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American Society of Hematology 2019 guidelines for immune thrombocytopenia
**Recommendation 1a**

The panel identified the following research needs:

- Natural history studies of adults with newly diagnosed ITP and a platelet count of $<30 \times 10^9 /L$ managed with observation.

**Recommendation 1b**

The panel prioritized the following research needs:

- Better delineation of risks of bleeding in elderly patients and those treated with anticoagulant and antiplatelet drugs;
- Determination of platelet thresholds for procedures

**Recommendation 2a/Recommendation 2b – N/A**

**Recommendation 3 – N/A**

**Recommendation 4**

The panel identified the following research needs:

- Properly designed studies with controlled dosing regimens that report total patient corticosteroid exposure during the study period;
- Assessment of differences in platelet count variability during treatment with dexamethasone compared with prednisone and need for rescue therapy;
- Assessment of the magnitude and impact of adverse effects associated with corticosteroid use;
- Application of prioritized outcomes such as HRQoL in RCTs and use of standardized outcomes with regard to platelet count outcomes;
- Understanding difference in management with regard to elderly patients (>60 years old)

**Recommendation 5**

The panel identified the following research needs:

- Properly designed studies with controlled dosing regimens, longer term follow-up, and adequate reporting of adverse effects;
- Studies assessing total corticosteroid exposure as an outcome;
- Inclusion of prioritized outcomes such as HRQoL in RCTs;
- Detailed cost-effectiveness analysis.

**Recommendation 6**

The panel identified the following research needs:

- Ongoing comparative effectiveness research of the different TPO-RAs, inclusive of newer agents such as avatrombopag, which is now approved by the US Food and Drug Administration (FDA) for chronic ITP
Recommendation 7/ Recommendation 8/ Recommendation 9

The panel identified the following research priorities:

- Obtaining data to determine whether patients are able to achieve and maintain an acceptable platelet count off treatment with TPORAs. Preliminary data from TPO-RAs clinical trial suggests that approximately one-third of patients (32%) are able to maintain a platelet count of >50 X 10^9 /L for 24 consecutive weeks off treatment;
- Defining predictors of durable response to rituximab;
- Establishing research models on how to understand, assess, and support patient values and preferences in shared decision making;
- Comparison and increased data on additional novel agents such as fostamatinib, a splenic tyrosine kinase inhibitor that was recently approved by the FDA for chronic ITP and has been studied primarily in the third-line setting but whose role as a second-line agent has not been established;
- Ongoing comparative effectiveness research of the different TPO-RAs, inclusive of newer agents such as avatrombopag, which is now approved by the FDA for chronic ITP.

Recommendation 10a/ Recommendation 10b

The panel prioritized the following research needs:

- Understanding the impact of pathway of care and types of encounters on short- and long-term patient outcomes such as HRQoL, patient experience, disease perception, and bleeding;
- Determination of impact of initial outpatient management on patient outcomes, family comfort with disease diagnosis, and HRQoL.

Recommendation 11

The panel identified the following research needs:

- Better classification of bleeding and identification of factors that influence bleeding to identify children at risk of bleeding who would benefit from treatment;
- Determination of biologic markers that may predict response to treatment;
- Application of prioritized outcomes such as HRQoL in RCTs;
- Detailed cost-effectiveness analysis

Recommendation 12

The panel identified the following research needs:

- Adequate assessment of the side effects associated with IVIG use;
- Better classification of bleeding and identification of factors that influence bleeding to identify children at risk of bleeding who would benefit from treatment;
- Determination of biologic markers that may predict response to treatment;
- Application of prioritized outcomes such as HRQoL in RCTs;
- Detailed cost-effectiveness analysis.

Recommendation 13
The panel identified the following research needs:

- Adequate assessment of side effects associated with anti-D immunoglobulin use;
- Better classification of bleeding and identification of factors that influence bleeding to identify children at risk of bleeding who would benefit from treatment;
- Determination of biologic markers that may predict response to treatment;
- Application of prioritized outcomes such as HRQoL in RCTs;
- Detailed cost-effectiveness analysis

**Recommendation 14**

The panel identified the following research needs:

- Properly designed studies applying more modern short-course dosing regimens;
- Assessment of the magnitude and impact of adverse effects associated with corticosteroid use;
- Application of prioritized outcomes such as HRQoL in RCTs

**Recommendation 15**

The panel identified the following research needs:

- Determination of an age or clinical scenario when children may benefit from adult guidelines;
- Randomized trials with patient-reported outcomes such as tolerability, side effects, and potential effect on platelet pathophysiology of the 2 drugs.

**Recommendation 16**

The panel identified the following research needs:

- Comparative effectiveness trials of first-line agents that account not only for efficacy but also for cost, side effects, and patient reported outcomes;
- Determination of upfront treatment selection on long-term outcomes;
- Biologic studies to predict treatment response;
- Assessment of other treatments (eg, TPO-RAs) for use in newly diagnosed patients to minimize side effects and potentially modify disease

**Recommendation 17**

The panel identified the following research needs:

- Comparative effectiveness trials of first-line agents that account not only for efficacy but also for cost, side effects, and patient reported outcomes;
- Determination of upfront treatment selection on long-term outcomes;
- Biologic studies to predict treatment response;
- Assessment of other treatments (eg, TPO-RAs) for use in newly diagnosed patients to minimize side effects and potentially modify disease

**Recommendation 18**

The panel identified the following research needs:
• Comparative effectiveness trials of first-line agents that account not only for efficacy but also for cost, side effects, and patient reported outcomes;
• Determination of upfront treatment selection on long-term outcomes;
• Biologic studies to predict treatment response;
• Assessment of other treatments (eg, TPO-RAs) for use in newly diagnosed patients to minimize side effects and potentially modify disease.

Recommendation 19
The panel identified the following research needs:

• Assessment of impact of treatments on patient-reported outcomes such as fatigue, HRQoL, and bleeding;
• Cost analysis of second-line therapies;
• Determination of patient and parent preferences that influence treatment selection;
• Biologic studies to predict treatment response and investigate the effect of agents on immunomodulation;
• Randomized trial or observational trials to assess long-term outcomes;
• Additional studies of novel second-line agents in children.

Recommendation 20
The panel identified the following research needs:

• Assessment of impact of treatments on patient-reported outcomes such as fatigue, HRQoL, and bleeding;
• Cost analysis of second-line therapies;
• Determination of patient and parent preferences that influence treatment selection;
• Biologic studies to predict treatment response and investigate the effect of agents on immunomodulation;
• Randomized trials or observational trials to assess long-term outcomes;
• Additional studies of novel second-line agents in children.

Recommendation 21
The panel identified the following research needs:

• Assessment of impact of treatments on patient-reported outcomes such as fatigue, HRQoL, and bleeding;
• Cost analysis of second-line therapies;
• Determination of patient and parent preferences that influence treatment selection;
• Biologic studies to predict treatment response and investigate the effect of agents on immunomodulation;
• Randomized trials or observational trials to assess long-term outcomes;
• Additional studies of novel second-line agents in children.
American Society of Hematology 2018 guidelines for management of venous thromboembolism: diagnosis of venous thromboembolism

The panel did not identify additional research questions.
American Society of Hematology 2018 guidelines for management of venous thromboembolism: prophylaxis for hospitalized and non-hospitalized medical patients
Recommendation 1/ Recommendation 2/ Recommendation 3

The panel identified the following additional research questions:

- Better information on baseline risk assessment of thrombosis and bleeding in medical inpatients is needed, in particular whether risk varies over the course of admission;
- More information on the optimal dosing of parenteral anticoagulation to prevent VTE in medical inpatients is needed. In particular, can lower or higher doses be used in different settings (perhaps dependent on baseline risk), and should dosing be adjusted in obese patients, underweight patients, and patients with renal disease?

Recommendation 4 – N/A

Recommendation 5 – N/A

Future research should address:

- Tools for quantitative risk assessment for VTE and bleeding in critically ill medical patients;
- Determination of the acceptable balance between bleeding and thrombosis risk in the context of selecting the optimal thromboprophylaxis in critically ill medical patients.

Recommendation 6/ Recommendation 7/ Recommendations 8 and 9/ Recommendation 10

Research question identified:

- Better information on bleeding risk in medical inpatients to inform decisions about use of mechanical compared with pharmacological VTE prophylaxis.

Recommendation 7

The panel also felt that more research should be conducted to elucidate:

- Net health benefit of mechanical prophylaxis in a lower-risk medical inpatient population;
- Utility of outpatient use of mechanical prophylaxis in those at risk of VTE;
- Direct comparisons between graduated compression stockings and pneumatic compression devices in medical inpatients;
- Impact of use of pneumatic compression devices in medical inpatients at high bleeding risk or with active bleeding

Recommendation 8

The panel felt that more research should be conducted to:

- Provide more direct evidence on combined mechanical and pharmacological prophylaxis compared with mechanical prophylaxis alone via clinical trials on efficacy, harms, and adherence to the intervention, particularly in high-risk medical inpatients in whom the balance of potential benefits vs harms might be more favorable than among lower-risk patients;
• Obtain patient preferences for mechanical or pharmacological prophylaxis by studying feasibility, equity, and acceptability; c Determine current utilization rate of combined mechanical and pharmacological prophylaxis in practice;
• Compare combined mechanical and pharmacological prophylaxis with mechanical prophylaxis alone utilizing comparative effectiveness research studies

Recommendation 9 – N/A

Recommendation 10 – N/A

With regard to research, the panel felt that:

• A systematic review of observational studies and a large comparative RCT are needed to increase the evidence available comparing pneumatic compression devices to graduated compression stockings in acutely or critically ill medical patients.
• Studies of pneumatic compression devices compared with graduated compression stockings are needed in acutely or critically ill medical patients with contraindications to pharmacological prophylaxis or those at high bleeding risk.

Recommendation 11/ Recommendation 12

The panel suggested that future research should address:

• DOAC use among medical inpatients or for extended prophylaxis after discharge in larger trials assessing symptomatic VTE and bleeding end points, and in more selected patients based on predicted risk of VTE and of bleeding;
• Evaluation of lower-dose DOAC regimens in medical inpatients or for extended use after discharge, to determine whether this might mitigate bleeding risk while preventing VTE.

Recommendation 13/ Recommendation 14

With regard to future research, the panel suggests:

• Studies of risk assessment tools for guidance on defining high-risk status for VTE and bleeding at discharge;
• Trials of pharmacological or nonpharmacological interventions in selected high-risk medical patients for VTE at discharge;
• Studies that evaluate dose adjustments or lower doses of anticoagulants that might maximize benefit while minimizing harm when used for extended treatment to prevent VTE after hospital discharge.

Recommendation 15

The panel suggested future research:

• Studies on identification of high-risk subgroups of chronically ill medical patients who could benefit from VTE prophylaxis, with consideration given to those who are immobilized;
• Studies of low-dose anticoagulant approaches, including use of DOACs or aspirin in chronically ill medical patients;
• Research on current clinical practices for VTE prevention and patient preferences for VTE prevention in chronically ill medical inpatients or nursing home residents.

**Recommendation 16**

The panel felt that the following research areas would be helpful:

• Development of risk-assessment methods to determine absolute risk of VTE in outpatients with minor provoking VTE risk factors
• Trials of interventions (pharmacological or nonpharmacological) in a high-risk population of outpatients with minor provoking VTE risk factors.

**Recommendation 17/ Recommendation 18/ Recommendation 19**

With regard to research needs, the panel identified:

• Risk-assessment methods to define travelers at sufficiently high VTE risk to warrant VTE prophylaxis intervention;
• Large pragmatic trials of interventions to prevent VTE in travelers, particularly those at high VTE risk;
• Evidence on effectiveness and safety of DOACs to prevent VTE in travelers at risk of VTE.
American Society of Hematology 2018 guidelines for management of venous thromboembolism: optimal management of anticoagulation therapy
**Recommendation 1**

The panel identified the following additional research priority:

- comparative evidence for different LMWH initiation dosing strategies in obese VTE patients.

**Recommendation 2**

The panel identified the following additional research question:

- What are the patient-important outcomes associated with concomitant administration of DOACs with P-gp/CYP3A4 inhibitors/inducers compared with DOACs alone or compared with other anticoagulants coadministered with strong P-gp or CYP3A4 inhibitors/inducers?

**Recommendation 3**

The panel identified the following additional research questions:

- What is the effectiveness of PST compared with DOAC therapy?
- What is the effectiveness of PST compared with other INR-testing strategies specifically for patients with VTE?

**Recommendation 4**

The panel identified the following additional research questions:

- What is the effectiveness of PSM of VKA compared with DOAC therapy?
- What is the effectiveness of PSM compared with other INR management strategies, specifically for patients with VTE?
- What minimum competencies are required to engage in PSM and what is the most effective way to train patients to perform PSM?

**Recommendation 5**

The panel identified the following additional research questions:

- Does a strategy of using 1-week recall intervals for INRs that are farther out of range (eg, >4.0 or <1.5) and 2- to 3-week recall intervals following INRs that are only slightly out of range (eg, 3.1-4.0 or 1.5-1.9) reduce the risk of mortality, recurrent VTE, and bleeding?
- Could pharmacogonemic testing inform INR recall intervals by helping to predict the time required for a given patient to reach a new steady state following VKA dose adjustments?

**Recommendation 6**

The panel identified the following additional research questions:

- What is the comparative effectiveness of 6- to 12-week INR recall intervals compared with a 4-week recall interval in real-world patients during periods of stable INR control? Given the low risk of adverse events in stable patients, a very large patient sample will likely be required to answer this question.
What is the cost-effectiveness of 6- to 12-week INR recall intervals compared with a 4-week recall interval from the societal perspective?

Recommendation 7

The panel identified the following additional research questions:

- What are the anti–factor Xa concentration cutoffs (determined in a manner that ensures accuracy and reproducibility) that correlate with risk of recurrent VTE and bleeding events?
- What percentage change in LMWH dose in response to an out-of-range anti–factor Xa concentration is optimal to return the concentration to the therapeutic range?
- What is the comparative effectiveness of adjusting LMWH doses based on the results of anti–factor Xa concentrations (performed in a manner that ensures accuracy and reproducibility) vs no such monitoring for patients with estimated creatinine clearance values of <30 mL/min requiring treatment of VTE?

Recommendation 8

The panel identified the following additional research questions:

- What are the anti–factor Xa concentration cutoffs (determined in a manner that ensures accuracy and reproducibility) that correlate with risk of recurrent VTE and bleeding events?
- What percentage change in LMWH dose in response to an out-of-range anti–factor Xa concentration is optimal to return the concentration to the therapeutic range?
- What is the comparative effectiveness of adjusting LMWH doses based on the results of anti–factor Xa concentrations (performed in a manner that ensures accuracy and reproducibility) vs no such monitoring for patients with obesity requiring treatment of VTE?

Recommendation 9

The panel identified the following additional research priorities:

- Developing validated specific DOAC effect tests, particularly those that can be performed rapidly and, ideally, at the point of care;
- Testing the effect on clinical outcomes of using a validated specific DOAC test for patients with bleeding; and
- Assessing the cost-effectiveness, acceptability, and feasibility of implementing a validated specific DOAC test during bleeding management.

Recommendation 10

The panel identified the following research priority:

- sufficiently powered pragmatic clinical trials comparing thromboembolic and bleeding outcomes for DOAC overlap vs LMWH-bridging therapy for patients transitioning from DOAC to VKA.

Recommendation 11

With regard to research priorities, the panel determined that RCT evidence needs to be strengthened to be considered superior to the reported observational evidence. Cluster RCTs are needed that are
appropriately randomized, enroll patients before unblinding of allocation, are sufficiently powered to
detect a difference in clinical outcomes using blinded outcome assessment (including the follow-up time
after dropping out of AMS care), use a consistent definition or elements of AMS, and address the impact
of AMS for patients receiving DOAC therapy.

**Recommendation 12**

The panel identified the following additional research priorities:

- Identifying a standardized definition of what constitutes a patient education intervention and
- Acquiring more information regarding DOAC educational interventions.

**Recommendation 13a/ Recommendation 13b/ Recommendation 13c/ Recommendation 13d**

The panel identified the following additional research priority:

- Development and testing of adherence interventions that are acceptable, feasible, and
  affordable, especially for patients on DOAC or on VKA and not considered eligible for PST or
  PSM, and determining the impact of those interventions on clinical outcomes and cost-
effectiveness

**Recommendation 14**

The panel identified the following additional research priority:

- Sufficiently powered RCTs comparing LMWH/UFH bridging vs VKA interruption alone in VTE
  patients at high recurrent VTE risk undergoing an invasive procedure.

**Recommendation 15**

The panel identified the following additional research priorities:

- Developing validated specific DOAC effect tests, particularly those that can be performed rapidly
  and, ideally, at the point of care;
- Testing the effect on clinical outcomes of using a validated specific DOAC test with prespecified
  thresholds at which patients on DOACs can safely proceed to surgery or invasive diagnostic
  procedures;
- Assessing the cost-effectiveness, acceptability, and feasibility of implementing a validated
  specific DOAC test.

**Recommendation 16**

The panel identified the following additional research questions:

- Is withholding VKA alone a safe and effective option for patients presenting with INRs of >10.0 in
  the absence of bleeding?
- What is the minimum amount of oral vitamin K required to reverse the hypoprothrombinemic
  effect of VKA?
- Can dietary sources of vitamin K (eg, broccoli, spinach, etc) be used to manage excessive VKA
  anticoagulation in nonbleeding patients?
**Recommendation 17**

The panel identified the following additional research questions:

- What is the cost-effectiveness of 4-factor PCC vs FFP from the payer perspective in various health care systems?
- What is the true magnitude of increased thromboembolic risk associated with 4-factor PCC administration compared with the same risk for patients treated with FFP?

**Recommendation 18a**

The panel identified the following additional research questions:

- What clinical parameters define the need for intervention with 4-factor PCC over withholding oral direct Xa inhibitor alone?
- What is the comparative effectiveness of 4-factor PCC in real-world patients presenting with potentially life-threatening oral direct Xa inhibitor-associated bleeding vs withholding direct Xa inhibitor alone?

**Recommendation 18b**

The panel identified the following additional research questions:

- What is the comparative effectiveness of administration of coagulation factor Xa (recombinant), inactivated-zhzo in the setting of direct Xa inhibitor-associated life-threatening bleeding compared with cessation of direct Xa inhibitor alone?
- What is the cost-effectiveness of administration of coagulation factor Xa (recombinant), inactivated-zhzo using pharmacoeconomic modeling based on comparative data and the actual costs of the intervention?
- What is the relative benefit of coagulation factor Xa (recombinant), inactivated-zhzo compared with alternate interventions such as nonspecific procoagulants (antifibrinolytics and/or PCCs)?
- Would a rapidly available test for anti-Xa effect prevent administration of coagulation factor Xa (recombinant), inactivated-zhzo to patients who do not have significant Xa inhibitor concentrations?

**Recommendation 19 – N/A**

**Recommendation 20**

The panel identified the following additional research question:

- What is the comparative effectiveness of protamine administration for management of life-threatening bleeding in VTE or other patients on UFH/LMWH compared with UFH/LMWH cessation alone?

**Recommendation 21**

The panel identified the following additional research questions:

- What is the optimal timing of and what patient-specific factors should influence anticoagulation therapy resumption?
For patients who developed major bleeding during oral anticoagulant therapy, how does transition to an alternative anticoagulant influence the risk of bleeding recurrence?

What is the impact on mortality, recurrent VTE risk, and recurrent bleeding risk associated with resumption of anticoagulation therapy following extracranial bleeding from sites other than the gastrointestinal tract?

Is resuming anticoagulation therapy following major bleeding a cost-effective strategy?
American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients
Recommendation 1

- The panel determined that it would be valuable to have further high-quality studies comparing these interventions outside of the orthopedic setting to confirm the generalizability of the results across surgical domains. The panel would also welcome high-quality studies to determine the effectiveness of mechanical prophylaxis administered outside the hospital setting. The panel identified the need for more and better studies on how patients value the various outcomes in the perioperative setting and to what degrees these values vary by patients as a future research priority.

Recommendation 2

- The panel recognizes that there is a need for high-quality clinical trials using clinically relevant end points to improve the certainty of the evidence supporting this recommendation, particularly outside the orthopedic setting. However, this is likely a lower priority for research than studies evaluating mechanical prophylaxis in combination with pharmacological prophylaxis.

Recommendation 3

- In settings where pneumatic compression devices are not available, the use of graduated compression stockings is reasonable, because mechanical prophylaxis is an acceptable and feasible option. Further well-designed studies using clinically relevant end points are required to improve the quality of evidence related to this question. Studies outside the field of orthopedics would be particularly useful.

Recommendation 4

- Further high-quality research studies using clinically important outcomes comparing combination pharmacological and mechanical methods with pharmacological methods alone are required to provide greater certainty about this recommendation. Studies addressing this question outside the orthopedic setting are most needed.

Recommendation 5

- Further high-quality research studies using clinically important outcomes to identify patients with high baseline risk for VTE in whom combined pharmacological and mechanical prophylaxis would be of value, particularly outside the orthopedic setting, are needed.

Recommendation 6

- Further studies quantifying the non-thrombotic risks of IVC filters would also be of value.

Recommendation 7

- Given the very low certainty in the evidence of effects this is based upon, there is a critical need for higher-quality studies comparing extended vs short-term prophylaxis using clinically important outcomes in contemporary surgical practices, which are marked by early patient mobilization and shorter hospital stays. There is particularly a need for studies outside the general hip and knee arthroplasty and cancer general surgical settings to confirm the benefits of
extended prophylaxis in other settings. There also appears to be a need for further research to determine the optimal duration of extended prophylaxis.

Recommendation 8

- The panel was particularly interested in seeing future high-quality studies of early vs late pharmacological prophylaxis studies in high-risk bleeding patients, examining the benefits and risks of later intervention (days following surgery) once the bleeding risk had greatly subsided.

Recommendation 9

- The panel identified that there is a need for large well-designed clinical trials using clinically important end points comparing ASA with other pharmacological methods following total hip and knee arthroplasty. The panel noted that such studies are underway.

Recommendation 10

- The panel recommended a need for large clinical trials using clinically relevant end points comparing different DOACs. Further studies regarding the optimal timing of the initiation of postoperative dosing of DOACs are warranted.

Recommendation 11

- Given the lack of direct comparative evidence, the panel identified an important need for high-quality head-to-head studies comparing different DOACs for the prevention of VTEs following total hip or knee arthroplasty.

Recommendation 12

- Further high-quality studies using clinically important outcomes would be of value to improve the certainty in the recommendation. However, given the availability of DOACs as oral agents that do not require anticoagulant monitoring or dose adjustment, further clinical trials using warfarin are not regarded as a high priority at this time.

Recommendation 13

- The guideline panel determined that there is moderate certainty evidence for a net health benefit/harm from using LMWH over UFH. Future large studies using clinically relevant end points would help to better inform this recommendation, although this research question would not be regarded as high priority.

Recommendation 14

- Given the overall very low certainty in the evidence, the panel indicated that there remains an important need for large high-quality RCTs using clinically important end points to determine the optimal role of ASA or anticoagulant pharmacological prophylaxis in this patient population. However, higher priority would be comparative studies of different antithrombotic regimens for the prevention of VTEs in these patients requiring repair of hip fracture.

Recommendation 15
• Large RCTs using clinically important outcomes are needed to better define the relative benefits and risks of LMWH compared with UFH following hip fracture surgery

Recommendation 16

• Further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to these recommendations. However, such studies would not be considered as high priority by the panel.

Recommendation 17

• In light of the very low certainty in the evidence, further high-quality comparative studies, using appropriate clinical outcomes, would be of value to add more certainty to this recommendation. However, such comparative studies are not regarded as high priority at this time.

Recommendation 18

• Further research into pharmacological prophylaxis following laparoscopic cholecystectomy was not regarded as high priority given the low baseline incidence of VTE complications in this patient population.

Recommendation 19

• There is a great need for the performance of large RCTs evaluating pharmacological prophylaxis following major neurosurgical procedures, and using clinically important end points, to add certainty to this recommendation. The panel acknowledges that the current recommendation may not reflect standard practice in some centers.

Recommendation 20

• The research priorities following major neurosurgical procedures are to better establish the benefits and risks of any pharmacological prophylaxis compared with no pharmacological prophylaxis. For patients considered at very high risk of postoperative VTE and at low bleeding risk, high-quality comparative studies of LMWH vs UFH using clinically important outcome measures would be of value.

Recommendation 21

• Given the very low baseline risks of VTE following this procedure and the increasing use of alternative modalities to treat lower urinary tract symptoms attributed to benign prostatic hyperplasia, further RCTs conducted on patients undergoing TURP do not appear to be a major priority.

Recommendation 22 - N/A

Recommendation 23

• Further studies on patient values regarding prevention of VTEs and bleeding would allow for optimal shared decision making regarding thromboprophylaxis for radical prostatectomy.

Recommendation 24
• There is a need for high-quality randomized trials specific to patients undergoing radical prostatectomy, particularly those treated with robotically assisted laparoscopic prostatectomy, the most widely used surgical approach for clinically localized prostate cancer.

Recommendation 25

• The panel supported that further research, in the form of well-designed RCTs using clinically important end points, is needed to determine the role of pharmacological prophylaxis in the prevention of VTEs following cardiac and major vascular surgery. Further research on the incremental impact of postoperative UFH and LMWH exposure on the development of HIT in this patient population is also warranted.

Recommendation 26

• The panel supported that the more important research question for this patient population is the role of pharmacological prophylaxis vs no pharmacological prophylaxis for the prevention of VTEs following cardiac and major vascular surgery. Further research on the incremental impact of postoperative UFH and LMWH exposure on the development of HIT in this patient population would also be of value.

Recommendation 27a/ Recommendation 27b

• Well-designed trials using clinically important VTE end points are required for patients at low to moderate risk for bleeding following trauma to determine the incremental benefits of pharmacological prophylaxis beyond mechanical methods alone. Well-designed studies are also needed to determine the benefits and risks of introducing delayed pharmacological prophylaxis for patients experiencing major bleeding, including intracranial hemorrhage as a consequence of major trauma, as the bleeding risk subsides.

Recommendation 28

• The panel judged that the research priorities in major trauma related to establishing the effectiveness and the timing of intervention with pharmacological prophylaxis for patients receiving mechanical prophylaxis following major trauma, rather than comparative studies of LMWH vs UFH.

Recommendation 29

• There is a need for large high-quality clinical trials using clinically relevant end points to determine the benefit of pharmacological prophylaxis following gynecological procedures. These studies should include detailed clinical characteristics of the patient populations.

Recommendation 30

• There is a need for large high-quality clinical trials using clinically relevant end points to determine the relative benefits of LMWH vs UFH pharmacological prophylaxis following gynecological procedures. These studies should include detailed clinical characteristics of the patient populations.
American Society of Hematology 2018 Guidelines for management of venous thromboembolism: treatment of pediatric venous thromboembolism
Recommendation 1/ Recommendation 2
The panel identified the following research topics:

- Determining the natural history of asymptomatic VTE in children and, hence, the benefits of treatment vs no treatment remains a high research priority;
- Determining the role of radiological screening for asymptomatic VTE is a related, but separate, important question;
- Understanding subgroups in whom the approach to the first 2 questions might be different.

The panel identified the following additional research questions:

- The role of thrombolysis in large VTE, sub-massive PE, and massive PE remains unknown in children, and further studies to identify the risk/benefit of thrombolysis compared with anticoagulation alone considering all outcomes of interest are required.
- The role of catheter-directed thrombolysis and the minimal infrastructure, experience, and annual case load to offer this therapy in children compared with systemic thrombolysis need to be determined.
- The natural history of VTE or large PE in children (including subgroup analysis [eg, intracardiac thrombi]) treated with anticoagulation alone needs to be understood to enable the first 2 questions to be properly addressed.

Recommendation 6/ Recommendation 7
The panel identified the following additional research questions:

- Further studies to identify subgroups who might benefit from thrombectomy or IVC filter;
- Further studies to identify the optimal methods of performing thrombectomy (eg, open surgical vs catheter thrombus retrieval) in appropriate cases;
- Further studies to determine the minimal infrastructure and operator experience required for safe placement of IVC filters especially in smaller children.

Recommendation 8a/ Recommendation 8b
The panel identified the following additional research issue:

- Use of AT-replacement therapy in pediatric patients, in addition to anticoagulation (heparinoid), in the treatment of VTE in a variety of subgroups.

The panel identified the following additional research questions:

- The optimal timing of CVAD removal (delayed by what duration vs immediate) once CVAD-associated VTE is diagnosed needs to be established.
- Subgroup studies are needed to identify specific patient populations in whom the approach might vary, including consideration of risk of CVAD-associated sepsis.

Recommendation 13
The panel identified the following additional research questions:
• Further studies are required to elucidate the minimal infrastructure requirements for services to support parents and families to optimize therapy with either low-molecular-weight heparin or vitamin K antagonists.
• Further studies are required to determine the impact of vitamin K antagonists vs low-molecular-weight heparin on bone density, especially for longer durations of therapy.
• Further studies are required to understand the factors influencing patient preferences for either therapy and the optimal ways to mitigate negative factors.

**Recommendation 14**
The panel identified the following additional research questions:
• Studies to determine the impact of differing provoking factors to optimal duration of therapy;
• Studies to determine the impact of age on optimal duration of therapy for provoked VTE;
• Studies to determine the required improvement in outcomes for patients and families compared with the perceived increased burden of care from prolonged therapy

**Recommendation 15**
The panel identified the following additional research question:
• With the increasing use of peripherally inserted central catheters in a wide range of pediatric care scenarios, the frequency of superficial vein CVAD VTE will increase, and studies of the natural history and role of anticoagulation treatment are required.

**Recommendation 16**
The panel identified the following additional research question:
• With the increasing use of peripherally inserted central catheters in a wide range of pediatric care scenarios, the frequency of superficial vein CVAD VTE will increase, and studies of the natural history and role of anticoagulation treatment are required.

**Recommendation 17/ Recommendation 18**
The panel identified the following additional research questions:
• The natural history of right atrial thrombosis in different patient subgroups needs to be determined.
• The impact of thrombosis size and mobility on natural history needs to be determined.

**Recommendation 19/ Recommendation 20a/ Recommendation 20b**
The panel identified the following additional research questions:
• More high-quality evidence for baseline risks, duration of treatment, and agents used, as well as better data to assess anticoagulation vs no anticoagulation in RVT
• Better subgroup data to identify the children who would benefit most from thrombolysis.

**Recommendation 21a/ Recommendation 21b**
The panel identified the following additional research question:
• studies to determine the outcomes, with or without anticoagulation, in clinical subgroups of PVT are required.
Recommendation 22a/ Recommendation 22b/ Recommendation 23
The panel identified the following additional research questions:

- Further studies focusing on specific subgroups (hemorrhagic vs non-hemorrhagic, infarct vs no infarct, neonatal vs older child) to determine whether different treatment strategies are required for different subgroups
- Further studies to determine whether catheter-directed thrombolysis has a different risk benefit ratio from systemic thrombolysis

Recommendation 24/ Recommendation 25/ Recommendation 26

- The panel identified the following additional research question: more information about the long-term outcomes and the comparative success of management options, as well as the optimal age for introducing those options, is required. Given the rarity of the disease, further information is more likely to come from observational studies and registries, which are of paramount importance in this disease
American Society of Hematology 2018 guidelines for management of venous thromboembolism: venous thromboembolism in the context of pregnancy
Recommendation 1/ Recommendation 2

The panel identified the following additional research need:

- More data are required regarding the safety of fondaparinux and the direct oral anticoagulants during pregnancy

Recommendation 3

The panel identified the following additional research need:

- More data are required regarding the dose and duration of LMWH if used in this context.

Recommendation 4

The panel identified the following additional research needs:

- Further evidence regarding the risks, benefits, and acceptability of once-per-day vs twice-per-day LMWH dosing for treatment of acute VTE, specifically in the pregnant patient population, should be sought.
- Investigations should be performed to determine whether there is any benefit to twice-per-day dosing of LMWH for the treatment of VTE in the acute (ie, first month) setting, followed by de-escalation to once-per-day dosing for the remainder of the treatment period.

Recommendation 5

The panel identified the following additional research needs:

- Larger and higher-quality studies examining the role of anti-FXa monitoring in this patient population are required to obtain more precise estimates of effect.
- Studies evaluating the role of anti-FXa level monitoring in the acute treatment period followed by a standard weight-based dosing approach should be performed.

Recommendation 6

The panel identified the following additional research needs:

- More information from high-quality research on the safety and efficacy of catheter-directed thrombolysis in the pregnant population, including in those with limb-threatening DVT, is required.
- More data regarding patient values and preferences for the potential benefits and drawbacks of this intervention are required.
- More data on estimated fetal radiation exposure and associated potential harms would be useful.

Recommendation 7/ Recommendation 8

The panel identified the following additional research needs:

- More information is required from high-quality direct studies on the safety and efficacy of thrombolysis for pulmonary embolism in the pregnant population, including in those with sub-massive pulmonary embolism and right ventricular dysfunction alone.
• More data on patient values and preferences for potential benefits and drawbacks of this intervention are required.

**Recommendation 9**

The panel identified the following additional research needs:

• Studies should be performed that will provide pregnancy-specific data for stratifying risk for complications associated with treatment of VTE, and clinical prediction rules should be developed to identify pregnant patients who require hospital admission for initial management of DVT and pulmonary embolism.
• Studies examining rates of hospital admission after initiation of outpatient therapy in pregnant patients should be undertaken.

**Recommendation 10**

The panel identified the following additional research needs:

• More outcome data that examines different anticoagulant regimens at the time of delivery, including transitioning to intravenous UFH, would be helpful.
• Data should be obtained that assess other critical outcomes for pregnant women with therapeutic anticoagulation interruption around the time of delivery (including access to epidural analgesia and frequency of epidural hematomas, cesarean delivery, and maternal and neonatal morbidity and mortality).

**Recommendation 11**

The panel identified the following additional research need:

• Data should be obtained that examine other critical outcomes for pregnant women with prophylactic anticoagulation interruption around the time of delivery.

**Recommendation 12/ Recommendation 13**

The panel identified the following additional research need:

• More data are required regarding the safety of the direct-acting oral anticoagulants in this population.

**Recommendation 14/ Recommendation 15**

The panel identified the following additional research needs:

• More data are required regarding the baseline risk of VTE with assisted reproductive technology in specific patient populations, including those with prior VTE, thrombophilia, and other risk factors for VTE.
• More data are also required regarding the potential benefits and risks of antithrombotic therapy in reducing the risk of VTE in women using assisted reproductive technologies.

**Recommendation 16/ Recommendation 17**

The panel identified the following additional research needs:
• More data are required regarding optimal intensity of LMWH prophylaxis in this setting. Additional information would be helpful regarding the impact of thrombophilia status and precipitating risk factors with prior venous thromboembolic events on the risk of antepartum recurrent VTE.

Recommendation 18
The panel identified the following additional research needs:

• More data are required regarding optimal intensity of LMWH prophylaxis in this setting. More information regarding optimal duration of postpartum prophylaxis should be gathered.
• Investigators should explore whether there are certain subgroups of patients more likely to derive benefit from postpartum prophylaxis.

Recommendation 19/ Recommendation 20/ Recommendation 21
The panel identified the following additional research needs:

• More data are required on patient values and preferences in this setting.
• Studies examining the risks and benefits of antepartum prophylaxis in women with thrombophilia and a family history of VTE are needed.

The panel identified the following additional research needs:

• More data are required regarding patient values and preferences in this setting.
• Studies examining the risks and benefits of postpartum prophylaxis in women with thrombophilia are needed.

Recommendation 27
The panel identified the following additional research needs:

• More data should be gathered on the absolute risk of VTE with combinations of risk factors.
• Information on the impact of applying risk scoring systems and predictive models with respect to thrombosis prevention and bleeding risks as assessed by randomized trials would be helpful.

Recommendation 28/ Recommendation 29
The panel identified the following additional research needs:

• Further evidence is required regarding the risks and benefits of intermediate- vs standard-dose LMWH prophylaxis. The panel noted that the ongoing Comparison of Low and Intermediate Dose Low-Molecular-Weight Heparin to Prevent Recurrent Venous Thromboembolism in Pregnancy (NCT01828697) trial will provide valuable information when it is completed.
• Further investigations should be performed to determine whether there are specific patient subgroups most likely to benefit from higher-dose prophylaxis.

Recommendation 30
The panel identified the following additional research need:

- The role of D-dimer testing and clinical prediction rules in limiting the need for radiologic tests in pregnant women with suspected pulmonary embolism needs to be evaluated in well-designed management studies

Recommendation 31

The panel identified the following additional research needs:

- More data are required on the safety of excluding DVT in pregnant women on the basis of a negative initial whole-leg compression ultrasound with imaging of the iliac veins.
- The role of D-dimer testing and clinical prediction rules in the management of pregnant women with suspected DVT needs to be evaluated in well-designed management studies.
American Society of Hematology 2018 guidelines for management of venous thromboembolism: heparin-induced thrombocytopenia
Recommendation 1.1.a / Recommendation 1.1.b – N/A

Recommendation 2.1 / Recommendation 2.2

Research priorities include implementation analyses and identification of barriers to the use of the recommended strategy and in particular the use of the 4Ts score. Our modeling and recommendations apply to the PF4/heparin ELISA. Assessment of other currently available immunoassays should be conducted. Research should also include the development of novel assays that overcome the limitations of currently available assays, such as immunoassays with enhanced specificity and functional assays with enhanced feasibility.

Recommendation 2.3 / Recommendation 2.4.a / Recommendation 2.4.b / Recommendation 2.5.a / Recommendation 2.5.b / Recommendation 2.6

Research could focus on the perceived barriers to managing patients according to the 4Ts score.

Recommendation 2.7 / Recommendation 2.8 / Recommendation 2.9 / Recommendation 2.10

The panel identified the effect of different ELISA OD thresholds on clinical outcomes as a research priority.

Recommendation 3.1

More research is needed on treatment of acute HIT with DOACs, including encouraging physicians to present outcome data when using DOACs, creating an international registry to capture treatment with DOACs, and conducting studies that compare DOACs and parenteral non-heparin anticoagulants.

Recommendation 3.2 – N/A

Recommendation 3.3

Future research may be needed to identify whether there are benefits of combining antiplatelet therapy and anticoagulation among patients with HIT.

Recommendation 3.4 – N/A

Recommendation 3.5 – N/A

Recommendation 3.6 – N/A

Recommendation 3.7.a / Recommendation 3.7.b

Research is needed to determine whether a strategy of screening and treatment of asymptomatic DVT in patients with acute isolated HIT influences outcomes important to patients such as symptomatic thromboembolism, major bleeding, and death.

Recommendation 3.8

The panel agreed that studies comparing different lengths of therapy would be useful for determining the optimal duration of treatment in patients with isolated HIT.

Recommendation 3.9
The panel agreed that an international registry of patients with subacute HIT A treated with a DOAC would provide important information.

**Recommendation 4.1.b**

Direct comparison of treatment options for intraoperative anticoagulation in patients with HIT is an important research priority. Anticoagulation in HIT patients with ventricular assist devices or those who use extracorporeal membrane oxygenation is also worthy of investigation.

**Recommendation 4.2**

Research priorities include development of a registry on the use of heparin during cardiac surgery among patients with subacute HIT B or remote HIT.

**Recommendation 5.1** - N/A

**Recommendation 5.2** - N/A

**Recommendation 6.1** - N/A

**Recommendation 6.2** – N/A

**Recommendation 7.1** – N/A

**Recommendation 8.1.a** – N/A
American Society of Hematology 2019 guidelines for sickle cell disease: cardiopulmonary and kidney disease
Recommendation 1

The panel identified the following additional types of research that are needed:

- 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
- 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.

Recommendation 2a/ Recommendation 2b

The panel identified the following additional types of research that are needed:

- 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;
- Prospective studies to better characterize the risk factors for development and natural history of PH in children and adults with SCD;
- 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;
- Prospective studies to determine the prognosis of PH and its subtypes, as well as their relationship to treatment, in children and adults with SCD.

Recommendation 3a/ Recommendation 3b

The panel identified the following additional types of research that are needed:

- 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;
- 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;
- 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;
- 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.

Recommendation 4

The panel identified the following additional types of research that are needed:
• Well-designed prospective, longitudinal multicenter studies to evaluate the natural history of lung function across the lifespan for patients with SCD;
• Prospective studies to evaluate the factors that contribute to decline in lung function among patients with SCD;
• Prospective studies to evaluate the relationship between lung function and clinical as well as patient-important outcomes in SCD;
• 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.

Recommendation 5

The panel identified the following additional types of research that are needed:

• 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);
• Prospective studies to evaluate the acceptability and impact of treating sleep-disordered breathing and its subtypes on patient-important outcomes for patients with SCD;
• Studies to develop a validated tool for identifying patients with SCD at risk for sleep-disordered breathing; and
• 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.

Recommendation 6

The panel identified the following additional types of research that are needed:

• 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,
• Prospective studies to understand the natural history of progression of albuminuria to endstage renal disease for patients with SCD,
• RCTs of renal protective medications to determine the appropriate therapy for patients with SCD with severe albuminuria,
• RCTs of placebo vs renal protective medications for patients with moderate albuminuria to evaluate progression to severe albuminuria or end-stage renal disease.

Recommendation 7

The panel identified the following additional types of research that are needed:

• Prospective studies evaluating patient-important outcomes after renal transplant compared with ongoing dialysis for patients with SCD;
• Studies to evaluate disparities in kidney transplant referral among patients with SCD and end-stage renal disease;
• 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;
• Studies to evaluate strategies for optimizing and preserving renal function following renal transplant, including determining transfusion goals and immunosuppression regimens

Recommendation 8

The panel identified the following additional types of research that are needed:

• 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;
• Studies to examine the synergistic effects of erythropoiesis-stimulating agents and hydroxyurea on hemoglobin level and patient-important outcomes for patients with SCD;
• 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.

Recommendation 9

The panel identified the following additional types of research that are needed:

• 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;
• Implementation studies to evaluate adherence to blood pressure guidelines in the SCD population;
• 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.

Recommendation 10a/ Recommendation 10b/ Recommendation 10c

The panel identified the following additional types of research that are needed:

• Prospective studies to evaluate the incidence and recurrence of VTE and determine the associated risk factors in children and adults with SCD;
• Studies to evaluate bleeding risk and consequences of bleeding in children and adults with SCD treated with anticoagulation;
• Studies to evaluate the efficacy and effectiveness of various anticoagulants for treatment of VTE in children and adults with SCD;
• 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
• Studies to develop and evaluate validated tools to support shared patient decision-making in VTE management in children and adults with SCD.
American Society of Hematology 2020 guidelines for sickle cell disease: transfusion support
**Recommendation 1**

The guideline panel identified the following additional areas of research that are needed:

- Prospective studies to determine the effect on transfusion outcomes when an extended blood group antigen profile is obtained for patients with SCD at the first encounter
- Prospective, randomized studies to determine the effect on transfusion outcomes when a red cell profile is obtained by molecular vs serologic methods.

**Recommendation 2**

The guideline panel identified the following research priorities:

- The role of serologic vs genotypic matching, most notably for the Rh system,
- The development and study of universally available transfusion registries to reduce alloimmunization-related sequelae, such as delays in transfusion and DHTRs because of the high rate of multisite transfusion and known antibody evanescence patterns.

**Recommendation 3**

The panel identified the following research priorities:

- Design of tools or models for rapidly and accurately predicting the clinical relevance of alloantibodies in a given patient;
- Studies to elucidate the mechanism or mechanisms of HTRs after incompatible red cell transfusion with distinct alloantigen targets in an effort to develop more effective approaches to prevent HTRs;
- High-quality studies evaluating the efficacy of currently available immunomodulatory agents in preventing AHTRs or DHTRs in patients deemed at risk.

**Recommendation 4**

The panel identified the following research priorities:

- High-quality studies to determine the efficacy of immunomodulatory agents (IVIg, steroids, eculizumab, and rituximab) for the treatment or prevention of hemolytic transfusion reactions, with or without hyperhemolysis;
- Studies on the mechanisms and consequences of alloantibody-mediated clearance of transfused red cells and the pathophysiology of hyperhemolysis;
- Studies of interventions to prevent the deleterious consequences of hemolysis itself, such as the use of plasma-derived haptoglobin and hemopexin in patients with excessive hemolysis.

**Recommendation 5**

The panel identified the following research priorities:

- Optimal peripheral access techniques (eg, ultrasound guidance) and central venous access devices and techniques for maintaining patency and sterility;
Individualized strategies (e.g., based on reticulocyte count, target hematocrit, and target HbS%) to minimize endogenous erythropoiesis, iron loading, and progression of SCD-related complications;

Novel RCE techniques to reduce red cell unit usage and procedure frequency.

**Recommendation 6a/ Recommendation 6b**

The guideline panel identified the following research priorities:

- Development and validation of a prognostic score and definitions of severe, moderate, and mild ACS and
- A prospective, controlled trial of patients with severe and moderate ACS randomly assigned to treatment with RCE vs simple transfusion.

**Recommendation 7**

The panel identified the following research priorities:

- High-quality studies comparing IHD-RCE with conventional RCE in regard to red cell unit use, maintenance of the target HbS level, iron loading, safety with different indications for chronic transfusion, risk for cerebral infarcts, and cost savings.

**Recommendation 8**

The panel identified the following research priorities:

- A randomized trial of scheduled transfusions vs on-demand transfusions in pregnant women with SCD,
- Studies to determine the timing of optimal initiation of regular transfusions,
- Studies to determine whether simple transfusion or RCE is more effective. The panel acknowledges that SCD is a rare disease and that sample size will be a challenge, thus necessitating a multicenter study.

**Recommendation 9**

The panel identified the following as priority research questions:

- Determining whether preoperative transfusion benefits patients with non-HbSS/SB0 genotypes undergoing low-, moderate-, and high-risk surgery;
- Determining whether the benefits of perioperative cell salvage in patients with SCD outweigh its risks;
- Determining the optimal preoperative HbS% in patients undergoing high-risk surgery (cardiac surgery or neurosurgery);
- Identifying other modalities to optimize preoperative hemoglobin in patients with SCD (i.e., erythroid-stimulating agents or hydroxyurea);
- Determining whether HbF% affects postoperative outcome for similar levels of preoperative total hemoglobin.

**Recommendation 10a/ Recommendation 10b**
The panel identified the following research priorities:

- Prospective studies to understand the clinical significance of varying degrees of iron overload in patients with SCD, including correlation with organ dysfunction, SCD-related complications, and mortality;
- A prospective, randomized trial of deferasirox compared with deferiprone for the treatment of transfusion iron overload in SCD;
- Prospective studies of the prevalence of abnormal cardiac T2* MRI, including investigation of potential risk factors such as genetic predisposition and chelator type.
American Society of Hematology 2020 guidelines for sickle cell disease: prevention, diagnosis, and treatment of cerebrovascular disease in children and adults

The panel identified the following additional areas in need of research.

- Best practices and implementation strategies for primary stroke prevention after using TCD as a screening tool should be determined. Over a 6-year study period among 4775 children with HbSS or HbSb0 thalassemia from 6 US states, 22% to 44% of children received TCD screening.
- Alternative options for primary stroke prevention other than initial regular blood transfusion therapy for a year for some, then followed by maximum tolerated dose of hydroxyurea therapy, should be identified for children living in high-income settings.
- Imaging strategies to identify the subgroup of children with an abnormal TCD measurement who are most likely to have a stroke should be improved. The current number needed to treat is 7 (ie, 7 children with abnormal TCD measurements must receive at least monthly blood transfusion therapy for at least a year to prevent 1 stroke). Strategies to personalize the risk of stroke for children with abnormal TCD measurements would be preferred to the current standard of red blood cell transfusion therapy for at least a year for children living in high-income settings for at least a year.
- The optimal hydroxyurea dose (20 mg/kg per day vs 10 mg/kg per day vs the maximum tolerated dose of hydroxyurea) for primary stroke prevention in children with abnormal TCD measurement living in low-middle-income settings should be determined.
- Use of a liquid formulation of hydroxyurea that is stable at room temperature when stored at home and can be provided to children 5 years of age unable to swallow a capsule is needed.
- The best strategies to partner with local, state, and federal health care authorities in low-middle-income settings to provide hydroxyurea therapy for primary stroke prevention programs should be determined.
- Training and quality assurance of TCD practitioners to increase the pool of qualified TCD practitioners, particularly in low-middle-income settings, are needed.

Recommendation 4.1/ Recommendation 4.2

The panel identified the following additional areas in need of research.

- Evidence to define the optimal interval between onset of ischemic stroke or TIA and transfusion is needed. The time point at which there is no longer a benefit or at which risk outweighs benefit is unknown.
- Development of additional therapeutic strategies or alternatives to blood transfusion is needed for better prevention of progressive brain injury after an initial acute ischemic stroke.
- A more precise understanding of the mechanisms of cerebral hemodynamics in children and adults with SCD is needed to develop targeted therapies and to improve risk stratification for initial and subsequent cerebral infarct and cerebral hemorrhage.

Recommendation 5

The panel identified the following additional areas in need of research.
• Optimal therapeutic strategies for secondary stroke prevention in children and adults (blood transfusion therapy vs blood transfusion therapy plus revascularization surgery vs HSCT) with long-term follow-up in children and adults with SCD are needed.
• Optimal therapeutic strategies or secondary stroke prevention in low-middle-income settings where blood transfusion therapy is not available are needed.
• Optimal transfusion targets and methods for secondary stroke prevention are needed.
• Risk stratification to identify the group of children and adults with strokes likely to have infarct recurrence should be carried out.
• Optimal treatment and stroke recurrence rate for children and adults other than those with HbSS or HbSβ0 thalassemia should be determined.

Recommendation 6

The panel identified the following additional areas in need of research.

• Rigorous studies that include longitudinal outcomes after revascularization surgery for moyamoya syndrome in SCD are needed.
• Multicenter prospective studies or registries for individuals with SCD and moyamoya syndrome should be conducted and implemented as a first step to collect outcome data.

Recommendation 7

The panel identified the following additional areas in need of research.

• Rigorous studies of the safety of tPA use in individuals confirmed to have SCD and acute ischemic stroke are needed.
• Systematic data collection in adults with SCD receiving IV tPA that includes stroke risk factors, presumed stroke etiology after workup, and outcomes should be carried out.
• Implementation science studies designed to identify the optimal clinical practice for administering both tPA and acute blood transfusion therapy to adults with SCD presenting to the emergency department with acute ischemic strokes are needed.

Recommendation 8.1/ Recommendation 8.2/ Recommendation 8.3/ Recommendation 8.3

The panel identified the following additional areas in need of research.

• Better documentation of the prevalence and progression of cognitive impairments in adults with SCD is needed.
• Evaluation of screening and surveillance approaches for cognitive and developmental concerns assessed within the SCD population should be developed, rather than relying on data from broader populations.
• Research evaluating implementation practices that produce the best access to screening, surveillance, and assessment for developmental delays and cognitive impairments, or both, is needed.
• Future research is required to determine which development and cognitive-screening tools have the highest clinical utility in low-middle- and high-income settings.

Recommendation 9.1/ Recommendation 9.2
The panel identified the following additional areas in need of research.

- Testing of specific cognitive rehabilitation strategies for people with SCD is needed.
- The optimal setting for cognitive rehabilitation therapy should be identified.
- The individuals most likely to benefit from cognitive rehabilitation therapy should be identified.

**Recommendation 10.1/ Recommendation 10.2**

The panel identified the following additional areas in need of research.

- A therapeutic strategy for primary prevention of silent cerebral infarcts is needed.
- Imaging strategies to identify subgroups of children and adults likely to have infarct recurrence are needed.
- Alternative treatment strategies, other than regular blood transfusion, for secondary prevention of infarct recurrence in children and adults with silent cerebral infarcts should be developed.
- The clinical benefit of HSCT or gene therapy vs regular blood transfusion therapy for secondary prevention of cerebral infarcts in children and adults with preexisting silent cerebral infarct should be determined.
- The optimal treatment and infarct recurrence rate for children and adults with SCD phenotypes other than HbSS or HbSβ0 thalassemia, and with silent cerebral infarcts should be determined.
- The clinical utility of screening for silent cerebral infarcts in low-middle–income settings with MRI scans is unknown. Furthermore, the neuroradiology expertise is far less available. If feasible, screening for silent cerebral infarcts in children and adults with HbSS in a low-middle–income country should be done for the same reason that the screening occurs in high-income settings.
American Society of Hematology 2020 guidelines for sickle cell disease: management of acute and chronic pain
Recommendation 1a/ Recommendation 1b

The panel identified the following additional areas of research that are needed:

- Additional research focused on patients’ values and preferences in addition to patient-reported outcomes,
- Dissemination and implementation research to assess and address the system-level barriers and facilitators to pain treatment delivery in the ED
- Research focused on the role of delivery of nonopioid analgesic alternatives to opioid analgesia for acute pain management in the ED.

Recommendation 2a/ Recommendation 2b/ Recommendation 2c/ Recommendation 2d/ No Recommendation

The panel identified the following additional areas of research that are needed:

- Delineating nonopioid pharmacological interventions that most robustly affect care and improve outcomes, including multimodal combination therapies;
- Integrating the patient voice into research; there is a need to assess the impact of these interventions on patient-reported outcomes, satisfaction with care, and patient values and preferences;
- Developing new definitions of acute and chronic pain specific to SCD to improve study design and potential of a successful trial;
- Conducting formal cost-effectiveness studies to evaluate the economic impact of nonopioid interventions; these should be updated for evolving costs, take a broader system-level view, and incorporate both patient and societal costs, including long-term chronic complications associated with the interventions;
- Conducting comparative-effectiveness research that reduces risk of bias.

Recommendation 3/ No Recommendation

The panel identified the following additional areas of research that are needed:

- Delineating the impact that these therapies have on patients in acute pain, because few nonpharmacological therapies have been rigorously evaluated in patients with SCD;
- Evaluating the impact that these nonpharmacological approaches have on important patient-reported health outcomes, such as HRQOL or return to baseline pain;
- Determining if nonpharmacological approaches may be effective for the prevention of acute pain in SCD, the treatment of acute pain when it occurs, and the prevention of the development of chronic pain;
- Developing protocols that operationalize the delivery of these therapies in the hospital and ambulatory settings.

Recommendation 4

The panel identified the following areas of research that are needed:
• Delineate aspects of the intervention that most robustly affect care and improve outcomes; many studies include multifaceted interventions for non-ED based care that are often part of a larger comprehensive SCD care model;
• Integrate the patient voice into research; there is a need to assess the impact of these care delivery models on patient-reported outcomes, satisfaction with care, and patient values and preferences;
• Investigate protocols to operationalize personalized treatment in SCD-specific hospital-based acute care facilities;
• Assess integration and efficacy of other nonopioid and nonpharmacological pain treatments in these care delivery models;
• Compare utilization patterns in systems that rely on ED-based care and those that rely on SCD-specific hospital-based acute care facilities; in addition, studies that assess long-term outcomes linked to SCD-specific hospital-based acute care facilities compared with traditional ED-based care are needed;
• Carry out more formal cost-effectiveness studies to evaluate the economic impact of SCD-specific hospital-based acute care facilities; these should be updated for evolving costs and take a broader system-level view and incorporate both patient and societal costs;
• Conduct comparative research to reduce the risk of bias. As a matter of policy, the panel agreed that the development of infrastructure and funding models to support such interventions and investigations into their efficacy and effectiveness is needed. Furthermore, there is a need for research into system barriers and solutions to these barriers to provide the evidence base that can facilitate successful implementation of this recommendation.

**Continuous basal opioid infusion for acute SCD pain treatment - No recommendation**

Because of the absence of data addressing the efficacy, effectiveness, and harms of basal opioid infusions in addition to on-demand opioid treatment in individuals with SCD and the inability of the panel to make a recommendation, the panel discussed the following research priorities for children, adolescents, and adults living with SCD:

• Study benefits and harms associated with basal opioid infusions in children, adolescents, and adults with inclusion of patient-reported outcomes and length of stay as patient-centered end points;
• Comparative-effectiveness research with existing data to determine benefits and harms of basal opioid infusions;
• Safety registries to monitor adverse events in hospitals that administer basal opioid infusions in addition to on-demand opioid PCA strategies.

**Recommendation 6a/ Recommendation 6b/ No recommendation/ No recommendation**

Because of the absence of direct data addressing the efficacy, effectiveness, and harms of nonopioid pharmacological therapies for chronic SCD pain with an identifiable cause, the panel discussed the following research priorities for children, adolescents, and adults living with SCD:

• Conduct RCTs of these nonopioid pharmacological medications in individuals living with SCD to delineate their efficacy, effectiveness, and risks for chronic SCD pain as result of avascular necrosis, leg ulcers, and other etiologies with an identifiable cause,
• Conduct large-scale observational studies to assess the risks/harms of NSAID use in patients with SCD.

**Recommendation 7a/ Recommendation 7b/ Recommendation 7c**

Because of the absence of data addressing the efficacy, effectiveness, and harms of chronic nonopioid therapy in individuals with chronic SCD pain without an identifiable cause beyond SCD, the panel discussed the following research priorities for children, adolescents, and adults living with SCD:

• Research focused on investigations into the use of all nonopioid drugs in patients with SCD;
• Comparative-effectiveness studies between COT and nonopioid pharmacological therapies in chronic SCD pain;
• Research focused on investigations into the use of medical cannabis, cannabis derivatives, and synthetic cannabinoids for chronic pain in patients with SCD. In addition to efficacy, this research should

**Recommendation 8a/ Recommendation 8b/ No recommendation**

The panel identified the following additional area of research that is needed:

• Larger-scale, adequately controlled clinical trials of physical activities and exercise and movement-based programs for chronic pain in SCD to determine the efficacy, safety, and effectiveness of these interventions.

**Recommendation 9a/ Recommendation 9b**

Because of the absence of data addressing the efficacy, effectiveness, and harms of COT in individuals with SCD, the panel discussed the following research priorities for children, adolescents, and adults living with SCD:

• Investigations into the efficacy and effectiveness of COT for chronic pain;
• Investigations into the harms of COT;
• Investigations into patients' values and preferences regarding COT;
• Comparative-effectiveness studies between full agonist opioids and partial agonist opioid therapy, such as buprenorphine therapy;
• Comparative-effectiveness studies between COT and nonopioid pharmacological therapies.

**Recommendation 9c**

The panel identified the following additional area of research that is needed:

• Larger-scale, adequately controlled clinical trials of physical activities and exercise and movement-based programs for chronic pain in SCD to determine the efficacy, safety, and effectiveness of these interventions.

**Recommendation 10**

The panel identified the following additional areas of research that are needed:

• Comparative-effectiveness research to compare chronic transfusions with hydroxyurea and other disease-modifying therapies for recurrent acute and chronic pain;
• Research on the impact of chronic transfusion therapy on the patient-centered outcomes outlined above, including HRQOL;
• Investigations that identify the appropriate trough hemoglobin S percentage for the treatment of recurrent acute or chronic SCD pain.

No recommendation

The panel identified the following additional types of research that are needed:

• Impact of chronic transfusion therapy on chronic pain–related morbidity with assessment of patient-centered outcomes, including HRQOL;
• The impact of chronic transfusion therapy on COT;
• The impact of chronic transfusion therapy on measures of pain sensitization.