Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension of Sickle Cell Disease

Online Supplement

Elizabeth S. Klings*[1, 15], Roberto F. Machado*[2], Robyn J. Barst[3+], Claudia R. Morris[4], Kamal K. Mubarak[5], Victor R. Gordeuk[6], Gregory J. Kato[7], Kenneth I. Ataga[8], J. Simon Gibbs[9], Oswaldo Castro[6], Erika B. Rosenzweig[3], Namita Sood[10], Lewis Hsu[11], Kevin C.Wilson[1,12,15], Marilyn J. Telen[13], Laura M. DeCastro[13], Lakshmanan Krishnamurti[14], Martin H. Steinberg[15], David B. Badesch[16], Mark T. Gladwin[17]

[1]The Pulmonary Center, Boston University School of Medicine, [2]Section of Pulmonary, Critical Care Medicine, Sleep and Allergy, University of Illinois Chicago, [3]Department of Pediatrics and Medicine, Columbia University, [4]Department of Pediatrics, Division of Pediatric Emergency Medicine, and the Emory Children's Center for Developmental Lung Biology, Emory University School of Medicine, [5]Division of Pulmonary and Critical Care, University of Florida, [6]Center for Sickle Cell Disease, Howard University, [7]Hematology Branch, National Heart, Lung and Blood Institute, [8]Division of Hematology/Oncology, University of North Carolina, [9]National Heart & Lung Institute, Imperial College London, [10]Division of Pulmonary and Critical Care, Ohio State University, [11]Division of Pediatric Hematology-Oncology, Children's Hospital of the University of Illinois, [12] UpToDate, Waltham, MA, [13]Division of Hematology, Duke University, [14]Division of Pediatric Hematology, Children's Hospital of Pittsburgh, [15]Department of Medicine, Boston University School of Medicine, [16]Division of Pulmonary Sciences and Critical Care Medicine, University of Colorado HSC, [17]Division of Pulmonary, Allergy and Critical Care Medicine and the Vascular Medicine Institute, University of Pittsburgh

[+]Deceased

Address Correspondence To:
Elizabeth S. Klings, MD
Associate Professor of Medicine
Boston University School of Medicine
The Pulmonary Center, R-304
72 East Concord Street
Boston, MA 02118
(617) 638-4860
Fax: (617) 638-5227
E-mail: klingon@bu.edu

TABLE OF CONTENTS

METHODS:

Committee Composition:

This document was approved and funded by the American Thoracic Society (ATS). The project chair (ESK) and co-chairs (RM and MTG) selected 24 committee members based upon their expertise in SCD, PH, or both. The committee consisted of seven adult pulmonologists, six adult hematologists, four pediatric hematologists, two adult cardiologists, two pediatric cardiologists, one pediatric pulmonologist, one adult pulmonologist/methodologist and one pediatric emergency medicine physician. All committee members disclosed their potential conflicts of interest to the ATS and the project chair.

Identifying, appraising and synthesizing the evidence:

To identify evidence relevant to each clinical question, systematic reviews of the literature were performed. The pre-specified search strategies and study selection criteria are described in the online supplemental appendix. The systematic reviews were periodically updated and are current through February 15, 2013. The identified evidence was appraised using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (1-3). In the four level grading system (high, moderate, low, and very low quality evidence), randomized trials begin with the assumption of high quality evidence, whereas well-conducted observational studies (e.g., cohort studies, case-control studies) begin with an assumption of low quality evidence (4). The quality of evidence can be downgraded or upgraded on the basis of the criteria shown in Table E1. Evidence tables were constructed using GRADEpro (available at http://ims.cochrane.org/revman/gradepro).

Formulating recommendations:

Recommendations were formulated to answer the clinical questions created by the group. The decision of whether to recommend an intervention was made by consensus and based upon four criteria: the quality of evidence, the balance of desirable and undesirable consequences, patient values and preferences related to the intervention and outcomes, and resource use (4). A strong recommendation was made when there was certainty about the balance of desirable and undesirable consequences of an intervention, whereas a weak recommendation was made when there was less certainty or the balance of desirable and undesirable consequences was finely balanced.

Disclosure of Conflicts of Interest:

All committee members disclosed their potential conflicts of interest to the ATS and the committee chair. The committee chair reviewed all potential conflicts of interest, discussed them with the chair of the Ethics and Conflict of Interest Committee of the ATS, and resolved them with individual committee members. Committee members were required to refrain from discussing topics related to their potential conflicts of interest both at the face-to-face meetings and in preliminary drafts of the document.

Sub-Committees:

Two subcommittees were formed to identify important clinical questions related to: (1) screening and diagnosis and (2) treatment. These questions were subsequently discussed during an initial face-to-face meeting at the 2009 ATS International Conference. A writing committee was subsequently formed and divided into subgroups. Each subgroup was charged with preparing a

portion of the guidelines, which entailed identifying, appraising, and synthesizing the evidence, as well as formulating recommendations and writing.

Document preparation:

The drafts from the various subgroups were integrated by the committee chairs. The document was distributed for discussion at two face-to-face meetings (the 2009 American Society of Hematology International Conference and the 2010 ATS International Conference) and periodically by e-mail and conference calls. All of the committee members had the opportunity to discuss and express any concerns about the document or the recommendations.

PH of SCD as a Systemic Vascular Disorder and Associated Conditions

Although defined as a genetic hemoglobinopathy, SCD is a complex vascular disorder. SCD patients typically have lower systemic blood pressures than normal volunteers, possibly related to a variety of mechanisms involving arterial stiffness and ischemic events to the renal medulla (5). Relative systemic hypertension in SCD defined by either systolic blood pressures (SBP) between 120-139 mmHg or diastolic blood pressures (DBP) between 70-89 mmHg, was observed in 37% of patients with a TRV $\geq$ 2.5 m/sec. Additionally, 93% of those with systemic hypertension by routine definitions (SBP $\geq$ 140 or DBP $\geq$90 mmHg) had co-existent elevations in TRV suggesting that there is a relationship between the degree of systemic hypertension and this echocardiographic finding (6).

Although all SCD patients share the same genetic hemoglobin defect, the clinical heterogeneity in this population supports the notion that factors unrelated to the hemoglobin mutation play a

role in the development of clinical phenotypes. These factors include hemolysis, hypoxia, oxidative stress, dysregulated nitric oxide (NO) metabolism, genetic predisposition, and altered coagulation. Over the past decade, a growing body of evidence has supported the notion that complications of SCD can be dichotomized into those that are either primarily vasoocclusive or hemolytic in etiology (7). While these pathophysiological limbs must be linked, this deconstruction of disease mechanisms has value for understanding pathophysiology. The severity of anemia and hemolysis are significantly associated with PH in SCD and other chronic hereditary and acquired hemolytic anemias. In stark contrast, a lower rate of hemolysis and increased baseline hemoglobin concentrations are associated with risk of hospitalization for vasoocclusive pain crisis (VOC) and ACS. Hemolysis, via the liberation of heme, has been shown to scavenge NO directly, generate reactive oxygen species and release erythrocytic enzymes such as arginase I into the bloodstream, with profound effects on NO bioavailability and endothelial function, potentially affecting pulmonary vascular remodeling (8-10). Lactate dehydrogenase (LDH), a marker of hemolysis, has been found to be an important biomarker associated with an elevated TRV. LDH levels were increased in patients with hemolytic complications of SCD including leg ulcers and priapism and there appeared to be an association between the degree of LDH elevation, NO resistance within the vasculature and the likelihood of having an elevated TRV by echocardiography (11). All three recent RHC-based screening studies (12-14) have confirmed a link between the degree of hemolytic anemia with a diagnosis of PH, thereby confirming this hypothesis.

Other important risk factors linked to the development of PH in SCD include renal insufficiency, iron overload, cholestatic hepatic dysfunction, and possibly, functional asplenia and

thromboembolic disease. PH in SCD is thought to occur by a variety of mechanisms including hypoxic vasoconstriction, thrombosis, and decreased nitric oxide bioavailability. The relative contribution of each of these mechanisms to the elevated pulmonary arterial or venous pressures observed in individual patients is variable and remains unclear.

Echocardiography in Sickle Cell Disease:

Echocardiography is a non-invasive way to screen SCD patients for structural cardiac abnormalities suggestive of PH. An estimation of the pulmonary artery systolic pressure can be made via assessment of the TRV. The typically thin body habitus of SCD patients accompanied by their dilated, hyperdynamic heart chambers allows for relatively easy measurement of the regurgitation of blood across the tricuspid valve during right ventricular systole. The Bernoulli equation includes the addition of the estimated right atrial pressure to $4(TRV)^2$. Estimation of right atrial pressure in different echocardiography laboratories occurs in a variety of ways including measurement of inferior vena cava diameter and its response to deep inspiration, clinical estimation of jugular venous pressure, or by assuming it to be 5, 10 or 15 mm Hg based on clinical patient characteristics. PASP is then assumed to be equivalent to RVSP as long as there is no pulmonary outflow tract obstruction. In the presence of the anemia and associated high cardiac output in SCD, there can be a measurable gradient across the right ventricular outflow track due to increased flow without true pulmonary stenosis. This turbulence across the right ventricular outflow track can also interfere with the accuracy in measuring the TRV. A TRV greater than or equal to 2.5 m/sec corresponds to an estimated PASP of $\geq$35 mm Hg, which is approximately two standard deviations above normal; for SCD patients less than 40 years of age, the normal reference mean Doppler echocardiographic estimated PASP is 27.5 ± 4.2 mmHg (95% CI 19.3 to 35.5 mm Hg) (15, 16). In other populations, a more traditional

echocardiographic definition of suspected PH would be a TRV of greater than or equal to 3.0 m/sec. However, in SCD patients, the risk of death associated with a TRV $\geq$ 2.5 m/sec rises linearly. Although the label "pulmonary hypertension" has been used in echocardiographic studies of SCD, many of these patients have not undergone RHC to confirm this diagnosis.

As a consequence, there is no direct translation of echocardiographically estimated RVSP to measured mean PAP (or even an estimated mean PAP) as used to define PH by right heart catheterization. The false positive rate of diagnosing PH by echocardiography has received much attention, particularly in the last decade. A recent meta-analysis evaluated 29 studies conducted between 1984 and 2009 amongst 1998 non-SCD patients comparing the accuracy of echocardiography in determining PASP and diagnosing PH with the gold standard right heart catheterization. The correlation of PASP by these two modalities was modest with a r=0.70 (95% CI 0.67-0.73) as was echocardiography's ability to diagnose PH. Echocardiography had a sensitivity of 83% (95% CI 73-90%) and specificity of 72% (95% CI 53-85%) (17). As a result, patients with a TRV $\geq$2.5 m/s who have not undergone RHC should be considered to have "an increased tricuspid regurgitation velocity" but not necessarily PH as many of these patients will likely not have PH. Only patients who have undergone RHC and meet the diagnostic hemodynamic criteria should be given the diagnosis of PH.

Echocardiography has also been used to assess diastolic function of the left ventricle as estimated by the E/A ratio. An abnormal E/A ratio suggestive of left ventricular diastolic dysfunction was reported in 18% of adult SCD patients and was an independent risk factor for death with a risk

ratio of 3.5. Both an abnormal E/A ratio and an elevated TRV were observed in 11% of patients and increased the risk ratio for death to 12.0 (18).

Question: What does a mildly elevated TRV (2.5-2.8 m/s) on an echocardiogram represent? Several studies have suggested that a peak TRV ≥2.5 m/s in SCD patients is associated with a greater risk of death (19-21). The odds ratio for death in the NIH screening cohort was 4.4 if TRV was 2.5 - 2.9 m/s (95% CI, 1.6-12.2; $p<0.001$) supporting the need for identifying these patients (19). One potential explanation for this increased mortality is the suggestion that these patients may have a more diffuse vasculopathy. Compared to SCD patients with a peak TRV <2.5 m/s, patients with a TRV ≥ 2.5 m/sec are older, have an increased prevalence of systemic hypertension and proteinuria, increased hemolysis with worsening anemia and are more likely to be on chronic transfusion therapy (6, 11, 22, 23). Exercise capacity is also often impaired in these patients as reflected by a decreased 6 minute walk distance (6MWD) and a decreased peak oxygen consumption compared to those with a TRV <2.5 m/s (24). Contrary to previous assumptions, a chronically raised TRV is not associated with a patient-reported history of increased vasoocclusive crises, ACS or the presence of osteonecrosis in SCD adults. The pediatric literature is conflicted in this regard; while almost all studies confirm the association with hemolytic anemia, the associations with ACS are variable; three studies note an association between an elevated TRV and a history of ACS (25-27) while others do not (28, 29). Interestingly, during ACS the TRV increases transiently (30), but this does not predict a steady-state increased peak TRV in adults (18).

Although this increased mortality risk has not been observed in SCD children with an elevated TRV, far less data are available for pediatric patients than for adults; however, there are associations between an increased TRV with increased hemolysis and anemia, more frequent blood transfusions, stroke, sepsis and a progressive decline in exercise capacity over time. An elevated TRV in the pediatric population may be a marker for a more severe phenotype with possible associations with asthma, obstructive sleep apnea, hypoxemia and/or ACS (25, 27, 28, 31).

Diagnosis of PH in SCD

History and Physical Examination:

Patients with SCD often present a diagnostic conundrum in terms of evaluating for PH. Frequent PH symptoms include dyspnea on exertion, fatigue, chest pain, lower extremity edema, syncope or near-syncope and palpitations, many of which can be observed in SCD patients unrelated to any degree of PH. Worsening anemia in SCD can produce exertional dyspnea, fatigue, palpitations, light-headedness and syncope/near-syncope. Chest pain can occur during VOC and may be difficult to discern in SCD patients who often have chronic pain. We recommend performing oximetry at rest and with exertion on all patients. Measuring ambulatory oximetry on both a flat surface and stair climbing is critical for identifying hypoxemic patients for whom a more complete PH workup is needed. Other physical examination findings reflective of increased PA and right-sided pressures include an accentuated pulmonic component of S_2, a mid-systolic ejection murmur or a holosystolic murmur at the left sternal border suggestive of tricuspid insufficiency, a left parasternal lift, an elevated jugular venous pulse, a pulsatile liver, a right ventricular S_4, hepatosplenomegaly and peripheral edema (32, 33). Some of these findings

may be difficult to appreciate in SCD patients who can have hyperdynamic heart sounds and a systolic ejection murmur due to anemia in the absence of PH.

Chest Radiography: Chest radiographs in SCD patients with PH may have cardiomegaly, particularly of the right atrium and right ventricle with prominent pulmonary arteries. However, cardiomegaly can also occur merely due to the presence of anemia alone. Peripheral hypovascularity or vascular pruning may be observed as well in PH but is a late finding.

Echocardiography: When PH is suspected, an echocardiogram is the next appropriate study. Echocardiograms can provide insights into potential etiologies of suspected elevated PAPs and can assess right atrial and right ventricular size and function, which in the absence of suspected elevated pulmonary pressures, may trigger an additional workup. Common echocardiographic features of PH are presented in Figure 1. Accurate assessment of the TRV requires time, patience and a skilled echocardiographer who can assess all views (subcostal, left parasternal right ventricular inlet, short axis at the aortic valve level, and apical 3 and 4 chamber views). Over-estimations of the TRV can occur if the tricuspid regurgitation is measured after an ectopic beat, if there is confusion with either mitral regurgitation or the tricuspid valve slap or interception of the aortic valve flow in the apical view. Under-estimations of the TRV are less frequent but can occur if the TR jet is eccentric or if variations with the respiratory cycle occur.

Laboratory Studies and Biomarkers:

Laboratory studies in SCD patients with an elevated TRV are useful in identifying associated medical conditions that may impact prognosis. In keeping with diagnostic recommendations for

other patients with suspected PH, all patients with an elevated TRV should be screened for co-existent connective tissue disease, chronic thromboembolic disease, congenital heart disease, HIV and/or liver disease (32, 33). Additionally, we recommend an assessment of the degree of hemolysis (serum LDH) and renal dysfunction (11, 23, 34).

Measurement of NT-pro-BNP levels can be used both to screen SCD patients for PH and for risk stratification as elevated levels are associated with increased mortality both in SCD patients as well as those with IPAH (35-38).

Studies of Exercise Capacity: The 6MWT is a well-established objective measure of exercise endurance in the evaluation of PAH patients and is an independent predictor of survival (32, 39). Although SCD patients can have other factors such as prior strokes, osteonecrosis of the hip and lower extremity ulcers that may limit mobility, the 6MWT is useful in this population as well. In PH of SCD patients, the distance walked correlates with PH severity and improves with a favorable therapeutic response, making it a useful endpoint in clinical trials (40, 41). When compared to age, gender and hemoglobin concentration-matched SCD patients without PH, individuals with a TRV $\geq$ 2.5 m/sec have a lower 6MWD (435 ± 31 versus 320 ± 20 meters; p=0.002) and lower peak oxygen consumption assessed by cardiopulmonary exercise testing (50 ± 3% versus 41 ± 2% of predicted; p=0.02) (41). In addition, in SCD patients, the PVR sharply rises with exercise consistent with pulmonary vascular disease being at least partially related to their functional limitations (24). Recently, a prospective study evaluating 483 subjects enrolled as part of the Walk-PHaSST (Pulmonary Hypertension and Sickle Cell Disease with Sildenafil

Therapy) clinical trial demonstrated that TRV was an independent predictor of 6MWD (p=0.019) (42).

Evaluation for Other Co-Existent Cardiopulmonary Disease

Pulmonary Function Testing: Pulmonary function testing (PFTs) is abnormal in most SCD patients. The largest study of HbSS adults to date evaluated 310 patients recruited as part of the Cooperative Study of Sickle Cell Disease; normal PFTs were present in only 31 of 310 (10%). Overall, HbSS adults had decreased total lung capacities (70.2 $\pm$ 14.7% predicted) and diffusion capacities for carbon monoxide (D_LCO) (64.5 $\pm$ 19.9% predicted). The most common PFT patterns were restrictive physiology (in 74%), and an isolated low D_LCO (in 13%) (43). PFTs performed on a small number of SCD patients with (n=26) and without (n=17) an elevated TRV (defined as $\geq$ 2.5 m/sec) demonstrated that those with an elevated TRV were more likely to have both restrictive physiology and a decreased D_LCO (41).

PFTs in children and adolescents with SCD are also frequently abnormal. In contrast to adults, there is a high prevalence of airway hyper-reactivity and obstructive physiology in children with SCD suggestive of asthma (25, 44-50). Of interest, a recent study of 99 children with SCD reported few typical features of allergic asthma associated with a positive methacholine challenge, suggesting a non-atopic mechanism of disease pathobiogenesis in these children. However, increased methacholine responsiveness correlated strongly with plasma LDH levels, potentially linking asthma to increased hemolytic rate in SCD (46). In several small studies, a reduced forced expiratory volume in the first second (FEV_1) (51) or the presence of asthma (25) were associated with an elevated TRV in SCD children supporting the notion that this finding

may identify a subset of the pediatric population at greater risk for cardiopulmonary disease. Complete pulmonary function testing for SCD patients includes spirometry, lung volumes and measurement of a D_LCO.

Evaluation For Thromboembolic Disease: In the general population, an evaluation for co-existent thromboembolic disease is essential for patients suspected of having PH as chronic thromboembolic PH (CTEPH) occurs in 3-4% of those with a prior history of pulmonary embolism (PE) and more importantly, up to 50% of those who are ultimately diagnosed with CTEPH have no known history of a prior PE. In SCD, this issue becomes more complicated. The consensus is that SCD is a hypercoagulable state based upon studies demonstrating increased markers of thrombin generation and an increased prevalence of thrombotic complications in SCD patients as compared to controls (52-55). Yet the published literature is less clear when examining the link between PH and thromboembolic disease in SCD (56-59). There appears to be a larger than anecdotal link between the two entities and as such, we recommend that all SCD patients being evaluated for PH also undergo screening for co-existent acute or chronic thromboembolic disease with radionuclide scanning (32). In some SCD patients, this may be abnormal or uninterpretable due to prior episodes of ACS or co-existent parenchymal lung disease. In those patients, selective pulmonary angiography is preferable to a CT angiogram (which has a 7% false negative rate in the presence of documented CTEPH) (32).

<u>Invasive Hemodynamic Evaluation of Pulmonary Hypertension</u>

A RHC is required to correctly diagnose and classify PH. Although some concern has been raised about the invasiveness of this procedure, in experienced centers, this is considered to be

safe with low associated morbidity and mortality rates. The largest study to date evaluated 7,218 RHCs performed either retrospectively or prospectively and found that serious adverse events occurred in 76 (1.1%, 95% confidence interval 0.8% to 1.3%). The most frequent adverse events related to venous access (hematomas or pneumothorax), arrhythmias or hypotension related to vagal reactions or acute vasoreactivity testing (AVT) (60). The diagnosis of PH includes wedging a balloon-directed occlusion catheter into several segments of the pulmonary vasculature to measure the PCWP, reflective of the left atrial pressure (as long as there is no obstruction within the pulmonary vasculature), measured at the end of expiration in patients breathing spontaneously. AVT is most useful in patients with idiopathic PAH; its clinical utility in patients with SCD related PH remains unclear. As such, we would not recommend performing AVT on SCD patients at this time.

Summary of Diagnostic Testing for PH in SCD

A diagnostic algorithm for SCD patients with an elevated TRV and suspected PH is presented in Figure 2 of the main document.

Long-term Follow-up of the PH in SCD Patient

Clinical indicators with prognostic implications in PH include NYHA Functional Class, 6MWD, NT-pro-BNP, and specific hemodynamic parameters, e.g. cardiac index, mean right atrial pressure and PVR. The frequency of follow-up depends on the clinical status of the patient and may vary between centers. Patients with SCD related PH are most often seen for clinical follow-up every 1-3 months. Stable patients may only need to be followed as infrequently as every 6 months. At each visit, an assessment of symptoms, physical examination including oximetry at

rest and with ambulation, and NYHA Class is usually performed. Most clinicians would repeat 6MWT and NT-pro-BNP levels every 6-12 months (as an objective measure of functional status). Echocardiography is generally done on an annual basis (for stable patients) as a non-invasive estimate of PH as well as right heart size and function. Repeat RHC should be considered for progression of symptoms or echocardiographic findings as well as to assess response to therapies.

PH in the Pediatric SCD Population: Special Considerations

The link between an elevated TRV and long term adverse outcomes and survival are also unknown in the pediatric population. Preliminary studies suggest differences compared with adults, largely secondary to the overall low mortality rate in SCD children currently (< 0.6% deaths/year). No deaths occurred in 15 children with a TRV ≥ 2.5 m/sec compared to 18 deaths in 81 adults with an elevated TRV from a SCD cohort followed over an 8 year period post-screening echocardiography (25). More recently, data from a prospective cohort study that included 88 children reported after 3 years of follow-up, all 18 subjects with a TRV ≥ 2.5 m/sec were alive (61). In the PUSH study, of the first 360 children and adolescents screened by echocardiography, 230 were followed for a median of 21 months with 3 deaths. In two of the children who died, the baseline TRV was <2.5 m/sec and in the third, the TRV was not detectable. These data suggest factors unrelated to an elevated TRV as the cause of death. Two of the children who died had an elevated hemolytic rate and a history of stroke at time of entry in the study (31). Moreover, none of the 11% of subjects with an elevated TRV (2.6 m/sec or higher) died within the 21 months of follow-up. Although preliminary studies suggest that short-term mortality risk in SCD is not increased in children with an elevated TRV compared to adults,

these children may still be at greater risk for complications in young adulthood and warrant close observation.

Although the PUSH study did not find that children with an increased TRV on screening had a shorter 6MWD at the time of screening, they had an increased history of ACS, blood transfusions and a greater decline in systemic arterial oxygen saturation during exercise than children without a TRV elevation (27). Longitudinal observations are essential in determining the clinical significance of an elevated TRV in children. The PUSH study found, in 160 HbSS children and adolescents, single screening determinations of TRV, 6MWD and hemolytic profile correlate with repeat determinations two years later ($r \geq 0.4$; $p < 0.0001$ for each comparison). Both baseline hemolytic rate ($p=0.008$) and elevation of mitral E/E_{tdi} ratio (a marker of left ventricular diastolic dysfunction) ($p = 0.039$) were independent predictors of new TRV elevation on follow-up; 27% of children with a higher hemolytic rate (defined as a 2 SD increase in the hemolytic index over the median) had a new TRV elevation on follow-up compared to 7% of children with a lower hemolytic rate. The hemolytic index in this study was derived by a principal component analysis of levels of LDH, aspartate aminotransferase and bilirubin and reticulocyte count. The frequency of a 10% or greater decline in the 6MWD during follow-up was 47% in participants with an elevated TRV compared to 21% in those without an elevated TRV ($p = 0.033$). By logistic regression, an elevated baseline TRV was associated with an estimated 4.4-fold increase in the odds of a 10% or greater decline in 6MWD after 22 months of follow-up (95% CI = 1.3–14.5; $p=0.015$) (31).

In summary, evaluation of the TRV and hemolytic rate in children with SCD may predict a decline in exercise capacity over 2 years. Whether or not further decline in cardiopulmonary function over longer follow-up will occur, remains unknown. However, this finding is important as younger patients may be more amenable to reversal of PH when TRV elevations are mild and vascular remodeling is less (62). **Thus, while mortality is an important endpoint in adult patients, it may not be the most appropriate outcome measure to assess for the pediatric population, and should not be considered as the only outcome measure of value for SCD (regardless of age).**

Pregnancy in PH of SCD

Two epidemiologic studies have recently addressed the issue of pregnancy in SCD patients in the United States (63, 64). The first looked retrospectively at hospital discharges with the International Classification of Diseases, 9th revision (ICD-9) codes related to pregnancy and SCD. Comparing 17,952 deliveries amongst SCD women to 16,756,944 amongst women without SCD, women with SCD had an increased risk of cesarean delivery, infections and thromboembolic events. Additionally, women with SCD had a mortality rate of 72.4 deaths per 100,000 deliveries compared with 12.7 deaths per 100,000 for women without SCD (64). A second study following 410 pregnancies prospectively in 190 women between 2002 and 2007 reported that 221 (53.9%) resulted in live births while 121 (29.5%) ended in spontaneous abortions and 68 (16.6%) were voluntarily terminated (63).

The presence of PH poses an additional hemodynamic risk to these patients. During pregnancy, the circulating blood volume increases 30-50%, reaching its maximum at approximately week 34

of gestation. Cardiac output also increases after the 5th week of gestation by approximately 50% and can, in many instances, increase an additional 50-80% during delivery and the post-partum period. These factors and the associated hypercoagulability of pregnancy are thought to be responsible for the 30-50% maternal mortality rate observed in IPAH (65). Additionally, the endothelin receptor antagonists, frequently used to treat PAH, are teratogenic. But regardless of any teratogenic risks, based on all of these factors, pregnancy is contraindicated in PAH. Even if a patient is able to survive pregnancy and the post-partum period, the likelihood that the patient's PAH will be worse than prior to the pregnancy is significant. Furthermore, with the additional risks incurred with co-existent SCD, it seems most prudent at this point, to recommend prevention of pregnancies in patients with RHC-confirmed PH and SCD. All SCD patients with an elevated TRV who become pregnant should be strongly considered for undergoing a RHC for risk assessment. The presence of an elevated TRV alone should trigger a consultation with experienced clinicians in the care and treatment of patients with PH and SCD as well as those in high-risk obstetrics. Joint management by these specialists should help lower morbidity and mortality risks for both the mother and her baby.

REFERENCES

1. Schunemann HJ, Jaeschke R, Cook DJ, Bria WF, El Solh AA, Ernst A, Fahy BF, Gould MK, Horan KL, Krishnan JA, Manthous CA, Maurer JR, McNicholas WT, Oxman AD, Rubenfeld G, Turino GM, Guyatt G. An official ats statement: Grading the quality of evidence and strength of recommendations in ats guidelines and recommendations. *AmJRespirCrit Care Med* 2006;174:605-614.

2. Schunemann HJ, Oxman AD, Brozek J, Glasziou P, Jaeschke R, Vist GE, Williams JW, Jr., Kunz R, Craig J, Montori VM, Bossuyt P, Guyatt GH. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ* 2008;336:1106-1110.

3. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, Raskob G, Lewis SZ, Schunemann H. Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an american college of chest physicians task force. *Chest* 2006;129:174-181.

4. Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schunemann HJ. What is "quality of evidence" and why is it important to clinicians? *BMJ* 2008;336:995-998.

5. Rodgers GP, Walker EC, Podgor MJ. Is "relative" hypertension a risk factor for vaso-occlusive complications in sickle cell disease? *AmJMedSci* 1993;305:150-156.

6. Gordeuk VR, Sachdev V, Taylor JG, Gladwin MT, Kato G, Castro OL. Relative systemic hypertension in patients with sickle cell disease is associated with risk of pulmonary hypertension and renal insufficiency. *AmJHematol* 2008;83:15-18.

7. Kato GJ, Gladwin MT, Steinberg MH. Deconstructing sickle cell disease: Reappraisal of the role of hemolysis in the development of clinical subphenotypes. *Blood Rev* 2007;21:37-47.

8. Morris CR. New strategies for the treatment of pulmonary hypertension in sickle cell disease : The rationale for arginine therapy. *TreatRespirMed* 2006;5:31-45.

9. Morris CR, Kato GJ, Poljakovic M, Wang X, Blackwelder WC, Sachdev V, Hazen SL, Vichinsky EP, Morris SM, Jr., Gladwin MT. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. *JAMA* 2005;294:81-90.

10. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO, III, Schechter AN, Gladwin MT. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *NatMed* 2002;8:1383-1389.

11. Kato GJ, McGowan V, Machado RF, Little JA, Taylor J, Morris CR, Nichols JS, Wang XD, Poljakovic M, Morris SM, Gladwin MT. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension and death in patients with sickle cell disease. *Blood* 2005;106:891A-891A.

12. Mehari A Fau - Alam S, Alam S Fau - Tian X, Tian X Fau - Cuttica MJ, Cuttica Mj Fau - Barnett CF, Barnett Cf Fau - Miles G, Miles G Fau - Xu D, Xu D Fau - Seamon C, Seamon C Fau - Adams-Graves P, Adams-Graves P Fau - Castro OL, Castro Ol Fau - Minniti CP, Minniti Cp Fau - Sachdev V, Sachdev V Fau - Taylor Vi JG, Taylor Vi Jg Fau - Kato GJ, Kato Gj Fau - Machado RF, Machado RF. Hemodynamic predictors of mortality in adults with sickle cell disease.

13. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, Loko G, Habibi A, Bennani S, Savale L, Adnot S, Maitre B, Yaici A, Hajji L, O'Callaghan DS, Clerson P, Girot R, Galacteros F, Simonneau G. A hemodynamic study of pulmonary hypertension in sickle cell disease. *NEnglJMed* 2011;365:44-53.

14. Fonseca GH, Souza R, Salemi VC, Jardim CV, Gualandro SF. Pulmonary hypertension diagnosed by right heart catheterization in sickle cell disease. *EurRespirJ* 2011.

15. Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. *NEnglJMed* 2008;359:2254-2265.

16. McQuillan BM, Picard MH, Leavitt M, Weyman AE. Clinical correlates and reference intervals for pulmonary artery systolic pressure among echocardiographically normal subjects. *Circulation* 2001;104:2797-2802.

17. Janda S, Shahidi N, Gin K, Swiston J. Diagnostic accuracy of echocardiography for pulmonary hypertension: A systematic review and meta-analysis. *Heart* 2011.

18. Sachdev V, Machado RF, Shizukuda Y, Rao YN, Sidenko S, Ernst I, St Peter M, Coles WA, Rosing DR, Blackwelder WC, Castro O, Kato GJ, Gladwin MT. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. *JAmCollCardiol* 2007;49:472-479.

19. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, Minter K, Brown B, Coles WA, Nichols JS, Ernst I, Hunter LA, Blackwelder WC, Schechter AN, Rodgers GP, Castro O, Ognibene FP. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med* 2004;350:886-895.

20. Ataga KI, Moore CG, Jones S, Olajide O, Strayhorn D, Hinderliter A, Orringer EP. Pulmonary hypertension in patients with sickle cell disease: A longitudinal study. *BrJHaematol* 2006;134:109-115.

21. Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: Cardiac catheterization results and survival. *Blood* 2003;101:1257-1261.

22. Stuart MJ, Nagel RL. Sickle-cell disease. *Lancet* 2004;364:1343-1360.

23. De Castro LM, Jonassaint JC, Graham FL, Ashley-Koch A, Telen MJ. Pulmonary hypertension associated with sickle cell disease: Clinical and laboratory endpoints and disease outcomes. *AmJHematol* 2008;83:19-25.

24. Machado RF, Kyle MA, Martyr S, Barnett C, Macarthur P, Sachdev V, Ernst I, Hunter LA, Coles WA, Nichols JP, Kato GJ, Gladwin MT. Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. *BrJHaematol* 2006.

25. Hagar RW, Michlitsch JG, Gardner J, Vichinsky EP, Morris CR. Clinical differences between children and adults with pulmonary hypertension and sickle cell disease. *BrJHaematol* 2008;140:104-112.

26. Dham N, Ensing G, Minniti C, Campbell A, Arteta M, Rana S, Darbari D, Nouraie M, Onyekwere O, Lasota M, Kato GJ, Gladwin MT, Castro O, Gordeuk V, Sable C. Prospective echocardiography assessment of pulmonary hypertension and its potential etiologies in children with sickle cell disease. *AmJCardiol* 2009;104:713-720.

27. Minniti CP, Sable C, Campbell A, Rana S, Ensing G, Dham N, Onyekwere O, Nouraie M, Kato GJ, Gladwin MT, Castro OL, Gordeuk VR. Elevated tricuspid regurgitant jet velocity in children and adolescents with sickle cell disease: Association with hemolysis and hemoglobin oxygen desaturation. *Haematologica* 2009;94:340-347.

28. Ambrusko SJ, Gunawardena S, Sakara A, Windsor B, Lanford L, Michelson P, Krishnamurti L. Elevation of tricuspid regurgitant jet velocity, a marker for pulmonary hypertension in children with sickle cell disease. *PediatrBlood Cancer* 2006;47:907-913.

29. Kato GJ, Onyekwere OC, Gladwin MT. Pulmonary hypertension in sickle cell disease: Relevance to children. *PediatrHematolOncol* 2007;24:159-170.

30. Mekontso DA, Leon R, Habibi A, Nzouakou R, Roudot-Thoraval F, Adnot S, Godeau B, Galacteros F, Brun-Buisson C, Brochard L, Maitre B. Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. *AmJRespirCrit Care Med* 2008;177:646-653.

31. Gordeuk V, Minniti CP, Nouraie M, Campbell AD, Rana S, Luchtman-Jones L, Sable C, Dham N, Ensing G, Prchal JT, Kato GJ, Gladwin MT, Castro OL. Elevated tricuspid regurgitation velocity and decline in exercise capacity over 22 months of follow-up in children and adolescents with sickle cell anemia. *Haematologica* 2010.

32. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. 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. *Circulation* 2009.

33. McLaughlin VV, Archer SL, Badesch DB, Barst RJ, Farber HW, Lindner JR, Mathier MA, McGoon MD, Park MH, Rosenson RS, Rubin LJ, Tapson VF, Varga J. 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. *JAmCollCardiol* 2009;53:1573-1619.

34. Ataga KI, Brittain JE, Moore D, Jones SK, Hulkower B, Strayhorn D, Adam S, Redding-Lallinger R, Nachman P, Orringer EP. Urinary albumin excretion is associated with pulmonary

hypertension in sickle cell disease: Potential role of soluble fms-like tyrosine kinase-1. *EurJHaematol* 2010.

35. Machado RF, Anthi A, Steinberg MH, Bonds D, Sachdev V, Kato GJ, Taveira-DaSilva AM, Ballas SK, Blackwelder W, Xu X, Hunter L, Barton B, Waclawiw M, Castro O, Gladwin MT. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. *JAMA* 2006;296:310-318.

36. Machado RF, Hildesheim M, Mendelsohn L, Remaley AT, Kato GJ, Gladwin MT. Nt-pro brain natriuretic peptide levels and the risk of death in the cooperative study of sickle cell disease. *BrJHaematol* 2011;154:512-520.

37. Fijalkowska A, Kurzyna M, Torbicki A, Szewczyk G, Florczyk M, Pruszczyk P, Szturmowicz M. Serum n-terminal brain natriuretic peptide as a prognostic parameter in patients with pulmonary hypertension. *Chest* 2006;129:1313-1321.

38. Nagaya N, Nishikimi T, Uematsu M, Satoh T, Kyotani S, Sakamaki F, Kakishita M, Fukushima K, Okano Y, Nakanishi N, Miyatake K, Kangawa K. Plasma brain natriuretic peptide as a prognostic indicator in patients with primary pulmonary hypertension. *Circulation* 2000;102:865-870.

39. Miyamoto S, Nagaya N, Satoh T, Kyotani S, Sakamaki F, Fujita M, Nakanishi N, Miyatake K. Clinical correlates and prognostic significance of six-minute walk test in patients with primary pulmonary hypertension. Comparison with cardiopulmonary exercise testing. *AmJRespirCrit Care Med* 2000;161:487-492.

40. Machado RF, Martyr S, Kato GJ, Barst RJ, Anthi A, Robinson MR, Hunter L, Coles W, Nichols J, Hunter C, Sachdev V, Castro O, Gladwin MT. Sildenafil therapy in patients with sickle cell disease and pulmonary hypertension. *BrJHaematol* 2005;130:445-453.

41. Anthi A, Machado RF, Jison ML, Taveira-DaSilva AM, Rubin LJ, Hunter L, Hunter CJ, Coles W, Nichols J, Avila NA, Sachdev V, Chen CC, Gladwin MT. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *AmJRespirCrit Care Med* 2007;175:1272-1279.

42. Sachdev V, Kato GJ, Gibbs JS, Barst RJ, Machado RF, Nouraie M, Hassell KL, Little JA, Schraufnagel DE, Krishnamurti L, Novelli EM, Girgis RE, Morris CR, Rosenzweig EB, Badesch DB, Lanzkron S, Castro OL, Taylor JG, Hannoush H, Goldsmith JC, Gladwin MT, Gordeuk VR. Echocardiographic markers of elevated pulmonary pressure and left ventricular diastolic dysfunction are associated with exercise intolerance in adults and adolescents with homozygous sickle cell anemia in the united states and united kingdom. *Circulation* 2011;124:1452-1460.

43. Klings ES, Wyszynski DF, Nolan VG, Steinberg MH. Abnormal pulmonary function in adults with sickle cell anemia. *AmJRespirCrit Care Med* 2006;173:1264-1269.

44. Leong MA, Dampier C, Varlotta L, Allen JL. Airway hyperreactivity in children with sickle cell disease. *JPediatr* 1997;131:278-283.

45. Sylvester KP, Patey RA, Rafferty GF, Rees D, Thein SL, Greenough A. Airway hyperresponsiveness and acute chest syndrome in children with sickle cell anemia. *PediatrPulmonol* 2007;42:272-276.

46. Field JJ, Stocks J, Kirkham FJ, Rosen CL, Dietzen DJ, Semon T, Kirkby J, Bates P, Seicean S, DeBaun MR, Redline S, Strunk RC. Airway hyperresponsiveness in children with sickle cell anemia. *Chest* 2011;139:563-568.

47. Knight-Madden JM, Forrester TS, Lewis NA, Greenough A. Asthma in children with sickle cell disease and its association with acute chest syndrome. *Thorax* 2005;60:206-210.

48. Boyd JH, DeBaun MR, Morgan WJ, Mao J, Strunk RC. Lower airway obstruction is associated with increased morbidity in children with sickle cell disease. *PediatrPulmonol* 2009;44:290-296.

49. Boyd JH, Macklin EA, Strunk RC, DeBaun MR. Asthma is associated with increased mortality in individuals with sickle cell anemia. *Haematologica* 2007;92:1115-1118.

50. Morris CR. Asthma management: Reinventing the wheel in sickle cell disease. *AmJHematol* 2009;84:234-241.

51. Onyekwere OC, Campbell A, Teshome M, Onyeagoro S, Sylvan C, Akintilo A, Hutchinson S, Ensing G, Gaskin P, Kato G, Rana S, Kwagyan J, Gordeuk V, Williams J, Castro O. Pulmonary hypertension in children and adolescents with sickle cell disease. *PediatrCardiol* 2008;29:309-312.

52. Ataga KI, Key NS. Hypercoagulability in sickle cell disease: New approaches to an old problem. *Hematology AmSocHematolEducProgram* 2007:91-96.

53. Adedeji MO, Cespedes J, Allen K, Subramony C, Hughson MD. Pulmonary thrombotic arteriopathy in patients with sickle cell disease. *ArchPatholLab Med* 2001;125:1436-1441.

54. Rothman SM, Fulling KH, Nelson JS. Sickle cell anemia and central nervous system infarction: A neuropathological study. *AnnNeurol* 1986;20:684-690.

55. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE. Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. *AmJMed* 2006;119:897-811.

56. van Beers EJ, Spronk HM, Ten Cate H, Duits AJ, Brandjes DP, van Esser JW, Biemond BJ, Schnog JB. No association of the hypercoagulable state with sickle cell disease related pulmonary hypertension. *Haematologica* 2008;93:e42-e44.

57. Mokhtar GM, Adly AA, El Alfy MS, Tawfik LM, Khairy AT. N-terminal natriuretic peptide and ventilation-perfusion lung scan in sickle cell disease and thalassemia patients with pulmonary hypertension. *Hemoglobin* 2010;34:78-94.

58. Machado RF. Sickle cell anemia-associated pulmonary arterial hypertension. *JBrasPneumol* 2007;33:583-591.

59. Graham JK, Mosunjac M, Hanzlick RL, Mosunjac M. Sickle cell lung disease and sudden death: A retrospective/prospective study of 21 autopsy cases and literature review. *AmJForensic MedPathol* 2007;28:168-172.

60. Hoeper MM, Lee SH, Voswinckel R, Palazzini M, Jais X, Marinelli A, Barst RJ, Ghofrani HA, Jing ZC, Opitz C, Seyfarth HJ, Halank M, McLaughlin V, Oudiz RJ, Ewert R, Wilkens H, Kluge S, Bremer HC, Baroke E, Rubin LJ. Complications of right heart catheterization procedures in patients with pulmonary hypertension in experienced centers. *JAmCollCardiol* 2006;48:2546-2552.

61. Lee MT, Small T, Khan MA, Rosenzweig EB, Barst RJ, Brittenham GM. Doppler-defined pulmonary hypertension and the risk of death in children with sickle cell disease followed for a mean of three years. *BrJHaematol* 2009;146:437-441.

62. Pashankar FD, Carbonella J, Bazzy-Asaad A, Friedman A. Longitudinal follow up of elevated pulmonary artery pressures in children with sickle cell disease. *BrJHaematol* 2009;144:736-741.

63. Adam S, Jonassaint J, Kruger H, Kail M, Orringer EP, Eckman JR, Ashley-Koch A, Telen MJ, De Castro LM. Surgical and obstetric outcomes in adults with sickle cell disease. *AmJMed* 2008;121:916-921.

64. Villers MS, Jamison MG, De Castro LM, James AH. Morbidity associated with sickle cell disease in pregnancy. *AmJObstetGynecol* 2008;199:125-125.

65. Madden BP. Pulmonary hypertension and pregnancy. *IntJObstetAnesth* 2009;18:156-164.

Table E1. Risk stratification by measurement of the tricuspid regurgitant velocity (TRV) via Doppler Echocardiography in adults with sickle cell disease.

Bibliography:

a. Gladwin, MT, Sachdev, V, Jison, ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004; 350(9):886-95;

b. De Castro, LM, Jonassaint, JC, Graham, FL, et al. Pulmonary hypertension associated with sickle cell disease: clinical and laboratory endpoints and disease outcomes. Am J Hematol 2008; 83(1):19-25;

c. Sachdev, V, Machado, RF, Shizukuda, Y, et al. Diastolic dysfunction is an independent risk factor for death in patients with sickle cell disease. J Am Coll Cardiol 2007; 49(4):472-479;

d. Gordeuk VR, Minniti CP, Nouraie M, et al. Elevated tricuspid regurgitant velocity and decline in exercise capacity over 22 months of follow-up in children and adolescents with sickle cell anemia. Haematologica 2011; 96(1):33.

Ref.	Type of study	Type of patients (n)	Numerator	Denominator	Mortality risk	Comments
a	Observational study evaluating the risk of death	Consecutive patients with SCD (195)	Mortality among patients with a TRV ≥2.5 m/s	Mortality among patients with a TRV <2.5 m/s	RR 10.1 (95% CI 2.2-47.0) 16.1 versus 1.6%	Adults
b	Observational study evaluating the risk of death	Consecutive patients with SCD (125)	Mortality among patients with a TRV ≥2.5 m/s	Mortality among patients with a TRV <2.5 m/s	RR 5.9 (95% CI 1.7-20.8) 21 versus 4 %	Adults
c	Observational study evaluating the risk of death	Consecutive patients with SCD (232)	Mortality among patients with a TRV ≥2.5 m/s	Mortality among patients with a TRV <2.5 m/s	RR 5.1 (95% CI 2.0-13.3) Absolute values not reported	Adults
d	Observational study evaluating the risk of death	Consecutive patients with SCD (149)	Mortality among patients with a TRV ≥2.6 m/s	Mortality among patients with a TRV <2.6 m/s	RR not estimable 0.0 versus 0.8%	Children and adolescents

TRV: Tricuspid regurgitant velocity, as measured by Doppler echocardiography. SCD: Sickle cell disease.

Table E2. Risk stratification by measurement of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels in adults with sickle cell disease.

Bibliography:

a. Machado RF, Anthi A, Steinberg MH, et al. N-terminal pro-brain natriuretic peptide levels and risk of death in sickle cell disease. JAMA 2006; 296(3):310-318.

b. Machado RF, Hildesheim M, Mendelsohn L, et al. NT-pro brain natriuretic peptide levels and the risk of death in the cooperative study of sickle cell disease. Br J Haematol 2011; 154(4):512-520.

Ref	Type of study	Type of patients (n)	Numerator	Denominator	Mortality risk
a	Observational study evaluating the risk of death	Two cohorts, consecutive patients with SCD (230 & 121).	Mortality among patients with an NT-pro-BNP ≥160 pg/mL	Mortality among patients with an NT-pro-BNP <160 pg/mL	RR 5.1 (95% CI 2.1-12.5) in cohort #1 RR 2.9 (95% CI 1.2-6.6) in cohort #2 Absolute values not provided
b	Observational study evaluating the risk of death	Consecutive patients with SCD (758).	Mortality among patients with an NT-pro-BNP ≥160 ng/L	Mortality among patients with an NT-pro-BNP <160 ng/L	Adjusted RR 6.87 (95% CI 3.0-16.0) Absolute values not provided

NT-pro-BNP: N-terminal pro-brain natriuretic peptide. SCD: Sickle cell disease.

Table E3. Evidence table for hydroxyurea in patients with sickle cell disease who have an increased risk for mortality, defined as a tricuspid regurgitant velocity ≥2.5 m/s, an NT-pro-BNP level ≥160 pg/ml, or RHC-confirmed pulmonary hypertension.

Bibliography: 1) Charache S, Terrin M, Moore RD. N Engl J Med 1995; 332:1317-1322; 2) Ferster A, Vermylen C, Cornu G, et al. Blood 1996; 88:1960; 3) Steinberg MH, Barton F, Castro O, et al. JAMA 2003; 289:1645-1651; 4) Steinberg MH, McCarthy WF, Castro O. et cal. Am J Hematol 2010; 85:403; 5) Wang WC, Ware RE, Miller ST, et al. Lancet 2011; 377(9778):1663-1672; and, 6) Ballas SK, Barton FB, Waclawiw MY, et al. Health Qual Life Outcomes 2006: 4:59.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Hydroxyurea	control	Relative (95% CI)	Absolute		
Mortality (9 year) [1]												
1	observational study[1]	no serious limitations	no serious inconsistency	serious indirectness[2]	no serious imprecision	none	46/219 (21.0%)[3]	29/80 (36.3%)[3]	RR 0.58 (0.39 to 0.85)[3]	15 fewer per 100 (from 27 fewer to 4 fewer)[3]	⊕OOO VERY LOW	CRITICAL
Hospitalizations												
2	randomized trials[4]	no serious limitations	no serious inconsistency	serious indirectness[5]	no serious imprecision	none	75/118 (63.6%)	103/119 (86.6%)	RR 0.73 (0.63 to 0.86)	23 fewer per 100 (from 12 fewer to 33 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Frequency of acute chest syndrome												
2	randomized trials[6]	no serious limitations	no serious inconsistency	serious indirectness[5]	no serious imprecision	none	32/248 (12.9%)	69/244 (28.3%)	RR 0.46 (0.31 to 0.67)	15 fewer per 100 (from 8 fewer to 22 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Frequency of sickle cell crises												
2	randomized trials[6]	no serious limitations	no serious inconsistency	serious indirectness[5]	no serious imprecision	none	Not pooled[7]	Not pooled[7]	Not pooled[7]	Not pooled[7]	⊕⊕⊕O MODERATE	CRITICAL
Quality of life (measured with SF-36; scores range from 0-100; higher scores correspond to better health status or well-being)												
1	randomized	no serious	no serious	serious	no serious	none	49.1±2.5	43.7±1.9	–	Mean difference 5.40 (4.73 to 6.07)[9]	⊕⊕⊕O	IMPORTANT

	trials[8]	limitations	inconsistency	indirectness[2]	imprecision		(n=69)[9]	(n=133)[9]			MODERATE	
Stroke (9 year)												
1	observational study[10]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[11]	none	11/219 (5.0%)[12]	3/80 (3.8%)[12]	RR 1.34 (0.38 to 4.68)[12]	13 more per 1000 (from 58 fewer to 58 more)[12]	⊕⊕OO LOW	IMPORTANT
Infection/sepsis (9 year)												
1	observational study[10]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[11]	none	22/219 (13.2%)[13]	9/80 (11.2%)[13]	RR 1.18 (0.58 to 2.38)[13]	20 more per 1000 (from 76 fewer to 93 more)[13]	⊕⊕OO LOW	IMPORTANT
Neoplasia/leukemogenesis (9 year)												
1	observational study[10]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[11]	none	2/219 (0.9%)[14]	0/80 (0.0%)[14]	Not estimatable[14]	Not estimatable[14]	⊕⊕OO LOW	IMPORTANT
Neutropenia (i.e., absolute neutrophil count <1249/mm^3)												
1	Randomized trials[15]	no serious limitations	no serious inconsistency	serious indirectness[2]	no serious imprecision	none	45/96 (46.9%)[16]	18/97 (18.6%)[16]	RR 2.53 (1.58 to 4.03)[16]	283 more per 1000 (from 152 more to 401 more)[16]	⊕OOO VERY LOW	IMPORTANT

[1] Mortality was reported by a randomized trial (Charache S, Terrin ML, Moore RD, et al. N Engl J Med 1995; 332:1317-1322) and an extension study that reported two time-points, 9 years (Steinberg MH, Barton F, Castro O, et al. JAMA 2003; 289:1645-1651) and 17 years (Steinberg MH, McCarthy WF, Castro O. et cal. Am J Hematol 2010; 85:403). We chose to present the 9-year results because, in patients whose 40-month survival is generally only 40%, a 9-year survival benefit is extremely important to patients. During the 2 years of follow-up in the randomized trial, 7 patients died (RR: 0.39 95% CI 0.09–1.70). During the 17 years of observation, 129 of 299 patients died – 69 of those originally randomized to placebo and 60 of those who received HU (RR: 0.84, 95% CI: 0.65–1.09).

[2] Indirectness: The data are from SCD patients with recurrent vasoocclusive crises, but the clinical question and recommendation are for patients with an elevated tricuspid regurgitant velocity, an elevated NT-pro-BNP level, or right heart catheterization-confirmed pulmonary hypertension. The committee recognizes that the impact of this indirectness is highly controversial, with some individuals contending that the indirectness is so minor that it should have no impact on our confidence in the estimated effects and others arguing that the indirectness is so profound that the evidence should not be used. The final judgment of the committee was to compromise; that is, to apply the evidence in our decision-making, but to lower the quality of evidence to reflect the indirectness of the population.

[3] The data presented are from the 9 year time-point. The initial randomized trial found no difference in mortality among patients treated with hydroxyurea, compared with placebo (1.3 versus 3.4 percent, RR 0.39, 95% CI 0.08-1.96). However, at 9 years, the subsequent observational study found a significant decrease in mortality when patients who received hydroxyurea (HU) for ≥1 year were compared with those who either did not receive HU or who received HU for <1 year (21.0 versus 36.3 percent, RR 0.58, 95% CI 0.39-0.85). At 17 years, there was also a significant decrease in mortality when patients who received HU for ≥5 years were compared with those who either did not receive HU or who received HU for <5 years (30.4 versus 51.1 percent, RR 0.60, 95% CI 0.44-0.81). At both 9 and 17 years, there was no significant difference in mortality when patients who received HU for any duration were compared to patients who never received HU.

[4] Hospitalizations were reported by two randomized trials (Ferster A, Vermylen C, Cornu G, et al. Blood 1996; 88:1960-1964 and Wang WC, Ware RE, Miller ST, et al. Lancet 2011; 377(9778):1663-1672).

[5] Indirectness: The clinical question and recommendation are for patients with an elevated tricuspid regurgitant velocity, an elevated NT-pro-BNP level, or right heart catheterization-confirmed pulmonary hypertension, but the evidence is from patients who have three or more painful vasoocclusive crises per year or at least one episode of acute chest syndrome in one trial and from very young children <18 months in the other trial. The committee recognizes that the impact of this indirectness is highly controversial, with some individuals contending that the indirectness is so minor that it should have no impact on our confidence in the estimated effects and others arguing that the indirectness is so profound that the evidence should not be used. The final judgment of the committee was to compromise; that is, to apply the evidence in our decision-making, but to lower the quality of evidence to reflect the indirectness of the population.

[6] Frequency of acute chest syndrome and frequency of sickle cell crises were reported by two randomized trials (Charache S, Terrin M, Moore RD. N Engl J Med 1995; 332:1317-1322 and Wang WC, Ware RE, Miller ST, et al. Lancet 2011; 377(9778):1663-1672).

[7] The data could not be pooled because they were reported differently and the crude data were not provided. In Charache, et al., hydroxyurea decreased the frequency of sickle cell crises from a median of 4.5 crises per year to a median of 2.5 crises per year. In Wang, et al, hydroxyurea decreased sickle cell crises from occurring in 55/97 (57%) of patients to 37/96 (39%) of patients (RR 0.67, 95% CI 0.50-0.92).

[8] The quality of life (QOL) data is from a randomized trial (Charache S, Terrin ML, Moore RD, et al. N Engl J Med 1995; 332:1317-1322 from which the QOL findings were reported in Ballas SK, Barton FB, Waclawiw MY, et al. Health Qual Life Outcomes 2006: 4:59).

[9] Patients who received hydroxyurea (and responded with an increased fetal hemoglobin level) had better social function (74.7±3.1 [n=69] versus 71.2±2.4 [n=133]), pain recall (57.6±3.2 [n=69] versus 49.5±2.3 [n=133]), and general health perception (shown above) at 2 years than patients who received placebo, as measured by short form-36.

[10] The stroke, infection/sepsis, and neoplasia/leukemogenesis data are from an observational study that reported two time-points, 9 years (Steinberg MH, Barton F, Castro O, et al. JAMA 2003; 289:1645-1651) and 17 years (Steinberg MH, McCarthy WF, Castro O. et al. Am J Hematol 2010; 85:403). The observational study is an extension of a randomized trial (Charache S, Terrin ML, Moore RD, et al. N Engl J Med 1995; 332:1317-1322). In addition, a separate randomized trial (Ferster A, Vermylen C, Cornu G, et al. Blood 1996; 88:1960) reported data on stroke and sepsis.

[11] Imprecision: For stroke and sepsis/infection, the ends of the confidence intervals led to different clinical decisions; for neoplasia/leukemogenesis, there were only two events.

[12] The data presented are for the 9 year time-point. The initial randomized trial found no difference in the stroke rate among patients treated with hydroxyurea, compared with placebo (data was not shown). At 9 years, the subsequent observational study found no significant difference in the stroke rate when patients who received hydroxyurea (HU) for ≥1 year were compared with those who either did not receive HU or who received HU for <1 year (5.0 versus 3.8 percent, RR 1.34, 95% CI 0.38-4.68), or when patients who received HU for any duration were compared to patients who never received HU (5.2 versus 2.1 percent, RR 2.42, 95% CI 0.32-18.1). At 17 years, there was similarly no significant difference in the stroke rate when patients who received HU for ≥5 years were compared with those who either did not receive HU or who received HU for <5 years (5.2 versus 6.5 percent, RR 0.80, 95% CI 0.31-2.07), or when patients who received HU for any duration were compared to patients who never received HU. In a separate randomized trial (Ferster A, Vermylen C, Cornu G, et al. Blood 1996; 88:1960), there was no significant difference in stroke when patients treated with HU were compared to those treated with placebo (0/189 [0%] versus 1/185 [0.5%]).

[13] The data presented are for the 9 year time-point. The initial randomized trial did not report the rate of infection or sepsis. At 9 years, the subsequent observational study found no significant difference in the infection/sepsis rate when patients who received HU for ≥1 year were compared with those who either did not receive HU or who received HU for <1 year (13.2 versus 11.2 percent, RR 1.18, 95% CI 0.58-2.38), or when patients who received HU for any duration were compared to patients who never received HU (13.9 versus 6.4 percent, RR 2.18, 95% CI 0.70-6.78). At 17 years, there was similarly no significant difference in the stroke rate when patients who received HU for ≥5 years were compared with those who either did not receive HU or who received HU for <5 years (21.7 versus 16.3 percent, RR 1.33, 95% CI 0.83-2.15), or when patients who received HU for any duration were compared to patients who never received HU (20.4 versus 6.8 percent, RR 3.00, 95% CI 0.98-9.16). In a separate randomized trial (Ferster A, Vermylen C, Cornu G, et al. Blood 1996; 88:1960), there was no significant difference in sepsis when patients treated with HU were compared to those treated with placebo (2/189 [1.0%] versus 5/185 [2.7%]).

[14] The data presented are for the 9 year time-point. The initial randomized trial did not identify any cases of neoplasia. At 9 years, the subsequent observational study found no significant difference in the neoplasia rate when patients who received HU for ≥1 year were compared with those who either did not receive HU or who received HU for <1 year (2/219 [0.9%] versus 0/80 [0%]), or when patients who received HU for any duration were compared to patients who never received HU (2/252 [0.8%] versus 0/47 [0%]). At 17 years, there was similarly no significant difference in the stroke rate when patients who received HU for ≥5 years were compared with those who either did not receive HU or who received HU for <5 years (1.7 versus 0.5 percent, RR 3.20, 95% CI 0.29-34.9), or when patients who received HU for any duration were compared to patients who never received HU (3/225 [0.8%] versus 0/44[0%]).

[15] Bone marrow suppression was reported by three randomized trials (Charache S, Terrin ML, Moore RD, et al. N Engl J Med 1995; 332:1317-1322); Ferster A, Vermylen C, Cornu G, et al. Blood 1996; 88:1960; and, Wang WC, Ware RE, Miller ST, et al. Lancet 2011; 377(9778):1663-1672).

[16] The data presented are from Wang, et al. Ferster et al., reported a significant decrease in the neutrophil count from 12.47x109/L to 8.90 x109/L following the initiation of HU. And, Charache et al. incompletely reported "bone marrow suppression" saying, "Treatment was temporarily stopped in almost all patients in the hydroxyurea group because of marrow depression; blood counts usually recovered within two weeks", but not providing any data. None of the trials found a significant decrease in platelets or red blood cells.

Table E4. Evidence table for chronic transfusion therapy in patients with sickle cell disease who have an increased risk for mortality, defined as a tricuspid regurgitant velocity (TRV) ≥2.5 m/s, an NT-Pro-BNP level ≥160 pg/ml, or RHC-confirmed pulmonary hypertension.

Bibliography: 1) Adams RJ, Brambilla D. N Engl J Med 2005; 353:2769; 2) Adams RJ, McKie VC, Hsu L, et al. N Engl J Med 1998; 339:5; 3) Wang WC, Morales KH, Scher CD, et al. J Pediatr 2005; 147:244; and, 4) Miller ST, Wright E, Abboud M, et al. J Pediatr 2001; 139:785, 5) Files B, Brambilla D, Kutlar A, et al. J Pediatr Hematol Oncol 2002; 24:284.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Chronic transfusion	control	Relative (95% CI)	Absolute		
Mortality												
2	randomized trials[1]	no serious limitations	no serious inconsistency	serious indirectness[2]	very serious imprecision[3]	none	1/101 (1.0%)[4]	0/108 (0.0%)[4]	RR 3.32 (0.13 to 84.01)[4]	1 more per 100 (from 2.5 fewer to 5.4 more)[4]	⊕OOO VERY LOW	CRITICAL
Stroke												
2	randomized trials[1]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[5]	none	1/101 (1.0%)[4]	13/108 (12.0%)[4]	RR 0.10 (0.02 to 0.58)[4]	11 fewer per 100 (from 4 fewer to 18 fewer)[4]	⊕⊕OO LOW	CRITICAL
Hospitalizations												
0	-	-	-	-	-	-	-	-	-	-	–	CRITICAL
Frequency of acute chest syndrome												
1	randomized trial[6]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[7]	none	2/59 (3.4%)	14/65 (21.5%)	RR 0.16 (0.04 to 0.66)	18 fewer per 100 (from 6 fewer to 30 fewer)	⊕⊕OO LOW	CRITICAL
Frequency of sickle cell crises												

1	randomized trial[6]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[8]	none	6/59 (10.2%)	12/65 (18.5%)	RR 0.55 (0.22 to 1.37)	8 fewer per 100 (from 20 fewer to 4 more)	⊕⊕OO LOW	CRITICAL
Growth velocity for weight												
1	randomized trial[9]	no serious limitations	no serious inconsistency	serious indirectness[2]	no serious imprecision	none	0.41±0.22 kg/mo (n=42)	0.25±0.10 kg/mo (n=36)	Not estimatable	Mean difference 0.16 (0.09 to 0.23)	⊕⊕⊕O MODERATE	IMPORTANT
Minor adverse effects (febrile reactions, allergic reactions, hemolytic reactions, and volume overload)												
2	randomized trials[1]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[10]	none	15/101 (15.0%)	0/108 (0.0%)	Not estimatable	15 more per 100 (from 8 more to 23 more)	⊕⊕OO LOW	IMPORTANT
Alloimmunizations												
2	randomized trials[1]	no serious limitations	no serious inconsistency	serious indirectness[2]	serious imprecision[11]	none	11/101 (11.0%)	0/108 (0.0%)	Not estimatable	11 more per 100 (from 5 more to 18 more)	⊕⊕OO LOW	IMPORTANT
Iron overload (serum ferritin >3000 ng/mL)												
1	series[12]	no serious limitations	no serious inconsistency	serious indirectness[13]	serious imprecision[14]	none	14/45 (31%)	uncontrolled	Not estimatable	Not estimatable	⊕OOO VERY LOW	IMPORTANT

[1] Mortality, stroke rate, and adverse effects were measured in two randomized trials, STOP-1 (Adams RJ, McKie VC, Hsu L, et al. N Engl J Med 1998; 339:5) and STOP-2 (Adams RJ, Brambilla D. N Engl J Med 2005; 353:2769).

[2] The clinical question and recommendation are intended for SCD patients with right heart catheterization-confirmed pulmonary hypertension, a tricuspid regurgitant velocity ≥2.5 m/s, or an NT-pro-BNP level ≥160 pg/ml, but the evidence is from SCD patients who have an increased risk of stroke. The committee recognizes that the impact of this indirectness is highly controversial, with some individuals contending that the indirectness is so minor that it should have no impact on our confidence in the estimated effects and others arguing that the indirectness is so profound that the evidence should not be used. The final judgment of the committee was to compromise; that is, to apply the evidence in our decision-making, but to lower the quality of evidence to reflect the indirectness of the population.

[3] There was only one event in the STOP-1 and STOP-2 trials combined, plus the ends of the confidence interval lead to differing conclusions.

[4] We did not perform our own meta-analysis. Rather, we relied upon a published meta-analysis by Hirst C and Wang WC. Cochrane Database System Rev 2002; 1:CD003146.

[5] There were only four events in the STOP-1 and STOP-2 trials combined.

[6] The acute chest syndrome and vasoocclusive crises data are from the STOP-1 trial (Adams RJ, McKie VC, Hsu L, et al. N Engl J Med 1998; 339:5), but were reported separately (Miller ST, Wright E, Abboud M, et al. J Pediatr 2001).

[7] There were only 16 events in the STOP-1 trial.

[8] There were only 18 events in the STOP-1 trial and the ends of the confidence interval lead to different clinical decisions.

[9] The growth data are from the STOP-1 trial (Adams RJ, McKie VC, Hsu L, et al. N Engl J Med 1998; 339:5), but were reported separately (Wang WC, Morales KH, Scher CD, et al. J Pediatr 2005; 147:244).

[10] There were only 15 events in the STOP-1 and STOP-2 trials combined.

[11] There were only 11 events in the STOP-1 and STOP-2 trials combined.

[12] An uncontrolled, longitudinal follow-up of patients in the STOP trial who received chronic transfusions (Files B, Brambilla D, Kutlar A, et al. J Pediatr Hematol Oncol 2002; 24:284).

[13] The clinical question and recommendation are intended for SCD patients with right heart catheterization-confirmed pulmonary hypertension, a tricuspid regurgitant velocity ≥2.5 m/s, or an NT-pro-BNP level ≥160 pg/ml, but the evidence is from SCD patients who have an increased risk of stroke. In addition, the outcome is a surrogate (ferritin level) for a patient-important outcome (liver fibrosis).

[14] There were only 45 patients in the series.

Table E5. Evidence table for lifelong anticoagulant therapy in patients with confirmed sickle cell disease-related pulmonary hypertension and venous thromboembolism.

Bibliography: 1) Kearon C, Gent M, Hirsh J, et al. N Engl J Med 1999; 340:901; 2) Palereti G, Cosmi B, Legnani C, et al. N Engl J Med 2006; 355:1780; 3) Ridker PM, Goldhaber SZ, Danielson E, et al. N Engl J Med 2003; 348:1425; 4) Schulman S, Granqvist S, Holmstrom M, et al. N Engl J Med 1997; 336:393.

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Indefinite anticoagulant therapy	control	Relative (95% CI)	Absolute		
Mortality												
4	randomized trials	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	16/570 (2.8%)	28/550 (5.1%)	RR 0.56 (0.31 to 1.01)	23 fewer per 1000 (from 47 fewer to 1 more)	⊕⊕OO LOW	CRITICAL
Recurrent venous thromboembolism												
4	randomized trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	very strong association[3]	20/570 (3.5%)	95/550 (17.3%)	RR 0.16 (0.06 to 0.41)	139 fewer per 1000 (from 174 fewer to 103 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Major bleeding												
4	randomized trials	no serious limitations	no serious inconsistency	serious[1]	no serious imprecision	strong association[4]	19/570 (3.3%)	5/550 (0.9%)	RR 3.14 (1.27 to 7.77)	24 more per 1000 (from 7 more to 43 more)	⊕⊕⊕O MODERATE	IMPORTANT

[1] The recommendation is intended for patients with confirmed SCD-related PH and venous thromboembolism, but the evidence is from heterogenous populations with venous thromboembolism.

[2] While the point estimate suggests that there is a clinically important mortality benefit, the ends of the confidence interval lead to opposite conclusions.

[3] The incidence of recurrent venous thromboembolic events was decreased approximately 6-times; however, these data did not influence the grading since the studies had other limitations.

[4] The incidence of major bleeding was increased approximately 3-times; however, these data did not influence the grading since the studies had other limitations.

Table E6. Pre-specified search strategy and study selection criteria for the use of the Tricuspid Regurgitant Velocity (TRV) to assess mortality risk in patients with sickle cell disease.

MEDLINE (PubMed) search strategy to identify evidence:

Step	Search term	Result
1	Anemia, sickle cell [mh]	16,602
2	Sickle cell anemia [tw]	16,434
3	Sickle cell disease [tw]	8,392
4	#1 OR #2 OR #3	18,961
5	Echocardiography, Doppler [mh]	20,329
6	Echocardiogram [tw]	7,716
7	Echocardiography [tw]	115,559
8	#5 OR #6 OR #7	118,833
9	#4 AND #8	186

The same search terms were adapted to strategies to search the Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews.

Study selection criteria

Studies were selected if they (a) enrolled patients with sickle cell disease, (b) compared patients who had their TRV measured via Doppler echocardiography to patients who did not have their TRV measured, and (c) measured patient-important outcomes. Alternatively, studies were selected if they measured the mortality risk among patients who had an elevated TRV, relative to those who had a normal TRV.

Table E7. Pre-specified search strategy and study selection criteria for the use of the N-terminal brain natriuretic peptide (NT-pro-BNP) to assess mortality risk in adults with sickle cell disease.

MEDLINE (PubMed) search strategy to identify evidence:

Step	Search term	Result
1	Anemia, sickle cell [mh]	16,602
2	Sickle cell anemia [tw]	16,434
3	Sickle cell disease [tw]	8,392
4	#1 OR #2 OR #3	18,961
5	Natriuretic peptide, brain [mh]	8,096
6	N-terminal pro-BNP [tw]	132
7	NT-proBNP [tw]	449
8	NTproBNP [tw]	135
9	proBNP [tw]	2,482
10	#5 OR #6 OR #7 OR #8 OR #9	8,882
11	#4 AND #10	14

*The same search terms were adapted to strategies to search the Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews.

Study selection criteria

Studies were selected if they (a) enrolled patients with sickle cell disease, (b) compared patients who had their NT-pro-BNP level measured to patients who did not have their NT-pro-BNP level measured, and (c) measured patient-important outcomes. Alternatively, studies were selected if they measured the mortality risk among patients who had an elevated NT-pro-BNP level, relative to those who had a normal NT-pro-BNP level.

Table E8. Pre-specified search strategy and study selection criteria for the use of hydroxyurea in patients with sickle cell disease and either RHC-confirmed pulmonary hypertension, a tricuspid regurgitant velocity ≥2.5 m/s, or an NT-Pro-BNP level ≥160 pg/ml.

MEDLINE (PubMed) search strategy to identify evidence:

Step	Search term	Result
1	Anemia, sickle cell [mh]	16,602
2	Sickle cell anemia [tw]	16,434
3	Sickle cell disease [tw]	8,392
4	#1 OR #2 OR #3	18,961
5	hydroxyurea [mh]	6,883
6	hydroxyurea [tw]	9,557
7	#5 OR #6	9,557
8	#4 AND #7	845

*The same search terms were adapted to strategies to search the Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews.

Study selection criteria

Studies were selected if they (a) enrolled patients with sickle cell disease, (b) compared patients who received hydroxyurea to patients who received no therapy or placebo, and (c) measured patient-important outcomes. Given the anticipated large volume of evidence, we initially sought published systematic reviews that included trials that met these selection criteria, with the plan to search step-wise for randomized trials and then observational studies if no suitable systematic reviews were identified. If such systematic reviews were identified, we planned to combine the systematic review with relevant studies published after the systematic review. Studies identified in this fashion were to be supplemented with unsystematic observations from the committee members.

Table E9. Pre-specified search strategy and study selection criteria for the use of chronic transfusion therapy in patients with sickle cell disease and either RHC-confirmed pulmonary hypertension, a tricuspid regurgitant velocity ≥2.5 m/s, or an NT-pro-BNP level ≥160 pg/ml.

MEDLINE (PubMed) search strategy to identify evidence:

Step	Search term	Result
1	Anemia, sickle cell [mh]	16,602
2	Sickle cell anemia [tw]	16,434
3	Sickle cell disease [tw]	8,392
4	#1 OR #2 OR #3	18,961
5	blood transfusion [mh]	75,968
6	blood transfusion [tw]	68,270
7	transfusion [tw]	101,139
8	red cell transfusion [tw]	582
9	5 OR #6 OR #7 OR #8	105,258
10	#4 AND #9	1,916

*The same search terms were adapted to strategies to search the Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews.

Study selection criteria

Studies were selected if they (a) enrolled patients with sickle cell disease, (b) compared patients who received chronic transfusion therapy to patients who received no chronic transfusion therapy, and (c) measured patient-important outcomes. Given the anticipated large volume of evidence, we initially sought published systematic reviews that included trials that met these selection criteria, with the plan search step-wise for randomized trials and then observational studies if no suitable systematic reviews were identified. If such systematic reviews were identified, we planned to combine the systematic review with relevant studies published after the systematic review. Studies identified in this fashion were to be supplemented with unsystematic observations from the committee members.

Table E10. Pre-specified search strategy and study selection criteria for the use of lifelong anticoagulant therapy in patients with sickle cell disease-related pulmonary hypertension and thromboembolic disease.

MEDLINE (PubMed) search strategy to identify evidence:

Step	Search term	Result
1	Anemia, sickle cell [mh]	16,602
2	Sickle cell anemia [tw]	16,434
3	Sickle cell disease [tw]	8,392
4	#1 OR #2 OR #3	18,961
5	hypertension, pulmonary [mh]	22,697
6	pulmonary hypertension [tw]	30,458
7	pulmonary artery hypertension [tw]	741
8	pulmonary arterial hypertension [tw]	4731
9	#5 OR #6 OR #7 OR #8	31,975
10	Pulmonary embolism [mh]	29,237
11	Venous thromboembolism [mh]	2,919
12	Venous thrombosis [mh]	41,591
13	#10 OR #11 OR #12	66,507
14	warfarin [mh]	12,823
15	heparin [mh]	53,868
16	anticoagulation [tw]	21,211
17	#14 OR #15 OR #16	78,967
18	#4 AND #9 AND #13 AND #17	0

*The same search terms were adapted to strategies to search the Cochrane Central Register of Controlled Clinical Trials, and the Cochrane Database of Systematic Reviews.

Study selection criteria

Studies were selected if they (a) enrolled patients with sickle cell disease-related pulmonary hypertension and venous thromboembolic disease, (b) compared patients who received lifelong anticoagulant therapy to patients who received a shorter duration of anticoagulant therapy, and (c) measured patient-important outcomes.

Figure E1. Flow of information through a systematic review that sought evidence relevant to the use of the Tricuspid Regurgitant Velocity (TRV) to assess mortality risk in patients with sickle cell disease.

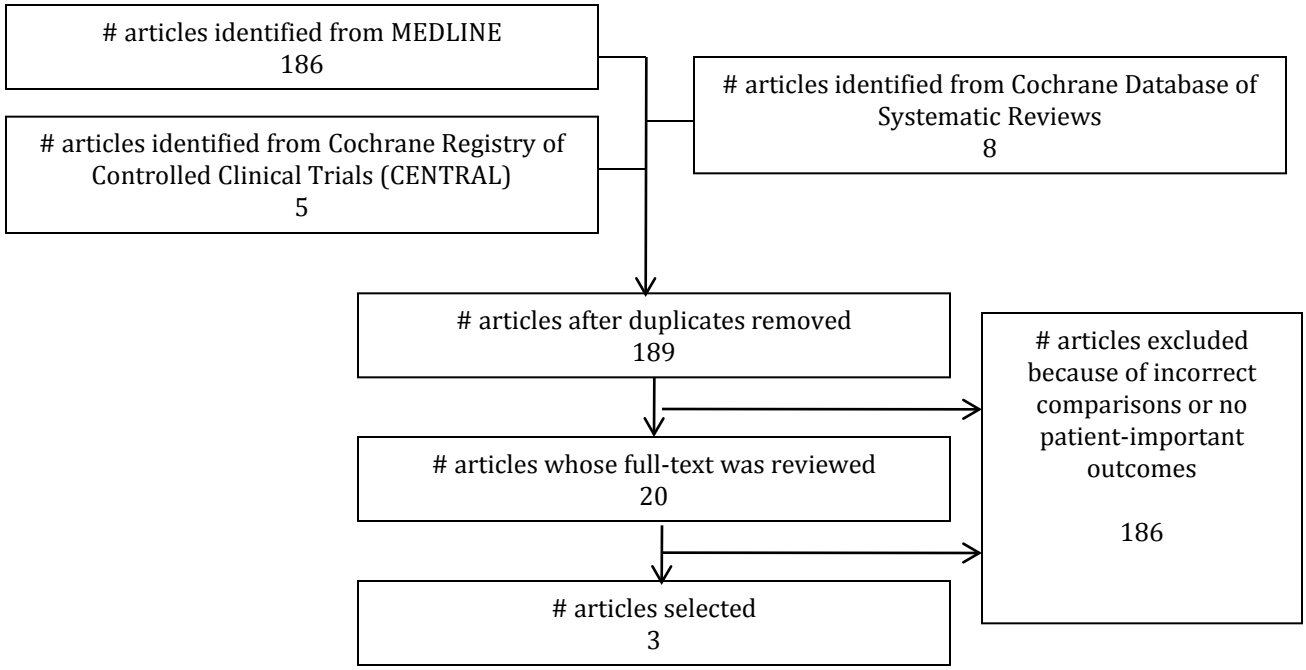

Figure E2. Flow of information through a systematic review that sought evidence relevant to the use of the N-terminal pro-brain natriuretic peptide (NT-pro-BNP) to assess mortality risk in patients with sickle cell disease.

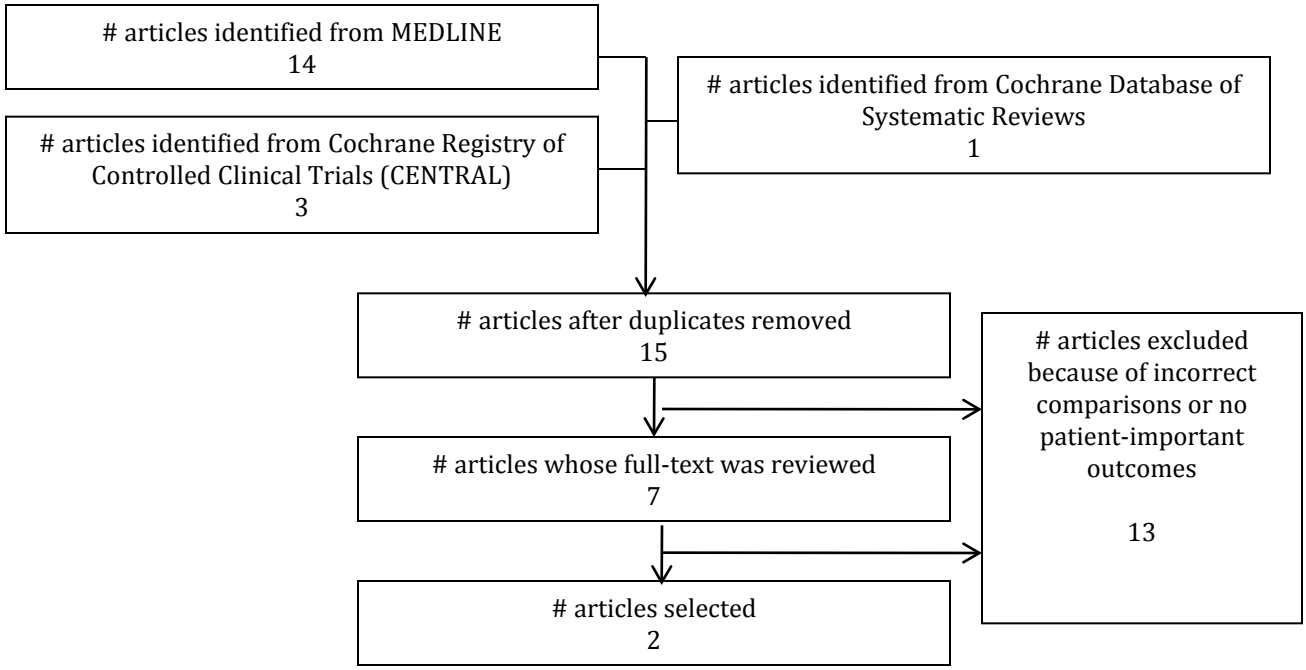

Figure E3. Flow of information through a systematic review that sought evidence relevant to the use of hydroxyurea in patients with sickle cell disease and either confirmed pulmonary hypertension, a tricuspid regurgitant velocity ≥2.5 m/s, or an NT-pro-BNP level ≥160 pg/ml.

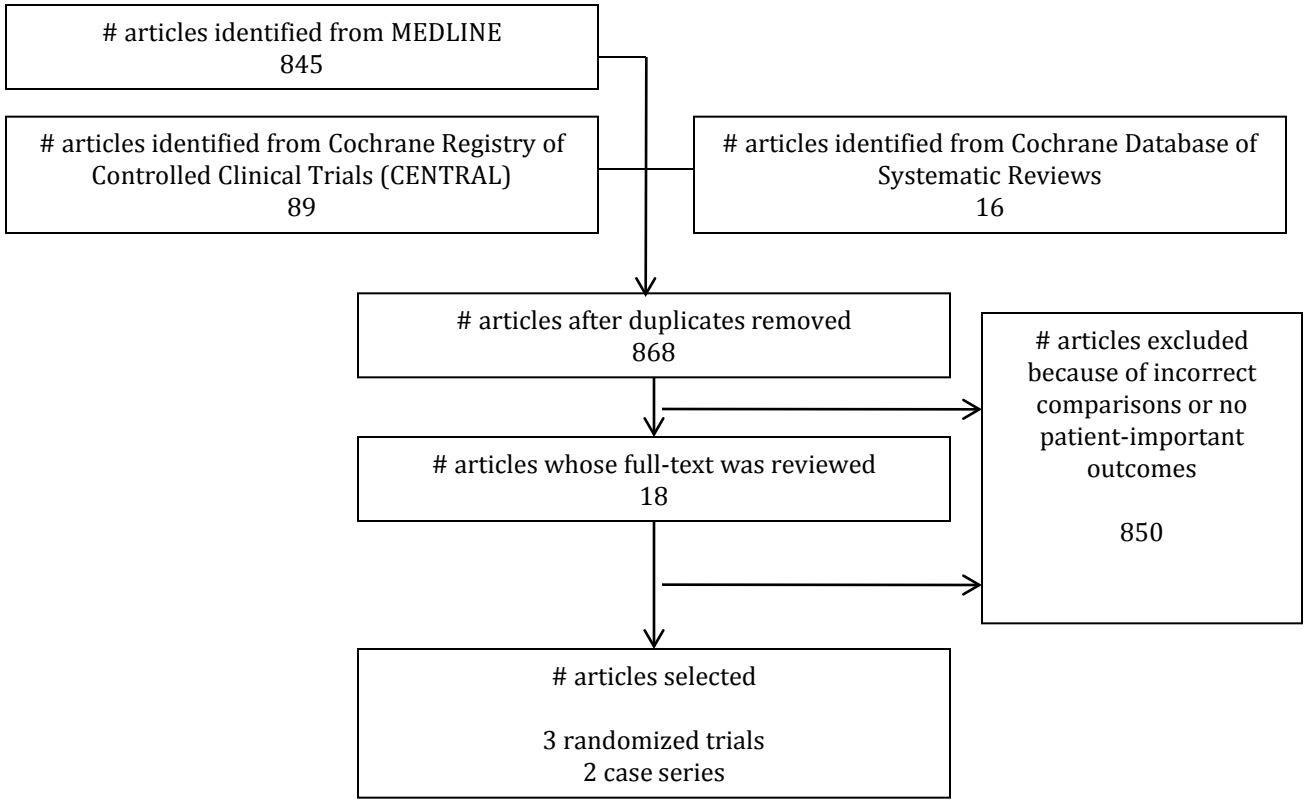

Figure E4. Flow of information through a systematic review that sought evidence relevant to chronic transfusion therapy in patients with sickle cell disease and either confirmed pulmonary hypertension, a tricuspid regurgitant velocity ≥2.5 m/s, or an NT-pro-BNP level ≥160 pg/ml.

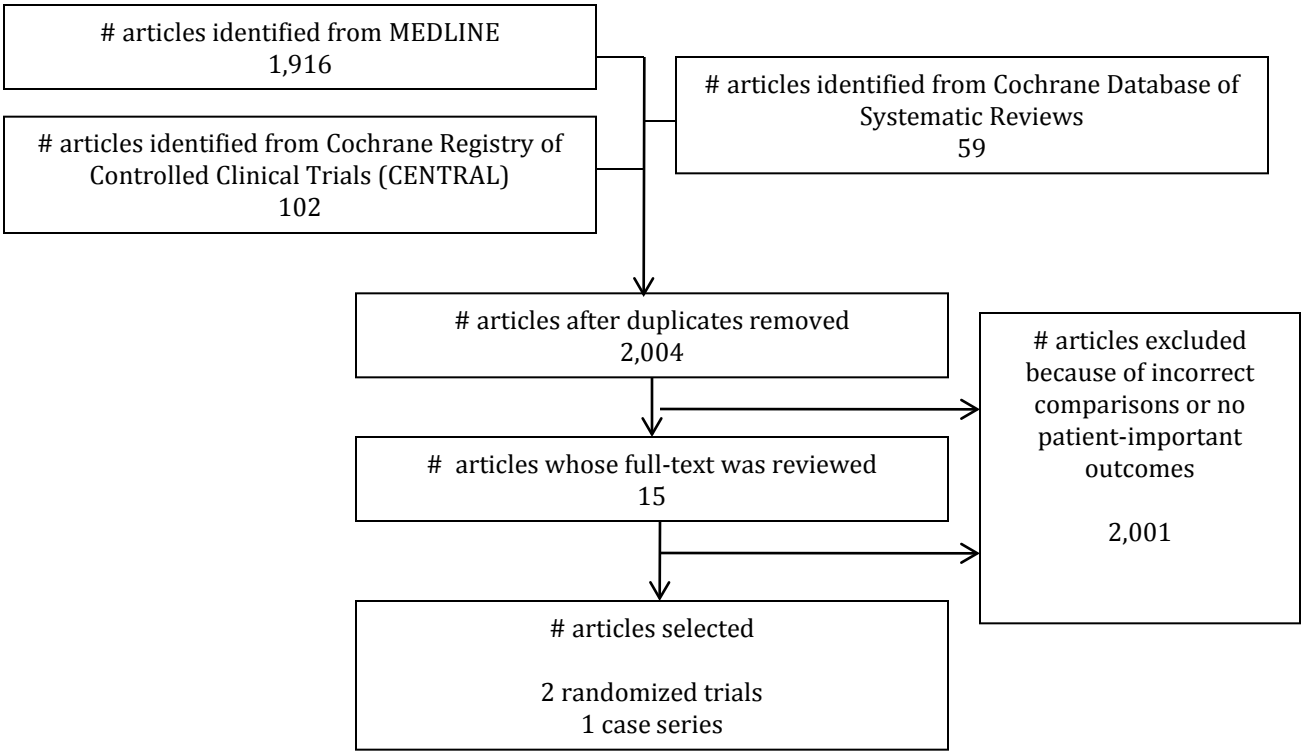

Figure E5. Flow of information through a systematic review that sought evidence relevant to targeted pulmonary artery hypertension (PAH) therapy in patients with sickle cell disease and confirmed PAH.