Arthritis & Rheumatology
Vol. 76, No. 5, May 2024, pp 777–782
DOI 10.1002/art.42791

American College of Rheumatology
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BRIEF REPORT

Performance of DETECT Pulmonary Arterial Hypertension Algorithm According to the Hemodynamic Definition of Pulmonary Arterial Hypertension in the 2022 European Society of Cardiology and the European Respiratory Society Guidelines

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Objective. The evidence-based DETECT pulmonary arterial hypertension (PAH) algorithm is frequently used in patients with systemic sclerosis (SSc) to help clinicians screen for PAH by using noninvasive data to recommend patient referral to echocardiography and, if applicable, for a diagnostic right-sided heart catheterization. However, the hemodynamic definition of PAH was recently updated in the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines. The performance of DETECT PAH in identifying patients with a high risk of PAH according to this new definition was assessed.

Methods. In this post hoc analysis of DETECT, which comprised 466 patients with SSc, the performance of the DETECT PAH algorithm in identifying patients with a high risk of PAH as defined in the 2022 ESC/ERS guidelines (mean pulmonary arterial pressure [mPAP] >20 mm Hg, pulmonary capillary wedge pressure [PCWP] ≤15 mm Hg, and pulmonary vascular resistance >2 Wood units) was assessed using summary statistics and was descriptively compared to the known performance of DETECT PAH as defined in 2014, when it was developed (mPAP ≥25 mm Hg and PCWP ≤15 mm Hg).

Results. The sensitivity of DETECT PAH in identifying patients with a high risk of PAH according to the 2022 ESC/ERS definition was lower (88.2%) compared to the 2014 definition (95.8%). Specificity improved from 47.8% to 50.8%.

Conclusion. The performance of the DETECT algorithm to screen for PAH in patients with SSc is maintained when PAH is defined according to the 2022 ESC/ERS hemodynamic definition, indicating that DETECT remains applicable to screen for PAH in patients with SSc.

INTRODUCTION

Patients with systemic sclerosis (SSc) have a high risk of pulmonary arterial hypertension (PAH), with an estimated prevalence of 4% to 12% based on right-sided heart catheterization (RHC).[1–4] Screening programs in patients with SSc are recommended and can lead to prompt PAH diagnosis, early treatment, and better prognosis.[3,5–7] This has recently been reflected in

ClinicalTrials.gov identifier: NCT00706082
Supported by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson and Johnson.
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Additional supplementary information cited in this article can be found online in the Supporting Information section (https://onlinelibrary.wiley.com/doi/10.1002/art.42791).

Author disclosures and graphical abstract are available at https://onlinelibrary.wiley.com/doi/10.1002/art.42791.

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Submitted for publication April 26, 2022; accepted in revised form December 22, 2023.

the 2022 European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines, which recommend the DETECT algorithm in adult patients with SSc of >3 years of disease duration, a forced vital capacity (FVC) ≥40%, and a pulmonary diffusing capacity for carbon monoxide (DLCO) <60% to identify asymptomatic patients with PAH.[5,6] The DETECT study (NCT00706082) developed an evidence-based detection algorithm for PAH in patients with SSc. DETECT uses clinical and laboratory data alongside echocardiography to recommend patient referral for RHC,[8] which is required to confirm PAH diagnosis.[9,10] The DETECT algorithm is highly sensitive, minimizes false negatives, and can help identify milder PAH.[8]

When the DETECT algorithm was developed, precapillary pulmonary hypertension (PH) was hemodynamically defined as mean pulmonary arterial pressure (mPAP) ≥25 mm Hg and pulmonary capillary wedge pressure (PCWP) as ≤15 mm Hg.[11] Subsequently, a proposal was made at the 6th World Symposium on PH (6WSPH) to update the hemodynamic definition of PH by lowering the mPAP threshold to >20 mm Hg and including pulmonary vascular resistance (PVR) ≥3 Wood units (WU) as part of the hemodynamic definition of precapillary PH.[12] Alternative PVR thresholds for precapillary PH were also discussed, because there is evidence that a PVR >2 WU is abnormal and associated with reduced long-term survival.[13,14] These proposed updates have recently been confirmed in the 2022 ESC/ERS guidelines, which updated the definition of PH to mPAP >20 mm Hg and included a PVR >2 WU in the definition of precapillary PH.[5,6]

The DETECT algorithm, developed based on the PH/PAH definition that prevailed at the time of its development, is established in clinical practice and widely used[15] to recommend echocardiography and diagnostic RHCs to patients with SSc when applicable.[8] In this analysis, we examined the performance of the DETECT algorithm in screening for PAH when PAH is hemodynamically defined according to the 2022 ESC/ERS guidelines.

PATIENTS AND METHODS

Study design. DETECT (NCT00706082) was a large, international, multicenter, real-world, cross-sectional study.[8] DETECT was the first study to develop an evidence-based algorithm using noninvasive data for PAH in patients with SSc. DETECT was conducted in accordance with the Declaration of Helsinki and its amendments, followed the International Conference on Harmonization Guideline for Good Clinical Practice, and was approved by local institutional review boards and ethics committees (Supplementary Table 1). All patients provided written informed consent.

The DETECT algorithm is a two-step, internally validated process for screening PAH in patients with SSc.[8] In Step 1, the patient is evaluated for nonechocardiographic variables and receives a risk score based on these variables. These include the FVC and DLCO percentage predicted, current and past telangiectasias, serum anticentromere antibodies, serum N-terminal probrain natriuretic peptide, serum urate, and right axis deviation (electrocardiogram). The total score of Step 1 determines whether the patient should be referred to echocardiography and thus undergo Step 2. In Step 2, two echocardiographic variables (right atrium area and tricuspid regurgitant jet velocity) are evaluated and combined with the previous risk score from Step 1. Step 1 can also directly be combined with Step 2. This overall risk score then recommends an RHC to confirm suspected PAH.

Patient population. DETECT[8] enrolled patients ≥18 years old with a diagnosis of SSc (diagnosed according to the American College of Rheumatology criteria[16]) with a duration of >3 years from the first non-Raynaud symptom and a predicted's DLCO of <60% (to increase the proportion of patients at higher risk of PAH). The exclusion criteria included confirmation of PH by RHC before enrollment, use of PH-specific therapy, an FVC <40% of predicted, renal insufficiency, previous evidence of clinically relevant left heart disease, or pregnancy. During DETECT, data were collected on a broad range of variables within the following four groups: (1) demographic and clinical parameters, (2) serum tests, (3) electrocardiography, and (4) echocardiography. The confirmatory diagnosis by RHC was performed after this data collection to minimize bias. RHC and echocardiography were conducted according to standardized procedures. All patients who had an RHC during the DETECT study[8] were included in this post hoc analysis. Patients were classified as non-PH, World Health Organization (WHO) Group 1 PH (PAH), WHO Group 2 PH, or WHO Group 3 PH.

For the main analysis, patients were classified according to the updated hemodynamic definitions for PAH recommended in the 2022 ESC/ERS guidelines[5,6] (Supplementary Table 2). Non-PH is defined as mPAP ≤20 mm Hg; PH as mPAP >20 mm Hg; and PAH as mPAP >20 mm Hg, PCWP ≤15 mm Hg, PVR >2 WU, and FVC >70% (or FVC 60% to 70% plus high-resolution computed tomography showing mild to moderate or no parenchymal lung disease). WHO Group 2 PH (PH caused by left heart disease) is defined as mPAP >20 mm Hg and PCWP >15 mm Hg. WHO Group 3 PH (PH caused by lung disease or hypoxia) is defined as mPAP >20 mm Hg, PCWP ≤15 mm Hg, PVR >2 WU, and FVC <60% (or FVC 60% to 70% plus high-resolution computed tomography not available or showing moderate to severe parenchymal lung disease). In an additional analysis, patients were classified as above but the PVR threshold ≥3 WU that was proposed at the 6WSPH was used to define PAH (6WSPH definition; Supplementary Table 2).[12]

Analysis and statistical methodology. In this post hoc study, the published algorithm, a Conformité Européenne–marked product, was evaluated without further development. The reported performance evaluation is research-based only and does not

apply to the claimed performance of the Conformité Européenne–marked product. The DETECT algorithm was applied to all patients as in the original publication[8]; missing values were not replaced or imputed when calculating the Step 1 and Step 2 scores of the patients with non-PH and PAH. If one of the six nonechocardiographic variables was missing, the total score of Step 1 could not be calculated, and the patient could not be classified. If the total score of Step 1 could be calculated with a result leading the patient to be referred to echocardiography but one of the two echocardiographic variables was missing, the total score of Step 2 could not be calculated, and the patient could not be classified. Performance summary statistics (Supplementary Methods) were then calculated from the observed algorithm decisions compared to diagnoses based on RHC. For comparison, results for patients classified using the hemodynamic definition in the prevailing guidelines[11,17,18] at the time of the DETECT publication (2014 definition; Supplementary Table 2) are also shown.

RESULTS

The 466 patients with SSc with RHC data who enrolled in DETECT were included in this analysis. Patient characteristics of the non-PH and PAH populations according to the 2022 ESC/ERS, 6WSPH, and 2014 definitions are shown in Supplementary Table 3. Patient classification using the 2022 ESC/ERS definition is summarized in Figure 1 alongside the distribution using the 2014 definition. The number of patients with non-PH decreased from 321 (2014 definition) to 242. Of the 79 patients who were re-classified from non-PH to PH by the 2022 ESC/ERS definition, 32 had an mPAP of 21 to 24 mm Hg and a PVR >2 WU and were classified as PAH (Supplementary Table 4). Of the 87 patients originally classified as PAH by the 2014 definition, 82 remained classified as PAH. Using a PVR threshold of >2 WU resulted in five patients classified as PAH using the 2014 definition now being grouped under nonclassified PH. The distribution of patients with mPAP 21 to 24 mm Hg stratified by PVR is summarized in Supplementary Figure 1. Altogether, classifying patients

2014 definition	**2022 ESC/ERS definition**					
Frequency	**Non-PH[f]**	**WHO Group 1 PH (PAH)[g]**	**WHO Group 2 PH (PH due to LHD)[h]**	**WHO Group 3 PH (PH due to lung disease / hypoxia)[i]**	**Non-classified PH[j]**	**Total**
Non-PH[a]	242	32	5	14	28	**321**
WHO Group 1 PH (PAH)[b]	0	82	0	0	5	**87**
WHO Group 2 PH (PH due to LHD)[c]	0	0	30	0	0	**30**
WHO Group 3 PH (PH due to lung disease / hypoxia)[d]	0	0	0	25	2	**27**
Non-classified PH[e]	0	0	0	0	1	**1**
Total	**242**	**114**	**35**	**39**	**36[k]**	**466**

Figure 1. Patient classification for the DETECT study population using the 2014 and 2022 ESC/ERS definitions. N = 466, all with right-sided heart catheterization performed. ESC/ERS, European Society of Cardiology/European Respiratory Society; FVC, forced vital capacity; HRCT, high-resolution computed tomography; LHD, left heart disease; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; WHO, World Health Organization; WU, Wood units. [a]mPAP <25 mm Hg. [b]mPAP ≥25 mm Hg, PCWP ≤15 mm Hg, and FVC >70% (or FVC 60%–70% plus HRCT showing mild-moderate or no parenchymal lung disease). [c]mPAP ≥25 mm Hg and PCWP >15 mm Hg. [d]mPAP ≥25 mm Hg, PCWP ≤15 mm Hg, and FVC <60% (or FVC 60%–70% plus HRCT not available or showing moderate-severe parenchymal lung disease). [e]mPAP ≥25 mm Hg and PCWP missing. [f]mPAP ≤20 mm Hg. [g]mPAP >20 mm Hg, PCWP ≤15 mm Hg, PVR >2 WU, and FVC >70% (or FVC 60%–70% plus HRCT showing mild-moderate or no parenchymal lung disease). [h]mPAP >20 mm Hg and PCWP >15 mm Hg. [i]mPAP >20 mm Hg, PCWP ≤15 mm Hg, PVR >2 WU, and FVC <60% (or FVC 60%–70% plus HRCT not available or showing moderate-severe parenchymal lung disease). [j]mPAP >20 mm Hg and either PCWP missing or PVR ≤2 WU. [k]Two patients had missing PCWP values, and 34 patients had PCWP ≤15 mm Hg and/or PVR ≤2 WU.

according to the 2022 ESC/ERS definition led to an increase in the number of patients classified as PAH from 87 to 114 patients.

Performance of DETECT. The sensitivity of the DETECT algorithm decreased from 95.8% to 88.2% (ie, an increase in the false negative rate from 4.2% to 11.8%), and specificity improved from 47.8% to 50.8% when PH and PAH was defined according to the 2022 ESC/ERS definition compared to the 2014 definition (Table 1, Figure 2). The positive predictive value improved from 34.8% to 46.9%, and the negative predictive value deteriorated from 97.5% to 89.7%. The referral rate for RHC was 62.1%, consistent with that for the 2014 definition.

An additional analysis was performed using the 6WSPH definition, which used a PVR cut-off of ≥3 WU (6WSPH definition; Supplementary Note). In this analysis, the sensitivity of DETECT slightly decreased from 95.8% to 92.7% (ie, an increase in the false negative rate from 4.2% to 7.3%), and the specificity slightly improved from 47.8% to 50.8% (Table 1, Supplementary Figure 2). There was a slight improvement in the positive predictive value from 34.8% to 35.4% and a decrease in the negative predictive value from 97.5% to 96.0%. The referral rate for RHC was 59.0% when PH and PAH was defined according to the 6WSPH definition versus 62.1% when defined according to the 2014 definition. For the 82 patients screened as true PAH positive using the DETECT algorithm with the 2022 ESC/ERS definition (Figure 2), the mean (SD) mPAP was 31.1 (8.5) mm Hg, and the mean (SD) PVR was 4.5 (2.6) WU. For the 69 patients screened as true PAH positive using the DETECT algorithm with the 2014 definition (Figure 2), the mean (SD) mPAP was 33.0 (8.0) mm Hg, and the mean (SD) PVR was 4.8 (2.6) WU. For the 51 patients screened as true PAH positive using the DETECT algorithm with the 6WSPH definition (Supplementary Figure 2), the mean (SD) mPAP was 35.0 (8.3) mm Hg, and the mean (SD) PVR was 5.7 (2.6) WU. The hemodynamics for the 11 false negative patients with PAH using the DETECT algorithm with the 2022 ESC/ERS definition are presented in Supplementary Table 5.

Table 1. Performance of the DETECT algorithm when applying the 2014, 6WSPH, and 2022 ESC/ERS definitions[a]

	2022 ESC/ERS definition (n = 282)[b]	2014 definition (n = 319)[b]	6WSPH definition (n = 244)[b]
Sensitivity, %	88.2	95.8	92.7
Specificity, %	50.8	47.8	50.8
PPV (RHC hit rate), %	46.9	34.8	35.4
NPV, %	89.7	97.5	96.0
False negative rate, %	11.8	4.2	7.3
Referral rate, %	62.1	62.1	59.0

[a] Pulmonary arterial hypertension is defined as mPAP >20 mm Hg, PCWP ≤15 mm Hg, and PVR >2 WU (2022 ESC/ERS definition); mPAP ≥25 mm Hg and PCWP ≤15 mm Hg (2014 definition); and mPAP >20 mm Hg, PCWP ≤15 mm Hg, and PVR ≥3 WU (6WSPH definition). Non–pulmonary hypertension is defined as mPAP ≤20 mm Hg (2022 ESC/ERS definition); mPAP <25 mm Hg (2014 definition); and mPAP ≤20 mm Hg (6WSPH definition).
[b] The "n" value is the total of patients with non-pulmonary hypertension and with pulmonary arterial hypertension with available data to enable application of DETECT; 74, 89, and 66 patients were removed because of missing data when applying the 2022 ESC/ERS, 2014, and 6WSPH definitions, respectively. ESC/ERS, European Society of Cardiology/European Respiratory Society; mPAP, mean pulmonary arterial pressure; NPV, negative predictive value; PCWP, pulmonary capillary wedge pressure; PPV, positive predictive value; PVR, pulmonary vascular resistance; RHC, right-sided heart catheterization; 6WSPH, 6th PH World Symposium; WU, Wood units.

DISCUSSION

Screening for PAH in patients with SSc improves early detection of PAH and is associated with better outcomes.[3,7] The DETECT algorithm is one of the most commonly used composite screening modalities for PAH in patients with SSc.[15] The hemodynamic definition of PAH has recently been updated in the 2022 ESC/ERS guidelines to include a lower mPAP threshold (mPAP >20 mm Hg vs mPAP ≥25 mm Hg) and a PVR cut-off (≥2 WU).[5,6,12] In support of this new definition, a recent study showed that an mPAP of 21 to 24 mm Hg and PVR >2 to ≤3 WU was associated with poorer survival in a PH referral population.[19] It is therefore important to understand how the DETECT algorithm performs in this new context. In this study, we took advantage of the large DETECT study dataset, which is unique because RHC, the gold standard diagnostic procedure for PAH, was performed in all patients after application of the DETECT algorithm and, therefore, allows testing of the false negative rate.

The DETECT algorithm performed well at identifying patients with PAH as defined in the 2022 ESC/ERS guidelines, which includes a PVR >2 WU. The specificity was comparable to that observed when PAH was defined according to the prevailing guidelines at the time of publication of DETECT[8] (50.8% vs 47.8%), although sensitivity was slightly lower (88.2% vs 95.8%). This slight decrease in sensitivity is likely due to patients with mildly elevated mPAP (21–24 mm Hg) and with a PVR between 2 and 3 WU, indicative of less advanced disease, being included in the PAH group when using the 2022 ESC/ERS definition. When applying the hemodynamic definition proposed at the 6WSPH, the DETECT algorithm also performed well with a sensitivity of 92.7% and specificity of 50.8%.

The results reported here are consistent with previous studies investigating patients with SSc with mPAP >20 mm Hg. One retrospective study evaluated the effect of the hemodynamic definition proposed at the 6WSPH on the PH classification of patients with SSc.[20] Similar to our findings, the update did not have a significant impact on the diagnosis of PH.[20] Furthermore, it has been shown that patients with SSc with mildly elevated mPAP (21–24 mm Hg) often have a PVR between >2 and <3 WU, have a preserved function at rest,[14,21] and can be distinguished from patients with normal mPAP (<21 mm Hg) and those with PAH (mPAP ≥25 mm Hg) based on clinical parameters.[22] Altogether,

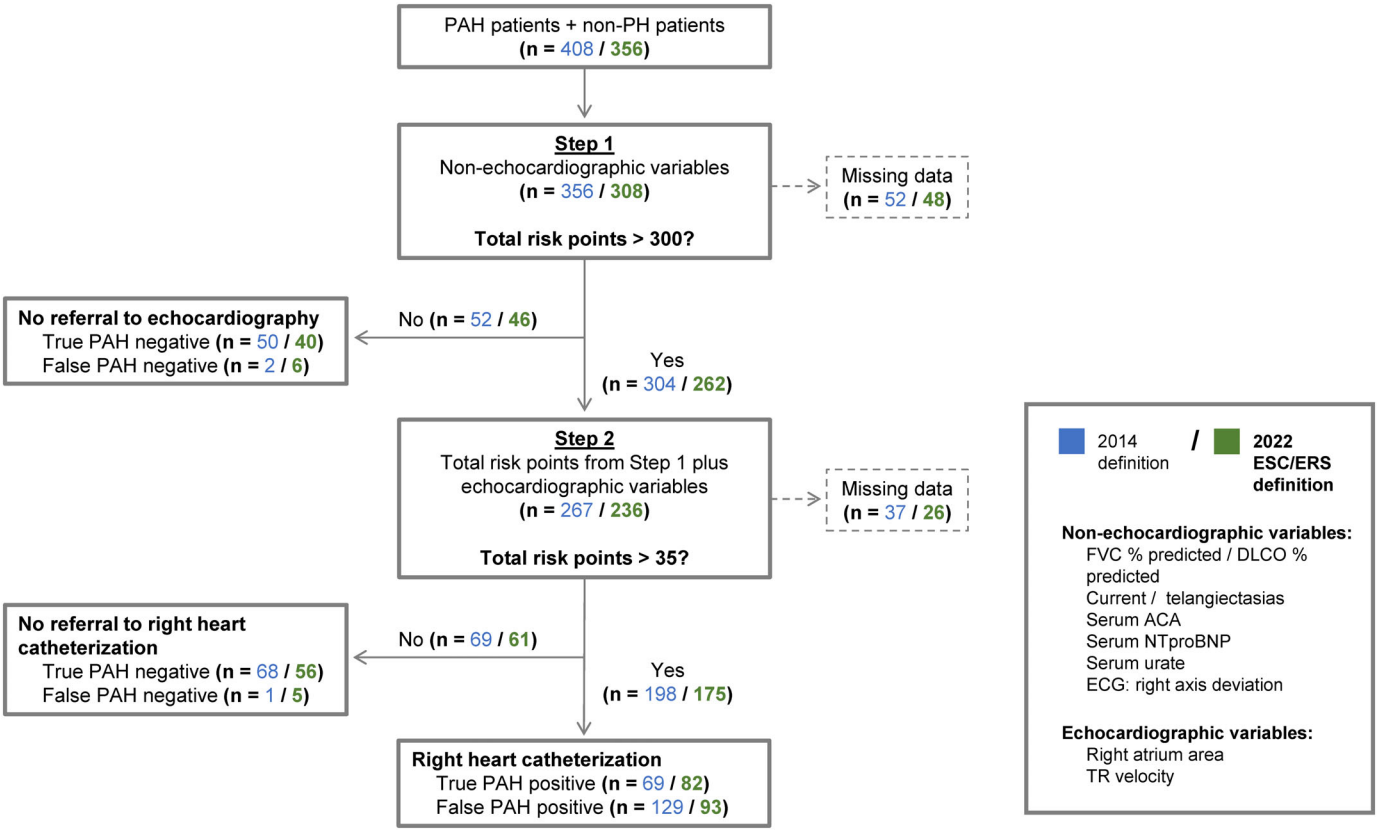

Figure 2. Two-step DETECT decision tree for patients with non-PH and PAH using the 2014 and 2022 ESC/ERS definitions. Data for the 2014 definition have been previously published.[8] PAH is defined as mPAP ≥25 mm Hg and PCWP ≤15 mm Hg (2014 definition) and mPAP >20 mm Hg, PCWP ≤15 mm Hg, PVR >2 Wood units (2022 ESC/ERS definition). Non-PH is defined as mPAP <25 mm Hg (2014 definition) and mPAP ≤20 mm Hg (2022 ESC/ERS definition). ACA, anticentromere antibody; DLCO, pulmonary diffusing capacity for carbon monoxide; ECG, electrocardiogram; ESC/ERS, European Society of Cardiology/European Respiratory Society; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; NTproBNP, N-terminal probrain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; TR, tricuspid regurgitant jet.

these results support the use of DETECT PAH as a clinical screening tool for PAH in patients with SSc.

This analysis provides insights on how the 2022 ESC/ERS guidelines and 6WSPH proceedings impact the number of patients in the DETECT study who would be classified as PH and, more importantly here, as PAH. Intuitively, lowering the mPAP threshold should lead to an increase in the number of patients classified as PAH. However, as demonstrated here, this was only true when this criterion was combined with a PVR of >2 WU and not when a PVR threshold of ≥3 WU was used to define PAH. This shows that, at least among patients with SSc, those with a low mPAP tend to also have a rather low PVR (ie, <3 WU). As such, lowering the mPAP threshold used to define PAH only significantly impacts the number of patients with PAH identified when the threshold for PVR is also lowered to >2 WU. Furthermore, although the 2022 ESC/ERS guidelines updated the definition of precapillary PH, they did not recommend use of a specific PAH therapy for the management of patients with PAH with a PVR of 2 to 3 WU; such patients may therefore be appropriate for close follow-up in the clinic as well as further investigation via a dedicated randomized clinical trial. Changing the hemodynamic definition of PH and PAH also led to an increase in the number of patients with PH not classified; however, this number was relatively modest with the definition recommended by the 2022 ESC/ERS guidelines. Hence, the size of this population can be expected to be small in clinical practice.

It is important to note that the DETECT cohort was recruited from 2008 to 2011[8] and may therefore not be fully representative of the contemporary patient population with SSc. Patients with a DLCO ≥60% were excluded from the DETECT study to enrich for patients at high risk of PAH; therefore, the results of this study may not be representative of the general population with SSc. However, patients with a DLCO ≥60% carry little risk of PAH and, this low prevalence combined with the current tools, renders routine screening ineffective.

In conclusion, the DETECT algorithm maintains good performance, with high sensitivity and reduced false negative rate, in

identifying patients with a high risk of PAH in SSc. The DETECT algorithm remains applicable in clinical practice as a screening tool for PAH.

ACKNOWLEDGMENTS

Medical writing assistance was provided by Anna Chapman-Barnes, Jatta Huotari and Emma Connolly (eluSCIdate ltd, Meggen, Switzerland) and funded by Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson, Allschwil, Switzerland.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr Distler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Distler, Hachulla.

Acquisition of data. Distler, Bonderman, Coghlan, Denton, Grünig, Khanna, McLaughlin, Müller-Ladner, Pope, Vonk, Hachulla.

Analysis and interpretation of data. Distler, Bonderman, Coghlan, Denton, Grünig, Khanna, McLaughlin, Müller-Ladner, Pope, Vonk, Di Scala, Lemarie, Perchenet, Hachulla.

ROLE OF THE STUDY SPONSOR

Actelion Pharmaceuticals Ltd had no role in the study design or in the collection, analysis, or interpretation of the data, the writing of the manuscript, or the decision to submit the manuscript for publication. Publication of this article was not contingent upon approval by Actelion Pharmaceuticals Ltd.

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