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ORIGINAL RESEARCH

CONGENITAL HEART DISEASE

Timely PAH Identification in Adults With Repaired Congenital Heart Disease? The ACHD-QuERI Registry Insights

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ABSTRACT

BACKGROUND The Quality Enhancement Research Initiative (QuERI) in adults with congenital heart disease (ACHD) was developed to improve detection of pulmonary arterial hypertension (PAH) after repair of systemic-to-pulmonary arterial shunt lesions.

OBJECTIVES This study sought to standardize use of accepted criteria for PAH diagnosis and evaluate utility in at-risk patients with ACHD.

METHODS Patients ≥18 years of age with ACHD repaired ≥1 year before enrollment and with additional risk factors for developing PAH were eligible. History, physical examination, electrocardiogram, transthoracic echocardiogram, World Health Organization functional class, and 6-minute walk distance were evaluated at baseline and yearly for 3 years. Pop-up reminders of patient-specific evidence-based recommendations for PAH detection appeared during data entry.

RESULTS Among 217 eligible patients, mean age (enrollment) was 44.0 ± 15.9 years, 72.3% were women, and 82.0% were World Health Organization functional class I. Electrocardiogram was performed in >80% and TTE in >70% of patients annually; capture of required transthoracic echocardiography (TTE) measures and alignment between study- and core-center interpretation improved over time, with more frequent assessment of pulmonary arterial flow acceleration time and documentation of right ventricular outflow tract Doppler notching. Approximately 40% of patients had ≥2 high-risk features for PAH on TTE, but only 7% (6/82) underwent right heart catheterization (RHC). Using current definitions, 2 patients were confirmed by RHC to have a diagnosis of PAH (maximum follow-up 3 years).

CONCLUSIONS A structured protocol may improve screening for patients with repaired ACHD at risk of developing PAH. RHC may be underutilized in patients with ACHD with TTE findings suggestive of PAH. (Adult Congenital Heart Disease Registry [QuERI]; NCT01659411) (JACC Adv 2023;2:100649) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

ACHD = adults with congenital heart disease

ASD = atrial septal defect

AVC = atrioventricular canal defect

CHD = congenital heart disease

ECG = electrocardiogram

PAH = pulmonary arterial hypertension

PDA = patent ductus arteriosus

PFT = pulmonary function test

PH = pulmonary hypertension

PVR = pulmonary vascular resistance

QuERI = Quality Enhancement Research Initiative

RHC = right heart catheterization

RV = right ventricle/ventricular

RVH = right ventricular hypertrophy

TTE = transthoracic echocardiography

VSD = ventricular septal defect

WHO FC = World Health Organization functional class

Adult survivors with congenital heart disease (CHD) have increased steadily in developed countries.[1-3] Pulmonary arterial hypertension (PAH), with elevation of pulmonary arterial pressure due to increased pulmonary vascular resistance (PVR), is a complication of various forms of CHD, including systemic-to-pulmonary arterial shunt lesions.[4,5] While early shunt closure may reduce the risk of developing heart failure, arrhythmia, and pulmonary vascular disease, a subset of patients develop pulmonary hypertension (PH) or PAH later in life, despite prior surgical or device intervention.[4,6,7] PH development in CHD is associated with a 3-fold increase in mortality.[8] This is of particular importance because of the relatively high prevalence, and often otherwise relatively uncomplicated clinical course, of congenital systemic-to-pulmonary arterial shunt-related CHD. Given the improved outcomes of PH and PAH with the use of pharmacologic and interventional therapies,[9-11] and potential for increased benefits when treatments are instated upon disease diagnosis,[12] the development and application of screening protocols for early identification and differential diagnosis of PH and PAH among adults with congenital heart disease (ACHD) may inform early therapeutic intervention and improve outcomes.

Risk factors for development of PAH in the context of CHD include type of anatomic lesion, degree of shunting prior to repair, and older age[13]; however, these have limited sensitivity, precision, and specificity.[14,15] Transthoracic echocardiography (TTE) is a powerful, noninvasive tool for identifying PH or risk of developing PAH.[16-18] Currently, right heart catheterization (RHC) remains necessary for definitive diagnosis of PAH and determining appropriate therapy.[19]

The Quality Enhancement Research Initiative (QuERI) program assesses clinical practice and outcomes in patients via longitudinal design and iterative feedback to participating clinicians based upon established care guidelines.[20] ACHD-QuERI was designed to standardize the evaluation and criteria for screening in adult patients with repaired systemic-to-pulmonary arterial shunts considered at high risk of PAH, and to determine the impact of specialist ACHD clinicians' responses to criteria and prompts on: 1) care practice (per established guidelines); and 2) depending on patient outcomes, patient health and survival. We present findings from the ACHD-QuERI program.

METHODS

ACHD-QuERI (NCT01659411) is a multicenter, observational, U.S.-based longitudinal program enrolling adults with repaired CHD considered at increased risk of developing PAH. Adults with CHD and systemic-to-pulmonary arterial shunt lesions repaired ≥1 year prior were enrolled between December 2011 and September 2015 from 59 U.S. specialist ACHD centers. The study originally enrolled only patients with historical or clinical features associated with increased risk of developing PAH, specific TTE criteria suggestive of right ventricular (RV) abnormalities, and history of anatomic or physiologic large defect prior to closure (Cohort 1). The study was amended to enroll a second cohort (Cohort 2) of patients with current signs or symptoms suggestive of high risk of developing PAH (ie, signs and symptoms of atrial fibrillation or flutter, right ventricular hypertrophy [RVH], right atrial enlargement, or right axis deviation).

The study protocol was approved by the Western Institutional Review Board and by the institutional review boards of participating institutions. The study was performed in accordance with the protocol, the Declaration of Helsinki, Guidelines for Good Pharmacoepidemiology Practice, International Council for Harmonisation Good Clinical Practices guidelines, and applicable regulatory requirements. All patients were made aware the study was voluntary, and written informed consent was obtained. All statistical analyses were performed by the Canadian Heart Research Centre, Toronto, Canada.

STUDY OBJECTIVES. Objectives were to characterize the demographics, clinical course, and clinical outcomes of a cohort of adults with repaired CHD considered to be at higher risk of developing PAH, and to assess clinicians' responses to pre-established criteria and prompts to standardize clinical practice. We hypothesized that enrollment in QuERI would lead to standardization of care and timely recognition of incident PAH, in accord with both PAH and ACHD expert and consensus-guidelines based criteria.

INCLUSION CRITERIA. Eligible patients in both cohorts were aged ≥18 years, had previously repaired systemic-to-pulmonary arterial shunt lesions (including atrial septal defect, ventricular septal defect, patent ductus arteriosus, or atrioventricular canal defect) ≥1 year before enrollment, and were expected to continue follow-up visits. Further

eligibility was based upon attribution of greater risk for development of PAH, which was assigned by an investigator through application of a stepwise schema based upon both clinically established and expert-consensus determined risks for PAH. Patients had ≥1 clinical high-risk feature, including age >40 years, later surgical repair (ie, ≥2 years for patent ductus arteriosus or ventricular septal defect, ≥1 year for atrioventricular canal defect, or ≥10 years for atrial septal defect), sinus venosus defect, ostium primum defect, World Health Organization functional class (WHO FC) >I, or atrial fibrillation or flutter. Patients also had ≥1 high-risk feature on TTE, including mild or greater tricuspid regurgitation, RV systolic dysfunction as per a tricuspid annular plane systolic excursion <2.0 cm, RV dilation, or an abnormality in the motion of the interventricular septum. In addition, there had to be presence of trans-tricuspid flow velocity of >3.0 m/s, pulmonary artery flow acceleration time of <100 milliseconds, or evidence of "notching" of the pulsed wave Doppler profile in the right ventricular outflow tract.

Patients in the historic high-risk cohort (Cohort 1) required evidence of a large defect prior to closure, defined as ≥1 of the following: increased anatomic size (atrial septal defect >2 cm, ventricular septal defect >1 cm, or patent ductus arteriosus >0.6 cm); systemic-to-pulmonary shunt 2:1 or greater; preoperative PH (pulmonary artery systolic pressure >40 mm Hg); shunt-related heart failure based on radiographic evidence; or preoperative atrial fibrillation or flutter.

Patients in the current high-risk cohort (Cohort 2) required evidence of ≥1 of the following: edema with elevated jugular venous pressure and also positive hepatojugular reflux, elevated brain natriuretic peptide or N-terminal probrain natriuretic peptide above the upper limit of normal, electrocardiogram (ECG) demonstrating right axis deviation and either RVH or right atrial enlargement, chest x-ray evidence of enlarged main and/or hilar pulmonary arterial shadows in association with RV enlargement, oxygen desaturation (≤92%) with exercise, a 6-minute walk distance (6MWD) of <380 m, or pulmonary function test (PFT) demonstrating diffusion capacity of the lung for carbon monoxide <70% predicted with forced expiratory volume in 1 second >70% predicted.

EXCLUSION CRITERIA. Patients were excluded if they had poor mental function, drug or substance abuse, or unstable psychiatric distress. Patients who had a diagnosis of PAH (confirmed by RHC or treatment with PAH-specific therapy) after surgical repair and prior to visit 1, or who had previously participated in the QuERI program, were also excluded.

PROGRAM DESIGN. At first visit (baseline), clinicians collected demographic information and medical history. Clinical data related to physical examination, ECG, history of arrhythmia, WHO FC, 6MWD, arterial oxygen saturation, vital signs, clinical outcomes (death, PAH development confirmed by RHC after visit 1, referral to another center for further management) were collected at baseline and every 12 months for 3 years. A TTE was required within 12 months prior to baseline and was to be repeated at either year 1 or 2 visits, and at year 3 visits. PAH development was confirmed by RHC or treatment with PAH-specific therapy in accord with WHO PAH care guidelines (with different criteria at the beginning of study and at completion of study). The development of TTE high-risk status was identified by the study-site principal investigator, with subsequent confirmation by core-center review required.

Clinicians used an electronic case report form to record patient data. Entry of certain data into the form triggered a pop-up recommendation to perform either a TTE (transthoracic echocardiogram) or RHC based on standardized guidelines (**Figure 1**). Patient management was per physician discretion, but clinicians were prompted to provide a reason if pop-up recommendations were not followed.

STATISTICAL ANALYSIS. Descriptive statistics were calculated for patient demographic variables, physical examination, medical history, and treatment profile including ECG and TTE characteristics, and clinician response to pop-up recommendations.

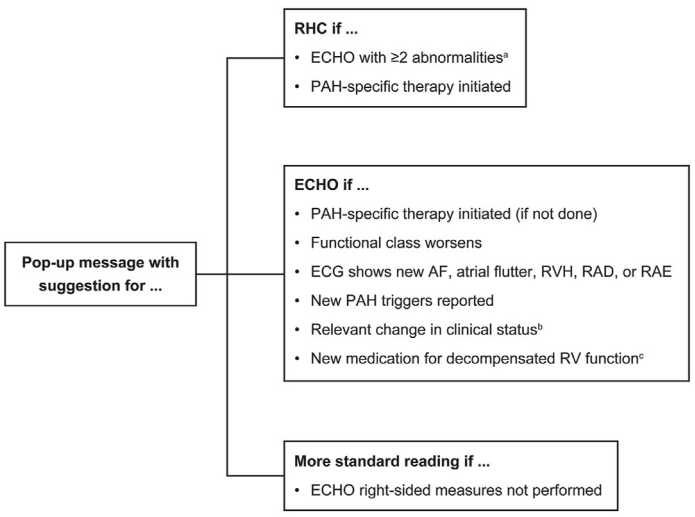
The association between prespecified TTE criteria and PAH development was assessed, with data interpreted at the local cardiology practice.

RESULTS

Overall, 240 patients were screened and 217 were eligible for analysis (**Figure 2**). Due to the small number of patients in Cohort 2, analyses were conducted using pooled Cohort 1 and 2 populations. Patient demographics, characteristics, and vital signs at baseline/screening are shown in **Table 1**.

CLINICAL COURSE OF REPAIRED ACHD DURING THE STUDY. **Figure 3** shows the clinical assessments captured during the study. The 6MWD test was performed in 22.1% of patients at baseline and only 3.2% in year 3. PFT was conducted within 1 year of the baseline visit in 3.7% of patients, and only 1 patient

FIGURE 1 Pop-Up Recommendation



Conditional pop-up recommendations (nonbulleted within white boxes) were triggered by recorded data (bulleted, within white boxes) based upon standardized care guidelines (see text for high-risk PAH: [a]echocardiographic abnormalities, [b]clinical changes, and [c]medications for right ventricular decompensation). AF = atrial fibrillation; ECG = electrocardiogram; ECHO = transthoracic echocardiogram; PAH = pulmonary arterial hypertension; RAD = right axis deviation; RAE = right atrial enlargement; RHC = right heart catheterization; RV = right ventricle; RVH = right ventricular hypertrophy.

had a PFT in years 1 to 3 (in year 2). Vital signs and symptoms associated with worsening of clinical status in the patients with CHD are described in **Table 2**. Across the 3-year study, WHO FC and mean ± SD arterial oxygen saturation remained stable from baseline. The appearance of PAH clinical triggers or new evidence suggestive of increased probability of PAH development are summarized in **Table 2**, captured in response to binary ("Yes/No") questions about specific clinical symptoms during patient visits. New peripheral edema, arrhythmias, and murmurs were the most commonly occurring new symptoms recorded. Around 2% of patients at each time point postbaseline had elevated brain natriuretic peptide or N-terminal probrain natriuretic peptide, although it is unknown what proportion underwent these tests.

Most patients received yearly ECGs from baseline (96.3%) to year 3 (81.5%); there were no clinically meaningful differences in ECG parameters from baseline to year 3 (Supplemental Table 1). Patients with high-risk features for PAH (atrial fibrillation or flutter; RVH, right atrial enlargement, or right axis deviation) were identified by ECG at each study visit (12.9% of patients at baseline; 5.9% at year 1, 12.2% at year 2, and 3.0% at year 3) (**Table 3**).

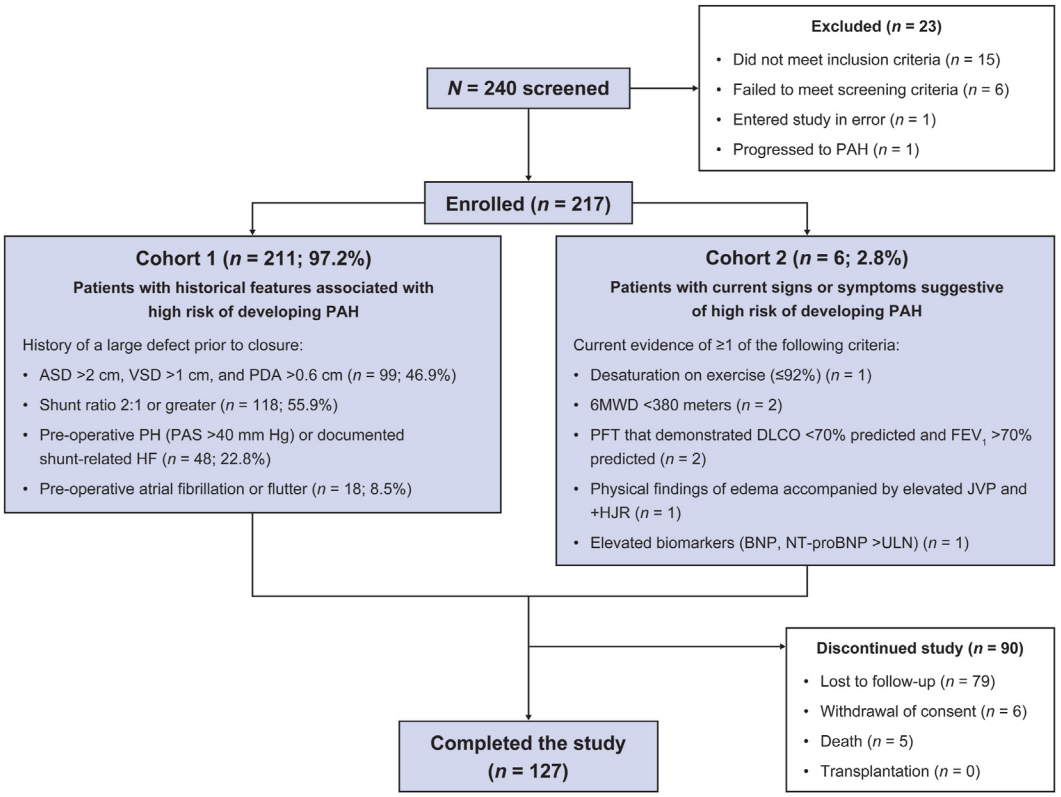
Summary data from longitudinal TTE recorded during the study are shown in Supplemental Table 2. Most patients had a yearly TTE. Among patients undergoing TTE, around 40% had ≥2 high-risk features for developing PAH, which included a trans-tricuspid flow velocity >3 m/s or RV outflow tract <100 ms, tricuspid annular plane systolic excursion ≤2.0 cm, RV dilation, systolic interventricular septal flattening, and "notching" of pulsed wave Doppler signal in the RV outflow tract.

There was a low rate of RHC performed during the study (Supplemental Table 3). Overall, RHC was recorded for 16 patients (including 1 who had RHC at the year 1 and year 3 visits). A total of 8 patients (3.7%) had RHC at the baseline visit, 2 (1.2%) at year 1, 1 (0.7%) at year 2, and 6 (4.8%) at year 3.

PAH OUTCOMES DURING THE STUDY. A total of 6 patients were reported as developing PAH between baseline and year 3 (**Table 3**), all of whom had a PAH diagnosis suggested by TTE (data not shown). An analysis of all patients with available RHC data (at any visit) was undertaken to confirm the reported PAH diagnosis (**Table 4**). Based on the definition of PAH at study initiation (ie, mean pulmonary artery pressure >25 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg and PVR >3 WU[21]) or on current definitions for PAH (ie, mean pulmonary artery pressure ≥20 mm Hg, pulmonary capillary wedge pressure ≤15 mm Hg, and PVR ≥3 WU[22]), 2 patients were confirmed to have a diagnosis of PAH (1 at baseline and 1 at year 1). Overall, 5 patients were identified with PH (2.3% of the overall study population (**Table 4**).

CLINICIANS' RESPONSES TO ELECTRONIC POP-UPS WITH CARE RECOMMENDATIONS. Guideline recommendations for PAH work-up appearing as pop-up comments in ACHD-QuERI were not closely followed by investigators (Supplemental Table 4). For example, at baseline, 38.0% of patients were recommended for RHC based upon TTE features suggesting a high PAH risk. Most had 2 or 3 high-risk features identified but only 7.3% were referred for RHC. Most clinicians indicated that they did not plan to follow the pop-up suggestion, most commonly (at baseline) because they considered their management appropriate (42/70 [60.0%]) (Supplemental Table 4). Similar patterns were observed at all study visits; however, at year 2 and year 3 visits, a higher proportion of clinicians indicated they would not follow

FIGURE 2 Patient Disposition



Flowchart showing the screening and selection of eligible patients for analysis. 6MWD = 6-minute walk distance; ASD = atrial septal defect; BNP = brain natriuretic peptide; DLCO = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; HF = heart failure; HJR = hepatojugular reflux; JVP = jugular venous pressure; NT-proBNP = N-terminal pro-brain natriuretic peptide; PAH = pulmonary arterial hypertension; PAS = pulmonary artery systolic; PDA = patent ductus arteriosus; PFT = pulmonary function test; PH = pulmonary hypertension; ULN = upper limit of normal; VSD = ventricular septal defect.

the recommendations as the abnormality was persistent and had been detected on a previous TTE.

DISCUSSION

Over the past decade, patient registries and multicenter trials have been designed, and guidelines developed, to standardize care practice and improve outcomes for ACHD/PAH.[6,23] Few studies have examined the effectiveness of clinical guidelines in ACHD.

ACHD-QuERI is the first prospective longitudinal observational study evaluating PAH in high-risk patients with ACHD with repaired systemic-to-pulmonary arterial shunt lesions. A standardized QuERI protocol was designed to enroll and follow a population of patients with ACHD at increased risk for PAH development, based upon established risk factors and additional risks identified through expert consensus recommendations. Guideline and expert recommendations were integrated to create management guides with digital pop-up recommendations appearing as clinicians reviewed patient clinical data at yearly consultations.

Patient characteristics at the baseline/screening visit, including age, defect type, and comorbidities, and current medications were as expected for a population with repaired ACHD and risk of PAH.[24-28]

ACHD-QuERI aimed to characterize demographics, clinical course, and clinical outcomes of patients at risk of developing PAH (**Central Illustration**). This included clinical signs and symptoms used to screen for PAH in other populations (eg, fatigue, dyspnea, palpitations and arrhythmia, volume retention, ECG changes), which are often noted in ACHD.[21,29-35] No clinically meaningful associations between patient

TABLE 1 Patient Demographics, Characteristics, and Vital Signs at Visit 1 (Screening/Baseline Visit) (N = 217)

Female	157 (72.3)
Age, y	44 ± 15.9
Race/ethnicity	
Caucasian	175 (80.7)
African American	15 (6.9)
Hispanic	10 (4.6)
Indian/other Asian	8 (3.7)
Other	6 (2.8)
Missing/unknown	3 (1.4)
CHD diagnosis	
ASD only	146 (67.3)
VSD only	25 (11.5)
AVC only	22 (10.1)
PDA only	0 (0)
Combination of lesions	24 (11.1)
WHO functional class	
I	178 (82.0)
II	31 (14.3)
III and IV	8 (3.7)
6MWD, m, (N = 48)	434 ± 109
Physical findings and vital signs	
BMI, kg/m^2	28.5 ± 6.2
Systolic BP, mm Hg	120.7 ± 14.0
Heart rate, beats/min	70.8 ± 13.0
O_2 saturation, %, (N = 201)	97.7 ± 4.4
Medical history and documented symptoms[a]	
Hypertension	52 (24.0)
Heart failure	26 (12.0)
Arrhythmia or arrhythmia symptoms, including palpitations, atrial fibrillation, or atrial flutter	111 (51.2)
Asthma/chronic obstructive pulmonary disease	26 (12.0)
Exertional light-headedness	24 (11.1)
Exertional dyspnea	62 (28.6)
Obstructive sleep apnea	22 (10.1)
Murmur suggestive of tricuspid regurgitation	28 (12.9)
Murmur suggestive of mitral regurgitation	31 (14.3)

Values are n (%) or mean ± SD. [a]Medical conditions reported in ≥10% of patients.

6MWD = 6-minute walk distance; ASD = atrial septal defect; AVC = atrioventricular canal defect; BMI = body mass index; BP = blood pressure; CHD = congenital heart disease; PDA = patent ductus arteriosus; VSD = ventricular septal defect; WHO = World Health Organization.

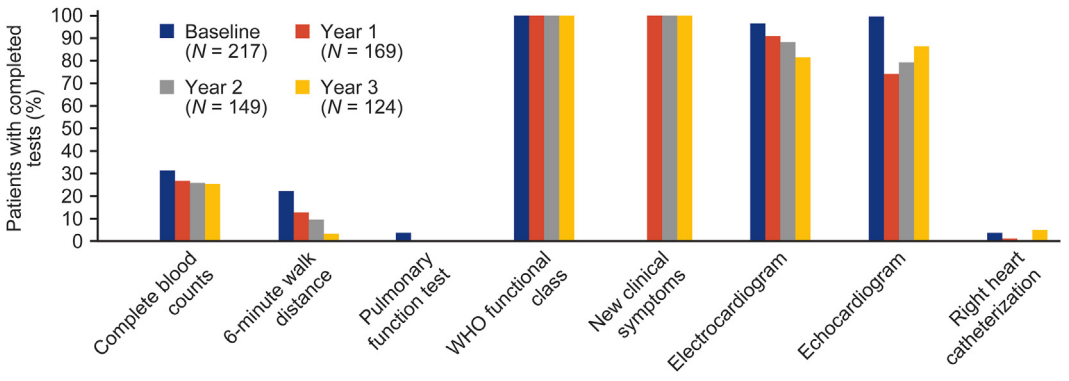
characteristics and clinical course or rate of newly-diagnosed PAH were identified from ACHD-QuERI data. We are cautious not to overextend this conclusion, as valid quantification of newly diagnosed PAH requires hemodynamic assessment via RHC, which was performed in a minority of patients. The very low PFT rate is notable, particularly as emerging evidence has suggested these data are strongly associated with outcomes in ACHD.

This study provides valuable new insights into the routine use of ECGs, TTE, and RHC in the clinical monitoring of patients with repaired ACHD. From baseline to year 3, the majority of patients had received an ECG and a TTE. ECG findings identified high-risk features in 3 to 13% of patients across all visits. Over 74% of patients had a yearly TTE, suggesting that there may be unwarranted overuse of TTE in clinical practice. American Heart Association/American College of Cardiology guidelines recommend yearly TTE only in people with ACHD in WHO FC III and IV; however, the majority of ACHD-QuERI patients were WHO FC I (86.5% at year 3), for whom TTE every 36 to 60 months is recommended.[35] By contrast, RHC appears to be underutilized. Overall, only 16 of 217 patients (7.4%) received an RHC, despite approximately 40% of those who underwent a TTE having ≥2 features indicative of a high risk of PAH. It is important to understand the drivers and barriers of the testing pattern observed. In ACHD-QuERI, patients were treated by ACHD specialist cardiologists, who have more experience with patients who have CHD-associated PAH compared with general cardiologists. They may be hesitant to refer patients for invasive testing, despite guideline recommendations and a strong evidence base on the safety and benefits of RHC in the general population, as well as awareness of improved outcomes with early PAH diagnosis.[36] Clinicians and patients may benefit from further education and support to overcome barriers to RHC use.

Based on current definitions, 2 patients were confirmed by RHC to have a diagnosis of PAH—1 patient by baseline RHC and 1 patient at year 1. This incidence of PAH is among patients who may not have been captured routinely in clinical practice; patients with a pre-existing diagnosis of PAH were excluded from the study. These findings suggest that the enrichment protocol may improve screening for PAH in this patient population by supporting a diagnosis of PAH in some patients at the screening visit and allowing early disease management. Although this appears a moderate proportion, over a longer time period this may have become more clinically relevant, as protocol adherence would be anticipated to increase based on the iterative use of ACHD-QuERI's standardized diagnosis and treatment algorithm. We identified 5 patients with PH (2.3%; including 2 with PAH), and epidemiological data indicate that more cases will develop with longer follow-up. PH is associated with a doubling of all-cause mortality and tripling of morbidity,[8] and early detection and intervention in ACHD are critical to improve long-term outcomes.

Despite pop-up recommendations appearing on electronic case report forms, many clinicians did not follow guideline-based testing protocols, most commonly because they considered their management appropriate. Failure to adhere to diagnosis and

FIGURE 3 Clinical Assessments Conducted From Baseline to Year 3



WHO = World Health Organization.

TABLE 2 Vital Signs and Clinical Symptoms in Follow-Up Visits

	Year 1 (n = 169)	Year 2 (n = 150)	Year 3 (n = 126)
WHO functional class			
I	146 (86.4)	131 (87.3)	109 (86.5)
II	19 (11.2)	15 (10.0)	13 (10.3)
III	4 (2.4)	3 (2.0)	4 (3.2)
IV	0	1 (0.7)	0
O_2 saturation, %	97.9 ± 3.5 (N = 155)	97.7 ± 4.55 (N = 130)	97.6 ± 2.03 (N = 105)
Responses to binary "Yes/No" questions on clinical parameters[a]			
Decline in systemic saturation >4% since last visit	1/159 (0.6)	0/132 (0)	4/106 (3.8)
New syncope	3/169 (1.8)	2/149 (1.3)	0/124 (0)
New CNS or peripheral embolization	3/169 (1.8)	1/149 (0.7)	1/124 (0.8)
New cyanosis	1/169 (0.6)	0/149 (0)	0/124 (0)
New ascites	0/169 (0)	1/149 (0.7)	1/124 (0.8)
New peripheral edema	4/169 (2.4)	5/149 (3.4)	3/124 (2.4)
New JVP elevation	2/169 (1.2)	0/149 (0)	0/124 (0)
New HJR	0/128 (0)	0/145 (0)	1/124 (0.8)
New P2 increase	1/169 (0.6)	0/149 (0)	0/124 (0)
New arrhythmia symptoms or diagnosis (atrial fibrillation/flutter)	4/169 (2.4)	5/149 (3.4)	4/124 (3.2)
New murmur	12/169 (7.1)	4/149 (2.7)	1/124 (0.8)
New PAH trigger: HIV infection	1/169 (0.6)	0/149 (0)	0/124 (0)
Desaturation on exercise (≤92%)	1/128 (0.8)[b]	0/146 (0)	0/126 (0)
6MWD <380 m	4/128 (3.1)[b]	1/146 (0.7)	1/126 (0.8)
ECG demonstrating RAD and RVH or RAE	1/128 (0.8)[b]	4/146 (2.7)	3/126 (2.4)
Physical findings of edema accompanied by elevated JVP and +HJR	0/128 (0)[b]	1/146 (0.7)	2/126 (1.6)
CXR evidence of enlarged main and/or hilar pulmonary arterial shadows in association with right ventricular enlargement	1/128 (0.8)[b]	1/146 (0.7)	0/126 (0)
Elevated biomarkers (BNP or NT-proBNP above upper limit of normal[c])	2/128 (1.6)[b]	3/146 (2.1)	3/126 (2.4)

Values are mean ± SD or n (%) unless otherwise indicated. Number of "Yes" responses/number of patients with data entered at each visit (%). [a]Denominators show the number of patients who came for the study visit and had data captured. Clinical parameters were captured as responses to binary ("Yes/No") questions. When the response was "No," it was not captured whether this was because the parameter had not been assessed (test not done) or whether there was no change since the last visit. [b]Variables with n = 128 as the denominator in year 1 were added after the study started and data were captured for fewer patients than completed the year 1 visit (n = 169 in total). [c]No thresholds were specified for the upper limit of normal. Sites answered "Yes" or "No" only.

6MWD = 6-minute walk distance; BNP = brain natriuretic peptide; CNS = central nervous system; CXR = chest x-ray; ECG = electrocardiogram; HIV = human immunodeficiency virus; HJR = hepatojugular reflux; JVP = jugular venous pressure; m = meters; NT-proBNP = N-terminal probrain natriuretic peptide; P2 = pulmonic valve closure; PAH = pulmonary arterial hypertension; RAD = right axis deviation; RAE = right atrial enlargement; RVH = right ventricular hypertrophy; WHO = World Health Organization.

TABLE 3 PAH Outcomes During the Study

	Baseline (Visit 1)	Year 1 (Visit 2)	Year 2 (Visit 3)	Year 3 (Visit 4)
ECG performed	209/217 (96.3)	152/168 (90.5)	131/149 (87.9)	101/124 (81.5)
Patients with high-risk features for PAH identified by ECG	27/209 (12.9)	9/152 (5.9)	16/131 (12.2)	3/101 (3.0)
Worsening of clinical parameters reported during a follow-up visit				
Worsening of O_2 saturation, WHO functional class, new murmur	-	11/169 (6.5)	7/150 (4.7)	7/126 (5.6)
As above, with new syncope; new CNS or peripheral embolization; new clubbing or cyanosis or JVP elevation or ascites or peripheral edema; new murmur; decline in systemic saturation >4% points	-	21/169 (12.4)	11/150 (7.3)	8/126 (6.4)
Most recent TTE performed	216/217 (99.5)	125/169 (74)	118/149 (79.2)	107/124 (86.3)
Patients with at least 2 high-risk features for PAH identified by TTE	82/216 (38.0)	51/125 (40.8)	46/118 (39.0)	40/107 (37.4)
RHC done[a]	8/217 (3.7)	2/168 (1.2)	1/149 (0.7)	6/124 (4.8)
RHC shows evidence consistent with PAH	1/8 (13)	1/2 (50)	0/1 (0)	0/6 (0)

Values are n/N (%). [a]Note: 1 patient underwent RHC at their Year 1 and Year 3 visits.

CNS = central nervous system; ECG = electrocardiogram; JVP = jugular venous pressure; PAH = pulmonary arterial hypertension; RHC = right heart catheterization; TTE = transthoracic echocardiogram; WHO = World Health Organization.

care recommendations may impact patient outcomes. Evidence suggests that clinicians may underestimate patient symptomatology and clinical disease severity, and overestimate patient survival.[37,38] These data and our current findings may further underscore the importance of adherence to standardized diagnostic and management protocols based on objective data-driven, expert-derived recommendations.

Certain limitations of this study should be noted. The data are largely observational and subject to confounding. Inclusion was based on historical patient data indicating high-risk features; consequently, survival and recall bias cannot be excluded. Some features considered high risk for PAH development in ACHD were determined by expert consensus and extrapolation from the study of other

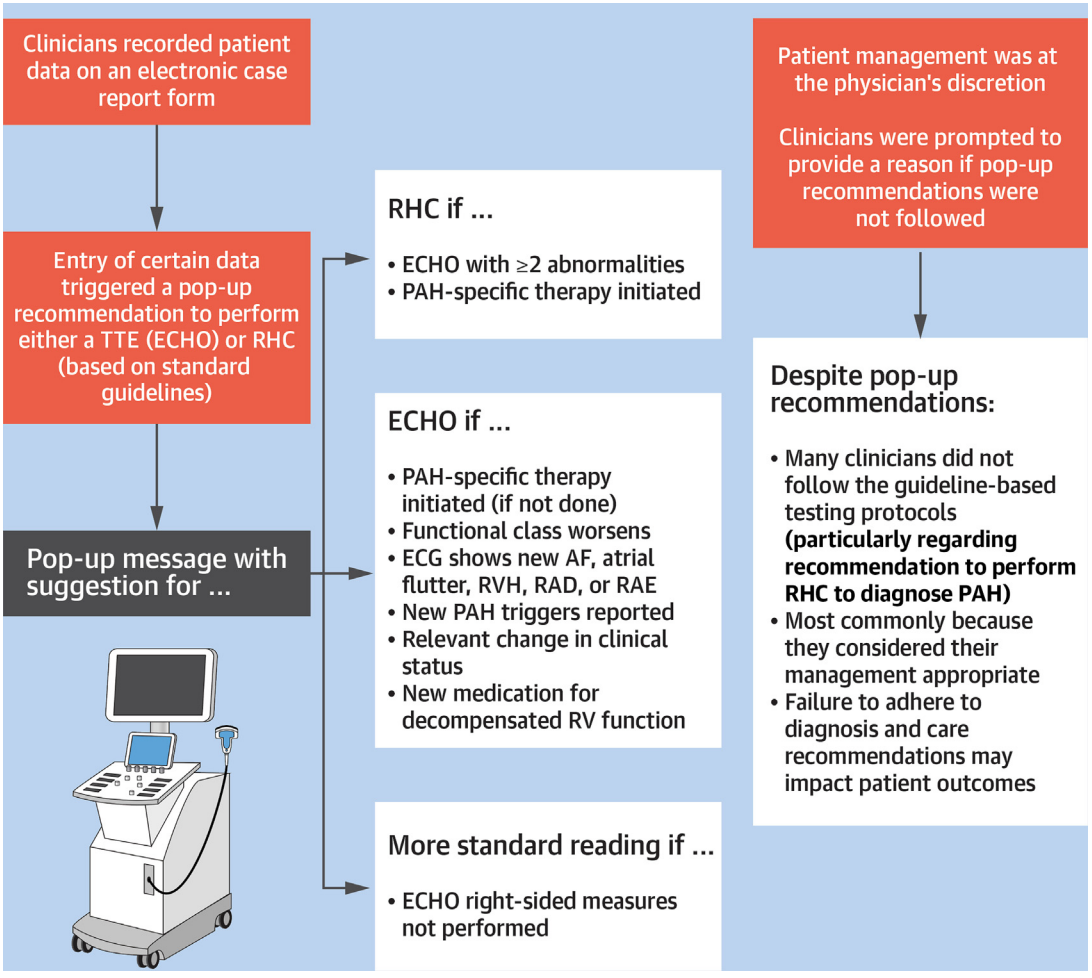
TABLE 4 Patients With a Diagnosis of PAH Based on RHC Data, According to Different Diagnostic Criteria

				PH Diagnosis: Definitions (At Rest)					
				Isolated Postcapillary PH		Combined Pre/Post Capillary PH		Precapillary PH: PAH	
	RHC Findings			At Study Start	Current	At Study Start	Current	At Study Start	Current
Patient (Visit)	mPAP (mm Hg)	PCWP (mm Hg)	PVR (WU)	mPAP ≥25 mm Hg PCWP >15 mm Hg PVR ≤3 WU[21]	mPAP >20 mm Hg PCWP >15 mm Hg PVR <3 WU[22]	mPAP ≥25 mm Hg PCWP >15 mm Hg PVR >3 WU[21]	mPAP >20 mm Hg PCWP >15 mm Hg PVR ≥3 WU[22]	mPAP ≥25 mm Hg PCWP ≤15 mm Hg PVR >3 WU[21]	mPAP >20 mm Hg PCWP ≤15 mm Hg PVR ≥3 WU[22]
1 (year 3)	33	14	1.6	No	No	No	No	No	No
2 (year 2)	17	10	4.1	No	No	No	No	No	No
3 (year 3)	14	4	1.2	No	No	No	No	No	No
4 (year 3)	27	18	1.3	Yes	Yes	No	No	No	No
5 (year 1)	20	8	1.0	No	No	No	No	No	No
5 (year 3)	17	14	10	No	No	No	No	No	No
6 (baseline)	33	22	1.5	Yes	Yes	No	No	No	No
7 (year 1)	38	13	8.0	No	No	No	No	Yes	Yes
8 (baseline)	18	10	2.9	No	No	No	No	No	No
9 (year 3)	38	19	3.3	No	No	Yes	Yes	No	No
10 (baseline)	24	15	2.0	No	No	No	No	No	No
11 (baseline)	51	10	5.7	No	No	No	No	Yes	Yes
12 (baseline)	23	11	2.3	No	No	No	No	No	No
13 (year 3)	24	14	2.5	No	No	No	No	No	No
14 (baseline)	14	6	1.6	No	No	No	No	No	No
15 (baseline)	17	12	1.0	No	No	No	No	No	No
16 (baseline)	12	6	1.1	No	No	No	No	No	No

Table color code: green = PAH; yellow = combined precapillary and postcapillary PH; blue = postcapillary PH.

mPAP = mean pulmonary artery pressure; PAH = pulmonary arterial hypertension; PCWP = pulmonary capillary wedge pressure; PH = pulmonary hypertension; PVR = pulmonary vascular resistance; RHC = right heart catheterization.

CENTRAL ILLUSTRATION **ACHD-QuERI: A Standardized Protocol Following a Population of Patients With Repaired ACHD at Increased Risk for PAH Development for 3 Years**



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ACHD = adults with congenital heart disease; AF = atrial fibrillation; ECG = electrocardiogram; ECHO = transthoracic echocardiogram; PAH = pulmonary arterial hypertension; QuERI = Quality Enhancement Research Initiative; RAD = right axis deviation; RAE = right atrial enlargement; RHC = right heart catheterization; RV = right ventricle; RVH = right ventricular hypertrophy.

patient populations. Their predictive value in ACHD remains untested and may contribute to clinician nonadherence to recommended diagnostic protocols. ACHD-QuERI methodology relied heavily on clinician implementation of expert- and consensus-care guidelines and electronic prompts to drive standardization of clinical practice. The low level of clinician application of this methodology limited the ability to accurately identify incident PAH and correlations between patient characteristics and clinical outcomes over the course of follow-up. Patient recruitment was lower than projected at study design and though pooled for analysis, participants from the 2 cohorts may differ. Also, a relatively high proportion of patients (36%) were lost to follow-up, potentially related to clinicians' perceptions that patients were less at-risk for PAH development than the study inclusion criteria would suggest. Nevertheless, ACHD-QuERI reports the largest longitudinal prospective cohort of adults after shunt repair and at increased risk of developing PAH.

CONCLUSIONS

ACHD-QuERI identified an opportunity to enhance risk stratification and monitoring of patients with repaired ACHD at high risk for development of PAH. It has done this through education on the benefits of adhering to guidelines, enrichment strategies for inclusion in care guidelines, and increased support for clinicians to engage patients in discussions and shared decision-making regarding PAH risk management.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The ACHD-QuERI initiative was developed to improve physicians' awareness and adherence to guidelines for the monitoring and detection of PAH after repair of systemic-to-pulmonary arterial shunt lesions.

TRANSLATIONAL OUTLOOK: ACHD-QuERI has identified an opportunity to enhance the risk stratification and monitoring of patients with repaired ACHD who are at high risk for development of PAH.

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KEY WORDS adult congenital heart disease, echocardiography, pulmonary arterial hypertension, right heart catheterization, septal defect

APPENDIX For supplemental tables, please see the online version of this paper.