ARTHRITIS & RHEUMATISM
Vol. 65, No. 12, December 2013, pp 3194–3201
DOI 10.1002/art.38172

Recommendations for Screening and Detection of Connective Tissue Disease–Associated Pulmonary Arterial Hypertension

Dinesh Khanna,[1] Heather Gladue,[1] Richard Channick,[2] Lorinda Chung,[3] Oliver Distler,[4] Daniel E. Furst,[5] Eric Hachulla,[6] Marc Humbert,[7] David Langleben,[8] Stephen C. Mathai,[9] Rajeev Saggar,[10] Scott Visovatti,[1] Nezam Altorok,[1] Whitney Townsend,[1] John FitzGerald,[5] and Vallerie V. McLaughlin[1]

Objective. **Pulmonary arterial hypertension (PAH) affects up to 15% of patients with connective tissue diseases (CTDs). Previous recommendations developed as part of larger efforts in PAH did not include detailed recommendations for patients with CTD-associated PAH. Therefore, we sought to develop recommendations for screening and early detection of CTD-associated PAH.**

Methods. **We performed a systematic review of the literature on the screening and diagnosis of PAH in CTD. Using the RAND/University of California, Los Angeles consensus methodology, we developed case scenarios followed by 2 stages of voting. First, international experts from a variety of specialties voted anonymously on the appropriateness of each case scenario. The experts then met face-to-face to discuss and resolve**

Funded by the Scleroderma Foundation and the Pulmonary Hypertension Association, which received unrestricted educational grants from Actelion, Gilead, and United Therapeutics to support development of these recommendations. Dr. Khanna's work was supported by the NIH (National Institute of Arthritis and Musculoskeletal and Skin Diseases grant K24-AR-063120-02). Dr. Chung's work was supported by the Scleroderma Research Foundation. Dr. Mathai's work was supported by the NIH and the Pulmonary Hypertension Association through a jointly sponsored grant (National Heart, Lung, and Blood Institute, K23-HL-093387).

[1]Dinesh Khanna, MD, MSc, Heather Gladue, DO (current address: Emory University, Atlanta, Georgia), Scott Visovatti, MD, Nezam Altorok, MD, Whitney Townsend, MLIS, Vallerie V. McLaughlin, MD: University of Michigan, Ann Arbor; [2]Richard Channick, MD: Massachusetts General Hospital, Boston; [3]Lorinda Chung, MD, MS: Stanford University School of Medicine, Stanford, California, and Palo Alto VA Health Care System, Palo Alto, California; [4]Oliver Distler, MD: University Hospital Zurich, Zurich, Switzerland; [5]Daniel E. Furst, MD, John FitzGerald, MD, PhD: David Geffen School of Medicine at University of California, Los Angeles; [6]Eric Hachulla, MD, PhD: Université Lille 2 and Hôpital Claude Huriez, Lille, France; [7]Marc Humbert, MD, PhD: Université Paris-Sud, INSERM U999, AP-HP, and Hôpital Bicêtre, Le Kremlin-Bicêtre, France; [8]David Langleben, MD: Jewish General Hospital and McGill University, Montreal, Quebec, Canada; [9]Stephen C. Mathai, MD, MHS: Johns Hopkins University School of Medicine, Baltimore, Maryland; [10]Rajeev Saggar, MD: St. Joseph's Hospital and Medical Center, Phoenix, Arizona.

Dr. Khanna has received consulting fees, speaking fees, and/or honoraria from United Therapeutics, Roche, Bristol-Myers Squibb, Gilead, Pfizer, Digna Biotech, and Impact Pharmaceutical Services (less than $10,000 each) and from Actelion (more than $10,000). Dr. Channick has received consulting fees, speaking fees, and/or honoraria from Actelion, United Therapeutics, and Bayer (less than $10,000 each). Dr. Chung has received consulting fees, speaking fees, and/or honoraria from Gilead (less than $10,000). Dr. Distler has received consulting fees, speaking fees, and/or honoraria from Bayer, Pfizer, ErgoNex, Bristol-Myers Squibb, Sanofi-Aventis, Sinoxa, United BioSource, Medac, Swedish Orphan Biovitrum, Boehringer Ingelheim Pharma, Novartis, and Active Biotech (less than $10,000 each) and from Actelion and 4D Science (more than $10,000 each); he also has a patent for the use of microRNA-29 for the treatment of systemic sclerosis. Dr. Hachulla has received consulting fees, speaking fees, and/or honoraria from Actelion, Pfizer, Lilly, United Therapeutics, and GlaxoSmithKline (less than $10,000 each). Dr. Humbert has received consulting fees, speaking fees, and/or honoraria from Actelion, Aires Pharmaceuticals, Bayer, GlaxoSmithKline, Novartis, and Pfizer (less than $10,000 each). Dr. Langleben has received consulting fees, speaking fees, and/or honoraria from Actelion, Bayer, Novartis, Pfizer, GlaxoSmithKline, Lilly, and United Therapeutics (less than $10,000 each). Dr. Mathai has received consulting fees, speaking fees, and/or honoraria from Bayer Healthcare, United Therapeutics, and Actelion (less than $10,000 each). Dr. Saggar has received consulting fees, speaking fees, and/or honoraria from United Therapeutics, Gilead, Actelion, and Bayer (less than $10,000 each). Dr. McLaughlin has received consulting fees, speaking fees, and/or honoraria from Merck (less than $10,000) and from Actelion, Bayer, Gilead, and United Therapeutics (more than $10,000 each); she also has received institutional grants and research support from Actelion, Bayer, and Novartis.

Address correspondence to Dinesh Khanna, MD, MSc, University of Michigan, Division of Rheumatology, Department of Internal Medicine, Suite 7C27, 300 North Ingalls Street, SPC 5422, Ann Arbor, MI 48109. E-mail: khannad@med.umich.edu.

Submitted for publication April 1, 2013; accepted in revised form August 22, 2013.

discrepant votes to arrive at consensus recommendations.

Results. **The key recommendation stated that all patients with systemic sclerosis (SSc) should be screened for PAH. In addition, patients with mixed connective tissue disease or other CTDs with scleroderma features (scleroderma spectrum disorders) should be screened for PAH. It was recommended that screening pulmonary function tests (PFTs) with single-breath diffusing capacity for carbon monoxide, transthoracic echocardiogram, and measurement of N-terminal pro–brain natriuretic peptide (NT-proBNP) be performed in all patients with SSc and scleroderma spectrum disorders. In patients with SSc and scleroderma spectrum disorders, transthoracic echocardiogram and PFTs should be performed annually. The full screening panel (transthoracic echocardiogram, PFTs, and measurement of NT-proBNP) should be performed as soon as any new signs or symptoms are present.**

Conclusion. **We provide consensus-based, evidence-driven recommendations for screening and early detection of CTD-associated PAH. It is our hope that these recommendations will lead to earlier detection of CTD-associated PAH and ultimately improve patient outcomes.**

Pulmonary arterial hypertension (PAH) affects 0.5–15% of patients with connective tissue diseases (CTDs) and is one of the leading causes of death in systemic sclerosis (SSc) and mixed connective tissue disease (MCTD) (1–5). Despite increasing recognition of PAH in CTDs, the diagnosis is often delayed, which may lead to unfavorable outcomes in these patients (2,6). International organizations have provided recommendations for screening and detection of PAH in CTDs, but these recommendations have been limited to the use of transthoracic echocardiography for patients with SSc (7–9). The established recommendations were developed as part of larger efforts in PAH and did not include detailed recommendations for patients with CTD-associated PAH. Therefore, we sought to develop recommendations for screening and early detection of CTD-associated PAH using rigorous data-driven and consensus-building methodology that has been used previously to develop recommendations.

These recommendations are designed to promote screening and early detection of CTD-associated PAH and to reflect best practice, as evaluated by a diverse group of experts who examined the current level of evidence. Important design limitations of the RAND/University of California, Los Angeles (UCLA) consensus methodology that was used in this study are the lack of inclusion of societal costs of health care and the absence of costs and cost-effectiveness of tests in the analyses (10). These recommendations are not meant to be prescriptive and are based on currently available evidence. The recommendations cannot and should not be substituted for individualized direct assessment of the patient, coupled with clinical decision-making by a competent health care practitioner. Importantly, the recommendations presented here are not intended to limit or deny third party payor coverage of health care costs for groups or individual patients.

MATERIALS AND METHODS

Project design and development of recommendations and grading of evidence. The RAND/UCLA consensus methodology, which was developed in the 1980s, incorporates both Delphi and nominal group methods and was successfully used to develop other guidelines and recommendations commissioned by the American College of Rheumatology (11–14). The purpose of this methodology is to reach a consensus among experts, with an understanding that published literature may not be adequate to provide sufficient evidence for day-to-day clinical decision-making. The RAND/UCLA method requires 2 groups of experts: a core expert panel that provides input into case scenario development and preparation of a scientific evidence report, and a task force panel that votes on these case scenarios. A systematic review of pertinent literature was performed that focused on PAH (15) and excluded articles that assessed World Health Organization (WHO) groups 2 and 3 (detailed in Supplementary Appendix 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38172/abstract), and the resulting scientific evidence report was given to the task force panel in conjunction with clinical scenarios representing a broad scope of disease. The scenarios illustrated multiple questions of interest and alternative options.

The core expert panel consisted of 2 experts on CTD-associated PAH (1 rheumatologist and 1 cardiologist), 2 trainees in rheumatology who conducted the systematic review, and 1 expert on the RAND/UCLA methodology. The task force panel consisted of a diverse group of experts: 3 rheumatologists, 1 internist, 4 pulmonologists, and 2 cardiologists, all with extensive experience and publications in the field of pulmonary vascular disease. There were 2 rounds of ratings. First, using the Delphi process, members of the task force panel anonymously ranked each of the potential elements of the recommendations on a risk–benefit basis ranging from 1 to 9 on a Likert scale. A vote of 1–3 was weighed as inappropriate—the risks clearly outweighed the benefits. A vote of 4–6 was considered uncertain—the risk/benefit ratio was uncertain. A vote of 7–9 was weighed as appropriate—the benefits clearly outweighed the risks. Votes on case scenarios were translated into recommendations if the median voting score was between 7 and 9 (“appropriate”) and if there was no significant disagreement, defined as no more than one-third of the votes between 1 and 3 (“inappropriate”) for the scenario.

For the second round of voting, the task force panel and the core expert panel convened for a face-to-face meeting to review the results of first-round voting. All task force panel members attended the meeting. During this meeting, a moderator experienced in the RAND/UCLA methodology (JF) led a discussion of the first-round voting results. Where areas of discrepancy were identified, discussion between members of the task force panel (and the core expert panel when requested by the task force panel) was used to clarify discrepant viewpoints and reach consensus where possible.

A priori, "appropriate" results (median vote 7–9, without significant disagreement [defined as no more than one-third of the votes between 1 and 3]) were included as recommendations. During the face-to-face task force panel meeting, some case scenarios were clarified for content based on task force panel discussion and voted on again by the task force panel as necessary.

To evaluate the risk of bias and quality of our studies, we used the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) evaluation tool (16,17). The QUADAS tool assesses the risk of bias in 4 domains, including patient selection, index test, reference standard, and flow and timing. Studies graded as low risk in all domains have the highest quality. Based on the results of the QUADAS evaluation, we also assessed the quality of evidence as proposed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group (18,19). Briefly, a recommendation is assessed as high quality if further research is unlikely to change the recommendations, moderate quality if further research is likely to affect our recommendations and may result in change, low quality if further research is very likely to affect our recommendations and likely result in change, and very low quality if recommendations are uncertain. The GRADE quality rating reflects the published evidence available to support a recommendation.

Definitions for the case scenarios. For these recommendations, screening is defined as "the presumptive identification of unrecognized disease by the application of tests, examinations, or other procedures which can be applied rapidly" (20). This assumes that a patient has no symptoms attributable to pulmonary hypertension (PH). Detection is defined as the identification of patients with signs and/or symptoms attributable to PH. The definition of a particular CTD was based on the criteria published by rheumatology associations such as the American College of Rheumatology (21) or different authors (22–25). However, the panel acknowledged that diagnosis of a CTD is based on the physician's evaluation of the patient, as classification and diagnostic criteria are not synonymous. In addition, it was agreed that patients could have more than 1 CTD if they met the published criteria. A glossary is provided for the terminology used in these recommendations (see Supplementary Appendix 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38172/abstract).

RESULTS

General recommendations (Table 1). The task force panel voted that every patient with SSc should be screened for PAH due to its high prevalence in SSc (moderate quality evidence) (1,2,26). In addition, patients with MCTD or other CTDs with prominent scleroderma features (such as sclerodactyly, nailfold capillary abnormalities, or scleroderma-specific autoantibodies), referred to hereafter as scleroderma spectrum disorders, should be screened for PAH due to high risk of PAH in these patients (very low quality evidence) (8,27). Screening was not recommended for patients with MCTD or CTDs without features of scleroderma, as the prevalence of PAH is either low or poorly defined in these patient populations (low-to-moderate quality evidence) (4,8,28). Right-sided heart catheterization (RHC) was voted as mandatory for the diagnosis of PAH in all patients (high quality evidence). It was emphasized that

Table 1. General recommendations, initial screening evaluation, and frequency of noninvasive tests for early detection of CTD-associated PAH*

General recommendations
All patients with SSc should be screened for PAH (Moderate)
Patients with MCTD or other CTDs with scleroderma features (scleroderma spectrum disorders) should be screened in a similar manner to patients with SSc (Very low)
Screening is not recommended for asymptomatic patients with MCTD or other CTDs (including SLE, rheumatoid arthritis, inflammatory myositis, Sjögren's syndrome) without features of scleroderma (Low to moderate)
For unexplained signs and symptoms of PH in patients with MCTD, SLE, or other CTDs without scleroderma features, one may consider the diagnostic algorithm evaluation for PH (Moderate)
All patients with SSc and scleroderma spectrum disorders with a positive results on a noninvasive screen (see below) should be referred for RHC (High)
RHC is mandatory for diagnosis of PAH (High)
Acute vasodilator testing is not required as part of the evaluation of PAH in patients with SSc, scleroderma spectrum disorders, or other CTDs (Moderate to high)
Initial screening evaluation
PFTs with DLCO (High)
Transthoracic echocardiogram (High)
NT-proBNP (Moderate)
DETECT algorithm if DLCO <60% predicted and disease duration >3 years (Moderate)
Frequency of noninvasive tests
Transthoracic echocardiogram annually as a screening test (Low)
Transthoracic echocardiogram if new signs or symptoms develop (High)
PFTs with DLCO annually as a screening test (Low)
PFTs with DLCO if new signs or symptoms develop (Low)
NT-proBNP if new signs or symptoms develop (Low)

* The quality of evidence, which was assessed according to the Grading of Recommendations Assessment, Development and Evaluation Working Group, is shown in parentheses at the end of each statement. CTD = connective tissue disease; PAH = pulmonary arterial hypertension; SSc = systemic sclerosis; MCTD = mixed connective tissue disease; SLE = systemic lupus erythematosus; PH = pulmonary hypertension; RHC = right-sided heart catheterization; PFTs = pulmonary function tests; DLCO = diffusing capacity for carbon monoxide; NT-proBNP = N-terminal pro–brain natriuretic peptide; DETECT = DETECTion of PAH in SSc.

PAH be defined by a mean pulmonary artery pressure (PAP) of ≥25 mm Hg with a pulmonary capillary wedge pressure of ≤15 mm Hg (28) on resting RHC. Additional diagnostic criteria may include a pulmonary vascular resistance of >3 Wood units (7) in the presence of either normal or reduced cardiac output. In all cases, chronic thromboembolic PH (WHO group 4) must be excluded by ventilation/perfusion lung scanning, helical computed tomography, or conventional pulmonary angiography (7). Ventilation/perfusion lung scanning is the preferred diagnostic test (29) but may be suboptimal with concomitant lung fibrosis. Patients with SSc and scleroderma spectrum disorders with positive findings on a noninvasive screen (as presented in the next section) should be referred for RHC (high quality evidence).

Initial evaluation in patients with SSc and scleroderma spectrum disorders. It was recommended that screening pulmonary function tests (PFTs; spirometry with lung volumes) with single-breath diffusing capacity for carbon monoxide (DLCO) (high quality evidence), transthoracic echocardiogram (high quality evidence), and measurement of N-terminal pro–brain natriuretic peptide (NT-proBNP) (moderate quality evidence) be performed in all patients with SSc and scleroderma spectrum disorders. The panel also endorsed the use of the DETECT (DETECTion of PAH in SSc) algorithm in these patients if their DLCO was <60% predicted and if the duration of their SSc was >3 years from the time of their first non–Raynaud's phenomenon symptom (moderate quality evidence) (30).

Frequency of noninvasive tests. The task force panel recommended that transthoracic echocardiogram and PFTs should be performed annually on all patients with SSc (low quality evidence) and scleroderma spectrum disorders (very low quality evidence). At the onset of any new signs or symptoms of PH, transthoracic echocardiogram (high quality evidence), PFTs (low quality evidence), and measurement of NT-proBNP (low quality evidence) should be performed.

Referral for RHC (Table 2). The task force panel recommended that acute vasodilator testing during RHC not be required as part of the evaluation of PAH, given the negligible proportion of patients in this population with both a positive vasodilator test result (defined as a reduction in mPAP by at least 10 mm Hg to an mPAP of <40 mm Hg in the setting of a normal cardiac output) and a long-term response to calcium-channel blockers (moderate to high quality evidence) (8,31). However, although this was not voted upon, it was discussed that there may be other reasons that individual physicians may wish to perform vasodilator challenge in these patients (e.g., insurance requirements).

Table 2. Recommendations for RHC for SSc and scleroderma spectrum disorders*

	Signs or symptoms required for RHC†	Quality of evidence
Transthoracic echocardiogram		
TR jet velocity		
2.5–2.8 meters/second	Yes	High
>2.8 meters/second	No	High
Right atrial or right ventricular enlargement (right atrium major dimension >53 mm and right ventricle midcavity dimension >35 mm), irrespective of TR jet velocity	No	High
PFTs		
FVC:DLCO ratio >1.6 and/or DLCO <60% predicted‡	Yes	High
FVC:DLCO ratio >1.6 and/or DLCO <60% predicted and NT-proBNP >2 times upper limit of normal‡	No	High
Composite measure		
Meets DETECT algorithm in patients with DLCO <60% predicted and disease duration >3 years‡	No	Moderate

* TR = tricuspid regurgitation; FVC = forced vital capacity (see Table 1 for other definitions).
† Signs include loud pulmonic sound and peripheral edema. Symptoms include dyspnea on rest or exercise, fatigue, presyncope/syncope, chest pain, palpitations, dizziness, and lightheadedness.
‡ Where a transthoracic echocardiogram did not reveal overt systolic dysfunction, greater than grade I diastolic dysfunction, greater than mild mitral or aortic valve disease, or evidence of PH (as defined in the transthoracic echocardiogram section).

The task force panel voted that patients with SSc and scleroderma spectrum disorders and signs and/or symptoms of PH who had a tricuspid regurgitation (TR) jet velocity of 2.5–2.8 meters/second (corresponding to a transtricuspid gradient of 25–31 mm Hg) should be referred for RHC (high quality evidence). In addition, all patients (with or without signs and/or symptoms of PH) with a TR jet velocity of >2.8 meters/second (corresponding to a transtricuspid gradient of >31 mm Hg) should be referred for RHC (high quality evidence). Moreover, all patients with right atrial or right ventricular enlargement (right atrium major dimension >53 mm and right ventricle midcavity dimension >35 mm), irrespective of TR jet velocity (including unmeasurable or <2.5 meters/second), should be referred for RHC (high quality evidence). RHC was recommended for patients with signs or symptoms of PH and a forced vital capacity % predicted to DLCO % predicted ratio of >1.6 and/or a DLCO of <60% predicted, where a transtho-

racic echocardiogram did not reveal overt systolic dysfunction, greater than grade I diastolic dysfunction, greater than mild mitral or aortic valve disease, or evidence of PH (high quality evidence). Other scenarios are shown in Table 2. In MCTD or other CTDs without scleroderma features, the presence of unexplained signs and symptoms of PH should lead to consideration of the published diagnostic algorithm for PH (low quality evidence).

Scenarios were discussed regarding the need for serial screening in patients with CTDs with normal RHC findings who might subsequently meet the above recommended indications for RHC during followup visits; however, firm recommendations could not be reached due to lack of published data. However, the panelists emphasized the need for clinical judgment on a patient-by-patient basis, along with further research in this area. The panelists did not provide recommendations on borderline mean PAP (21–24 mm Hg) or exercise-induced PH due to lack of long-term outcomes data and variability in exercise testing (32,33). The panelists did agree that this is an important research agenda for patients at high risk of PAH, such as those with SSc and scleroderma spectrum disorders. In addition, there was no consensus on the definition of moderate-to-severe interstitial lung disease (ILD) to classify a patient in WHO group 3. The panelists believed that further research is needed to define this and that current published definitions should be used for recommendations concerning ILD.

DISCUSSION

We present the first evidence- and consensus-based recommendations for screening and early detection of CTD-associated PAH. The recommendations are written for health care providers (such as rheumatologists and primary care physicians) who evaluate and treat patients with CTDs. The recommendations are presented to encourage screening, and therefore early diagnosis, of CTD-associated PAH. Screening is defined as the systematic testing of asymptomatic individuals for preclinical disease (20). The purpose of screening and early detection is to identify those with asymptomatic/preclinical disease and those with mild symptoms in order to prevent or delay progression of disease through early management. Screening programs play an important part in the detection of PAH in certain "at-risk" populations and may enable patients with PAH to be identified at an earlier stage than in routine clinical practice. This is particularly important in patients with CTDs, who may be relatively sedentary and may therefore not develop symptoms until their disease is quite advanced. However, screening tests are not meant to be diagnostic, and appropriate tests (RHC in the case of PAH) should be performed to make a diagnosis.

The prevalence of PAH is 8–12% in patients with SSc, and PAH is responsible for almost 30% of SSc-related deaths (34). In a single-center study of patients with MCTD, 64% of mortality was attributed to PAH at a mean followup of 15 years (3). Other CTDs have also been shown to be associated with PAH (4,5,35). The value of screening for PAH in patients with SSc has been highlighted by the recent work of Humbert and colleagues (2). In that prospective study, SSc patients whose PAH was identified in an early detection program (n = 16) were compared with SSc patients whose PAH was diagnosed during routine clinical practice (n = 16). At the time of PAH diagnosis, patients whose PAH was identified in an early detection program had less advanced pulmonary vascular disease than patients whose PAH was diagnosed during routine clinical practice (36). At diagnosis, 6% of patients whose PAH was detected by screening were in New York Heart Association (NYHA) functional class I (37) and 44% were in NYHA functional class II. These results contrast sharply with those for the patients whose PAH was diagnosed in routine practice, the majority of whom were already in NYHA functional class III or IV at the time of diagnosis (69% and 18.5%, respectively). Patients in the screening program had significantly greater survival rates at 8 years than patients whose PAH was identified in routine clinical practice (64% versus 17%; $P = 0.004$). The small sample size and effect of lead-time bias may have led to this effect, which needs to be confirmed in a larger study.

The resulting recommendations of the task force panel take into account recommendations from professional societies as well as systematic review of reported studies (15). The European Society of Cardiology/European Respiratory Society guidelines (8) recommend annual transthoracic echocardiogram screening of symptomatic SSc patients, and annual screening of asymptomatic SSc patients "may be considered" (7). Similar to our recommendations, the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association recommend yearly transthoracic echocardiogram and referral for RHC if transthoracic echocardiogram shows elevated PAP (high right ventricular systolic pressure [RVSP] estimates or enlargement of the right heart chambers) (7). The American College of Chest Physicians recommends transthoracic echocardiogram for clinical suspicion of PAH in order to evaluate for

elevated estimated RVSP and right atrial and ventricular enlargement (9).

However, none of the published recommendations includes use of other noninvasive screening tests (such as PFTs) or measurement of serum biomarkers (such as NT-proBNP) that have been shown to be associated with PAH in SSc patients (30,38–41). For example, the ItinérAIR-Sclérodermie PAH detection study screened 195 patients with symptoms consistent with SSc-associated PAH. Gas transfer analyses determined that DLCO was ≤60% predicted in 162 patients, of whom 13 (8%) had PAH (42). Also, in a recent prospective cohort, the presence of elevated NT-proBNP (>97th percentile of normal) and a DLCO/alveolar volume <70% predicted was associated with a hazard ratio of 47.2 for developing PAH at 36 months (40). Finally, measurement of NT-proBNP level was found to be a good screening test in 2 large SSc cohorts (39,41).

A combination of transthoracic echocardiogram and PFTs might be used to enrich the screening population of patients with SSc (30,40,43,44); a recent report proposed a representative algorithm of noninvasive tests for screening/early detection of SSc-associated PAH (30). In the DETECT study, which included patients with SSc and scleroderma spectrum disorders, an enriched cohort of 466 patients (adults with >3 years' disease duration from the first non–Raynaud's phenomenon symptom, and a DLCO <60% predicted) underwent noninvasive testing and RHC. Of those 466 patients, 87 (19%) had RHC-confirmed PAH (30). However, the DETECT study did not provide recommendations regarding patients with a DLCO ≥60% predicted or patients in whom the results of DETECT screening are negative, and its findings need to be validated in another cohort.

The task force panel recommended that patients with signs and/or symptoms of PH who had a TR jet velocity of 2.5–2.8 meters/second should be referred for RHC, and that all patients (with or without signs and/or symptoms of PH) with a TR jet velocity of >2.8 meters/second should be referred for RHC. This is supported by large cohort studies in which a TR jet velocity of >2.73–3.0 meters/second without signs or symptoms of PH or >2.5 meters/second with signs or symptoms of PH was used for referral for RHC (42,45–48). The RVSP on transthoracic echocardiogram can be estimated by the modified Bernoulli equation: RVSP = 4(TR jet velocity)^2 + right atrial pressure. Guidelines have been established for the estimation of right atrial pressure based on inferior vena cava diameter and respiratory variation, but these are most accurate at the extremes (49). However, in practice, there is variation from one laboratory to another and even among echocardiographers in the same laboratory as to how echocardiographers add the estimated right atrial pressure. TR jet velocities of 2.5 meters/second, 2.8 meters/second, and 3.0 meters/second correspond to transtricuspid gradients of 25 mm Hg, 31 mm Hg, and 36 mm Hg, respectively. Thus, the variation of 5–10 mm Hg for the estimated right atrial pressure has the potential to alter the decision-making process regarding an individual patient.

To reduce this variability, we chose to base criteria on the TR jet velocity rather than on the estimated RVSP. This approach, while methodologically sound, may not be applicable in broad clinical practice, as many echocardiography laboratories report the estimated RVSP as opposed to the TR jet velocity. For practical purposes, a TR jet velocity of 2.5 meters/second corresponds to an estimated RVSP of 30–35 mm Hg, assuming a right atrial pressure of 5–10 mm Hg.

The task force panel recommended performing noninvasive transthoracic echocardiogram and PFTs annually in patients with SSc and scleroderma spectrum disorders. Although there is a lack of evidence regarding the frequency of tests, a high incidence of PAH is observed in these patients. In addition, an annual transthoracic echocardiogram is consistent with some of the other recommendations in SSc (7,8). The societal economic costs of such recommendations are unclear. Early treatment may improve outcomes (acknowledging that knowledge gaps still exist in SSc-associated PAH). Caring for patients with milder disease could lower medical costs. However, medical costs to society could theoretically be increased by expensive medical therapies for PAH or through extended courses of care (because of greater longevity). The costs of screening and the potential impact of the results are complicated and are beyond the scope of this project. The RAND/UCLA method excludes cost-efficacy considerations, as this would require a separate literature data set for decision-making. Further research is needed in this area.

Our study has many strengths. We used an established consensus methodology (50) that has a foundation in rheumatology and has been used in recent guidelines supported by the American College of Rheumatology (11–13,51). In addition, we assessed the quality of the studies using the QUADAS evaluation tool. A majority (16 of 22) of our studies were cohort studies and were rated as having a high quality of evidence (low risk of bias or applicability concerns) on the QUADAS evalu-

ation scale (15). We followed the GRADE methodology to assign quality to the recommendations. The majority of the recommendations are of moderate-to-high quality. Also, we had a diverse group of experts (cardiologists, internist, pulmonologists, and rheumatologists) who participated as the panelists.

Limitations of the recommendations include the RAND/UCLA methodology used for this project, as it did not allow us to address the important societal implications of screening or early detection of PAH. For example, the costs of proposed screening tests are not considered in these recommendations. This is true of other recommendations published in medicine using this methodology. Also, treatment was not evaluated as part of these recommendations.

In conclusion, we provide consensus-based and evidence-driven recommendations for screening and early detection of CTD-associated PAH. It is our hope that these recommendations will lead to early detection of CTD-associated PAH and ultimately improve patient outcomes. As with any recommendations, these should be updated as more evidence becomes available.

ACKNOWLEDGMENTS

We thank Mr. Robert Riggs from the Scleroderma Foundation and Mr. Rino Aldrighetti from the Pulmonary Hypertension Association.

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. Khanna 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. Khanna, Gladue, Channick, Furst, Hachulla, Langleben, Mathai, Saggar, Townsend, McLaughlin.

Acquisition of data. Khanna, Gladue, Channick, Chung, Distler, Hachulla, Langleben, Mathai, Saggar, Visovatti, Altorok, Townsend, FitzGerald, McLaughlin.

Analysis and interpretation of data. Khanna, Gladue, Channick, Chung, Distler, Furst, Hachulla, Humbert, Langleben, Mathai, Saggar, FitzGerald, McLaughlin.

REFERENCES

1. Mukerjee D, St George D, Knight C, Davar J, Wells AU, Du Bois RM, et al. Echocardiography and pulmonary function as screening tests for pulmonary arterial hypertension in systemic sclerosis. Rheumatology (Oxford) 2004;43:461–6.
2. Humbert M, Yaici A, de Groote P, Montani D, Sitbon O, Launay D, et al. Screening for pulmonary arterial hypertension in patients with systemic sclerosis: clinical characteristics at diagnosis and long-term survival. Arthritis Rheum 2011;63:3522–30.
3. Burdt MA, Hoffman RW, Deutscher SL, Wang GS, Johnson JC, Sharp GC. Long-term outcome in mixed connective tissue disease: longitudinal clinical and serologic findings. Arthritis Rheum 1999; 42:899–909.
4. Ruiz-Irastorza G, Garmendia M, Villar I, Egurbide MV, Aguirre C. Pulmonary hypertension in systemic lupus erythematosus: prevalence, predictors and diagnostic strategy. Autoimmun Rev 2013;12:410–5.
5. Udayakumar N, Venkatesan S, Rajendiran C. Pulmonary hypertension in rheumatoid arthritis–relation with the duration of the disease. Int J Cardiol 2008;127:410–2.
6. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med 2009;179:151–7.
7. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, et al. ACCF/AHA 2009 expert consensus document on pulmonary hypertension: a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association developed in collaboration with the American College of Chest Physicians; American Thoracic Society, Inc.; and the Pulmonary Hypertension Association. J Am Coll Cardiol 2009;53:1573–619.
8. Galie N, Hoeper MM, Humbert M, Torbicki A, Vachiery JL, Barbera JA, et al, Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS). Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J 2009;34:1219–63.
9. Badesch DB, Champion HC, Sanchez MA, Hoeper MM, Loyd JE, Manes A, et al. Diagnosis and assessment of pulmonary arterial hypertension. J Am Coll Cardiol 2009;54:S55–66.
10. Fitch K, Bernstein SJ, Aguilar MS, Burnand B, LaCalle JR, Lazaro P, et al. The RAND/UCLA appropriateness method user's manual. Santa Monica (CA): RAND Corporation; 2001.
11. Khanna D, Khanna PP, FitzGerald JD, Singh MK, Bae S, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 2. Therapy and antiinflammatory prophylaxis of acute gouty arthritis. Arthritis Care Res (Hoboken) 2012;64:1447–61.
12. Khanna D, FitzGerald JD, Khanna PP, Bae S, Singh MK, Neogi T, et al. 2012 American College of Rheumatology guidelines for management of gout. Part 1. Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia. Arthritis Care Res (Hoboken) 2012;64:1431–46.
13. Grossman JM, Gordon R, Ranganath VK, Deal C, Caplan L, Chen W, et al. American College of Rheumatology 2010 recommendations for the prevention and treatment of glucocorticoid-induced osteoporosis [published erratum appears in Arthritis Care Res (Hoboken) 2012;64:464]. Arthritis Care Res (Hoboken) 2010; 62:1515–26.
14. Saag KG, Teng GG, Patkar NM, Anuntiyo J, Finney C, Curtis JR, et al. American College of Rheumatology 2008 recommendations for the use of nonbiologic and biologic disease-modifying antirheumatic drugs in rheumatoid arthritis. Arthritis Rheum 2008;59: 762–84.
15. Gladue H, Altorok N, Townsend W, McLaughlin V, Khanna D. Screening and diagnostic modalities for connective tissue disease-associated pulmonary arterial hypertension: a systematic review. Semin Arthritis Rheum 2013. E-pub 9/10/13.
16. Whiting P, Rutjes AW, Reitsma JB, Bossuyt PM, Kleijnen J. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003;3:25.
17. Whiting PF, Rutjes AW, Westwood ME, Mallett S, Deeks JJ, Reitsma JB, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155:529–36.
18. Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al, GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004;328:1490.
19. Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, et al, GRADE Working Group. Grading quality of

evidence and strength of recommendations for diagnostic tests and strategies. BMJ 2008;336:1106–10.
20. National Conference on chronic disease. Public Health Nurs 1951;43:344.
21. Subcommittee for Scleroderma Criteria of the American Rheumatism Association Diagnostic and Therapeutic Criteria Committee. Preliminary criteria for the classification of systemic sclerosis (scleroderma). Arthritis Rheum 1980;23:581–90.
22. Alarcon-Segovia D, Villareal M. Classification and diagnostic criteria for mixed connective tissue disease. In: Kasukawa R, Sharp G, editors. Mixed connective tissue disease and anti-nuclear antibodies. Amsterdam: Elsevier; 1987. p. 33–40.
23. Sharp GC, Irvin WS, Tan EM, Gould RG, Holman HR. Mixed connective tissue disease—an apparently distinct rheumatic disease syndrome associated with a specific antibody to an extractable nuclear antigen (ENA). Am J Med 1972;52:148–59.
24. Kahn MF, Appelboom T. Syndrom de Sharp. In: Kahn MF, Peltier AP, Meyer O, Piette JC, editors. Les maladies systemiques. 3rd ed. Paris: Flammarion; 1991. p. 545–556.
25. Kasukawa R, Tojo T, Miyawaki S. Preliminary diagnostic criteria for classification of mixed connective tissue disease. In: Kasukawa R, Sharp GC, editors. Mixed connective tissue disease and antinuclear antibodies. Amsterdam: Elsevier; 1987. p. 41–8.
26. Hachulla E, de Groote P, Gressin V, Sibilia J, Diot E, Carpentier P, et al, and the ItinerAIR-Sclerodermie Study Group. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum 2009;60:1831–9.
27. Yoshida S. Pulmonary arterial hypertension in connective tissue diseases. Allergol Int 2011;60:405–9.
28. Hoeper MM. Definition, classification, and epidemiology of pulmonary arterial hypertension. Semin Respir Crit Care Med 2009; 30:369–75.
29. Tunariu N, Gibbs SJ, Win Z, Gin-Sing W, Graham A, Gishen P, et al. Ventilation-perfusion scintigraphy is more sensitive than multidetector CTPA in detecting chronic thromboembolic pulmonary disease as a treatable cause of pulmonary hypertension. J Nucl Med 2007;48:680–4.
30. Coghlan JG, Denton CP, Grunig E, Bonderman D, Distler O, Khanna D, et al, on behalf of the DETECT Study Group. Evidence-based detection of pulmonary arterial hypertension in systemic sclerosis: the DETECT study. Ann Rheum Dis 2013. E-pub ahead of print.
31. Montani D, Savale L, Natali D, Jais X, Herve P, Garcia G, et al. Long-term response to calcium-channel blockers in non-idiopathic pulmonary arterial hypertension. Eur Heart J 2010;31:1898–907.
32. Saggar R, Khanna D, Furst DE, Shapiro S, Maranian P, Belperio JA, et al. Exercise-induced pulmonary hypertension associated with systemic sclerosis: four distinct entities. Arthritis Rheum 2010;62:3741–50.
33. Bae S, Saggar R, Bolster MB, Chung L, Csuka ME, Derk C, et al, for the Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma Investigators. Baseline characteristics and follow-up in patients with normal haemodynamics versus borderline mean pulmonary arterial pressure in systemic sclerosis—results from the PHAROS registry. Ann Rheum Dis 2012;71: 1335–42.
34. Walker UA, Tyndall A, Czirjak L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis 2007;66:754–63.
35. Launay D, Hachulla E, Hatron PY, Jais X, Simonneau G, Humbert M. Pulmonary arterial hypertension: a rare complication of primary Sjögren's syndrome: report of 9 new cases and review of the literature. Medicine (Baltimore) 2007;86:299–315.
36. Humbert M, Gerry Coghlan J, Khanna D. Early detection and management of pulmonary arterial hypertension. Eur Respir Rev 2012;21:306–12.
37. The Criteria Committee of the New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th ed. Boston: Little Brown; 1994. p. 253–6.
38. Rajaram S, Swift AJ, Capener D, Elliot CA, Condliffe R, Davies C, et al. Comparison of the diagnostic utility of cardiac magnetic resonance imaging, computed tomography, and echocardiography in assessment of suspected pulmonary arterial hypertension in patients with connective tissue disease. J Rheumatol 2012;39: 1265–74.
39. Stupi AM, Steen VD, Owens GR, Barnes EL, Rodnan GP, Medsger TA Jr. Pulmonary hypertension in the CREST syndrome variant of systemic sclerosis. Arthritis Rheum 1986;29:515–24.
40. Allanore Y, Borderie D, Avouac J, Zerkak D, Meune C, Hachulla E, et al. High N-terminal pro–brain natriuretic peptide levels and low diffusing capacity for carbon monoxide as independent predictors of the occurrence of precapillary pulmonary arterial hypertension in patients with systemic sclerosis. Arthritis Rheum 2008;58:284–91.
41. Thakkar V, Stevens WM, Prior D, Moore OA, Byron J, Liew D, et al. N-terminal pro-brain natriuretic peptide in a novel screening algorithm for pulmonary arterial hypertension in systemic sclerosis: a case-control study. Arthritis Res Ther 2012;14:R143.
42. Hachulla E, Gressin V, Guillevin L, Carpentier P, Diot E, Sibilia J, et al. Early detection of pulmonary arterial hypertension in systemic sclerosis: a French nationwide prospective multicenter study. Arthritis Rheum 2005;52:3792–800.
43. Meune C, Avouac J, Airo P, Beretta L, Dieude P, Wahbi K, et al. Prediction of pulmonary hypertension related to systemic sclerosis by an index based on simple clinical observations. Arthritis Rheum 2011;63:2790–6.
44. Gladue H, Steen V, Allanore Y, Saggar R, Saggar R, Maranian P, et al. Combination of echocardiographic and pulmonary function test measures improves sensitivity for the diagnosis of systemic sclerosis-associated pulmonary arterial hypertension: analysis of two cohorts. J Rheumatol 2013. E-pub 8/21/13.
45. Phung S, Strange G, Chung LP, Leong J, Dalton B, Roddy J, et al. Prevalence of pulmonary arterial hypertension in an Australian scleroderma population: screening allows for earlier diagnosis. Intern Med J 2009;39:682–91.
46. Ciurzynski M, Bienias P, Irzyk K, Rymarczyk Z, Kostrubiec M, Lichodziejewska B, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension in patients with systemic sclerosis. Eur Heart J 2010;31:869–70.
47. Jansa P, Becvar R, Ambroz D, Palecek T, Tomcik M, Skacelova S, et al. Pulmonary arterial hypertension associated with systemic sclerosis in the Czech Republic. Clin Rheumatol 2012;31:557–61.
48. Avouac J, Airo P, Meune C, Beretta L, Dieude P, Caramaschi P, et al. Prevalence of pulmonary hypertension in systemic sclerosis in European Caucasians and metaanalysis of 5 studies. J Rheumatol 2010;37:2290–8.
49. Rudski LG, Lai WW, Afilalo J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. J Am Soc Echocardiogr 2010;23:685–713.
50. Nair R, Aggarwal R, Khanna D. Methods of formal consensus in classification/diagnostic criteria and guideline development. Semin Arthritis Rheum 2011;41:95–105.
51. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625–39.