blood advances

American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease

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Background: Prevention and management of end-organ disease represent major challenges facing providers of children and adults with sickle cell disease (SCD). Uncertainty and variability in the screening, diagnosis, and management of cardiopulmonary and renal complications in SCD lead to varying outcomes for affected individuals.

Objective: These evidence-based guidelines of the American Society of Hematology (ASH) are intended to support patients, clinicians, and other health care professionals in their decisions about screening, diagnosis, and management of cardiopulmonary and renal complications of SCD.

Methods: ASH formed a multidisciplinary guideline panel that included 2 patient representatives and was balanced to minimize potential bias from conflicts of interest. The Mayo Evidence-Based Practice Research Program supported the guideline development process, including performing systematic evidence reviews up to September 2017. The panel prioritized clinical questions and outcomes according to their importance for clinicians and patients. The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, including GRADE evidence-to-decision frameworks, to assess evidence and make recommendations, which were subject to public comment.

Results: The panel agreed on 10 recommendations for screening, diagnosis, and management of cardiopulmonary and renal complications of SCD. Recommendations related to anticoagulation duration for adults with SCD and venous thromboembolism were also developed.

Conclusions: Most recommendations were conditional due to a paucity of direct, high-quality evidence for outcomes of interest. Future research was identified, including the need for prospective studies to better understand the natural history of cardiopulmonary and renal disease, their relationship to patient-important outcomes, and optimal management.

Summary of recommendations

The management of end-organ damage represents a major challenge facing individuals living with sickle cell disease (SCD), the majority of whom now survive into adulthood.[1] The prevention and treatment of SCD-related complications linked to cardiopulmonary and kidney disease are especially challenging for providers and thus are the focus of these guidelines. The American Society of Hematology (ASH) guideline panel addressed specific questions related to screening, diagnosis, and management of these complications, with special emphasis on the following areas: screening, monitoring, and management of pulmonary hypertension (PH) and pulmonary arterial hypertension (PAH); screening for chronic lung disease;

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screening for sleep-disordered breathing; management of hypertension; management of proteinuria and chronic kidney disease; and anticoagulation management of venous thromboembolism (VTE).

These guidelines are based on original and updated systematic reviews of evidence conducted under the direction of the Mayo Evidence-Based Practice Research Program. The panel followed best practice for guideline development recommended by the Institute of Medicine and the Guidelines International Network (GIN).[2-5] The panel used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach[6-12] to assess the certainty in the evidence and formulate recommendations.

Interpretation of strong and conditional recommendations

The strength of a recommendation is expressed as either strong ("the guideline panel recommends…") or conditional ("the guideline panel suggests…") and has the following interpretation.

Strong recommendation

- For patients: Most individuals in this situation would want the recommended course of action, and only a small proportion would not.
- For clinicians: Most individuals should follow the recommended course of action. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.
- For policy makers: The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.
- For researchers: The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation. On occasion, a strong recommendation is based on low or very low certainty in the evidence. In such instances, further research may provide important information that alters the recommendations.

Conditional recommendation

- For patients: The majority of individuals in this situation would want the suggested course of action, but many would not. Decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences.
- For clinicians: Different choices will be appropriate for individual patients, and you must help each patient arrive at a management decision consistent with the patient's values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences.
- For policy makers: Policy-making will require substantial debate and involvement of various stakeholders. Performance measures about the suggested course of action should focus on whether an appropriate decision-making process is duly documented.
- For researchers: This recommendation is likely to be strengthened (for future updates or adaptation) by additional research. An evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps.

Interpretation of good practice statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.[13] Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Recommendations

Screening echocardiography

RECOMMENDATION 1. In asymptomatic children and adults with SCD, the ASH guideline panel *suggests against* performing a routine screening echocardiogram (ECHO) to identify PH (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. A comprehensive history and review of systems are essential parts of the diagnostic strategy to identify patients with SCD for whom a low threshold should be considered for obtaining an ECHO.
2. Although the panel suggests no routine screening ECHO for asymptomatic patients with SCD, the following signs or symptoms may warrant a consultation with a PH expert or a diagnostic ECHO for patients who are otherwise in steady state (ie, not experiencing acute complications such as painful episodes or acute chest syndrome) to evaluate for PH:
   - Dyspnea at rest or with exertion that is out of proportion to known condition, increased compared with baseline or unexplained;
   - Hypoxemia at rest or with exertion that is out of proportion to known condition, increased compared with baseline or unexplained;
   - Chest pain at rest or with exertion that is out of proportion to known condition, increased compared with baseline or unexplained;
   - Increase in exercise limitation compared with baseline that is unexplained by other factors;
   - History of recurrent hypoxemia at rest or with exertion;
   - Evidence for sleep-disordered breathing with or without hypoxemia;
   - History of syncope or presyncope;
   - Evidence for loud P2 component of second heart sound or unexpected or new murmur on examination;
   - Signs of heart failure and/or fluid overload on examination;
   - History of pulmonary embolism.
3. A diagnostic ECHO should be considered for patients with SCD who also have comorbid conditions (eg, connective tissue disease) or disease complications (eg, leg ulcers, priapism) known to be associated with PH when signs or symptoms of PH are present.
4. Evaluation of 6-minute walk distance (6MWD) and/or N-terminal pro-B-type natriuretic peptide (NT-BNP) may also be useful in individuals with SCD and suspected PH based on an abnormal ECHO (eg, elevated tricuspid regurgitant jet velocity [TRJV]).

5. PH is defined hemodynamically by right-heart catheterization using a mean pulmonary artery pressure threshold of >20 mm Hg, which has recently been reduced from ≥25 mm Hg. However, the mean pulmonary artery pressure alone does not distinguish PAH from other forms of PH. Additional criteria for the diagnosis of PAH include a pulmonary artery wedge pressure of ≤15 mm Hg and a pulmonary vascular resistance of ≥3 Wood units (240 dyn × seconds × cm^{-5}).

Management of abnormal echocardiography

RECOMMENDATION 2a. For asymptomatic children and adults with SCD and an isolated peak TRJV of ≥2.5 to 2.9 m/s, the ASH guideline panel *suggests against* right-heart catheterization (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

RECOMMENDATION 2b. For children and adults with SCD and a peak TRJV of ≥2.5 m/s who also have a reduced 6MWD and/or elevated NT-BNP, the ASH guideline panel *suggests* right-heart catheterization (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. Repeating ECHOs demonstrating elevated peak TRJV are important prior to referral for right-heart catheterization under the guidance of a PH expert because reproducibility of TRJV measurements may vary due to technical factors, severity of anemia, or increased cardiac output.
2. For patients with peak TRJV of ≥2.5 m/s who are asymptomatic, the addition of NT-BNP and 6MWD may help to improve the diagnostic accuracy for PH. Abnormal cutoff values for NT-BNP and 6MWD have not been firmly determined for patients with SCD. However, NT-BNP values of ≥160 pg/mL and 6MWD values of <333 m represent reasonable thresholds for adults with SCD based on published studies in this population. Referrals for right-heart catheterization should also account for clinical judgment and discussion with a PH expert.
3. For patients with peak TRJV of ≥2.5 m/s who have normal 6MWD and NT-BNP, serial noninvasive monitoring with ECHOs should be considered if clinically indicated (see list of symptoms in remarks for recommendation 1).
4. Consultation with a PH expert regarding the need for a right-heart catheterization should be considered for patients with TRJV of >2.9 m/s who have normal 6MWD and NT-BNP or other findings on ECHO, in addition to elevated peak TRJV, which could suggest significant PH (eg, right-atrial enlargement, pericardial effusion, right-ventricular failure, or septal flattening).
5. PH is defined hemodynamically by right-heart catheterization using a mean pulmonary artery pressure threshold of >20 mm Hg, which represents a recent reduction from ≥25 mm Hg. However, the mean pulmonary artery pressure alone does not distinguish PAH from other forms of PH. Additional criteria for the diagnosis of PAH include a pulmonary artery wedge pressure of ≤15 mm Hg and a pulmonary vascular resistance of ≥3 Wood units (240 dyn × seconds × cm^{-5}).

Treatment of PAH

RECOMMENDATION 3a. For children and adults with SCD who do not have PAH confirmed by right-heart catheterization, the ASH guideline panel *recommends against* the use of PAH-specific therapies (strong recommendation, low certainty in the evidence about effects ⊕⊕◯◯).[14]

RECOMMENDATION 3b. For children and adults with SCD and a diagnosis of PAH confirmed by right-heart catheterization, the ASH guideline panel *suggests* the use of PAH-specific therapies under the care of a PH specialist given the lack of alternative treatment options and associated high morbidity and mortality (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

1. Although different subtypes of PH may develop in individuals with SCD, this recommendation refers only to PAH and not other subtypes of PH.
2. Treatment options may differ based on the subtype of PH as classified by findings on right-heart catheterization and clinical evaluation by a PH specialist.
3. PH is defined hemodynamically by right-heart catheterization using a mean pulmonary artery pressure threshold of >20 mm Hg, which was recently reduced from ≥25 mm Hg. However, the mean pulmonary artery pressure alone does not distinguish PAH from other forms of PH. Additional criteria for the diagnosis of PAH include a pulmonary artery wedge pressure of ≤15 mm Hg and a pulmonary vascular resistance of ≥3 Wood units (240 dyn × seconds × cm^{-5}).
4. Improvements in cardiopulmonary hemodynamics, as determined by right-heart catheterization, and clinical status, such as a change in PAH symptoms or functional status, initiation of other PAH drugs, or diuretic requirements (eg, in the setting of right-heart failure), are important additional end points for monitoring the benefits of PAH-specific therapy started for patients with PAH confirmed by right-heart catheterization.
5. It is appropriate to refer patients with SCD and PAH confirmed by right-heart catheterization to treatment centers with expertise in PH and SCD, given the possibility of increased side effects (eg, pain) with PAH-specific therapy such as sildenafil.
6. It is important to consider initiation and/or optimization of disease-modifying therapy such as hydroxyurea or chronic transfusions for patients with PAH confirmed by right-heart catheterization.
7. It is important to consider potential differences in the pathophysiologic basis of PAH (eg, contribution of chronic anemia and high-output cardiac states) and differences in side-effect profiles (eg, pain) when determining treatment options for PAH confirmed by right-heart catheterization in SCD.
8. The recommendation for PAH-specific therapy in SCD applies to patients with SCD who have no other clear reason for their PAH confirmed by right-heart catheterization (eg, obstructive sleep apnea, significant lung disease, left-heart failure).

Screening pulmonary function testing

RECOMMENDATION 4. For asymptomatic children and adults with SCD, the ASH guideline panel *suggests against* performing routine screening pulmonary function testing (PFT) (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. A comprehensive respiratory history and review of systems are an essential part of the diagnostic strategy to identify patients with

SCD for whom a low threshold should be considered for obtaining PFT.

2. Although the panel suggests no routine screening PFT for asymptomatic patients with SCD, the following signs, symptoms, or diagnoses may warrant a diagnostic PFT for patients who are otherwise in steady state (ie, healthy) to evaluate for abnormal lung function:
   - Wheezing or increased cough at rest or with exertion;
   - Wheezing or increased cough during episodes of acute upper respiratory infection;
   - Dyspnea at rest or with exertion that is increased compared with baseline or that is unexplained;
   - Chest pain at rest or with exertion that is out of proportion to known condition, that is increased compared with baseline or that is unexplained;
   - Increase in exercise limitation compared with baseline or that is unexplained (eg, sickle cell pain or musculoskeletal disease);
   - Abnormal 6-minute walk test defined by either reduced 6MWD or oxygen desaturation during test;
   - History of recurrent hypoxemia at rest or with exertion;
   - History of syncope or presyncope;
   - History of recurrent acute chest syndrome;
   - History of pulmonary embolism.
3. Comprehensive PFT should include full spirometry as well as complete evaluation of diffusion capacity and lung volumes.

Screening for sleep-disordered breathing

RECOMMENDATION 5. For asymptomatic children and adults with SCD, the ASH guideline panel *suggests against* screening with formal polysomnography (sleep study) for sleep-disordered breathing (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. A comprehensive sleep history and review of systems are essential parts of the diagnostic strategy to identify patients with SCD for whom a low threshold should be considered for obtaining a formal sleep study. Whenever appropriate, validated tools (eg, Epworth Sleepiness Scale or Pittsburgh Sleep Quality Index) should be used to further identify patients who should be considered for formal sleep testing.
2. Although the panel suggests no routine screening sleep study in asymptomatic patients with SCD, the following signs or symptoms may warrant a diagnostic sleep study for patients who are otherwise in steady state (ie, healthy) to evaluate for sleep-disordered breathing:
   - Snoring;
   - Witnessed apneas or respiratory pauses;
   - Nonrestorative sleep and/or excessive daytime sleepiness;
   - Obesity;
   - Early morning headaches;
   - Unexplained desaturation or hypoxemia during sleep, while awake, or with exertion;
   - Carbon dioxide retention on arterial blood gas;
   - History of poorly controlled hypertension or congestive heart failure;
   - History of nocturnal enuresis in an older child (eg, ≥10 years old);
   - History of recurrent priapism or frequent daytime or nocturnal vaso-occlusive pain;
   - History of PH confirmed by right-heart catheterization;
   - History of ischemic stroke without evidence for vasculopathy;
   - History of memory loss, difficulty with concentration, or unexplained episodes of mental confusion;
   - Symptoms of attention deficit-hyperactivity disorder, poor academic achievement, and performance or behavior problems in children.
3. For patients for whom a sleep study is warranted, the American Academy of Sleep Medicine guidelines currently recommend in-laboratory, "attended" sleep studies for children and for adults with chronic disease and known comorbidities, specifically cardiopulmonary. Additionally, it is important for formal sleep studies to be conducted in a certified sleep center that meets standards as required by accreditation groups (The Joint Commission, American Academy of Sleep Medicine).

Management of albuminuria

RECOMMENDATION 6. For children and adults with SCD and albuminuria, the ASH guideline panel *suggests* the use of angiotensin-converting enzyme inhibitors (ACEi's) or angiotensin II receptor blockers (ARBs) (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. The initiation of ACEi's and ARBs for patients with SCD requires adequate follow-up and monitoring of side effects (eg, hyperkalemia, cough, hypotension).
2. As recommended by the Kidney Disease Improving Global Outcomes guidelines for the general population, the following attention to baseline and changes in renal function are appropriate when prescribing ACEi's or ARBs for patients with SCD:
   - Start medication at a lower dose in individuals with a glomerular filtration rate (GFR) of <45 mL/min/1.73 m^2;
   - Assess GFR and measure serum potassium within 1 week of starting medication or following any dose escalation;
   - Temporarily suspend medication during interval illness, planned IV radiocontrast administration, or bowel preparation for colonoscopy or prior to major surgery.
3. The ASH guideline panel did not assess the evidence to inform decisions about albuminuria screening. The Kidney Disease Improving Global Outcomes guidelines state that albuminuria should be confirmed by either a first morning urine sample or 2 consecutive untimed urine samples. The National Heart, Lung, and Blood Institute (NHLBI) 2014 expert panel report states

that screening for albuminuria should occur annually beginning at 10 years of age for patients with SCD. However, more recent evidence suggests a potential benefit of earlier screening.[15,16]

Renal transplant for end-stage renal disease

RECOMMENDATION 7. For children and adults with SCD and advanced chronic kidney disease or end-stage renal disease, the ASH guideline panel *suggests* referral for renal transplant (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. It is essential that providers adhere closely to general guidelines and recommendations for perioperative transfusion requirements for surgery in adults with SCD.[17]
2. Judicious use of corticosteroids as part of the posttransplant immunosuppression regimen is advised given the potential relationship between steroid exposure and vaso-occlusive pain for patients with SCD.

Use of hydroxyurea and erythropoiesis-stimulating agents for chronic kidney disease

RECOMMENDATION 8. In children and adults with SCD and worsening anemia associated with chronic kidney disease, the ASH guideline panel *suggests* combination therapy with hydroxyurea and erythropoiesis-stimulating agents (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. This recommendation is based on evidence available only from patients with hemoglobin SS or S/β^0 thalassemia, for whom erythropoiesis-stimulating-agent dosing in the studies reviewed was higher than that typically used in the general population.
2. For patients already on steady-state hydroxyurea, erythropoiesis-stimulating agents are appropriate in the setting of chronic kidney disease when there is a simultaneous drop in hemoglobin and absolute reticulocyte count.
3. Optimizing adherence to hydroxyurea therapy while on erythropoiesis-stimulating agents may help maximize fetal hemoglobin responses for patients treated with combination therapy.
4. For patients with SCD undergoing treatment with erythropoiesis-stimulating agents, a conservative hemoglobin threshold is advised above which treatment should be decreased or held. The ASH guideline panel advises not exceeding a hemoglobin threshold of 10 g/dL (hematocrit of 30%) to reduce the risk of vaso-occlusion–related complications, stroke, and VTE.

Management of blood pressure

RECOMMENDATION 9. For adults with SCD, the ASH guideline panel *recommends* a blood pressure goal of ≤130/80 mm Hg over a goal of ≤140/90 mm Hg (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks:

1. There is a lack of evidence to suggest that blood pressure goals should differ for individuals with and without SCD. The impact of hypertension on patient-important outcomes is significant for African American individuals and therefore requires adherence to guidelines developed for the general population independent of having SCD.

Management of VTE

RECOMMENDATION 10a. For adults with SCD and first unprovoked VTE, the ASH guideline panel *suggests* indefinite anticoagulation over shorter, defined periods of anticoagulation (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

RECOMMENDATION 10b. For adults with SCD and first, surgically, or nonsurgically provoked VTE, the ASH guideline panel *suggests* defined periods of anticoagulation (3-6 months) over indefinite anticoagulation (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

RECOMMENDATION 10c. In adults with SCD and recurrent provoked VTE, the ASH guideline panel *suggests* indefinite anticoagulation over shorter, defined periods of anticoagulation (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

1. The panel considers SCD to be a chronic underlying risk factor for initial and recurrent VTE.
2. The type, strength, and duration of the provoking events are important to take into account when considering indefinite anticoagulation for patients with SCD and recurrent provoked VTE.
3. The decision to remain on anticoagulation should be made through shared decision-making based on patient values/preferences and be subject to regular reevaluation.
4. Discussions of the benefits vs harms of anticoagulation, as well as duration of therapy, should consider bleeding risk, including from existing use of other medications that could further increase risk of bleeding (eg, nonsteroidal anti-inflammatory drugs).
5. Indefinite anticoagulation is not recommended for first provoked VTE such as secondary to a central venous line. However, anticoagulation should continue as long as any provoking risk factor, including central venous line, continues to be present.
6. Anticoagulant selection for patients with SCD should account for comorbidities such as renal impairment that may affect drug clearance. For example, because of the potential for decreased efficacy of edoxaban in the setting of increased creatinine clearance (CrCl), alternative anticoagulants should be considered for SCD patients with CrCl of >95 mL/min.

Values and preferences. Overall, the ASH guideline panel on cardiopulmonary and renal disease placed a higher value on outcomes related to mortality, survival, progression of disease-related complications, and health-related quality of life when making recommendations. Panel members considered the balance between the benefits and harms for all recommendations, especially those related to screening procedures and direct therapies. However, the panel recognized that there could be variability among patients and providers in their values and preferences related to both patient-important outcomes and these recommendations.

Explanations and other considerations. These recommendations take into consideration acceptability, feasibility, cost-effectiveness, and impact on health equity. The ASH guideline panel acknowledged variability in patient and provider knowledge as well as variability in their perceptions of tradeoffs between harms vs benefits when developing these recommendations.

Good practice statements

Good practice statement 1. Given the risk for cardiopulmonary disease in individuals with SCD, it is good practice to routinely take a targeted history for signs and symptoms that might indicate a need for further evaluation, including consideration for a diagnostic ECHO.

Good practice statement 2. It is good practice to consult with a cardiologist, pulmonologist, or an expert in PH when interpreting results of right-heart catheterization and considering therapeutic options based on type of PH and presumed pathophysiology.

Good practice statement 3. It is good practice to base decisions about the need for right-heart catheterization on ECHOs obtained at steady state and not during acute illness, such as hospitalization for pain or acute chest syndrome.

Good practice statement 4. It is good practice to adopt a multidisciplinary (ie, hematology, PH specialist, pulmonary medicine, or cardiology) approach when considering PAH-specific therapies for SCD patients who have PAH confirmed by right-heart catheterization.

Good practice statement 5. It is good practice for providers to understand the importance of educating patients, discussing patient and caregiver priorities, and incorporating shared decision-making when considering obtaining PFT.

Introduction

Aim(s) of these guidelines and specific objectives

The purpose of these guidelines is to provide evidence-based recommendations for cardiopulmonary and renal complications of SCD. The primary goals of these guidelines are to review, critically appraise, and implement evidence-based recommendations aimed at improving the diagnosis and management of cardiopulmonary and renal complications of SCD, while minimizing harms associated with unnecessary screening, testing and interventions. Through improved provider and patient education using the available evidence and evidence-based recommendations, these guidelines aim to provide clinical decision support for shared decision-making that will result in improved cardiopulmonary and renal outcomes for individuals with SCD.

The target audience includes patients, hematologists, general practitioners, internists, other clinicians, and decision-makers. Policy makers interested in these guidelines include those involved in developing local, national, or international programs with the goal of improving the lives of people living with SCD. This document may also serve as the basis for adaptation by local, regional, or national guideline panels.

Description of the health problem(s)

As the majority of people living with SCD in developed nations survive into adulthood, a major challenge in disease management is the treatment and prevention of end-organ disease.[1] Although SCD complications may occur in any organ, this panel specifically addressed practice gaps related to cardiopulmonary and renal complications of the disease. Given the broad scope of topics, the panel chose to focus on providing guidance to questions related to screening and management that would have the most impact on the day-to-day care of people living with SCD. The panel's questions focused on screening, diagnosis, and management recommendations.

The approach to the diagnosis and management of cardiopulmonary complications in SCD, such as PH, abnormal lung function, and sleep-disordered breathing, remains difficult. The role of the screening ECHO to assess for PAH in asymptomatic patients with SCD has been a particularly controversial topic. Establishing thresholds for right-heart catheterization to confirm PAH and determining treatment of confirmed PAH in SCD represent other areas of uncertainty. For these reasons, the panel believed that a thorough evaluation of the published data was necessary to assist clinicians and other stakeholders in understanding these aspects of PAH. Similarly, the panel evaluated the evidence related to screening for sleep-disordered breathing and the use of screening PFT in asymptomatic individuals, given growing concerns about sleep-disordered breathing and chronic lung disease in SCD.

There is increasing recognition that renal disease affects morbidity and mortality as individuals with SCD age. Several aspects of renal disease in SCD remain poorly understood, including the diagnosis and management of early and late renal disease and its complications.[18] This led the panel to evaluate evidence for both the management of proteinuria and the approach to renal transplant for individuals with SCD and end-stage renal disease. Despite the importance of hydroxyurea as disease-modifying therapy in SCD, its use for patients with chronic kidney disease may be challenging due to its suppressive effects on red blood cell production in the setting of decreased endogenous erythropoietin production. Thus, the panel also evaluated evidence for the use of combination therapy with erythropoiesis-stimulating agents and hydroxyurea in SCD patients with chronic kidney disease. Relative systemic hypertension has been a well-recognized complication of SCD since it was defined during the Cooperative Study of Sickle Cell Disease, yet guidance on what blood pressure thresholds should be targeted in the SCD population is lacking. As such, the panel evaluated the evidence to determine the optimal blood pressure threshold above which to initiate therapy for patients with SCD.

Finally, there is increasing recognition that VTE, including pulmonary embolism, is a frequent complication of SCD and contributes to significant morbidity in individuals with SCD. The risk of VTE recurrence in individuals with SCD is also high. Therefore, the panel chose to address questions related to the appropriate duration of anticoagulation therapy in individuals with SCD in the setting of either provoked or unprovoked VTE events.

Methods

The guideline panel developed and graded the recommendations and assessed the certainty of the supporting evidence following the GRADE approach.[6-12] The overall guideline development process, including funding of the work, panel formation, management of conflicts of interest, internal and external review, and organizational approval, was guided by ASH policies and procedures derived from the GIN-McMaster Guideline Development Checklist (http://cebgrade.mcmaster.ca/guidecheck.html) and was intended to meet recommendations for trustworthy guidelines by the Institute of Medicine and the GIN.[2-5]

Organization, panel composition, planning, and coordination

The work of this panel was coordinated with 4 other guideline panels (addressing other aspects of SCD) by ASH and the Mayo Evidence-Based Practice Research Center (funded by ASH under a paid agreement). Project oversight was provided by a coordination panel, which reported to the ASH Guideline Oversight Subcommittee. ASH vetted individuals and appointed them to the guideline panel. The Mayo Center vetted and retained researchers to conduct systematic reviews of evidence and coordinate the guideline development process, including the use of the GRADE approach. The membership of the panels and the Mayo Center team is described in supplemental File 1.

The panel included adult and pediatric hematologists, cardiologists, pulmonologists, and nephrologists who all had clinical and research expertise on the guideline topic. The panel also included 2 patient representatives. Two co-chairs were content experts, and another co-chair was a nephrologist and expert in guideline development methodology.

In addition to synthesizing evidence systematically, the Mayo Center supported the guideline development process, including determining methods, preparing meeting materials, and participating in panel discussions of evidence. The panel's work was done using web-based tools (www.surveymonkey.com and www.gradepro.org) and via face-to-face and online meetings.

Guideline funding and management of conflicts of interest

Development of these guidelines was wholly funded by ASH, a nonprofit medical specialty society that represents hematologists. Most members of the guideline panel were members of ASH. ASH staff supported panel appointments and coordinated meetings but had no role in choosing the guideline questions or determining the recommendations.

Members of the guideline panel received travel reimbursement for attendance at in-person meetings, and the patient representatives received honoraria of $100 per day for in-person meetings and $25 per conference call. The panelists received no other payments. Through the Mayo Clinic Evidence-Based Practice Research Program, some researchers who contributed to the systematic evidence reviews received salary or grant support. Other researchers participated to fulfill requirements of an academic degree or program.

Conflicts of interest of all participants were managed through disclosure, panel composition, and recusal, according to recommendations of the Institute of Medicine[19] and the GIN.[5] Participants disclosed all financial and nonfinancial interests relevant to the guideline topic. ASH staff and the ASH Guideline Oversight Subcommittee reviewed the disclosures and composed the guideline panel to include a diversity of expertise and perspectives and avoid a majority of the panel having the same or similar conflicts. Greatest attention was given to direct financial conflicts with for-profit companies that could be directly affected by the guidelines. A majority of the panel, including the co-chairs, had no such conflicts. None of the Mayo-affiliated researchers who contributed to the systematic evidence reviews or who supported the guideline development process had any such conflicts.

Recusal was also used to manage conflicts of interest.[5,20-22] During deliberations about recommendations, any panel member with a current, direct financial conflict in a commercial entity that marketed any product that could be affected by a specific recommendation participated in discussions about the evidence and clinical context but was recused from making judgments or voting about individual domains (eg, magnitude of desirable consequences) and the direction and strength of the recommendation. The evidence-to-decision (EtD) framework for each recommendation describes which individuals were recused from making judgments about each recommendation.

In 2019, after the guideline panel had agreed on recommendations, it was discovered that 1 panelist had a direct financial conflict with an affected company (a meal in 2017) that had not been previously reported. Members of the Guideline Oversight Subcommittee reviewed the guidelines in relation to this late disclosure and agreed that this conflict was unlikely to have influenced any of the recommendations.

Supplemental File 2 provides the complete disclosure-of-interest forms of all panel members. In part A of the forms, individuals disclosed direct financial interests for 2 years prior to appointment; in part B, indirect financial interests were disclosed; and in part C, not mainly financial interests were disclosed. Part D describes new interests disclosed by individuals after appointment. Part E summarizes ASH decisions about which interests were judged to be conflicts and how they were managed, including through recusal.

Supplemental File 3 provides the complete disclosure-of-interest forms of researchers who contributed to these guidelines.

Table 1. Questions prioritized by the ASH Guideline Panel on Cardiopulmonary and Kidney Disease

Prioritized questions
Q1. Should screening ECHO vs no screening be performed to identify PH in asymptomatic patients with SCD?
Q2. Should right-heart catheterization vs serial noninvasive monitoring be performed for patients with SCD suspected to have PH based on an abnormal ECHO?
Q3. Should targeted therapy for PAH or chronic transfusions vs no targeted therapy or chronic transfusions be used for patients with SCD and right-heart catheterization–defined PAH?
Q4. Should screening for abnormal pulmonary function vs no screening be performed for asymptomatic patients with SCD?
Q5. Should screening using formal polysomnography (sleep study) for sleep-disordered breathing vs no screening be performed for asymptomatic patients with SCD?
Q6. Should angiotensin inhibition vs no angiotensin inhibition be used for patients with SCD and albuminuria?
Q7. Should proceeding with renal transplant vs remaining on dialysis be considered for patients with SCD and end-stage renal disease?
Q8. Should combination therapy with hydroxyurea and erythropoiesis-stimulating agents vs hydroxyurea alone be used for patients with SCD and nephropathy?
Q9. Should the target blood pressure in adults with SCD be ≤130/80 mm Hg vs ≤140/90 mm Hg?
Q10. Should indefinite anticoagulation vs short-term (≤6 mo) anticoagulation be used for adults with SCD who have first unprovoked, first provoked, or recurrent provoked VTE?

Formulating specific clinical questions and determining outcomes of interest

The panel met in person and via conference calls to generate possible questions to address. The panel then used an iterative process to prioritize the questions described in Table 1.

The panel selected outcomes of interest for each question a priori, following the approach described in detail elsewhere.[23] In brief, the panel first brainstormed all possible outcomes before rating their relative importance for decision-making following the GRADE

approach.[23] While acknowledging considerable variation in the impact on patient outcomes, the panel considered the outcomes in Table 2 critical for clinical decision-making across questions.

Evidence review and development of recommendations

For each guideline question, the Mayo Center prepared a GRADE EtD framework, using the GRADEpro Guideline Development Tool.[6,7,12] The EtD table summarized the results of systematic reviews of the literature that were updated or performed for this guideline. The EtD table addressed effects of interventions, resource utilization (cost-effectiveness), values and preferences (relative importance of outcomes), equity, acceptability, and feasibility. The guideline panel reviewed draft EtD tables before, during, and after the guideline panel meeting and made suggestions for corrections and identified missing evidence. To ensure that recent studies were not missed in addition to searches presented in supplemental File 4, panel members were asked to suggest any studies that might have been considered missed and fulfilled the inclusion criteria for the individual questions.

Under the direction of the Mayo Center, researchers followed the general methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions (handbook.cochrane.org) for conducting updated or new systematic reviews of intervention effects. When existing reviews were used, judgments of the original authors about risk of bias were either randomly checked for accuracy and accepted or conducted de novo if they were not available or not reproducible. For new reviews, risk of bias was assessed at the health outcome level using the Cochrane Collaboration's risk-of-bias tool for randomized trials or nonrandomized studies. In addition to conducting systematic reviews of intervention effects, the researchers searched for evidence related to baseline risks, values, preferences, and costs, and summarized findings within the EtD frameworks.[6,7,12] Subsequently, the certainty of the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed for each effect estimate of the outcomes of interest following the GRADE approach based on the following domains: risk of bias, imprecision, inconsistency, indirectness, risk of publication bias, presence of large effects, dose-response relationship, and an assessment of the effect of residual, opposing confounding. The certainty was categorized into 4 levels ranging from very low to high.[8-10]

During a 2-day in-person meeting followed by online communication and conference calls, the panel developed clinical recommendations based on the evidence summarized in the EtD tables. For each recommendation, the panel took a population perspective and came to consensus on the following: the certainty in the evidence, the balance of benefits and harms of the compared management options, and the assumptions about the values and preferences associated with the decision. The panel also explicitly took into account the extent of resource use associated with alternative management options. The panel agreed on the recommendations (including direction and strength), remarks, and qualifications by consensus or, in rare instances, by voting (an 80% majority was required for a strong recommendation), based on the balance of all desirable and undesirable consequences. The final guidelines, including recommendations, were reviewed and approved by all members of the panel. The approach is described in detail in an article describing the methods of development.

Methodological considerations for screening questions

In addition to the known challenge related to the paucity of evidence in the SCD population, the ASH cardiopulmonary and kidney disease panel faced special challenges when addressing screening questions. The GRADE approach has laid out guidance about judging the certainty of evidence and making recommendations about health care–related tests and diagnostic strategies.[12,24-26] However, this approach typically addresses a framework to support decision-making when data based on direct comparison are lacking but test accuracy results are available.[12,27] During review of the body of evidence informing screening questions, it became evident that test accuracy results either are lacking or, when available, have serious limitations hindering the panel's ability to make judgments. Consequently, the systematic review team identified any other data that could potentially support developing recommendations. These additional data were mostly in the form of association studies that reported specific results of some patient-important outcomes among patients who received the screening tests.

To allow consistent decisions among the different screening questions, the ASH guideline panel developed a framework that supported forming recommendations based on association studies. The framework was informed by the GRADE diagnosis EtD framework, the World Health Organization, and the US Preventive Services Task Force criteria and manual for screening tests.[12,28,29] Table 3 summarizes the framework and the criteria used to determine when screening is justified.

The cardiopulmonary and kidney disease panel placed high value on meeting 2 criteria for the screening test to be considered: (1) the panel must have high certainty that individuals with a positive screening test would receive different management than those with a negative test and (2) the panel must have high certainty that there is an effective treatment/management for the condition that improves outcomes if administered earlier rather than when the condition is clinically apparent.

Interpretation of strong and conditional recommendations

The recommendations are labeled as either "strong" or "conditional" according to the GRADE approach. The words "the ASH guideline panel recommends" are used for strong recommendations, and "the ASH guideline panel suggests" for conditional recommendations. Table 4 provides GRADE's interpretation of strong and conditional recommendations by patients, clinicians, health care policy makers, and researchers.

Interpretation of good practice statements

As described by the GRADE Guidance Group, good practice statements endorse interventions or practices that the guideline panel agreed have unequivocal net benefit yet may not be widely recognized or used.[13] Good practice statements in these guidelines are not based on a systematic review of available evidence. Nevertheless, they may be interpreted as strong recommendations.

Document review

Draft recommendations were reviewed by all members of the panel, revised, and then made available online on 24 September 2018 or for external review by stakeholders including allied organizations, other

Table 2. Outcomes prioritized by the ASH Guideline Panel on Cardiopulmonary and Kidney Disease

Critical outcomes for decision-making
Q1.
• Test accuracy of ECHO to diagnose PH compared with cardiac catheterization
• Mortality
• Change in patient management
• Patient desire to know about abnormal screening
• Rate of cardiac catheterization
• Anxiety related to abnormal test
Q2.
• Appropriate treatment in appropriate patients
• Mortality
• Time to diagnosis
• Complications related to cardiac catheterization (eg, bleeding, clots, infection, arrhythmia, and pain)
• Progression of cardiac dysfunction
Q3.
• Mortality
• Quality of life
• PH therapy side effects (eg, hypotension, flushing/headache, injection-related pain, liver dysfunction)
• Oxygen requirement
• Dyspnea, exercise tolerance, 6MWD, and NYHA functional class
• Transfusion side effects (eg, alloimmunization, need for and complications related to IV access, iron overload)
• Change in pain episodes
• Burden of treatment
• Cardiac function
• Hospitalization rate
• Syncope
Q4.
• Rate of cardiac catheterization
• Mortality
• Change in patient management
• Patient desire to know about abnormal screening
• Anxiety related to abnormal test
Q5.
• Quality of life
• Mortality
• Cardiovascular outcomes
• Acute and chronic pain rate
• Acute chest syndrome rate
• Nocturnal enuresis
• Priapism
• Burden of treatment
• Patient desire to know about abnormal screening
Q6.
• End-stage renal disease
• Mortality
• Quality of life/function
• Burden of treatment
• Worsening proteinuria
• Hospitalization rate
• Hyperkalemia
• Hypotension
• Acute kidney injury
Q7.
• Overall mortality
• Transplant organ survival
• Quality of life
• Transplant-related mortality
• Treatment burden related to transplant vs dialysis
• Improvement in anemia
• Hospitalization
• Pain episodes
Q8.
• Mortality
• Quality of life
• Improvement in renal function
• Improvement in hemoglobin
• Acute and chronic pain rate
• Burden of treatment
• Bone marrow suppression
• Hypertension
• Thrombosis
Q9.
• Mortality
• Stroke
• Cardiovascular events
• Worsening renal function
• Quality of life/function
• Hypotension
• Burden of treatment (eg, emergency department visits, adherence, monitoring)
• Medication side effects
• Hospitalization rate
Q10.
• Major bleeding
• Risk of recurrent pulmonary embolism
• Risk of recurrent deep vein thrombosis
• Quality of life
• Mortality
• SCD-related complications
• Treatment burden
• Postthrombotic syndrome

medical professionals, patients, and the public. Seventeen individuals or organizations submitted comments. The document was revised to address pertinent comments, but no changes were made

to recommendations. The guidelines were reviewed by the ASH Guideline Oversight Subcommittee on 21 August 2019. On 27 August 2019, the ASH Committee on Quality confirmed that the defined guideline development process was followed, and on 3 September 2019, the officers of the ASH Executive Committee approved submission of the guidelines for publication under the imprimatur of ASH. The guidelines were then subjected to peer review by *Blood Advances*.

How to use these guidelines

ASH guidelines are primarily intended to help clinicians make decisions about diagnostic and treatment alternatives. Other purposes are to inform policy, education, and advocacy and to state future research needs. They may also be used by patients. These guidelines are not intended to serve or be construed as a standard of care. Clinicians must make decisions on the basis of the clinical presentation of each individual patient, ideally through a shared process that considers the patient's values and preferences with respect to the anticipated outcomes of the chosen option. Decisions may be constrained by the realities of a specific clinical setting and local resources, including but not limited to institutional policies, time limitations, or availability of treatments. These guidelines may not include all appropriate methods of care for the clinical scenarios described. As science advances and new evidence becomes available, recommendations may become outdated. Following these guidelines cannot guarantee successful outcomes. ASH does not warrant or guarantee any products described in these guidelines.

Statements about the underlying values and preferences as well as qualifying remarks accompanying each recommendation are its integral parts and serve to facilitate more accurate interpretation. They should never be omitted when quoting or translating recommendations from these guidelines. Implementation of the guidelines will be facilitated by forthcoming decision aids.

Recommendations

Screening echocardiography

Question: Should screening ECHO vs no screening be performed to identify PH in asymptomatic patients with SCD?

Recommendation 1

In asymptomatic children and adults with SCD, the ASH guideline panel *suggests against* performing routine screening ECHO to identify PH (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Good practice statement

The panel agreed that given the risk for cardiopulmonary disease in individuals with SCD, it is good practice to routinely take a targeted history for signs and symptoms that might indicate a need for further evaluation, including consideration for a diagnostic ECHO.

Remarks:

1. A comprehensive history and review of systems are essential parts of the diagnostic strategy to identify patients with SCD for whom a low threshold should be considered for obtaining an ECHO.
2. Although the panel suggests no routine screening ECHO for asymptomatic patients with SCD, the following signs or symptoms may warrant a consultation with a PH expert or a diagnostic ECHO for patients who are otherwise in steady state (ie, not experiencing acute complications such as painful episodes or acute chest syndrome) to evaluate for PH:
   - Dyspnea at rest or with exertion that is out of proportion to known condition, increased compared with baseline or unexplained;
   - Hypoxemia at rest or with exertion that is out of proportion to known condition, increased compared with baseline or unexplained;
   - Chest pain at rest or with exertion that is out of proportion to known condition, increased compared with baseline or unexplained;
   - Increase in exercise limitation compared with baseline that is unexplained by other factors;
   - History of recurrent hypoxemia at rest or with exertion;
   - Evidence for sleep-disordered breathing with or without hypoxemia;
   - History of syncope or presyncope;
   - Evidence for loud P2 component of second heart sound or unexpected or new murmur on examination;
   - Signs of heart failure and/or fluid overload on examination;
   - History of pulmonary embolism.
3. A diagnostic ECHO should be considered for patients with SCD who also have comorbid conditions (eg, connective tissue disease) or disease complications (eg, leg ulcers, priapism) known to be associated with PH when signs or symptoms of PH are present.
4. Evaluation of 6MWD and/or NT-BNP may also be useful in individuals with SCD and suspected PH based on an abnormal ECHO (eg, elevated TRJV).
5. PH is defined hemodynamically by right-heart catheterization using a mean pulmonary artery pressure threshold of $>$20 mm Hg, which has recently been reduced from $\geq$25 mm Hg. However, the mean pulmonary artery pressure alone does not distinguish PAH from other forms of PH. Additional criteria for the diagnosis of PAH include a pulmonary artery wedge pressure of $\leq$15 mm Hg and a pulmonary vascular resistance of $\geq$3 Wood units (240 dyn $\times$ seconds $\times$ cm^{-5}).

Background. Elevated peak TRJV, as measured by Doppler ECHO, is common among adults with SCD and is associated with an increased risk of mortality.[30] Elevated peak TRJV may also predict PH, which is diagnosed by right-heart catheterization. Despite the utility of Doppler ECHO as a diagnostic aid for

Table 3. Making decisions about screening: when is screening justified

Criterion
The condition should be an important health problem (either sufficiently prevalent or having significant consequences)
Individuals with a positive screening test would get a different management than those with a negative test
The condition being screened for should have a natural history that is understood and a recognized latent or early symptomatic stage
There should be an effective treatment/management for the condition that improves outcomes if administered before the condition is clinically apparent
The improvement in outcomes based on management according to screening results should outweigh harms of screening
There should be high- or moderate-quality evidence for a sufficient accuracy of the test (acceptable low rates of false-positives and -negatives)
Screening should be cost-effective
Screening should be acceptable to patients
Screening should be feasible to implement

individuals with signs and symptoms suggestive of PH, its utility as a screening tool for PH in asymptomatic individuals with SCD is not clear. The impact of results from screening on patient-important outcomes is also unknown.

Summary of the evidence. There were no direct head-to-head comparisons of benefits and harms in children and adults with SCD who underwent screening ECHO to identify PH vs those who did not. Instead, studies that included patients with SCD were examined for the following outcomes of interest: mortality, accuracy of ECHO as a screening tool to identify PH, quality of life, and functional capacity and other outcomes (eg, anxiety related to abnormal test, patient desire to know about abnormal results, rate of cardiac catheterization, and change in patient management). The relationship between mortality and peak TRJV elevation measured on screening ECHO was reported in 15 studies, which demonstrated an increased risk of death associated with elevated peak TRJV $\geq$2.5 m/s.[30-44] A total of 4 studies (total n = 1082) estimated the prevalence of PH and PAH among patients undergoing screening ECHO and reported on the accuracy of ECHO to screen for both complications.[37,39,40,45] Of those who underwent ECHO screening, 231 with peak TRJV elevation proceeded to right-heart catheterization. Among all patients undergoing screening ECHO, PH was confirmed by right-heart catheterization in 96 of 1082 (8.9%), with PAH diagnosed in 48 of 1082 (4.4%). Among patients with TRJV elevation, PH was confirmed in 96 of 231 (41.6%), with PAH diagnosed in 48 of 231 (20.8%). The remaining patients did not proceed with further investigation to confirm or rule out PH. It is important to note that the diagnosis of PH and PAH by right-heart catheterization in these studies does not reflect the decision made at the recent 6th World Symposium of Pulmonary Hypertension to lower the mean pulmonary arterial pressure threshold from $\geq$25 mm Hg to >20 mm Hg.[46] There were no direct comparisons of quality of life or functional capacity in children and adults who underwent ECHO screening for PH vs those who did not. However, 1 study (n = 398) examined the relationship of TRJV elevation to New York Heart Association (NYHA) classification and 6MWD.[40] No direct comparisons were available for all other clinical outcomes.

Benefits, harms, and burden. Despite the absence of data demonstrating direct benefits of ECHO screening, possible benefits could include the potential to use peak TRJV as a general prognostic biomarker for mortality and the opportunity to optimize disease-modifying therapy for patients with SCD based on results of screening (considered by the panel to be small to moderate for adults and minimal for children). Screening ECHOs may also provide additional information beyond peak TRJV measurements, such as that gained from examining parameters that reflect left-ventricular diastolic dysfunction or right-ventricular size and function. Obtaining ECHOs for these indications, however, should be considered separately from its use as a screening tool for PH in asymptomatic patients with SCD but may be reasonable for patients with signs, symptoms, or a clinical course that warrants evaluation.

Despite the absence of data on direct harms related to ECHO screening, possible harms could include the inability to know how to use the information obtained from screening, the potential for anxiety for patients as a result of the information, the potential for increasing health care costs from excessive and unnecessary testing without impacting changes in management, the risks associated with inappropriate referral for right-heart

Table 4. Interpretation of strong and conditional recommendations

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not; decision aids may be useful in helping patients to make decisions consistent with their individual risks, values, and preferences
Clinicians	Most individuals should follow the recommended course of action; formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences	Different choices will be appropriate for individual patients, and you must help each patient arrive at a management decision consistent with the patient's values and preferences; decision aids may be useful in helping individuals to make decisions consistent with their individual risks, values, and preferences
Policy makers	The recommendation can be adopted as policy in most situations; adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator	Policy-making will require substantial debate and involvement of various stakeholders; performance measures should assess whether decision-making is appropriate
Researchers	The recommendation is supported by credible research or other convincing judgments that make additional research unlikely to alter the recommendation; on occasion, a strong recommendation is based on low or very low certainty in the evidence; in such instances, further research may provide important information that alters the recommendations	The recommendation is likely to be strengthened (for future updates or adaptation) by additional research; an evaluation of the conditions and criteria (and the related judgments, research evidence, and additional considerations) that determined the conditional (rather than strong) recommendation will help identify possible research gaps

catheterization due to high false-positive rates associated with ECHO screening, and the potential adverse effects associated with inappropriate treatment targeted at PH (considered by the panel to be moderate for adults and moderate to large for children).

Rationale and key drivers for recommendation. The balance of benefits vs harms probably favors the comparison (ie, not performing a screening ECHO) based on the overall very low certainty of evidence of effects (see the EtD framework for question 1 in supplemental File 5). This was primarily due to the absence of direct head-to-head comparisons of the intervention (eg, screening vs no screening ECHO for PH) with regard to patient-important outcomes. Other reasons for low certainty of evidence include the following: (1) diagnostic limitations of peak TRJV by ECHO as a screening test (ie, high false-positive rates) for PH, (2) inability to determine how results from ECHO impact subsequent changes in management decisions (eg, right-heart catheterization), (3) lack of sufficient evidence regarding which therapies constitute appropriate management of elevated peak TRJV and/or PH in SCD, (4) inability to determine whether changes in management based on screening ECHO results actually affect outcomes, and (5) evidence for death by causes other than PH for patients who were found to have either peak TRJV elevation on screening ECHO or PH confirmed by right-heart catheterization and who later died. It is important to note that the discussion of balance of effects was focused solely on evidence and outcomes related to ECHO in the setting of screening for PH alone.

Other EtD criteria and considerations. The panel acknowledged that there is variability in patient vs provider desire for knowledge of screening results and that this may be influenced by differences in acceptance of potential management based on culture, age, and other factors. This may impact individual provider decisions about screening in asymptomatic patients given the known limitations of peak TRJV measurements and unclear impact on subsequent changes in management. The panel agreed that inequity may be increased for adults not currently insured if screening by ECHO was recommended for all asymptomatic patients. The panel also agreed that diagnostic ECHO studies should be covered by third-party payers when signs or symptoms dictate a need for testing. Finally, feasibility of ECHO screening may vary given the technical aspects and skills required for accurate measurement of peak TRJV. The panel acknowledged the potential value of peak TRJV on ECHO as a general biomarker of disease severity, given the relationship between elevated peak TRJV and increased mortality in adults with SCD.[47] In this way, baseline peak TRJV may inform a greater understanding of disease severity in adults with SCD and influence shared decision-making regarding general management strategies, including initiation or optimization of disease-modifying therapies such as hydroxyurea and chronic transfusions.

Conclusions and research needs for this recommendation. The guideline panel determined that there is a very low certainty of evidence for a net health benefit related to patient-important outcomes associated with ECHO screening to identify PH among asymptomatic children and adults with SCD due to the absence of direct head-to-head comparison data that are published. The panel identified the following additional types of research that are needed: (1) prospective comparative studies to evaluate the impact of screening vs no screening ECHO in asymptomatic patients with SCD on patient-important outcomes, including the relationship of findings on ECHO (eg, peak TRJV, right-ventricular function and parameters assessing left-ventricular diastolic function) and changes in management to these outcomes and (2) studies to further standardize and validate findings on ECHO, including determining the range of "normal" vs "abnormal" findings, including peak TRJV measurements, for children and adults with SCD.

Management of abnormal echocardiography

Question: Should right-heart catheterization vs serial noninvasive monitoring be performed for patients with SCD suspected to have PH based on an abnormal ECHO?

Recommendation 2a

For asymptomatic children and adults with SCD and an isolated peak TRJV of ≥2.5 to 2.9 m/s, the ASH guideline panel *suggests against* right-heart catheterization (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Recommendation 2b

For children and adults with SCD and a peak TRJV of ≥2.5 m/s who also have a reduced 6MWD and/or elevated NT-BNP, the ASH guideline panel *suggests* right-heart catheterization (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Good practice statement

The panel agreed that it is good practice to consult with a cardiologist, pulmonologist, or an expert in PH when referring patients with SCD for a right-heart catheterization, interpreting results of right-heart catheterization, and/or considering therapeutic options based on type of PH and presumed pathophysiology.

Good practice statement

The panel agreed that it is good practice to base decisions about the need for right-heart catheterization on ECHOs obtained at steady state and not during acute illness, such as hospitalization for pain or acute chest syndrome.

Remarks:

- Repeating ECHOs demonstrating elevated peak TRJV is important prior to referral for right-heart catheterization under the guidance of a PH expert because reproducibility of TRJV measurements may vary due to technical factors, severity of anemia, or increased cardiac output.
- For patients with peak TRJV of ≥2.5 m/s who are asymptomatic, the addition of NT-BNP and 6MWD may help to improve the diagnostic accuracy for PH. Abnormal cutoff values for NT-BNP and 6MWD have not been firmly determined for patients with SCD. However, NT-BNP values of ≥160 pg/mL and 6MWD values of <333 m represent reasonable thresholds for adults with SCD based on published studies in this population. Referrals for right-heart catheterization should also account for clinical judgment and discussion with a PH expert.
- For patients with peak TRJV of ≥2.5 m/s who have normal 6MWD and NT-BNP, serial noninvasive monitoring with ECHOs should be considered if clinically indicated (see list of symptoms in remarks for recommendation 1).
- Consultation with a PH expert regarding the need for a right-heart catheterization should be considered for patients with TRJV of >2.9 m/s who have normal 6MWD and NT-BNP or other findings on ECHO, in addition to elevated peak TRJV, which could suggest significant PH (eg, right-atrial enlargement, pericardial effusion, right-ventricular failure, or septal flattening).
- PH is defined hemodynamically by right-heart catheterization using a mean pulmonary artery pressure threshold of >20 mm Hg, which represents a recent reduction from ≥25 mm Hg. However, the mean pulmonary artery pressure alone does not distinguish PAH from other forms of PH. Additional criteria for the diagnosis of PAH include a pulmonary artery wedge pressure of ≤15 mm Hg and a pulmonary vascular resistance of ≥3 Wood units (240 dyn × seconds × cm^{-5}).

Background. Elevated peak TRJV, frequently defined as ≥2.5 m/s, is a common finding on Doppler ECHO among individuals with SCD and may predict the presence of PH. Although right-heart catheterization represents the gold standard for diagnosing PH, the utility of serial monitoring by noninvasive measures such as peak TRJV in individuals suspected to have PH based on an abnormal ECHO is not clear. The impact of serial monitoring by Doppler ECHO vs right-heart catheterization is also unknown.

Summary of the evidence. Studies that included patients with SCD were examined for the following outcomes: mortality, adverse events associated with right-heart catheterization, and accuracy of ECHO as a screening tool for PH. A total of 3 studies examined mortality among selected patients with elevated peak TRJV who underwent right-heart catheterization for suspected PH.[37,39,40] In these studies, only patients with peak TRJV values of ≥2.5 m/s on screening ECHO underwent right-heart catheterization (total n = 206). Among patients who underwent right-heart catheterization, 29 of 206 (14.1%) died, compared with 54 of 795 (6.8%) who died among those who did not undergo right-heart catheterization. In the only study that reported adverse events associated with right-heart catheterization in SCD patients, vaso-occlusive crisis occurred in 3 of 96 patients (3%) shortly after catheterization, necessitating brief hospitalizations.[40] There were no permanent sequelae related to these events. A total of 4 studies (total n = 1082) estimated the prevalence of PH and PAH among patients undergoing screening ECHO and reported on the accuracy of ECHO to screen for both complications.[37,39,40,45] Of those who underwent ECHO screening, 231 with peak TRJV elevation proceeded to right-heart catheterization. Among all patients undergoing screening ECHO, PH was confirmed by right-heart catheterization in 96 of 1082 (8.9%), with PAH diagnosed in 48 of 1082 (4.4%). Among patients with TRJV elevation, PH was confirmed in 96 of 231 (41.6%), with PAH diagnosed in 48 of 231 (20.8%). The remaining patients did not proceed with further investigation to confirm or exclude PAH. It is important to note that the diagnosis of PH and PAH by right-heart catheterization in these studies does not reflect the decision made at the recent 6th World Symposium of Pulmonary Hypertension to lower the mean pulmonary arterial pressure threshold from ≥25 mm Hg to >20 mm Hg.[46]

Benefits, harms, and burden. There were no direct prospective, head-to-head comparisons of direct health benefits in children or adults with SCD who underwent right-heart catheterization vs serial ECHO for suspected PH based on an abnormal ECHO and peak TRJV elevation. Any potential benefits derived from right-heart catheterization depend on the diagnostic accuracy of screening ECHO to identify patients at high risk for PH. The diagnostic accuracy of using a peak TRJV of ≥2.5 m/s on screening ECHO as the sole criterion for identifying PH or determining need for right-heart catheterization is suboptimal but may be improved when combined with other signs (eg, reduced 6MWD or increased NT-BNP) or symptoms suggestive of PH.[37,39,40,48]

The potential harms associated with the high false-positive rate of using a peak TRJV of ≥2.5 m/s on screening ECHO as the sole criterion for identifying PH or determining need to undergo right-heart catheterization were considered by the panel to be moderate to large. These potential harms include the possibility of inappropriate treatment of patients with PAH-specific therapy or unnecessary exposure to right-heart catheterization. However, the panel considered the potential harm associated with right-heart catheterization to be small because the complication rate for this procedure in general is low in adults.

Rationale and key drivers for recommendation. The balance of benefits vs harms favors not performing right-heart catheterization for an isolated peak TRJV of ≥2.5 to 2.9 m/s found on an ECHO obtained in otherwise asymptomatic patients with SCD (see the EtD framework for question 2 in supplemental File 5). This is based primarily on the overall very low certainty of evidence of effects due to the absence of direct head-to-head comparisons of the impact of the intervention (ie, right-heart catheterization vs serial noninvasive monitoring) on patient-important outcomes. Other reasons for very low certainty of evidence include the following: (1) variability in criteria (ie, peak TRJV alone vs other signs and symptoms) used in existing studies to determine which patients underwent right-heart catheterization, (2) diagnostic limitations of peak TRJV by ECHO as a screening test (ie, high false-positive rates), and (3) inability to determine whether the decision to proceed with right-heart catheterization or its results led to subsequent change in management that affected outcomes. However, the balance of

benefits vs harms favors performing right-heart catheterization for patients with peak TRJV of ≥2.5 on screening ECHO accompanied by reduced 6MWD or increased NT-BNP.

Other EtD criteria and considerations. The panel acknowledged that there is likely variability in provider and patient values regarding the risks associated with undergoing right-heart catheterization for patients with SCD, thus requiring the application of shared decision-making to management of abnormal ECHO studies and peak TRJV elevation. The panel also agreed that there is likely variability in patient access to specialists with expertise in PH who may provide guidance in the interpretation and management of abnormal ECHO studies, TRJV elevation and/or signs and symptoms suggestive of PH requiring further invasive evaluation, such as right-heart catheterization.

Conclusions and research needs for this recommendation. The panel determined that there is a very low certainty of evidence for a net health benefit related to patient-important outcomes associated with performing right-heart catheterization in asymptomatic patients with SCD and isolated peak TRJV of ≥2.5 to 2.9 m/s on ECHO. However, there may be a net benefit related to patient-important outcomes to performing right-heart catheterization for patients with SCD and peak TRJV of ≥2.5 m/s who also have reduced 6MWD or elevated NT-BNP. The panel identified the following additional types of research that are needed: (1) prospective studies evaluating the utility of adding NT-BNP and 6MWD to findings on ECHO, including peak TRJV, to improve diagnostic yield for patients with SCD undergoing evaluation for PH; (2) prospective studies to better characterize the risk factors for development and natural history of PH in children and adults with SCD; (3) prospective comparative studies to examine the relationship between revised hemodynamic thresholds defining PH and PAH on right-heart catheterization and clinical outcomes, including mortality, in SCD; and (4) prospective studies to determine the prognosis of PH and its subtypes, as well as their relationship to treatment, in children and adults with SCD.

Treatment of PAH

Question: Should targeted therapy for PAH or chronic transfusions vs no targeted therapy or chronic transfusions be used for patients with SCD and right-heart catheterization–defined PAH?

Recommendation 3a

For children and adults with SCD who do not have PAH confirmed by right-heart catheterization, the ASH guideline panel *recommends against* the use of PAH-specific therapies (strong recommendation, low certainty in the evidence about effects ⊕⊕◯◯).[14]

Recommendation 3b

For children and adults with SCD and a diagnosis of PAH confirmed by right-heart catheterization, the ASH guideline panel *suggests* the use of PAH-specific therapies under the care of a PH specialist given the lack of alternative treatment options and associated high morbidity and mortality (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Good practice statement

The panel agreed that it is good practice to adopt a multidisciplinary (ie, hematology, PH specialist, pulmonary medicine, or cardiology) approach when considering PAH-specific therapies in SCD patients who have PAH confirmed by right-heart catheterization.

Remarks:

- Although different subtypes of PH may develop in individuals with SCD, this recommendation refers only to PAH and not other subtypes of PH.
- Treatment options may differ based on the subtype of PH as classified by findings on right-heart catheterization and clinical evaluation by a PH specialist.
- PH is defined hemodynamically by right-heart catheterization using a mean pulmonary artery pressure threshold of >20 mm Hg, which was recently reduced from ≥25 mm Hg. However, the mean pulmonary artery pressure alone does not distinguish PAH from other forms of PH. Additional criteria for the diagnosis of PAH include a pulmonary artery wedge pressure of ≤15 mm Hg and a pulmonary vascular resistance of ≥3 Wood units (240 dyn × seconds × cm^{-5}).
- Improvements in cardiopulmonary hemodynamics, as determined by right-heart catheterization, and clinical status, such as a change in PAH symptoms or functional status, initiation of other PAH drugs, or diuretic requirements (eg, in the setting of right-heart failure), are important additional end points for monitoring the benefits of PAH-specific therapy started for patients with PAH confirmed by right-heart catheterization.
- It is appropriate to refer patients with SCD and PAH confirmed by right-heart catheterization to treatment centers with expertise in PH and SCD, given the possibility of increased side effects (eg, pain) with PAH-specific therapy such as sildenafil.
- It is important to consider initiation and/or optimization of disease-modifying therapy such as hydroxyurea or chronic transfusions for patients with PAH confirmed by right-heart catheterization.
- It is important to consider potential differences in the pathophysiologic basis of PAH (eg, contribution of chronic anemia and high-output cardiac states) and differences in side effect profiles (eg, pain) when determining treatment options for PAH confirmed by right-heart catheterization in SCD.
- The recommendation for PAH-specific therapy in SCD applies to patients with SCD who have no other clear reason for their PAH confirmed by right-heart catheterization (eg, obstructive sleep apnea, significant lung disease, left-heart failure).

Background. PH, confirmed by right-heart catheterization, is associated with increased mortality among adults with SCD.[39] However, several aspects of PH, including PAH, in the SCD population remain unclear, including its exact pathophysiology, natural history, and optimal treatment. Treatment of PH in individuals with a diagnosis confirmed by right-heart catheterization may include therapy targeted specifically at PAH or disease-modifying therapy in SCD, such as monthly transfusions. The impact of either strategy on patient-important outcomes is not known.

Summary of the evidence. Studies that included patients with SCD were examined for the following patient-important outcomes: (1) exercise tolerance and 6MWD, (2) treatment side effects, (3) mortality, (4) blood pressure changes, (5) NYHA classification (ie, symptoms), (6) oxygen requirement, and (7) health-related quality of life. In the only randomized controlled trial (RCT) that examined the effect of PAH-specific therapy on exercise tolerance or 6MWD in adults with PH, including PAH, confirmed by right-heart catheterization, the efficacy of bosentan vs placebo could not be determined due to early trial termination secondary to slow accrual and limitations of a small sample size.[49] However, the RCT was limited by a small sample size, and the trial was terminated early secondary to slow accrual. The effect of PAH-specific therapy (total n = 71) on 6MWD was also examined in 5 observational studies and 1 additional RCT, although in this RCT and 3 of the observational studies, PH was not confirmed by right-heart catheterization.[50-55] It is important to note that the diagnosis of PH and PAH by right-heart catheterization in these studies does not reflect the decision made at the recent 6th World Symposium of Pulmonary Hypertension to lower the mean pulmonary arterial pressure threshold from ≥25 mm Hg to >20 mm Hg.[46] Improvements in 6MWD were variable in degree and significance across these studies of PAH-specific therapies (ie, sildenafil, arginine, bosentan, and prostacyclin). However, there was an overall suggestion that treatment of PAH could be associated with increases in 6MWD. Treatment side effects associated with PAH-specific therapies were reported in 1 RCT and 4 observation studies (total n = 88),[50-52,54,55] and mortality was reported in 3 studies (total n = 111), in which there were 4 deaths.[49,54,55] For all other outcomes, blood pressure changes, NYHA classification, and health-related quality of life were each reported in 1 study of PAH-specific therapies,[51,52] and oxygen requirement was reported in 3 studies (2 for PAH-specific therapies and 1 for regular automated red blood cell exchange).[52,53,56] However, there were no major treatment effects across studies for these outcomes.

Benefits, harms, and burden. There was an absence of high-quality, direct evidence for benefits related to PAH-specific therapy for patients with SCD and right-heart catheterization–confirmed PAH. The direct evidence for benefits of treatment related to patient-important outcomes is considered by the panel to be minimal due to the following: (1) paucity of direct evidence from RCTs for the use of PAH-specific therapy or disease-modifying treatment (eg, hydroxyurea or chronic transfusions), (2) reliance of several studies on end points such as 6MWD and oxygen requirement alone without evidence for improvement in right-heart catheterization–defined hemodynamics or mortality associated with PAH, (3) inclusion in several studies of patients with elevated TRJV rather than PAH confirmed by right-heart catheterization, and (4) absence of data on treatment effects in other subtypes of PH besides PAH.

However, the panel relied on indirect evidence related to various classes of PAH-specific therapies to guide decision-making given the high mortality associated with untreated PAH and the lack of alternative therapies.[57] In general, indirect evidence from a meta-analysis suggests a treatment benefit related to 6MWD for some classes of PAH-specific therapies, including endothelin receptor antagonists, phosphodiesterase-5 inhibitors, prostacyclin receptor agonists, and combination therapy (eg, endothelin receptor antagonists plus phosphodiesterase-5 inhibitors) compared with placebo. However, the applicability of indirect evidence from other populations with PAH to patients with SCD is uncertain due to lack of evidence that either confirms similar pathophysiology or provides a clear picture of the harms and benefits of PAH-specific therapy in the SCD population with PAH or other forms of PH.

The potential harms associated with therapy are considered by the panel to be moderate based on data from 2 RCTs and 5 observational studies investigating PAH-specific therapy (eg, sildenafil, bosentan, prostacyclin, and L-arginine) as well as 1 observational study on chronic transfusions for patients with SCD and presumed PAH. In the only completed RCT for patients with SCD, sildenafil or placebo was administered to patients with SCD and elevated peak TRJV on screening ECHO, but the trial was terminated early due to a higher percentage of participants experiencing hospitalization for sickle cell pain in the treatment arm.[55] The panel also relied on indirect evidence to examine the undesirable effects associated with PAH-specific treatment. In general, the risk of adverse events leading to discontinuation of PAH-specific therapy was negligible for most therapies.

Rationale and key drivers for recommendation. The balance of benefits vs harms is against the intervention (ie, PAH-specific therapy) in individuals with SCD who do not have PAH confirmed by right-heart catheterization. The panel made this a strong recommendation because of low certainty in the evidence for benefits in this setting but high certainty in the evidence for potential harm associated with treatment in the general population.[14] On the other hand, the balance of benefits vs harms probably favors the intervention (ie, PAH-specific therapy) for treatment of PAH confirmed by right-heart catheterization in individuals with SCD (see the EtD framework for question 3 in supplemental File 5). The panel arrived at this recommendation despite the absence of high-quality, direct evidence for treatment benefits. It is important to note that the high morbidity and mortality associated with PAH in SCD and the lack of alternative therapies influenced the panel's decision-making and final recommendation. However, the overall certainty of the effects is low for sildenafil and very low for all other PAH-specific or disease-modifying therapies based on the following: (1) only 2 RCTs of PAH-specific therapies have been conducted in the SCD population, with the rest of the evidence being based on observational studies; (2) there is inconsistency in using right-heart catheterization to diagnose PH or PAH in these studies; (3) the determination of effects is imprecise due to the small sample size in the available studies; (4) the evidence of effects is indirect, being derived from other patient populations, which may or may not be appropriate to extrapolate to SCD given potential differences in the pathophysiology of PAH and a poor understanding

of subtypes other than PAH in SCD; and (5) there is reliance on surrogate and unvalidated end points, such as functional capacity (eg, 6MWD or NYHA functional class), health-related quality of life or oxygen requirement, without evidence for improvement in right-heart catheterization–defined hemodynamics or mortality associated with PAH. Nonetheless, the reliance on surrogate end points is common to studies of PAH treatment in the general population and, thus, represents a standard limitation.

Other EtD criteria and considerations. The panel acknowledged that there is some variability in patient perceptions of some of the side effects of PAH-specific therapies. Costs associated with PAH treatment will likely vary depending on the specific therapy and access to and duration of therapy. The panel agreed that acceptability of treatment may also vary across providers and patients depending on values, symptoms, and acceptance of treatment side-effect profiles.

Conclusions and research needs for this recommendation. Despite the reliance on low-certainty evidence based mostly on indirect evidence, the panel determined that there may be a net health benefit related to patient-important outcomes associated with treatment using PAH-specific therapy in children and adults with SCD and PAH confirmed by right-heart catheterization. The panel identified the following additional types of research that are needed: (1) prospective studies to evaluate the effect of chronic transfusion and/or hydroxyurea, either as primary therapy or as an adjuvant to PAH-specific therapy, in PAH confirmed by right-heart catheterization for patients with SCD; (2) well-designed RCTs for PAH-specific therapy for patients with SCD and PAH confirmed by right-heart catheterization that examine benefits vs harms as well as relevant patient-important outcomes; (3) a registry study of patients with SCD and PAH confirmed by right-heart catheterization to longitudinally follow patient-important outcomes, including functional capacity, quality of life, and mortality, as well as the impact of treatment on these outcomes; and (4) prospective studies of other adjuvant therapies (eg, supplemental oxygen and anticoagulation) on patient-important outcomes for patients with SCD and PAH confirmed by right-heart catheterization.

Screening PFT

Question: Should screening for abnormal pulmonary function vs no screening be performed for asymptomatic patients with SCD?

Recommendation 4

For asymptomatic children and adults with SCD, the ASH guideline panel *suggests against* performing routine screening PFT (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Good practice statement

The panel agreed that it is good practice for providers to understand the importance of educating patients, discussing patient and caregiver priorities, and incorporating shared decision-making when considering carrying out PFT.

Remarks:

1. A comprehensive respiratory history and review of systems are essential parts of the diagnostic strategy to identify patients with SCD for whom a low threshold should be considered for obtaining PFT.
2. Although the panel suggests no routine screening PFT for asymptomatic patients with SCD, the following signs, symptoms, or diagnoses may warrant a diagnostic PFT for patients who are otherwise in steady state (ie, healthy) to evaluate for abnormal lung function:
   - Wheezing or increased cough at rest or with exertion;
   - Wheezing or increased cough during episodes of acute upper respiratory infection;
   - Dyspnea at rest or with exertion that is increased compared with baseline or that is unexplained;
   - Chest pain at rest or with exertion that is out of proportion to known condition, increased compared with baseline or that is unexplained;
   - Increase in exercise limitation compared with baseline or that is unexplained (eg, sickle cell pain or musculoskeletal disease);
   - Abnormal 6-minute walk test defined by either reduced 6MWD or oxygen desaturation during test;
   - History of recurrent hypoxemia at rest or with exertion;
   - History of syncope or presyncope;
   - History of recurrent acute chest syndrome;
   - History of pulmonary embolism.
3. Comprehensive PFT should include full spirometry as well as complete evaluation of diffusion capacity and lung volumes.

Background. Abnormal lung function or chronic lung disease, diagnosed by PFT, is relatively common among children and adults with SCD.[58,59] However, several aspects of abnormal lung function remain unclear in SCD, including its prevalence, natural history, relationship to disease severity, and optimal therapy. Despite the utility of PFT as a diagnostic tool for individuals with signs and symptoms suggestive of chronic respiratory impairment, its utility as a screening tool for asymptomatic individuals with SCD is not clear. The impact of results from screening on changing management and patient-important outcomes is also unknown.

Summary of the evidence. There were few direct head-to-head comparisons of benefits and harms in children and adults with SCD who underwent screening PFT vs those who did not. Studies were examined for the following patient-important outcomes: pain, acute chest syndrome, mortality, and decline in lung function. In 2 studies that examined pain and PFT in children and adults with SCD (total n = 1442), pain rates were not significantly different in individuals who underwent PFT vs those who did not.[60,61] In 3 studies that examined acute chest syndrome and PFT (total n = 1564), there was no consistent relationship between acute chest syndrome and either completion of PFT screening or findings on PFT.[60-62] In 2 observational

studies that included adults with SCD (total n = 1484), abnormal lung function, defined as percent-predicted low forced expiratory volume in 1 second, was associated with increased risk of death.[61,63] Despite this relationship, actual mortality rates did not differ for patients who underwent screening PFT and those who did not. In a total of 8 studies that examined decline in lung function measured by PFT among children and adults with SCD (total n = 758), there was an observable decline over time in various parameters on PFT between baseline and follow-up measurements.[64-71]

Benefits, harms, and burden. There was a paucity of direct head-to-head comparisons of benefits associated with undergoing screening PFT. The anticipated benefits of screening PFT for patients with SCD who are asymptomatic are likely minimal but potentially include knowledge about lung function gained from performing the test and the ability to better monitor lung function across the lifespan in individual patients with SCD undergoing serial testing. Of these, only some evidence related to the decline in lung function demonstrated by PFT screening is available in the existing literature.

Direct evidence is not available for any harms as a result of PFT screening for patients with SCD. Minor undesirable anticipated effects may include the possibility that patients with SCD or their parents or guardians may miss school or work, as well as the potential for increased anxiety for patients and their parents or guardians as a result of being given information about abnormal lung function. There may also be unintended harms associated with screening for abnormal lung function in individuals without respiratory symptoms, such as the initiation of treatments without known benefits or unnecessary further evaluation.

Rationale and key drivers for recommendation. The balance of benefits vs harms probably favors the comparison (ie, no screening PFT) in asymptomatic children and adults with SCD (see the EtD framework for question 4 in supplemental File 5). The panel's discussion of the balance of harms vs benefits was driven primarily by the acknowledgment of insufficient evidence that screening asymptomatic patients leads to changes in management that would directly result in improvement in patient-important outcomes, such as pain, acute chest syndrome or mortality. In addition to the absence of direct head-to-head comparisons of screening vs no screening PFT on patient-important outcomes, other reasons for the low certainty of effects in the SCD population included the following: (1) inability to determine how results from screening PFT affect subsequent changes in other management decisions for asymptomatic patients (eg, further testing or initiation of treatment); (2) inconsistent data on the relationship between abnormal lung function and outcomes such as pain, acute chest syndrome, and mortality; (3) lack of sufficient evidence for which therapies constitute appropriate management of abnormal findings on screening PFT in asymptomatic patients; and (4) inability to determine whether changes or no changes in management based on screening results themselves actually affect patient-important outcomes.

Other EtD criteria and considerations. The panel acknowledged that in the analyzed studies, screening PFT did not include bronchoprovocation studies, which are useful diagnostic tests in the general population for demonstrating airway hyperreactivity in the absence of airway obstruction during steady state. However, the significance and utility of demonstrating airway hyperreactivity in the SCD population is unclear. There may be variability in patient or caregiver feelings of helplessness, knowledge gaps, anxiety, or desire to know information gained from PFT screening. Rather than being universally available, PFT may be available only at tertiary-care centers with a pulmonary function laboratory or at outpatient practices with PFT equipment (ie, office-based spirometry).

Conclusions and research needs for this recommendation. The panel determined that there is a very low certainty of evidence for a net benefit related to patient-important outcomes associated with PFT screening among asymptomatic children and adults with SCD. Due to the absence of direct head-to-head comparison data that are published, however, the fact that the panel did not find evidence of an effect on these outcomes does not imply that such an effect does not exist. The panel identified the following additional types of research that are needed: (1) well-designed prospective, longitudinal multicenter studies to evaluate the natural history of lung function across the lifespan for patients with SCD; (2) prospective studies to evaluate the factors that contribute to decline in lung function among patients with SCD; (3) prospective studies to evaluate the relationship between lung function and clinical as well as patient-important outcomes in SCD; and (4) prospective studies to assess the utility of screening and its impact on patient-important outcomes, including change in management, and its influence on clinical end points as well as overall mortality.

Screening for sleep-disordered breathing

Question: Should screening using formal polysomnography (sleep study) for sleep-disordered breathing vs no screening be performed for asymptomatic patients with SCD?

Recommendation 5

For asymptomatic children and adults with SCD, the ASH guideline panel *suggests against* screening with formal polysomnography (sleep study) for sleep-disordered breathing (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. A comprehensive sleep history and review of systems are essential parts of the diagnostic strategy to identify patients with SCD for whom a low threshold should be considered for obtaining a formal sleep study. Whenever appropriate, validated tools (eg, Epworth Sleepiness Scale or Pittsburgh Sleep Quality Index) should be used to further identify patients who should be considered for formal sleep testing.
2. Although the panel suggests no routine screening sleep study in asymptomatic patients with SCD, the following signs or symptoms may warrant a diagnostic sleep study

for patients who are otherwise in steady state (ie, healthy) to evaluate for sleep-disordered breathing:
- Snoring;
- Witnessed apneas or respiratory pauses;
- Nonrestorative sleep and/or excessive daytime sleepiness;
- Obesity;
- Early morning headaches;
- Unexplained desaturation or hypoxemia during sleep, while awake, or with exertion;
- Carbon dioxide retention on arterial blood gas;
- History of poorly controlled hypertension or congestive heart failure;
- History of nocturnal enuresis in an older child (eg, ≥10 years old);
- History of recurrent priapism or frequent daytime or nocturnal vaso-occlusive pain;
- History of PH confirmed by right-heart catheterization;
- History of ischemic stroke without evidence for vasculopathy;
- History of memory loss, difficulty with concentration or unexplained episodes of mental confusion;
- Symptoms of attention deficit-hyperactivity disorder, poor academic achievement, and performance or behavior problems in children.

3. For patients for whom a sleep study is warranted, the American Academy of Sleep Medicine Guidelines currently recommend in-laboratory, "attended" sleep studies for children and for adults with chronic disease and known comorbidities, specifically cardiopulmonary. Additionally, it is important for formal sleep studies to be conducted in a certified sleep center that meets standards as required by accreditation groups (The Joint Commission, American Academy of Sleep Medicine).

Background. Sleep-disordered breathing, diagnosed by formal sleep polysomnography, may have significant consequences for outcomes in children and, potentially, adults with SCD. Sleep-disordered breathing is defined by abnormal respiratory patterns (eg, apneas and/or hypopneas and hypoventilation) during sleep resulting in daytime sleepiness or fatigue that interferes with an individual's ability to function and reduces quality of life. Several aspects of sleep-disordered breathing remain unclear in SCD, including its prevalence, natural history, relationship to SCD severity and progression, as well as optimal therapy. Despite the utility of sleep polysomnography as a diagnostic tool for individuals with signs and symptoms suggestive of sleep-disordered breathing, its utility as a screening tool for asymptomatic individuals with SCD is not clear. The impact of results from screening on patient-important outcomes is also unknown.

Summary of the evidence. There were no direct head-to-head comparisons of benefits and harms in children and adults with SCD who underwent a screening sleep study vs those who did not. Instead, studies were examined for the patient-important outcomes prevalence of sleep-disordered breathing as well as cardiovascular outcomes, nocturnal enuresis, pain crises, health-related quality of life, and lung function as they relate to findings on sleep study. A total of 7 studies reported the prevalence of sleep-disordered breathing in children and adults with SCD (total n = 489), which ranged from 42% in children to 46% in adults.[72-78] Using a higher apnea-hypopnea index cutoff in children with SCD resulted in a lower prevalence. In 2 studies that reported cardiovascular outcomes (total n = 115), sleep-disordered breathing was associated with a higher mean systolic blood pressure and evidence for impaired left-ventricular diastolic dysfunction, and lower nocturnal oxygen saturation was associated with a shorter time to first cerebrovascular event.[78,79] Sleep-disordered breathing was associated with nocturnal enuresis in 2 studies (total n = 311)[80,81] and worse health-related quality of life in 1 study (n = 20)[78] but not with pain episodes in 1 study (n = 140).[82] In 2 studies that reported on the relationship between sleep-disordered breathing and lung function (total n = 293), sleep-disordered breathing was not associated with differences in lung function in adolescents[65] but was associated with lower lung function in children with SCD.[75]

Benefits, harms, and burden. Given the lack of direct head-to-head comparisons of benefits associated with undergoing a screening sleep study, the panel did not identify any major benefits related to screening in asymptomatic patients despite agreement that there are clear interventions for sleep-disordered breathing, including obstructive or central sleep apnea, identified in sleep studies. Despite this, some potential benefits include knowledge about sleep characteristics gained from performing the test and the ability to better detect sleep-disordered breathing in the SCD population because relying solely on the presence of symptoms or validated tools to screen for individuals who should undergo a formal sleep study, as recommended for the general population, may be inadequate for patients with SCD. The ability to determine the impact of SCD and its complications on sleep hygiene represents another potential benefit.

Potential harms of screening sleep study may include the inconvenience of having to spend the night at a medical facility for the sleep study, missed school and work for patients and/or their providers, the potential for increased anxiety for patients and their parents or guardians as a result of being given information about an abnormal sleep study, and minor cosmetic considerations identified by patients, such as difficulty cleaning the gel used for lead placement out of patients' hair.

Rationale and key drivers for recommendation. The balance of benefits vs harms probably favors the comparison (ie, no screening sleep study) for asymptomatic children and adults with SCD (see the EtD framework for question 5 in supplemental File 5). The recommendation was driven primarily by insufficient evidence, especially in the adult SCD population, that screening of asymptomatic patients leads to changes in management that would directly result in improvement in patient-important outcomes such as pain, acute chest syndrome, cardiovascular outcomes, or mortality. The overall certainty in the evidence of effects was very low, given that there are no direct head-to-head comparisons of the intervention (eg, screening vs no screening for sleep-disordered breathing) on patient-important outcomes. Other reasons for very low certainty of evidence included (1) inadequate study design resulting in biased prevalence estimates, given that only 1 study was prospective with a large, unselected sample,[75] 2 research cohort studies had small sample sizes,[74,78] and the rest were retrospective, with clinically obtained sleep studies for either symptomatic patients or patients with unclear symptom status; (2) risk of imprecision given the small sample size of most of the studies available; (3) inconsistency in criteria used to define sleep-disordered breathing in children and adults across studies; (4) inconsistencies in the data examining the

association between sleep-disordered breathing and outcomes in children and adults with SCD; (5) insufficient evidence for how results from screening determine subsequent changes in management decisions in asymptomatic patients (ie, further testing or initiation of treatment); and (6) inability to determine whether changes or no changes in management based on screening itself affect outcomes in asymptomatic patients.

Other EtD criteria and considerations. The panel acknowledged that the extent to which patients or providers value the main outcomes may be affected by how well educated they are about sleep-disordered breathing and its consequences. Some of the consequences of sleep-disordered breathing in the SCD population are known (eg, poor sleep quality, excessive daytime sleepiness, and impaired physical and cognitive function), but others are inadequately studied and therefore not well understood (eg, impact of sleep-disordered breathing on disease severity and progression). The panel agreed that when a sleep study is being considered, costs related to testing, interpretation, and consultation with a sleep medicine specialist can be high. The panel further agreed that the intervention may not be feasible to implement broadly due to limited access to certified sleep laboratories, wait times and scheduling challenges, insurance authorization requirements, and the potential for lost patient or parent/caregiver wages given the overnight nature of the test. These factors may also reduce health equity.

Conclusions and research needs for this recommendation. The panel determined that there is a very low certainty of evidence for a net health benefit related to patient-important outcomes associated with screening sleep study among asymptomatic children and adults with SCD. Due to the absence of direct head-to-head comparison data that are published, however, the fact that the panel did not find evidence of an effect on these outcomes does not imply that such an effect does not exist. The panel identified the following additional types of research that are needed: (1) multicenter, prospective studies with adequate follow-up to screen a large cohort of children and adults regardless of SCD genotype or symptoms to better understand the prevalence of sleep-disordered breathing, its subtypes, and their relationship to outcomes (symptoms, disease manifestations, and other patient-important outcomes); (2) prospective studies to evaluate the acceptability and impact of treating sleep-disordered breathing and its subtypes on patient-important outcomes for patients with SCD; (3) studies to develop a validated tool for identifying patients with SCD at risk for sleep-disordered breathing; and (4) studies to validate home sleep apnea testing for patients with SCD to reduce the inconvenience and burden of overnight testing at a medical facility, including missed days of school or work.

Management of albuminuria

Question: Should angiotensin inhibition vs no angiotensin inhibition be used for patients with SCD and albuminuria?

Recommendation 6

For children and adults with SCD and albuminuria, the ASH guideline panel *suggests* the use of ACEi's or ARBs (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. The initiation of ACEi's and ARBs for patients with SCD requires adequate follow-up and monitoring of side effects (eg, hyperkalemia, cough, hypotension).
2. As recommended by the Kidney Disease Improving Global Outcomes guidelines for the general population, the following attention to baseline and changes in renal function is appropriate when prescribing ACEi's or ARBs for patients with SCD:
   - Start medication at a lower dose in individuals with a GFR of <45 mL/min/1.73 m^2;
   - Assess GFR and measure serum potassium within 1 week of starting medication or following any dose escalation;
   - Temporarily suspend medication during interval illness, planned IV radiocontrast administration, or bowel preparation for colonoscopy or prior to major surgery.
3. The ASH guideline panel did not assess the evidence to inform decisions about albuminuria screening. The Kidney Disease Improving Global Outcomes guidelines state that albuminuria should be confirmed by either a first morning urine sample or 2 consecutive untimed urine samples. The NHLBI 2014 expert panel report states that screening for albuminuria should occur annually beginning at 10 years of age in patients with SCD. However, more recent evidence suggests a potential benefit of earlier screening.[15,16]

Background. Albuminuria is a common finding among adults, and some children, with SCD and may be associated with progression of chronic kidney disease.[83,84] The exact pathophysiology, natural history, and optimal therapy of albuminuria in individuals with SCD, however, remain unclear. Angiotensin inhibition, with ACEi's or ARBs, represents a treatment strategy adopted in other conditions associated with albuminuria and chronic kidney disease. The impact of angiotensin inhibition on patient-important outcomes in SCD is not known.

Summary of the evidence. Studies that included patients with SCD were examined for the following patient-important outcomes associated with treatment: urine albumin, blood pressure, hyperkalemia, and renal function. Urine albumin was reported in 1 RCT (n = 22)[85] and 7 observational studies (total n = 114).[86-92] In the 6 studies that examined ACEi therapy, 53 of 84 patients (63%) who received ACEi therapy showed improvement in urine albumin.[86-88,90-92] Of those who improved while receiving ACEi therapy, 18 (34%) had severe albuminuria (macroalbuminuria), 6 (11%) had moderate albuminuria (microalbuminuria), and the rest did not have their degree of albuminuria specified. In the 2 studies of ARB, all 30 patients (100%) who received ARB (losartan) showed improvement in urine albumin level at some point during the study.[91,92] Of these, 18 (60%) had moderate albuminuria (microalbuminuria) and 12 (40%) had severe albuminuria (macroalbuminuria). A total of 6 observational studies reported the treatment effect on blood pressure.[85-87,89,91,92] In 4 studies, 8 of 72 patients (11%)

who received ACEi showed improvement in blood pressure. The rest showed either no difference in blood pressure compared with a placebo group or no difference in blood pressure after ACEi treatment. In 2 studies, 30 patients received ARB (losartan) with no significant change in blood pressure reported after treatment. No hypotension was reported with either ACEi or ARB therapy. In 1 RCT and 4 observational studies that reported potassium levels with either ACEi or ARB treatment (total n = 92),[85,86,89,91,92] potassium was elevated in 12 of 92 patients (13%). In 3 observational studies that examined changes in renal function after treatment (total n = 140),[89,92,93] 2 studies did not identify a significant change in renal function, but 1 study demonstrated a slower decline in estimated GFR, although the effect was lost after adjusting for hydroxyurea use. However, it is important to note that most of the patients included in these studies had early stages of chronic kidney disease.

Benefits, harms, and burden. The potential benefits related to improvement in albuminuria are moderate for the effect of ACEi or ARB treatment on severe albuminuria (macroalbuminuria) but minimal for the effect on moderate albuminuria (microalbuminuria). This is based on data from 8 studies in which 83 of 114 subjects (72.8%) treated with an ACEi or ARB had improvement in proteinuria.[85-92] The majority of subjects in these studies had severe albuminuria at the time of enrollment. Despite evidence for benefits in these studies, limitations of the available data include short follow-up, variability in classification of proteinuria, and unclear application of quality assurance to measurements of urine albumin. It is also unclear whether short-term reduction in proteinuria results in long-term benefits (eg, improvement in kidney function). There are no RCT data for patients with SCD supporting the effect of angiotensin inhibition on long-term kidney function or progression of existing chronic kidney disease.

The potential harms associated with ACEi or ARB treatment are minimal based on the absence of significant hypotension or hyperkalemia reported in published studies. Although no angioedema was reported in these studies, the incidence of angioedema for patients with SCD undergoing treatment with ACEi's or ARBs is expected to be similar to that observed in the general African American population. The panel believes that other risks of taking ACEi's or ARBs are similar for patients with and without SCD.

Rationale and key drivers for recommendation. The balance of benefits vs harms probably favors treatment with ACEi's or ARBs for patients with SCD and albuminuria (see the EtD framework for question 6 in supplemental File 5). However, the overall certainty of effects is very low based on the following: (1) imprecision due to limited data with small sample size, (2) indirectness of the outcome (ie, surrogate outcome) with only short follow-up, (3) suboptimal study design and reliance on non-RCT studies, and (4) the potential for selective reporting in the studies that were examined. The panel did not rely on indirect evidence from the diabetes literature because the pathophysiologic bases for proteinuria in diabetes and SCD are likely not comparable. Nonetheless, the panel highly values the possibility that reductions in albuminuria, demonstrated in both observational studies and 1 small RCT, could decrease the risk of progression to end-stage renal disease in SCD. This consideration, along with the minimal side effects and monitoring burden expected with treatment, supported a recommendation for the intervention. It is important to note, however, that the recommendation is based on stronger evidence of a reduction in albuminuria for patients with SCD and macroalbuminuria.

Other EtD criteria and considerations. The effect of using ACEi's and ARBs on reducing the risk of end-stage renal disease (ie, prevention of end-stage renal disease, dialysis, or renal transplant) is unknown for patients with SCD. However, the panel, including patient representatives, agreed that there is likely little variability for patients' desire to decrease the risk of end-stage renal disease. The panel acknowledged that implementation of this recommendation would be feasible and acceptable given that costs associated with ACEi and ARB treatment and their required monitoring are low, availability of once-daily dosing would enhance adherence, generic formulations are available, and most providers are familiar with prescribing these medications.

Conclusions and research needs for this recommendation. The panel determined that there is very low certainty of evidence for a net health benefit related to patient-important outcomes associated with ACEi and ARB treatment among children and adults with SCD and albuminuria. However, treatment in this setting is justified given the potential for decreasing risk of progression to end-stage kidney disease through reduction of albuminuria as well as the favorable side-effect profile of therapy. The panel identified the following additional types of research that are needed: (1) prospective studies to determine the temporal relationship between the development of moderate albuminuria (30-300 mg/g) and progression to severe albuminuria (>300 mg/g) for patients with SCD, (2) prospective studies to understand the natural history of progression of albuminuria to end-stage renal disease for patients with SCD, (3) RCTs of renal protective medications to determine the appropriate therapy for patients with SCD with severe albuminuria, and (4) RCTs of placebo vs renal protective medications for patients with moderate albuminuria to evaluate progression to severe albuminuria or end-stage renal disease.

Renal transplant for end-stage renal disease

Question: Should proceeding with renal transplant vs remaining on dialysis be considered for patients with SCD and end-stage renal disease?

Recommendation 7

For children and adults with SCD and advanced chronic kidney disease or end-stage renal disease, the ASH guideline panel *suggests* referral for renal transplant (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. It is essential that providers adhere closely to general guidelines and recommendations for perioperative transfusion requirements for surgery in adults with SCD.[17]
2. Judicious use of corticosteroids as part of the posttransplant immunosuppression regimen is advised given the potential relationship between steroid exposure and vaso-occlusive pain for patients with SCD.

Background. Chronic kidney injury and progression to end-stage renal disease are relatively common among adults with SCD and are associated with increased morbidity and mortality.[94] Remaining on

long-term dialysis vs proceeding with renal transplant represents the primary treatment strategy for individuals with end-stage renal disease. However, the decision-making process, risks vs benefits, and the impact of 1 strategy over the other on patient-important outcomes in individuals with SCD and end-stage renal disease are unknown.

Summary of the evidence. Studies were examined for the following patient-important outcomes related to renal transplant: overall survival, graft survival, graft rejection, frequency of pain episodes, and renal function. A total of 6 observational studies examined survival for patients with SCD after renal transplant (total n = 311).[95-99] Overall, 175 of 311 patients with SCD (56%) survived as reported by 5 studies.[95-98,100] However, survival was reported at different follow-up intervals in these studies, limiting the accuracy of the pooled summarized estimate. Survival at 1 year after renal transplant was reported for 268 of 307 patients with SCD (87%) in 6 studies, with a weighted and pooled estimate of 88% (95% confidence interval [CI], 80.1-95.5).[95-100] In 2 observational studies that examined graft status (total n = 118), cadaveric graft survival at 1 year was reported for 100 of 118 patients with SCD (85%). After 1 year, graft survival at 3 years was reported for only 39 of 82 patients with SCD (48%) in 1 study, which was less than the 60% graft survival rate reported for non-SCD patients with end-stage renal disease ($P = .055$).[98] In the other study, however, graft survival at 2, 5, and 10 years after transplant was comparable between sickle cell and non–sickle cell patients.[100] Graft rejection was reported for 21 of 90 patients (23%) in 5 studies, all of whom had different follow-up intervals.[96-99,101] Sickle cell pain episodes were reported for 9 of 14 patients with SCD (64%) in 2 studies, in which a decline in renal function following renal transplant was also observed.[96,101]

Benefits, harms, and burden. The potential benefits of renal transplant are moderate and include a trend toward better survival with transplant than with dialysis and the ability to avoid the burden of dialysis. These benefits are primarily based on data from 2 retrospective studies: (1) a study (n = 173) that reported increased mortality risk for patients with SCD undergoing renal transplant compared with the general population undergoing renal transplant (hazard ratio [HR], 2.03; 95% CI, 1.31-3.16) but improved survival in the recent era as well as a survival rate comparable to that of patients undergoing transplant for diabetic nephropathy (SCD, 73.1%; diabetes, 74.1%; $P = .44$)[95] and (2) a study (n = 82) that reported a trend toward improved survival in SCD patients who underwent transplant vs those who remained on dialysis (relative risk, 0.14; *P*, .056) as well as the potential for improvement in hemoglobin in those who underwent transplant.[98]

The potential harms related to renal transplant are moderate and include the risk of sickle cell pain (ie, from steroid use), infection from chronic immunosuppression and surgical/perioperative complications related to transplant surgery.

Rationale and key drivers for recommendation. The balance between benefits vs harms probably favors renal transplant for SCD patients with end-stage renal disease given that the panel considered the outcomes after renal transplant for patients with SCD to be comparable to outcomes seen for patients with diabetes and end-stage renal disease who undergo renal transplant (see the EtD framework for question 7 in supplemental File 5). However, the overall certainty in the evidence of effects is very low because of the following: (1) concerns about study design due to the lack of direct comparative studies and (2) imprecision due to small sample size in available studies. Despite the low certainty of evidence, additional key drivers for the panel's recommendation included the following considerations: (1) end-stage renal disease occurs at an earlier age in SCD than in other conditions causing end-stage renal disease; (2) a retrospective study demonstrated improved survival in a more modern cohort of patients undergoing renal transplant,[95] suggesting that survival would likely continue to improve with advancements in transplant technique and procedures; and (3) the panel believes that outcomes associated with dialysis remain poor for adults with SCD.

Other EtD criteria and considerations. The panel acknowledged that there may be important uncertainty or variability in how much people value the primary outcomes based on patient knowledge gaps in understanding the risks and benefits of renal transplant. Patients with SCD may also have different opinions about the risks of surgery and long-term immunosuppression. Despite limited organ availability, the panel considers the financial costs of renal transplant to be large due to lost work wages and the costs of surgery and posttransplant care, including costs of required medications and monitoring. However, the panel considered the costs associated with dialysis to be equally high. The panel recognized that policies for transplant eligibility and referrals may vary for SCD patients and that lower equity and health disparities associated with bias in referring SCD patients for renal transplant may exist. In general, African American individuals who are eligible for renal transplant have lower availability of potential living donors.

Conclusions and research needs for this recommendation. The panel determined that there is very low certainty of evidence for a net health benefit related to patient-important outcomes associated with renal transplant for patients with SCD and end-stage renal disease. Despite the absence of direct head-to-head comparison data that are published related to renal transplant vs dialysis, renal transplant is justified given the high burden associated with dialysis and the comparable outcomes for patients with SCD vs diabetes and end-stage renal disease. The panel identified the following additional types of research that are needed: (1) prospective studies evaluating patient-important outcomes after renal transplant compared with ongoing dialysis for patients with SCD; (2) studies to evaluate disparities in kidney transplant referral among patients with SCD and end-stage renal disease; (3) studies to evaluate the impact of posttransplant transfusions or hydroxyurea on patient-important outcomes for patients with SCD undergoing renal transplant for end-stage renal disease; and (4) studies to evaluate strategies for optimizing and preserving renal function following renal transplant, including determining transfusion goals and immunosuppression regimens.

Use of hydroxyurea and erythropoiesis-stimulating agents for chronic kidney disease

Question: Should combination therapy with hydroxyurea and erythropoiesis-stimulating agents or hydroxyurea alone be used for patients with SCD and nephropathy?

Recommendation 8

In children and adults with SCD and worsening anemia associated with chronic kidney disease, the ASH guideline panel *suggests* combination therapy with hydroxyurea and erythropoiesis-stimulating agents (conditional recommendation, very low certainty in the evidence about effects ⊕◯◯◯).

Remarks:

1. This recommendation is based on evidence available only from patients with hemoglobin SS or S/β^0 thalassemia, for whom erythropoiesis-stimulating-agent dosing in the studies reviewed was higher than that typically used in the general population.
2. For patients already on steady-state hydroxyurea, erythropoiesis-stimulating agents are appropriate in the setting of chronic kidney disease when there is a simultaneous drop in hemoglobin and absolute reticulocyte count.
3. Optimizing adherence to hydroxyurea therapy while on erythropoiesis-stimulating agents may help maximize fetal hemoglobin responses for patients treated with combination therapy.
4. For patients with SCD undergoing treatment with erythropoiesis-stimulating agents, a conservative hemoglobin threshold is advised above which treatment should be decreased or held. The ASH guideline panel advises not exceeding a hemoglobin threshold of 10 g/dL (hematocrit of 30%) to reduce the risk of vaso-occlusion–related complications, stroke, and VTE.

Background. Chronic kidney injury resulting in various degrees of nephropathy is relatively common among adults with SCD.[102] Various aspects of sickle cell nephropathy remain unclear, including its etiology, pathophysiologic contributors, natural history, and optimal treatment. Prevention of progression to end-stage renal disease and maintenance of hemoglobin to prevent worsening of anemia represent major therapeutic goals for individuals with SCD and nephropathy. Whether this may be achieved through the combination of hydroxyurea and erythropoiesis-stimulating agents vs either therapy alone is not clear. The impact of using combination therapy on patient-important outcomes for individuals with SCD and nephropathy is also unknown.

Summary of the evidence. Studies were examined for the following patient-important outcomes associated with combination treatment with hydroxyurea and erythropoiesis-stimulating agents in chronic kidney disease: treatment safety and improvement in hemoglobin. The panel was unable to find any observational or direct comparative studies that reported the outcomes of interest for combination therapy for patients with SCD and chronic kidney disease. Despite the absence of direct head-to-head comparisons of combination vs single therapy, some of the identified studies were relevant for examining erythropoiesis-stimulating-agent use for patients with chronic kidney disease. The safety of erythropoiesis-stimulating agents was examined in 3 studies (total n = 56).[103-105] Only 1 of 56 patients (1.8%) experienced worsening SCD-related symptoms or other adverse events. Improvement in hemoglobin or surrogates for improvement in hemoglobin were examined in 5 observational studies (total n = 29).[103,104,106-108] Benefits reported in 3 of the studies included improvements in total packed red blood cell volume transfused and increase in tagged red blood cell mass in 2 patients,[106] the allowance for more aggressive hydroxyurea dosing and subsequent higher fetal hemoglobin levels with the addition of erythropoiesis-stimulating agents,[104] and increased hemoglobin levels in 3 patients after combination therapy with erythropoiesis-stimulating agents and hydroxyurea as an alternative to transfusion prior to surgery.[103]

Benefits, harms, and burden. The potential benefits associated with combination therapy with hydroxyurea and erythropoiesis-stimulating agents are moderate and are based on a very small number of subjects from a case series (n = 52), suggesting that erythropoiesis-stimulating agents may have the desirable effect of more aggressive hydroxyurea dosing in high-risk patients with SCD in the setting of mild renal insufficiency.[104] The panel believes that higher hydroxyurea dosing could decrease complications from SCD and slow progression of end-organ damage. Additionally, 1 case report demonstrated that combination therapy led to reduced transfusion needs.[103]

The potential harms associated with combination therapy are probably minimal based on 3 studies in which only 1 of 56 patients (1.8%) experienced worsening sickle cell symptoms upon receiving the combination of hydroxyurea and erythropoiesis-stimulating agents.[103-105] Other potential undesirable effects, such as blood clots, adverse cardiovascular outcomes, and hypertension, were not observed. The panel acknowledges the need to consider indirect evidence from the general population when considering the harms of erythropoiesis-stimulating agents, especially the need for setting treatment thresholds for hemoglobin levels. The panel feels that treatment thresholds for hemoglobin levels may need to be set lower for individuals with SCD given the theoretical risk for increased pain with higher hemoglobin levels in SCD.

Rationale and key drivers for recommendation. The balance of benefits vs harms probably favors the intervention (ie, combination therapy with hydroxyurea and erythropoiesis-stimulating agents) based on the surrogate outcome of allowing continued or higher dosing of hydroxyurea with concomitant use of erythropoiesis-stimulating agents, potential for reduction in transfusion requirements, and the minimal side effects associated with combination therapy (see the EtD framework for question 8 in supplemental File 5). Hydroxyurea plays an important role in the treatment of people with SCD, and the panel considers the ability to safely maximize this therapy to be essential. With careful monitoring, the benefits of ongoing hydroxyurea use and improvement in anemia outweigh the potential risks of hyperviscosity and associated adverse effects from using concomitant erythropoiesis-stimulating agents. Despite the potential benefits of combination therapy, the overall certainty in the evidence of effects is very low based on the following: (1) imprecision from very limited numbers of patients in the studies examined, (2) absence of direct comparison studies and reliance on case reports, (3) limited follow-up after treatment of patients in studies, and (4) variability in type and dosing of erythropoiesis-stimulating agents used as well as level of chronic kidney disease in SCD patients undergoing treatment.

Other EtD criteria and considerations. The panel acknowledged that there is possibly important uncertainty or variability in how much patients value the main outcomes based on their treatment preferences for single vs combination therapy with hydroxyurea and erythropoiesis-stimulating agents. A study on therapy preferences among patients with SCD suggests that there is a potential preference for the use of hydroxyurea but there is variability among patients and caregivers.[109] In general, hematologists are comfortable with prescribing erythropoiesis-stimulating agents, which are also readily available. However, the panel considered medication-related costs, the need for prior

approval from insurance carriers, and the required outpatient follow-up to receive injections and undergo laboratory monitoring as potential burdens. The panel also acknowledged that there may be variability in acceptability of injections by patients with SCD, which may also differ for adults vs children.

Conclusions and research needs for this recommendation. The panel determined that there is very low certainty evidence for a net health benefit related to patient-important outcomes associated with combination therapy using hydroxyurea and erythropoiesis-stimulating agents in children and adults with SCD in the setting of chronic kidney disease. Despite the absence of direct head-to-head comparison data that are published, combination therapy with hydroxyurea and erythropoiesis-stimulating agents is justified based on the allowance for more aggressive dosing of hydroxyurea, a drug known to be beneficial in SCD, and the safety profile of combination therapy. The panel identified the following additional types of research that are needed: (1) studies to identify the appropriate dosing of erythropoiesis-stimulating agents for optimal response and to study the risks and benefits for patients with SCD and chronic kidney disease; (2) studies to examine the synergistic effects of erythropoiesis-stimulating agents and hydroxyurea on hemoglobin level and patient-important outcomes for patients with SCD; and (3) studies to determine appropriate hemoglobin thresholds for initiating, continuing, and holding the administration of erythropoiesis-stimulating agents in combination with hydroxyurea for patients with SCD and chronic kidney disease.

Management of blood pressure

Question: Should the target blood pressure in adults with SCD be ≤130/80 mm Hg vs ≤140/90 mm Hg?

Recommendation 9

For adults with SCD, the ASH guideline panel *recommends* a blood pressure goal of ≤130/80 mm Hg over a goal of ≤140/90 mm Hg (strong recommendation, moderate certainty in the evidence about effects ⊕⊕⊕◯).

Remarks:

1. There is a lack of evidence to suggest that blood pressure goals should differ for individuals with and without SCD. The impact of hypertension on patient-important outcomes is significant for African American individuals and therefore requires adherence to guidelines developed for the general population independent of having SCD.

Background. Treatment of hypertension and maintenance of optimal blood pressure control are important for otherwise healthy individuals as well as individuals with comorbid conditions such as SCD. Several aspects of blood pressure control in the SCD population remain unclear, including the pathophysiologic basis for lower baseline blood pressures, contributors to blood pressure elevation, natural history of blood pressure elevation, and relationship of elevated blood pressures to disease severity and other complications. The optimal treatment of elevated blood pressures, including optimal blood pressure target and its impact on patient-important outcomes in SCD, is also unknown.

Summary of the evidence. Studies were examined for the following patient-important outcomes related to blood pressure management: renal function, quality of life, stroke, cardiac events, burden of treatment, mortality, and hypotension. No identified studies reported any of the outcomes of interest in relationship to different strategies of blood pressure control. However, a total of 5 observational studies (total n = 4495) that included both children and adults with SCD were reviewed to determine the prevalence of hypertension for patients with SCD as well as to evaluate the relationship between blood pressure and risk of developing complications and overall mortality.[110-114] These studies demonstrated that for patients with hemoglobin SS disease, blood pressure was significantly lower than published norms for age, race, and sex, and that this difference increased with age. For patients with hemoglobin SC disease, blood pressure deviated from published norms to a lesser degree. A meta-analysis from the 2014 NHLBI Expert Panel Report on Evidence-Based Management of Sickle Cell Disease determined that individuals with hemoglobin SS disease had significantly lower diastolic (−8.37 mm Hg), systolic (−2.82 mm Hg), and mean (−8.41 mm Hg) blood pressure compared with age- and sex-matched healthy controls or patients with a confirmed hemoglobin AA genotype. There are no direct data on the effect of lowering blood pressure to any specific threshold for patients with SCD. However, data from 3 studies suggest an association between higher blood pressures and adverse outcomes for patients with SCD.[110,112,114] In the Cooperative Study of Sickle Cell Disease cohort (n = 3317), the risk of stroke increased with systolic but not diastolic blood pressure.[110] There was an association between higher blood pressure and all-cause mortality. The combined survival of male subjects in the low-blood-pressure and above-average-blood-pressure groups was significantly better than the survival of male subjects in the high-blood-pressure group for both systolic (P = .012) and diastolic (P = .007) blood pressure. There was a trend toward better survival among female subjects in the low and above-average groups compared with those in the high-blood-pressure group. Findings from another study (n = 163) suggest that a systolic blood pressure of 120 to 139 mm Hg or diastolic blood pressure of 70 to 89 mm Hg defines a category of relative systemic hypertension for patients with SCD that is associated with increased risk of PH and renal dysfunction.[112] Finally, in a study of children with hemoglobin SS or S/β^0 thalassemia (n = 814), higher systolic blood pressure was associated with increasing odds of silent cerebral infarct found on brain magnetic resonance imaging (P = .018).[114]

Benefits, harms, and burden. The potential benefits of targeting a blood pressure goal of ≤130/80 are largely based on indirect evidence from the general population that an intensive blood pressure target (ie, initiation of therapy at a blood pressure of 130/80) results in decreases in cardiovascular mortality, stroke, major cardiovascular events, and heart failure.[115] The panel has no reason to believe that there are differences in outcomes related to blood pressure management in individuals with SCD compared with the general population.

The potential harms associated with targeting a blood pressure goal of ≤130/80 are small and may be therapy related, including hypotension, acute kidney injury, hyperkalemia (ie, cumulative effects from multiple drugs and underlying renal disease), drug interactions, and other potential side effects.

Rationale and key drivers for recommendation. The balance of benefits vs harms favors the intervention (ie, targeting a blood pressure goal of ≤130/80 mm Hg) based on indirect evidence of benefits associated with intensive blood pressure control in the general population (see the EtD framework for question 9 in supplemental File 5). The certainty in the evidence of effects is very low in the SCD population due to the absence of direct comparative studies. However, the overall certainty in the evidence of effects for the panel's recommendation was considered to be moderate based on indirect evidence from the general population for outcomes related to intensive vs standard blood pressure targets. Higher blood pressure is associated with worse outcomes, including all-cause mortality, in individuals with SCD.[110] There are no data from a contemporary SCD cohort and no direct data on treatment effects in the SCD population. The panel chose therefore to evaluate data from the general population on outcomes related to intensive vs standard blood pressure targets.[115] The panel valued this indirect evidence because it draws from a diverse population that includes individuals of African descent, which is important given the known health disparities and poorer outcomes associated with blood pressure management among African American individuals. The panel also felt that there was no compelling reason that blood pressure goals should be different for individuals with SCD vs the general population.

Other EtD criteria and considerations. The panel acknowledged that there is probably no important uncertainty or variability in how much patients value the main outcomes important for blood pressure management, which include a decrease in overall mortality and cardiovascular events. The panel agreed that this recommendation will increase access to and optimize blood pressure management for an underserved population for which there is increased morbidity and mortality from hypertension-related complications. Despite the additional requirements for monitoring, the panel also agreed that the intervention will be acceptable based on the availability of daily dosing of medications and low costs associated with generic formulations as well as feasible given that providers are generally knowledgeable about therapies for blood pressure management.

Conclusions and research needs for this recommendation. The panel determined that there is very low certainty of evidence for a net health benefit related to patient-important outcomes associated with maintaining a blood pressure of ≤130/80 mm Hg in adults with SCD. Despite the absence of published direct head-to-head comparison data, this recommendation is justified given the evidence for benefits associated with more intensive blood pressure control in the general population, which should be applicable to the SCD population. The panel identified the following additional types of research that are needed: (1) studies to determine blood pressure thresholds and targets for initiating and maintaining therapy, respectively, given known lower baseline blood pressures in the SCD population, as well as their impact on patient-important outcomes; (2) implementation studies to evaluate adherence to blood pressure guidelines in the SCD population; and (3) prospective studies to determine the natural history of blood pressure changes, end-organ effects and pathophysiologic mechanisms underlying blood pressure regulation in children and adults with SCD.

Management of VTE

Question: Should indefinite anticoagulation vs short-term (≤6 months) anticoagulation be used for adults with SCD who have first unprovoked, first provoked, or recurrent provoked VTE?

Recommendation 10a

For adults with SCD and first unprovoked VTE, the ASH guideline panel *suggests* indefinite anticoagulation over shorter, defined periods of anticoagulation (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 10b

For adults with SCD and first, surgically, or nonsurgically provoked VTE, the ASH guideline panel *suggests* defined periods of anticoagulation (3-6 months) over indefinite anticoagulation (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Recommendation 10c

In adults with SCD and recurrent provoked VTE, the ASH guideline panel *suggests* indefinite anticoagulation over shorter, defined periods of anticoagulation (conditional recommendation, low certainty in the evidence about effects ⊕⊕◯◯).

Remarks:

1. The panel considers SCD to be a chronic underlying risk factor for initial and recurrent VTE.
2. The type, strength, and duration of the provoking events are important to take into account when considering indefinite anticoagulation for patients with SCD and recurrent provoked VTE.
3. The decision to remain on anticoagulation should be made through shared decision-making based on patient values/preferences and be subject to regular reevaluation.
4. Discussions of the benefits vs harms of anticoagulation, as well as duration of therapy, should consider bleeding risk, including from existing use of other medications that could further increase risk of bleeding (eg, nonsteroidal anti-inflammatory drugs).
5. Indefinite anticoagulation is not recommended for first provoked VTE such as secondary to a central venous line. However, anticoagulation should continue as long as any provoking risk factor, including central venous line, continues to be present.
6. Anticoagulant selection for patients with SCD should account for comorbidities such as renal impairment that may affect drug clearance. For example, because of the potential for decreased efficacy of edoxaban in the setting of increased CrCl, alternative anticoagulants should be considered for SCD patients with CrCl of >95 mL/min.

Background. The risk of VTE is increased among children and adults with SCD compared with the incidence observed in the general population.[116,117] Several aspects of VTE in the SCD population remain unclear, including risk of recurrence, associated risk factors for initial and recurrent VTE, and clinical consequences of VTE. Anticoagulation remains the mainstay for treatment of VTE in the general population. The optimum duration of anticoagulation, however, is unclear for individuals with SCD and either provoked or unprovoked VTE. The impact of anticoagulation duration on patient-important outcomes, including risk of bleeding, is also unknown.

Summary of the evidence. There was an absence of direct head-to-head comparison data related to the impact of treatment duration on patient-important outcomes for patients with SCD and VTE treated with anticoagulation. Instead, studies were examined for the following patient-important outcomes: (1) incidence and risk factors for VTE in adults and children with SCD and (2) safety of anticoagulation. A total of 3 studies reported on the incidence and risk factors of VTE in adults with SCD (total n = 7972).[116,118,119] From 2 large retrospective cohort studies, the incidence of VTE, including pulmonary embolism, ranged from 11.2% in all adults with SCD to 17.1% in adults with SCD and more severe disease (ie, hospitalization ≥3 times per year).[116,119] Female sex, more severe disease, and severe sickle cell genotype were associated with a greater risk of VTE. The 5-year recurrence rate of VTE is high among patients with SCD. Moreover, there is higher overall mortality associated with VTE for patients with SCD. Among pregnant women with SCD, the incidence of VTE is higher than that in the general pregnant population.[118] Higher risk of VTE among pregnant women with SCD is associated with pneumonia, vaso-occlusive crisis, and acute chest syndrome. A total of 2 studies reported on incidence and risk factors of VTE in children with SCD (total n = 10 868).[117,120] From these studies, the incidence of VTE among children with SCD ranged from 1.7% to 2.9%. Risk factors for VTE in children with SCD included presence of a central venous catheter, chronic renal disease, history of stroke, female sex, length of hospitalization, intensive care unit utilization, and older age. VTE was also independently associated with death in children with SCD.

A total of 3 published studies reported on safety of anticoagulation in adults with SCD.[121-123] In a retrospective study of patients with SCD receiving VTE prophylaxis (n = 116), anticoagulation was discontinued for hemorrhage in 5 of 116 patients (4.3%).[122] In a small retrospective cohort study of patients receiving oral anticoagulants (n = 37), 3 of 22 patients (14%) receiving direct oral anticoagulants developed nonmajor bleeding and none developed major bleeding. Of those on warfarin, 1 of 15 patients (7%) developed major bleeding and 2 of 15 (13%) developed nonmajor bleeding.[121] In another cohort study of individuals with SCD on anticoagulation (n = 877), the cumulative incidence of bleeding was 4.9% (95% CI, 3.5%-6.4%) at 6 months and 7.9% (95% CI, 6.2%-9.8%) at 1 year.[123]

Benefits, harms, and burden. The potential benefits of indefinite anticoagulation for patients with SCD requiring anticoagulation for VTE are moderate and primarily reflect the potential decrease in recurrent venous thrombotic events associated with indefinite anticoagulation in a population at high risk for recurrent VTE.

The potential harms associated with indefinite anticoagulation for patients with SCD requiring anticoagulation for VTE are moderate and reflect the increased risk of bleeding and need for ongoing monitoring associated with indefinite anticoagulation.

Rationale and key drivers for recommendation. The balance of benefits vs harms probably favors the intervention (ie, indefinite anticoagulation) for either first unprovoked or recurrent provoked VTE based primarily on evidence for a high VTE recurrence rate in adults with SCD and the recognition that SCD is considered a chronic risk factor for recurrent VTE (see the EtD framework for question 10 in supplemental File 5). However, the balance of benefits vs harms probably favors the comparison (ie, defined periods of anticoagulation) for first, surgically, or nonsurgically provoked VTE. Of note, the overall certainty in the evidence is low based on the absence of direct comparative studies for individuals with SCD but moderate based on indirect evidence from the general population. Due to the absence of direct data in SCD, the panel feels that it is appropriate to apply the VTE recommendations developed by ASH for the general population to patients with SCD.[124] The risk of VTE recurrence in SCD patients is at least as high as or higher than (ie, for frequently hospitalized patients) that in the general population. Concerns about the increased risk for recurrent VTE, however, need to be balanced against the potential higher risk of bleeding in individuals with SCD treated with anticoagulation.

Other EtD criteria and considerations. The panel acknowledged that there is possibly important uncertainty or variability in how much patients value the outcomes related to bleeding risks, anxiety from continuing on therapy vs fear of recurrence, and the burden of monitoring while on indefinite anticoagulation. The panel also considered medication costs (ie, newer vs older anticoagulants) as well as the costs related to required monitoring and follow-up while on anticoagulation. The panel acknowledged that acceptability may vary depending on individual patient activity level, ability to follow-up, and overall bleeding risk. Access to providers who can prescribe anticoagulation for patients with SCD is generally available, which supports the feasibility of these recommendations.

Conclusions and research needs for this recommendation. The panel determined that there is low certainty of evidence for a net health benefit related to patient-important outcomes associated with indefinite anticoagulation for both first unprovoked and recurrent provoked VTE, but not first provoked VTE, in adults with SCD. Despite the absence of published direct head-to-head comparison data, these recommendations were based on indirect evidence from the general population and are justified based on acknowledgment that SCD is considered a prothrombotic condition and is associated with a high VTE recurrence risk. Based on the paucity of direct and indirect evidence regarding duration of anticoagulation in children, the panel decided to limit recommendations to adults. The panel identified the following additional types of research that are needed: (1) prospective studies to evaluate the incidence and recurrence of VTE and determine the associated risk factors in children and adults with SCD; (2) studies to evaluate bleeding risk and consequences of bleeding in children and adults with SCD treated with anticoagulation;

(3) studies to evaluate the efficacy and effectiveness of various anticoagulants for treatment of VTE in children and adults with SCD; (4) studies to determine the additional contribution of other inherited or acquired risk factors (eg, antiphospholipid antibody) to VTE risk in children and adults with SCD; and (5) studies to develop and evaluate validated tools to support shared patient decision-making in VTE management in children and adults with SCD.

What are others saying and what is new in these ASH guidelines?

Although few guidelines currently exist for SCD, the recommendations from the ASH guideline panel should be considered in the setting of existing recommendations from other organizations and efforts. Existing guidelines considered most relevant to this panel included the (1) 2013 American Thoracic Society (ATS) Clinical Practice Guideline on Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension in Sickle Cell Disease; (2) 2014 NHLBI Expert Panel Report on the Evidence-Based Management of Sickle Cell Disease; (3) 2015 American Heart Association (AHA)/ATS Guidelines on Pediatric Pulmonary Hypertension; (4) 2018 ASH Guidelines for Management of VTE: Optimal Management of Anticoagulation Therapy; and (5) 2016 Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report. These guidelines allowed direct comparison of our recommendations to those existing recommendations primarily in select areas of cardiopulmonary and renal complications.

The ASH guideline panel's conditional recommendation against routine screening by ECHO for PAH in asymptomatic children and adults with SCD aligns with those from the 2014 NHLBI report and 2015 AHA/ATS pediatric PH guidelines, which recommend ECHO only for patients with symptoms and signs of PH or a history of frequent cardiorespiratory symptoms, respectively. In contrast, the 2014 ATS guidelines recommend routine screening ECHO for adults and children (ie, to establish a baseline) with SCD. Rather than focusing on the need to screen for PAH, these guidelines emphasize instead the need for risk stratification to justify their recommendation given the known relationship between elevated peak TRJV and mortality in adults with SCD. Overall, there is consistency between our guidelines and others related to the need for right-heart catheterization to confirm the diagnosis of PAH as well as the need to reserve PAH-specific therapies for right-heart catheterization–confirmed PAH.

The panel's recommendation against routinely performing screening PFT in asymptomatic children and adults with SCD aligns with the recommendation available in the 2014 NHLBI report. However, existing recommendations related to screening for sleep-disordered breathing were not available in the 2014 NHLBI report or elsewhere for direct comparison with our recommendation against routine screening in asymptomatic patients with SCD.

The panel's recommendations for renal complications were compared with those available from the 2014 NHLBI report. There is consistency for the recommendation of ACEi therapy for patients with SCD and evidence of albuminuria. However, there were differences for other recommendations. Although the 2014 NHLBI report recommends either renal transplant or dialysis for patients with SCD and end-stage renal disease, the ASH guidelines emphasize a preference for referral for renal transplant. Moreover, our recommendation to maintain a blood pressure target of $\leq$130/80 mm Hg contrasts with the target of $\leq$140/90 mm Hg in the 2014 NHLBI report, which reflects our reliance on more recent evidence and guidelines in the general population.

Finally, the panel's recommendations for management of VTE in individuals with SCD are aligned with the anticoagulation recommendations for individuals with chronic risk factors discussed in the 2018 ASH Guidelines for Management of VTE: Optimal Management of Anticoagulation Therapy and the 2016 Antithrombotic Therapy for VTE Disease: CHEST Guideline and Expert Panel Report.[125,126]

Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence identified for many of the questions. Where appropriate and specifically indicated in the guidelines, the ASH guideline panel relied on indirect evidence from the general population to inform decision-making and derive recommendations in the absence of evidence from the SCD population. In rare instances, where explicitly described, final recommendations were derived through voting by panel members when there were differences in opinion on the certainty of evidence or the relevance/application of evidence to a specific question. Given the limited number of questions addressed by the ASH guideline panel, the prioritized questions in these guidelines may not constitute the full list of questions considered by others to be clinically important in cardiopulmonary and renal disease in SCD.

Revision or adaptation of the guidelines

Plans for updating these guidelines

After publication of these guidelines, ASH will maintain them through surveillance for new evidence, ongoing review by experts, and regular revisions.

Updating or adapting recommendations locally

Adaptation of these guidelines will be necessary in many circumstances. These adaptations should be based on the associated EtD frameworks.[127]

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Authorship

Contribution: R.I.L. and S.L. wrote the first draft of the manuscript and revised the manuscript based on the coauthors' suggestions; guideline panel members (T.D.C., L.D., A.A.D., K.I.A., R.T.C., J.H., I.O., J.D.L., J.P.L., T.W., M.V., E.O., R.B., and R.A.M.) and members of the knowledge synthesis team (F.A. and A.K.) critically reviewed the manuscript and provided suggestions for improvement; members of the knowledge synthesis team (F.A. and A.K.) contributed evidence summaries to the guidelines; all authors approved of

the content; and R.I.L., S.L., and R.A.M. were the cochairs of the panel and led the panel meetings.

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