Table 1). 18-20 Thus in SSc, patients may have PAH, PH secondary to left heart disease, PH secondary to lung disease/hypoxaemia, CTEPH or a combination. 18,20 Targeted treatment for SSc associated PAH (SSc-PAH) is only indicated in the first group. PH secondary to left heart disease and pulmonary disease is being treated with conventional therapies for heart disease (see section above on myocardial disease) or pulmonary disease and are not discussed in this manuscript. In SSc, the diagnosis of PAH is made by RHC (the presence of precapillary PH with a pulmonary vascular resistance >3 Woods units) in the absence of arguments for lung disease/hypoxaemia or for CTEPH (Fig. 1). At the time of diagnostic RHC, vasoreactivity testing can identify patients who benefit from long-term treatment with calcium-channel blockers. Vasoreactivity testing is performed by inhalation of nitric oxide (NO) and a positive response is defined as a reduction in mPAP ≥10 mmHg to obtain an absolute mPAP value ≤40 mmHg with an increased or unchanged cardiac output (CO). Positive responders are the only PAH patients that can be treated safely with high dose of calcium-channel blockers. 18,20 Vasoreactivity testing at the time of diagnosis is recommended in idiopathic pulmonary arterial hypertension (IPAH), but is not recommended for patients with connective tissue disease associated PAH (CTD-PAH), since in CTD-PAH, the response rate is low (1%), high dose calcium-channel blockers are often not well tolerated and vasodilator responsiveness at diagnosis does not really predict long-term response to calcium-channel blockers in CTD-PAH. 18,20 However, in Belgium, vasoreactivity testing still is obligatory performed in CTD-PAH for reimbursement purposes.

Pathogenesis
The precise mechanisms and the initiating process involved in the pathogenesis of PAH remain unknown. There is a disequilibrium between vasoactive, proliferative mediators (thromboxane A2 and endothelin-1) and antiproliferative vasodilators (NO and prostacyclin) in the endothelium. This leads to vasoconstriction, inflammation and vascular remodelling (with intima proliferation, medial hypertrophy and adventitia thickening with inflammatory infiltrates and fibrotic changes) preferential in small pulmonary arteries. Additional prothrombotic conditions can lead to intraluminal thrombi. 20

Screening
Breathlessness, fatigue, weakness, angina, syncope, abdominal distension, peripheral oedema are aspecific symptoms of PAH, especially in SSc patients. 19,20 In heart diseases, the New York Heart Association (NYHA) functional classification (FC) is used for clinical evaluation of symptomatic severity. 9 In 1998, the World Health Organisation (WHO) FC for PH was defined, which is a modification of the NYHA FC, recognizing the importance of near syncope and syncope in the clinical evaluation of PH patients (Table 2a and b). 18 In practice, in patients with PAH, one can use either the NYHA FC or WHO FC for clinical evaluation, but the presence of near syncope and syncope is important in assessing these patients. The prevalence of PAH in SSc is 7 to 12%, 19,20 Both the LcSSc and DcSSc subtypes are at risk for development of PAH and PAH may occur early (within 5 years) after diagnosis of SSc. In both subgroups (in 41% of the DcSSc-PAH patients and 59% of the LcSSc-PAH patients the diagnosis of PAH was made within 5 years after the diagnosis of SSc). 21 Despite the current treatment modalities, mortality in SSc-PAH remains high (1- and 2-year survival 86 and 73%, respectively), with lower survival rates as compared to IPAH. 19,20,22-24 Mortality rates are the highest in the SSc patients who are most severely ill (as measured by the New York Heart Association functional class [NYHA FC]) at the moment of diagnosis of PAH (3-year survival
most of the patients are diagnosed in NYHA FC III or IV and only a minority of the SSc-PAH patients (16%) is in

rate 30–72% when NYHA FC III or IV vs. 3-year survival rate up to 80% when NYHA FC II (Table 2). However,

Table 1 Updated classification of pulmonary hypertension from the European Society of Cardiology/European respiratory Society Guidelines 2015

<table>
<thead>
<tr>
<th>1. PAH</th>
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<tbody>
<tr>
<td>1.1 Idiopathic PAH</td>
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<tr>
<td>1.2 Heritable PAH</td>
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<tr>
<td>1.2.1 BMPR2 mutation</td>
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<tr>
<td>1.2.2 Other mutations</td>
</tr>
<tr>
<td>1.3 Drug and toxin induced</td>
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<tr>
<td>1.4 Associated with</td>
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<tr>
<td>1.4.1 Connective tissue diseases</td>
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<tr>
<td>1.4.2 HIV infection</td>
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<td>1.4.3 Portal hypertension</td>
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<tr>
<td>1.4.4 Congenital heart disease</td>
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<tr>
<td>1.4.5 Schistosomiasis</td>
</tr>
</tbody>
</table>

1’. Pulmonary veno-occlusive disease and/or pulmonary capillary haemangiomatosis
1’.1 Idiopathic
1’.2 Heritable
1’.2.1 EIF2AK4 mutation
1’.2.2 Other mutations
1’.3 Drugs, toxins and radiation induced
1’.4 Associated with
1’.4.1 Connective tissue diseases
1’.4.1 HIV infection

1”’. Persistent PH of the newborn
2. PH due to left heart disease
2.1 Left ventricular systolic dysfunction
2.2 Left ventricular diastolic dysfunction
2.3 Valvular disease
2.4 Congenital/acquired left heart inflow/outflow tract obstruction and congenital cardiomyopathies
2.5 Congenital/acquired pulmonary veins stenosis

3. PH due to lung disease and/or hypoxaemia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep-disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental lung diseases

4. Chronic thromboembolic PH and other pulmonary artery obstructions
4.1 Chronic thromboembolic pulmonary hypertension
4.2 Other pulmonary artery obstructions
4.2.1 Angiosarcoma
4.2.2 Other intravascular tumors
4.2.3 Arteritis
4.2.4 Congenital pulmonary arteries stenoses
4.2.5 Parasites (hydatidosis)

5. PH with unclear and/or multifactorial mechanisms
5.1 Hematologic disorders: chronic haemolytic anaemia, myeloproliferative disorders, splenectomy
5.2 Systemic disorders: sarcoidosis, pulmonary histiocytosis, lymphangioleiomyomatosis
5.3 Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4 Others: pulmonary tumoral thrombotic microangiopathy, fibrosing mediastinitis, chronic renal failure (with/without dialysis), segmental PH

Source: Reproduced with permission from Galie et al.18
The echocardiographic ESC/ERS screening algorithm is based on maximal tricuspid regurgitation velocity (TRV). In patients with a TRV ≤2.8 metre per second (m/s) (estimated systolic pulmonary artery pressure [sPAP] ≤36 mmHg) without additional echocardiographic PH signs (AHA) and by the ESC/ERS guidelines on PH (class of recommendation 1, level of evidence C).18,26

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Table 2 The New York Heart Association functional classification and World health Organization functional classification

<table>
<thead>
<tr>
<th>Class</th>
<th>NYHA classification</th>
<th>WHO classification</th>
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<tbody>
<tr>
<td>I</td>
<td>No limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitations</td>
<td>Without limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or near syncope</td>
</tr>
<tr>
<td>II</td>
<td>Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitations</td>
<td>Slight limitation of physical activity. Comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope</td>
</tr>
<tr>
<td>III</td>
<td>Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in undue breathlessness, fatigue or palpitations</td>
<td>Marked limitation of physical activity. Comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope</td>
</tr>
<tr>
<td>IV</td>
<td>Unable to carry on any physical activity without discomfort. Symptoms at rest can be present. If any physical activity is undertaken, discomfort is increased</td>
<td>Inability to carry out any physical activity without symptoms. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity</td>
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NYHA FC II at diagnosis.20,22,25 Screening leads to early diagnosis (up to 50% in NYHA FC I or II at diagnosis in a French screening programme) and to earlier treatment and a better prognosis.19,21 Annual echocardiographic screening in asymptomatic SSc patients is recommended by an expert consensus of the American College of Cardiology Foundation (ACCF) and the American Heart Association (AHA) and by the ESC/ERS guidelines on PH (class of recommendation 1, level of evidence C).18,26

Figure 1 Diagnosis of pulmonary arterial hypertension by right heart catheterization.
Notes: RHC: right heart catheterization, nl: normal, mPAP: mean pulmonary artery pressure, PH: pulmonary hypertension, mmHg: millimeter of mercury, PCWP: pulmonary capillary wedge pressure, HRCT: high resolution computed tomography of the lungs, V/Q-scan: ventilation perfusion scintigraphy, PVR: pulmonary vascular resistance, PAH: pulmonary arterial hypertension.
(increased dimension of right atrium and/or right ventricle, increased right ventricular wall thickness, flattening of the interventricular septum, a short acceleration time of the right ventricular ejection in the main pulmonary artery, dilated pulmonary artery, dilated inferior caval vein with decreased inspiratory collapse), PH is unlikely and RHC is not justified. In patients with TRV >3.4 m/s (estimated sPAP >50 mmHg), PH is likely and RHC is indicated. In patients with TRV ≤2.8 m/s (estimated sPAP ≤36 mmHg) with additional echocardiographic PH signs or TRV between 2.9 and 3.4 m/s (estimated sPAP between 36 and 50 mmHg), further investigation with clinical judgement (presence of NYHA FC ≥ II, anginal pain, syncope/near syncope, peripheral oedema) is required to evaluate whether RHC is necessary.18,20 Recently the DETECT study introduced a 2-step diagnostic algorithm with clinical (current/past telangietasias), laboratory (serum urate, NT-proBNP and presence of anti-centromere antibodies), lung functional (forced vital capacity [%predicted]/diffusion lung capacity for carbon monoxide [DLCO] [%predicted]) and ECG parameters (right axis deviation) in step 1 and echocardiography (right atrium area and TRV) in step 2 to evaluate SSc patients at risk for PAH. This prospective, multicentre cross-sectional study is the first PAH detecting study performing RHC in all SSc patients and reporting information on a number of missed PAH diagnoses, (4% in DETECT vs. 29% in screening according to the ESC/ERS guidelines), positive predictive value (35% vs. 40%) and negative predictive value (98% vs. 89%). The high sensitivity (96% vs. 71%) is associated with a reduced specificity (48% vs. 69%) as compared to screening with the ESC/ERS guidelines.27 However, the DETECT study included only a subgroup of SSc patients at increased risk for PAH (SSc for >3 years and DLCO <60% of the predicted value) and further research is needed to validate the DETECT algorithm as a screening tool for the general SSc population.

**Treatment**

**General measures**

PAH patients should avoid excessive physical activity, but when in poor physical condition, supervised exercise rehabilitation is recommended (class of recommendation IIa, level of evidence B). Pregnancy is associated with high maternal mortality in PAH patients and should be avoided. Birth control is indicated in each premenopausal female PAH patient.18,20,28 Vaccination against pneumococcal pneumonia and influenza is recommended (Figure 2).18,20,28

**Supportive therapy**

Oxygen use is indicated when arterial blood oxygen pressure is below 60 mmHg. Treatment with diuretics alleviates fluid retention. Digoxin should be considered to slow ventricular rate in patients with atrial tachyarrhythmia.18,28 Although PAH patients are at risk for intraluminal thrombi, there are no RCTs evaluating the use of anticoagulants in CTD-PAH. The ESC/ERS guidelines advise in CTD-PAH to consider the use of anticoagulants on an individual base (class of recommendation IIb, level of evidence C), whereas the ACCF/AHA guidelines advise consideration of their use in CTD-PAH patients with advanced disease, especially with IV treatment (Supplementary file 1).18,26

**Calcium-channel blockers**

The use of high dose calcium-channel blockers in SSc-PAH is not recommended. As mentioned above, in CTD-PAH patients, vasodilator responsiveness does not appear to predict a favourable long-term response to calcium-channel blockers therapy and high dose calcium-channel blockers are often not well tolerated. However, 50–60% of the SSc patients already take calcium-channel blockers for the presence of a RP, and question is whether the calcium-channel blockers may be continued in low dose with intensive clinical follow-up of the patient.1,3

Although vasoreactivity testing is controversial in CTD-PAH, we still perform it in each CTD-PAH patient for local reimbursement purposes.

**Specific drug therapy**

The current treatment options for PAH interact with the prostacyclin (epoprostenol, treprostenil and iloprost), the endothelin (bosentan, macitentan and ambrisentan) and NO (sildenafil, tadalafil and riociguat) pathway. ESC-ERS guidelines advise to follow the same treatment algorithm for CTD-PAH as for IPAH.18 The treatment algorithm has been updated in the 2015 revised ESC/ERS guidelines (Fig. 2).18,20,28 Following the 2009 EULAR recommendations for the treatment of SSc-PAH, bosentan should be strongly considered to treat SSc-PAH and sildenafil should be considered when bosentan has been ineffective or cannot be used for safety reasons (e.g. liver function). Intravenous (IV) epoprostenol is recommended as the treatment of choice in SSc-PAH with severe PAH (NYHA FC III or IV) or with inadequate response to bosentan and/ or sildenafil.29

Evaluation of clinical response is based on a combination of different parameters including signs and symptoms of right ventricular failure, NYHA FC, exercise capacity, echocardiographic parameters, haemodynamic parameters and NT-proBNP plasma levels.18,28

In most of the RCTs on which approval of specific PAH therapy is based, both IPAH and CTD-PAH patients have been included (5–32% CTD-PAH). Focussing on CTD-PAH or SSc-PAH, there are some general remarks and limitations for the below described RCTs. First of all, RCTs on treatment of PAH in SSc and CTD are scarce. Second, RCTs including both IPAH and CTD-PAH patients not always perform subgroup analysis of CTD-PAH or SSc-PAH. Third, in most of these RCTs, the primary endpoint was a six minute walk test (6MWT) on short-term (after 12–16 weeks). Of note, the SSc community questions whether the 6MWT is an adequate performant parameter in SSc-PAH as it only reflects functional capacity.
(a measure of morbidity) whilst ideally, RCT’s on PAH should have both mortality and morbidity as outcome. Notably, only one recent long-term RCT in PAH patients with a combined primary endpoint of mortality and morbidity was published.30 Fourth, subgroup analyses of CTD-PAH show lower response rate in CTD-PAH as compared to IPAH.20 Finally, in SSc-PAH, mortality remains high, despite the currently accepted treatment options, which makes morbidity also an important endpoint. Stabilization or improvement of 6MWT, although sometimes rather small, can be a marker for functional capacity and comfort of the patient, which is an important morbidity parameter.

In the next section, the evidence-based treatment options for PAH are described, focussing on the RCTs or subgroup analyses of RCTs concerning CTD-PAH or SSc-PAH. In some trials, the level of significance is not reached, which could possibly be explained by the fact that subgroup analyses for CTD-PAH or SSc-PAH are underpowered to detect statistical significance (Table 3).
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<th>Drug</th>
<th>Reference</th>
<th>Type of study</th>
<th>Treatment</th>
<th>Comp</th>
<th>N PAH</th>
<th>N IPAH</th>
<th>N CTD</th>
<th>(1) primary endpoint</th>
<th>Effect in CTD-PAH or SSc-PAH</th>
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<td>(2) secondary endpoints</td>
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<td>Prostacyclins</td>
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<td>(N SSc-PAH)</td>
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<td>Epoprostenol</td>
<td>Badesch 2000&lt;sup&gt;32&lt;/sup&gt;</td>
<td>RCT</td>
<td>Epoprostenol continuous IV</td>
<td>Placebo</td>
<td>111</td>
<td>0</td>
<td>111 (111)</td>
<td>(1) placebo corrected Δmedi-an 6MW at week 12</td>
<td>SSc (1) 108 m (95%CI: 55.2 to 180 m)</td>
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<td>(2) Placebo corrected haemo-dynamics (mPAP, PVR, RAP CF, mixed venous oxygen saturation, SpO₂, RR, HR), Borg dyspnoea score, dyspnoea fatigue score, NYHA FC, RP severity score, new digital ulcers, survival at week 12</td>
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<td></td>
<td>(1) 1-, 2-, 3-year survival</td>
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<td>Treprostenil</td>
<td>Oudiz 2004&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Subgroup analysis of RCT</td>
<td>Treprostenil continuous SC</td>
<td>Placebo</td>
<td>90</td>
<td>0</td>
<td>90 (45)</td>
<td>(1) placebo corrected Δ6MW at week 12</td>
<td>CTD (1) 25 m (p = 0.055)</td>
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<td>(2) Dyspnoea fatigue score: 0.9 ± 0.2 vs. 0 ± 0.3 (p = 0.014), Borg dyspnoea score: −0.6 ± 0.5 vs. 0.2 ± 0.5, (p = 0.168), mPAP: −3 ± 1 vs. −1 ± 1 (p = 0.095), PVR: −4 ± 2 vs. 1±/-1 (p = 0.006), RAP: −2 ± 1 vs. 1 ± 1 (p = 0.056), CI²: 0.2 ± 0.1 vs. −0.1 ± 0.1 (p = 0.007), mixed venous oxygen saturation: 0 ± 2 vs. −3 ± 2 (p = 0.153), SpO₂: 0 ± 1 vs. 0 ± 1 (p = 0.464), RR: −1 ± 2 vs. −3 ± 2 (p = 0.082), HR: 0 ± 2 vs. −4 ± 0 ± 0.117, PCWP: −1 ± 1 vs. 1 ± 1 (p = 0.1)</td>
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<td>(2) Δdyspnoea fatigue score, borg dyspnoea score, haemodynamics (mPAP, PVR, RAP, CI², mixed venous oxygen saturation, SpO₂, RR, HR, PCWP, QoL score at week 12</td>
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(Continued)
## Table 3 (Continued)

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<th>Drug</th>
<th>Reference</th>
<th>Type of study</th>
<th>Treatment Inclusion criteria</th>
<th>Comp</th>
<th>N PAH</th>
<th>N IPAH</th>
<th>N CTD (N SSc-PAH)</th>
<th>(1) primary endpoint</th>
<th>(2) secondary endpoints</th>
<th>Effect in CTD-PAH or SSc-PAH</th>
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<tr>
<td>Bosentan</td>
<td>Rubin 2002</td>
<td>RCT</td>
<td>IPAH, CTD-PAH, WHO FC III/IV</td>
<td>125</td>
<td>213</td>
<td>150</td>
<td>63 (47)</td>
<td>(1) Δ 6MWT at week 16</td>
<td>(2) Borg dyspnoea score, WHO FC; TTCW</td>
<td>SSc</td>
</tr>
<tr>
<td></td>
<td>BREATHE°</td>
<td>RCT</td>
<td>IPAH, CTD-PAH, WHO FC III/IV</td>
<td>250</td>
<td>213</td>
<td>150</td>
<td>63 (47)</td>
<td>(1) Δ 6MWT at week 16</td>
<td>(2) Borg dyspnoea score, WHO FC; TTCW</td>
<td>CTD</td>
</tr>
<tr>
<td></td>
<td>Denton 2006</td>
<td>Subgroup analysis of and open-label extension of 2 RCT's</td>
<td>125</td>
<td>66</td>
<td>0</td>
<td>66 (52)</td>
<td>(1) placebo-corrected Δ 6MWT</td>
<td>(2) TTCW at week 12–16 survival in longterm extension</td>
<td>SSc</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pulido 2013</td>
<td>RCT</td>
<td>IPAH, CTD-PAH, others°</td>
<td>10 mg/day</td>
<td>742</td>
<td>404</td>
<td>224</td>
<td>(1) combined mortality/morbidity primary endpoint</td>
<td>(2) TTCW at week 12–16 survival in longterm extension</td>
<td>CTD</td>
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<tr>
<td></td>
<td>Galie 2008</td>
<td>2 RCTs</td>
<td>IPAH, CTD-PAH, others°</td>
<td>10 mg/day</td>
<td>201</td>
<td>126</td>
<td>62</td>
<td>(1) placebo-corrected Δ 6MWT</td>
<td>(2) WHO FC; Borg dyspnoea score, short form-36 health survey, BNP; TTCW</td>
<td>CTD</td>
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<td></td>
<td>(1) placebo-corrected Δ 6MWT at week 12</td>
<td>(2) WHO FC; Borg dyspnoea score, short form-36 health survey, BNP; TTCW</td>
<td>CTD</td>
<td></td>
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<tr>
<td>Sildenafil</td>
<td>Badesch 2007°</td>
<td>Subgroup Analysis of RCT CTD-PAH, WHO FC II-IV</td>
<td>20 mg 3×/day</td>
<td>84</td>
<td>0</td>
<td>84 (38)</td>
<td>(1) Placebo corrected Δ6MWT at week 12</td>
<td>(2) WHO FC, haemodynamics (mPAP, RAP, CO, PVR) at week 12</td>
<td>CTD</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Notes:
- N: number of.
- RCT: randomized controlled trial.
- PAH: pulmonary arterial hypertension.
- IPAH: idiopathic pulmonary arterial hypertension.
- CTD: connective tissue disease.
- SSc: systemic sclerosis.
- *: PAH defined as mean pulmonary arterial pressure $\geq 35$ mmHg.
- °: PAH defined as mean pulmonary arterial pressure $\geq 25$ mmHg.
- 6MWT: six minute walk test.
- m: metre.
- WHO: World Health Organization.
- FC: functional class.
- others: other causes of PAH than IPAH, CTD-PAH or SSc-PAH.
- IV: intravenous.
- SC: subcutaneous.
- po: per oral.
- mg: milligram.
- $\Delta$: delta.
- CI: confidence interval.
- %: per cent.
- NS: not significant.
- HR: hazard ratio.
- ERA: endothelin-1 receptor antagonist.
- NO: nitric oxide.
- comp: comparator.
- mPAP: mean pulmonary arterial pressure.
- PVR: pulmonary vascular resistance.
- RAP: right atrial pressure.
- PCWP: pulmonary capillary wedge pressure.
- QoL: quality of life.
- 6MWD: 6 minute walk distance.
- TTCW: time to clinical worsening.
- mPAP: mean pulmonary arterial pressure.
- CI: cardiac index.
- SpO$_2$: arterial oxygen saturation.
- RR: mean systemic arterial blood pressure.
- RP: Raynaud's phenomenon.

### Table 3

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Type of study</th>
<th>Treatment</th>
<th>Comp</th>
<th>N PAH</th>
<th>N IPAH</th>
<th>N CTD</th>
<th>(N SSc-PAH) (1) primary endpoint</th>
<th>Effect in CTD-PAH or SSc-PAH</th>
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<tbody>
<tr>
<td>Tadalafil</td>
<td>Galie 2009$^a$</td>
<td>RCT</td>
<td>Tadalafil po</td>
<td>Placebo</td>
<td>405</td>
<td>247</td>
<td>95</td>
<td>Placebo corrected Δ6MWT at week 16 2.5 mg, 10 mg, 20 mg, 40 mg</td>
<td>CTD (1.25 mg; 18 m (95% CI: −27 to 63 m), 10 mg: 22 m (95% CI: −13 to 56 m), 20 mg: 50 m (95% CI: 16–83 m), 40 mg: 49 m (95% CI: 15–83 m)) (2) NA</td>
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<td>2.5 mg/day</td>
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<td>(2) WHO FC, TTCW2, Borg dyspnoea score, QoL2, haemodynamics (mPAP, CI, PVR) at week 16 2.5 mg: 18 m (95% CI: −27 to 63 m), 10 mg: 22 m (95% CI: −13 to 56 m), 20 mg: 50 m (95% CI: 16–83 m), 40 mg: 49 m (95% CI: 15–83 m)</td>
<td>(2) NA</td>
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<td>10 mg/day</td>
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<td>20 mg/day</td>
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<td>6MWD 150–450 m</td>
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<td>WHO FC I-IV</td>
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<td>Riociguat</td>
<td>Ghofrani 2013$^a$</td>
<td>RCT</td>
<td>Riociguat po</td>
<td>Placebo</td>
<td>443</td>
<td>272</td>
<td>111</td>
<td>Placebo corrected Δ6MWT at week 12 2.5 mg 3×/day</td>
<td>CTD (1.27 m (95% CI: −7 to 61 m)) (2) NA</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2.5 mg 3×/day</td>
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<td></td>
<td></td>
<td></td>
<td>(2) WHO FC, TTCW2, Borg dyspnoea score, QoL3 at week 12 2.5 mg 3×/day</td>
<td>(2) NA</td>
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<td>1.5 mg 3×/day</td>
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**Continued**
Prostacyclin pathway

Prostacyclin analogues bind to the prostacyclin receptor leading to an increase in cyclic adenosine monophosphate, resulting in vasodilation, antiproliferative and antithrombotic effects. Three agents have been Food and Drug Administration (FDA) and European Medicines Agency (EMA) licensed for treatment of PAH: epoprostenol, treprostenil and iloprost. Beraprost, an oral prostanoïd analogue, is only approved in Japan and South Korea. Selexipag is a novel orally active, selective prostacyclin receptor agonist being under investigation (see further under section novel treatment options).

Epoprostenol (Flolan®)

A RCT with 111 SSc-PAH patients receiving IV epoprostenol additional to supportive therapy or supportive therapy alone during a period of 12 weeks, showed that epoprostenol therapy significantly improved 6MWT. After 12 weeks of therapy, there was no survival benefit of treatment with epoprostenol. However, the retrospective, open-label uncontrolled extension study of the above-mentioned RCT showed 1-, 2- and 3-year survival rates of 71, 52 and 48% which are better than those of historical controls (1-year survival rate of 50%).

Flolan® has an extremely short half-life (3–5 min) which implicates continuous IV infusion with a central venous catheter. Minor complications are diarrhoea, flushing, headache, nausea and vomiting. Catheter-related infection, thromboembolic events and episodes of worsening of PAH secondary to abrupt discontinuation of the infusion are feared complications. Flolan® must be prepared daily under sterile conditions and stored cold using ice packs.

Thermostable epoprostenol (Veletri®)

Recently, a novel epoprostenol formulation with greater room temperature stability has been FDA and EMA approved for treatment of PAH. In the EPITOME-2 study, with only 2 CTD-PAH patients out of 41 PAH patients, this new formulation has the same efficacy, tolerability and safety as compared to the previous formulation of epoprostenol.

Treprostenil

Treprostenil can be administered by continuous IV infusion, subcutaneous (SC) infusion or inhalation. Continuous SC infusion of treprostenil has a longer half-life (2–4 h) as compared to epoprostenol and is stable at room temperature. Subgroup analysis of 90 CTD-PAH patients (50% SSc-PAH) of a RCT on SC treprostenil compared to placebo, showed a non-significant improvement in 6MWT ($p = 0.055$). The use of SC treprostenil in SSc-PAH is rather limited because, due to skin thickening, SSc patients are at increased risk for the most common side effect, i.e. pain at the infusion site.

Iloprost

A RCT showed that aerolized iloprost is an effective therapy (improvement of combined primary endpoint of 6MWT and NYHA FC) in PAH (17% CTD-PAH), but no subgroup analysis of CTD-PAH was made. Aerolized iloprost should be administered 6–9 times a day and flushing and jaw pain are the most frequent side effects.

Selexipag

Selexipag is an oral, selective prostacyclin receptor agonist (see further section novel treatment options).

As recommended by the EULAR, IV epoprostenol (Flolan® or Veletri®) is the treatment of choice in SSc-PAH with severe PAH (NYHA functional class III or IV) or with inadequate response to ERA and/or phosphodiesterase 5-inhibitor (PDE5-I).

Endothelin pathway by endothelin-1 receptor antagonists

Endothelin-1 (ET-1) acts through two receptor subtypes namely ET receptor type A and B to which ET-1 binds with high affinity. ET-1 acts on the smooth muscle cells causing vasoconstriction and proliferation by binding to ET type A and B receptor and increases the NO and prostacyclin production by binding to ET type B receptor. Bosentan and macitentan are non-selective ET-1 receptor antagonists that block signalling mediated by type A and type B ET-1 receptors. Ambrisentan is a selective type A ET-1 receptor antagonist.

Bosentan

In the BREATHE-1 trial, 213 patients with IPAH or CTD-PAH (22% SSc-PAH) received bosentan or placebo during minimum 16 weeks. In the SSc-PAH subgroup, bosentan prevented deterioration in 6MWT.

In another RCT with 32 PAH patients (27 IPAH and 5 SSc-PAH), no subgroup analysis of the SSc-PAH was performed.

A subgroup analysis of the 2 above-mentioned clinical trials and their open-label extensions with 66 CTD-PAH patients (44 bosentan, 22 placebo) showed that treatment with bosentan for 12–16 weeks prevented deterioration in 6MWT. The secondary endpoint (time to clinical worsening [TTCW] which is a combined endpoint of death, lung transplantation, hospitalization for PAH, atrial septostomy and lack of improvement or worsening of PAH leading to discontinuation and/or need for additional therapy) is delayed without reaching the level of significance (after 16 weeks, 90% was event free in the bosentan treated group vs. 86% in the placebo group). The open label extension with mean duration of 1.6 year of bosentan treatment, with additional treatments if required, showed a 1-and 2-year survival of 86 and 73%, as compared to 45 and 35%, respectively, in a historical control cohort. Administration of bosentan is twice daily (bid).
<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Inclusion</th>
<th>Treatment</th>
<th>Comparator</th>
<th>N PAH</th>
<th>N CTD-PAH</th>
<th>Primary endpoint</th>
<th>Effect in PAH</th>
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<tbody>
<tr>
<td>Selexipag (oral prostanoid)</td>
<td>Simonneau 2012&lt;sup&gt;21&lt;/sup&gt;</td>
<td>Phase II IPAH, CTD-PAH, other 6MWT 150–500 m NYHA FC II–III</td>
<td>Selexipag po 2×/day</td>
<td>Placebo</td>
<td>43</td>
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<td>Change in PVR at week 17 (% baseline value, 95%CI)</td>
<td>PVR</td>
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<td>ClinicalTrials.gov NCT 01106014&lt;sup&gt;46,46&lt;/sup&gt;</td>
<td>Phase III IPAH, CTD-PAH, other 6MWT 50–450 m SSc-PAH NYHA II–IV</td>
<td>Selexipag po 2×/day</td>
<td>Placebo</td>
<td>1156</td>
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<td>Time to first mortality/morbidity event</td>
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<td>ClinicalTrials.gov NCT 00986540&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Phase II IPAH, CTD-PAH, other 6MWT &gt;100 m NYHA II–IV</td>
<td>IV Rituximab</td>
<td>Placebo</td>
<td>NA</td>
<td>NA</td>
<td>Placebo corrected ΔPVR at week 24</td>
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<td>Hoeper 2013&lt;sup&gt;48&lt;/sup&gt;</td>
<td>Phase III IPAH, CTD-PAH, other WHO-FC II–IV</td>
<td>Fasudil po 1×/day</td>
<td>Placebo</td>
<td>202</td>
<td>NA</td>
<td>Placebo corrected Δ6MWT at week 24</td>
<td>32 m (95% CI: 12–52 m)</td>
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<td>Fukumoto 2013&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Phase II IPAH, CTD-PAH, other 6MWT ≥150 m WHO FC I–III</td>
<td>Fasudil po 2×/day</td>
<td>Placebo</td>
<td>23</td>
<td>8</td>
<td>Placebo corrected Δ6MWT and haemodynamics (mPAP, CP, SpO₂, oxygen saturation of pulmonary artery) at week 12</td>
<td>6MWT p = 0.51</td>
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<td>Galie 2010&lt;sup&gt;50&lt;/sup&gt;</td>
<td>Phase II IPAH, CTD-PAH, other 6MWT 200–550 m WHO FC II–III</td>
<td>Aviptadil inhaled</td>
<td>Placebo</td>
<td>56</td>
<td>12</td>
<td>Acute ΔPVR after 1 inhalation</td>
<td>NS</td>
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<td></td>
<td>Ghofrani 2012&lt;sup&gt;52&lt;/sup&gt;</td>
<td>Phase II IPAH, CTD-PAH, other 6MWT &gt;150 m WHO FC II–III</td>
<td>Aviptadil po 50 μg or 200 μg 4×/day</td>
<td>Placebo</td>
<td>103</td>
<td>14</td>
<td>Placebo corrected ΔPVR at week 16</td>
<td>−39 dynes·sec/cm² (95% CI: −119 to 42 dynes·sec/cm²)</td>
</tr>
</tbody>
</table>

The starting dose is 62.5 mg bid with up titration after 4 weeks to 125 mg bid. Possible side-effects are headache, flushing, hypotension, palpitations and anaemia. In 10% of the subjects, an increase in hepatic aminotransferase levels is seen. This is dose-dependent and reversible after reduction or discontinuation. Monthly liver function and haemoglobin control should be performed.

Macitentan

Macitentan is a novel non-selective ERA recently approved for PAH. The SERAPHIN trial was the first trial on PAH using a combined mortality/morbidity primary endpoint, time from the initiation of treatment to the first event: death from any cause, initiation of treatment with IV or SC prostanoids, lung transplantation, atrial septostomy or worsening of PAH (decrease in 6MWT of at least 15% from baseline, worsening of symptoms of PAH [NYHA FC or signs of right heart failure not responding to diuretics] and need for additional treatment for PAH). In 742 PAH patients (31% CTD-PAH, 64% on concomitant treatment with PDE5-I or oral/inhaled prostanoid), macitentan 3 and 10 mg significantly reduced the combined primary endpoint compared to placebo (38% vs. 46% for 3 mg, hazard ratio [HR] 0.70 [95%CI 0.50–0.96], p = 0.01 and 31% vs. 46% for 10 mg, HR 0.55 [95%CI 0.32–0.76], p < 0.001). Worsening of PAH was the most frequent event. In the subgroup analysis of 224 CTD-PAH patients, there was a trend towards reduction of combined primary endpoint without reaching level of significance (for macitentan 10 mg HR 0.58 [95%CI 0.33–1.02], p = NS). Macitentan 10 mg once daily is the dose used for PAH and an increase in hepatic aminotransferase levels is seldom seen. Headache, nasopharyngitis and anaemia were more frequently associated with macitentan than with placebo.

Ambrisentan

In the ARIES-1 and ARIES-2 trials, treatment with 2.5, 5 or 10 mg ambrisentan improved the 6MWT in PAH patients (32% CTD-PAH). Subgroup analysis of CTD-PAH showed a more modest response (range 15–23 m) as compared to IPAH (range 50–66 m). Ambrisentan is administered once daily, with a starting dose of 5 mg, which can be increased to 10 mg/day. The incidence of abnormal liver function tests is low (0.8–3%) and there is no tendency for the development of abnormal liver function tests in patients who had previously liver function abnormalities on bosentan treatment. Monthly control of liver function and haemoglobin level is however advised.

Sitaxentan has been withdrawn worldwide because of fatal hepatotoxicity.

Although the RCTs show a more moderate response on 6MWT in CTD-PAH and SSc-PAH as compared to IPAH for all ERAs, TTCW is delayed and survival seems to improve. Both bosentan, macitentan and ambrisentan can be used in SSc-PAH. Until now, bosentan was the first choice of treatment, but macitentan is recently reimbursed in Belgium and ambrisentan can be used even after liver toxicity on bosentan treatment.

Nitric oxide pathway

Reduced NO availability is associated with PAH. NO induces vasodilation and inhibits vascular proliferation by increasing production of cyclic guanosine monophosphate (cGMP). Phosphodiesterases (PDEs) are enzymes that inactivate cGMP. PDE5-I (sildenafil and tadalafil and vardenafil) slow the breakdown of cGMP and the soluble guanylate cyclase agonist (riociguat) stimulates cGMP production. Vardenafil is not yet EMA approved for the treatment of PAH.

Inhaled NO

Inhaled NO is used for acute vasoreactivity testing, but the use in an outpatient clinic setting is limited.

Sildenafil

In the SUPER-1 trial, sildenafil (20, 40 or 80 mg 3 times daily [tid]) was compared to placebo in patients with PAH (IPAH, CTD-PAH or PAH associated with congenital heart disease). A subgroup analysis of 84 patients with CTD-PAH (45% SSc-PAH) showed an improvement in 6MWT after 12 weeks of treatment with sildenafil 20 and 40 mg tid, but not with 80 mg tid. The starting dose is 20 mg tid but uptitration is frequently needed. Most side-effects are mild and related to vasodilation (headache, flushing and epistaxis).

Tadalafil

The PHIRST trial is a RCT in 405 PAH patients (53% on bosentan therapy) treated with 2.5, 10, 20 or 40 mg tadala-fil once daily. Subgroup analysis of the CTD-PAH patients shows a significant improvement of 6MWT after 16 weeks of treatment with tadalafil 20 and 40 mg daily. With the dose of 2.5 and 10 mg, the level of significance was not reached. Tadalafil has the advantage of being administered once daily (40 mg/day). The side-effects are similar with those of sildenafil.

Riociguat

Riociguat is a novel soluble guanylate cyclase stimulator recently approved for the treatment of PAH. In the PATENT-1 trial, there is a significant difference in 6MWT after 12 weeks of treatment with riociguat 2.5 mg tid compared to placebo in 443 PAH patients of which 50% were on background therapy with ERA or prostanoid. In the CTD-subgroup, there was a benefit in 6MWT without reaching the level of significance. Both sildenafil and tadalafil show benefit in 6MWT in CTD-PAH, but there are no mortality data. Riociguat is only recently reimbursed in Belgium.
Combination therapy

Simultaneous use of more than one PAH-specific class of drugs may be applied sequentially (for patients responding inadequately to initial monotherapy) or initially (upfront). Sequential combination therapy is the most widely utilized strategy. Evaluation of clinical response is based on a combination of different parameters including signs and symptoms of right ventricular failure, NYHA FC, exercise capacity, echocardiographic parameters, haemodynamic parameters and NT-proBNP plasma levels.

A meta-analysis of 6 RCT’s on combination therapy including 858 PAH patients (predominantly IPAH) shows that combination therapy is safe and well tolerated, improves exercise capacity and haemodynamics and reduces risk of clinical worsening (defined as death, lung transplantation, atrial septostomy, hospitalization and lack of improvement, deterioration or need for additional treatment) as compared to monotherapy. However, no all-cause mortality benefit was noticed. The recently published AMBITION trial compared monotherapy with tadalafil or ambrisentan with initial combination therapy with tadalafil and ambrisentan. The risk for the primary endpoint (a composite endpoint of clinical events including death from any cause, hospitalization, PAH progression and unsatisfactory clinical response) was 50% lower in PAH patients receiving initially combination therapy than receiving monotherapy of either drug. As no data are available concerning combination therapy in SSc-PAH these results should be interpreted with caution.

Lung transplantation

Lung transplantation may be considered in carefully selected SSc-PAH patients who have severe symptoms and who do not respond to IV prostacyclines or to a combination therapy. In a retrospective study with 29 SSc patients (15 SSc-ILD, 11 SSc-PAH and 3 both), 38 IPAH patients and 70 patients with idiopathic pulmonary fibrosis who had undergone lung transplantation, mortality did not differ significantly between these three groups. Cumulative survival at 6 months was 69, 79 and 80%, respectively, and converged with similar cumulative survival after 2 years (61, 63 and 64%, respectively).

Balloon atrial septostomy

The creation of an interatrial right-to-left shunt can decompress the right heart chambers, increase left ventricular preload and increase CO. It improves systemic oxygen transport despite arterial desaturation. Atrial septostomy should be regarded as a bridging procedure to transplantation or in a palliative setting.

Novel treatment options (Table 4)

Several novel molecules, working by the traditional (prostacyclin pathway) and novel pathways are under investigation in clinical trials on PAH. In none of these trials, subgroup analyses of CTD-PAH or SSc-PAH were performed yet.

Selexipag

Selexipag is an oral, selective prostacyclin receptor agonist. A phase II study with 43 PAH patients, stable on treatment with ERA and/or PDE5-I, showed significant improvement in pulmonary vascular resistance (PVR) after 17 weeks of treatment with selexipag compared to placebo. Selexipag was well tolerated. The results of a phase III RCT on selexipag are underway. 1156 PAH patients were randomized to receive selexipag or placebo in addition to ERA and/or PDE5-I. Patients were treated up to 4.3 years. Preliminary data announced that selexipag decreased the risk of a morbidity/mortality event vs. placebo by 39% (p < 0.0001).

Immunosuppressive therapy

Rituximab, an anti-CD20 monoclonal antibody, for the treatment of SSc-PAH is currently being studied in a phase II RCT. Patients on prostanoids, ERA and/or PDE5-I receive IV rituximab or placebo and the primary endpoint is PVR at week 24.

Tyrosine kinase inhibitor

Platelet-derived growth factor (PDGF) is a growth factor for several cell types, including vascular smooth muscle cells, resulting in proliferation and hyperplasia. Imatinib is a tyrosine kinase inhibitor, initially developed for chronic myeloid leukaemia, which inhibits the PDGF receptor. In the IMPRES study, 202 symptomatic PAH patients on advanced therapy (at least 2 conventional PAH therapies), were randomized to receive additional oral imatinib or placebo. Significant improvement in 6MWT was observed in the group treated with imatinib, but side-effects (anaemia, vomiting, oedema, diarrhoea) were common and a third of the patients had to discontinue the treatment. In PAH patients treated with imatinib and oral anticoagulants, an increased incidence of subdural haematoma was observed.

Rho-kinase inhibitor

Rho-kinase is up-regulated by inflammatory stimuli and rho-kinase inhibition increases the endothelial NO synthase expression and inhibits inflammatory cell migration. Fasudil is a rho-kinase inhibitor that can be administered intravenously or orally. A phase II RCT in 23 PAH patients showed that oral treatment with fasudil did not significantly improve haemodynamics and 6MWT as compared to placebo.

Vasoactive intestinal peptide (VIP)

VIP is a neurotransmitter hormone with a vasodilatory, antiproliferative effect and induces as well an inhibition of platelet activation. In patients with IPAH, low serum
concentrations of VIP with increased receptor expression in the pulmonary vessels have been described. In a non RCT, inhalation of a single dose of aviptadil during RHC in 20 PH patients with various aetiologies (PAH, PH due to ILD and CTEPH) caused a significant, temporary pulmonary vasodilation, increase in stroke volume and increase in mixed venous oxygen saturation. However, results from an unpublished phase II study in 56 PAH patients receiving inhaled aviptadil or placebo in addition to an ERA and/or a PDE-5 inhibitor showed no significant benefit in haemodynamics after one inhalation.

Selective serotonin receptor inhibitor
Serotonin can induce pulmonary vasoconstriction and platelet aggregation. Terguride is an oral antagonist of serotonin receptors. In PAH, a phase II RCT showed no significant effect of terguride in addition to maximal two conventional non-intravenous PAH therapies, on PVR compared to placebo.

Conclusion
SSc is a devastating disease with high mortality and morbidity. Clinically evident cardiac involvement and SSc-PAH are associated with an increased risk of death. Both DcSSc and LcSSc are at risk for development of cardiac involvement and PAH. Screening for asymptomatic cardiac involvement should be performed on a regular base in order to start the conventional treatment options for heart failure in an early phase. However, until now, there are no RCTs on the treatment options and optimal screening methods for cardiac involvement in SSc patients. PAH can occur early in the disease course both in DcSSc and LcSSc. Screening for PAH should be performed routinely in SSc patients, since screening leads to earlier diagnosis and earlier treatment is associated with a better prognosis. Nowadays, screening is performed following the ESC/ERS guidelines by clinical judgement and echocardiography. Recently the DETECT algorithm, a 2-step screenings algorithm, was proposed in a subgroup of SSc patients at increased risk for PAH. This algorithm showed a higher sensitivity but lower specificity as compared to the ESC/ERS screening algorithm, but further research is needed for validation in the general SSc population. Mortality in SSc-PAH is higher than in IPAH, despite the currently accepted treatment options. The recommendations of the EULAR from 2009 can be followed for treatment of SSc-PAH: IV epoprostenol (Flolan® or Veletri®) as the treatment of choice in severe, therapy-resistant SSc-PAH. Alternatively, an ERA (bosentan or ambrisentan) or PDE-5-i (sildenafil or tadalafil) can be used. The novel molecules macitentan and riociguat have recently received FDA and EMA approval for use in PAH. Some novel, possibly promising drugs for PAH (selexipag, rituximab, imatinib, fasudil, aviptadil and terguride) are under investigation but larger phase III clinical trials and the subgroup analyses in CTD-PAH and SSc-PAH are still missing.
PC1 percutaneous coronary intervention
PDE5-I phosphodiesterase 5-inhibitor
PDGF platelet-derived growth factor
PH pulmonary hypertension
PVR pulmonary vascular resistance
RCT randomized controlled trial
RHC right heart catheterization
RP Raynaud’s phenomenon
SC subcutaneous
sPAP systolic pulmonary artery pressure
SPECT single-photon emission computed tomography
SSc systemic sclerosis
SSc-PAH systemic sclerosis associated pulmonary arterial hypertension
Tid ter in die, three times daily
TRV tricuspid regurgitation velocity
TTCW time to clinical worsening
WHO World Health Organisation

Conflicts of interest
None.

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