Relationships Among Sickle Cell Disease Complications and Their Implications for Cost-Effectiveness Modeling for Therapies With Curative Intent

EE310

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BACKGROUND

- In the United States, approximately 100,000 people have sickle cell disease (SCD), and it is most prevalent among African Americans.[1]
- SCD is caused by a single point mutation in the β-hemoglobin gene that results in the production of sickle hemoglobin.[2,3]
- SCD is a complex, multi-organ, multi-system disorder associated with hemolytic anemia, vaso-occlusion, and an intricate network of relationships among SCD-related events and complications that ultimately results in chronic end-organ damage and early death.[2]
- It is essential to capture the relationships among SCD events and complications in health economic models for SCD therapies, especially in models making lifetime predictions based on one-time therapies with curative intent.
- A comprehensive synthesis of the literature characterizing the relationships among key events and complications associated with SCD has not been performed.

OBJECTIVE

- Our objective was to assess the extent to which associations among select SCD events and complications have been quantified in the literature to inform cost-effectiveness modeling for SCD therapies with curative intent.

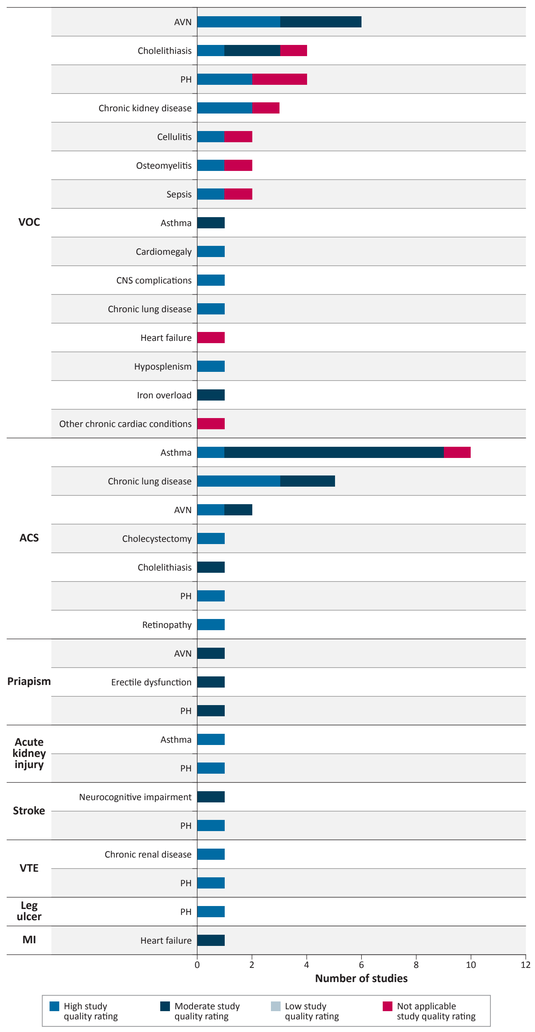
METHODS

- We sought information about associations between key SCD-related events (e.g., vaso-occlusive crisis [VOC], acute chest syndrome [ACS], priapism, splenic sequestration, venous thromboembolism, stroke, infections) and complications (e.g., chronic kidney disease, pulmonary hypertension [PH], retinopathy, cardiovascular disease, avascular necrosis), with a particular emphasis on relationships between VOCs and other events or complications. Although relevant, associations with mortality were not considered in this review.
- We conducted a structured review of the literature published from 2010 through 2020 by searching MEDLINE, conference abstracts, and Google Scholar for original, review, and health technology assessment (HTA) publications quantifying the associations among complications in patients with SCD. Landmark studies published before 2010 also were considered.
- Abstracts were screened against prespecified criteria, and full texts of eligible studies were assessed further for inclusion.
  - Studies were included if the association between select events and complications were investigated in patients with SCD.
  - Original research studies reporting significant findings ($p < 0.05$) were included.
- Original research studies were rated subjectively as high, moderate, or low-quality, and low-quality studies were excluded from further review. Reviews and HTAs without original research were included but did not receive quality ratings.

RESULTS

- Of 977 abstracts screened, 34 studies were included: 31 original research studies, 1 review, and 2 HTAs (see Supplemental Table 1 in the Supplemental Materials).
- VOCs and ACS had the greatest number of quantified associations with the other events and complications included in this review (Figure 1 and Figure 2).
  - Both VOCs and ACS were linked to PH, avascular necrosis, and cholelithiasis, and each was linked to multiple other complications separately.
  - Overall, VOCs were primarily found to be a risk factor for the other events and complications (e.g., recent VOCs increase the risk of pulmonary embolism, stroke, and chronic kidney disease, among other complications) (Figure 3).
  - In contrast, ACS was found to be influenced by the presence of other risk factors (e.g., PH increases the risk of ACS) and was itself a risk factor for other events and complications (e.g., prior ACS increases the risk of AVN) (Figure 4).
- PH also was found to be associated with multiple other events and complications included in this review (Figure 1 and Figure 5).
  - Similar to ACS, PH was found to be influenced by the presence of other risk factors (e.g., recent VOCs increase the risk of developing PH) and was itself identified as a risk factor for other events and complications (e.g., PH increases the risk of venous thromboembolism) (Figure 5).
- Comparatively fewer associations were identified for other cardiovascular and neurological complications (Figure 1 and Figure 2).

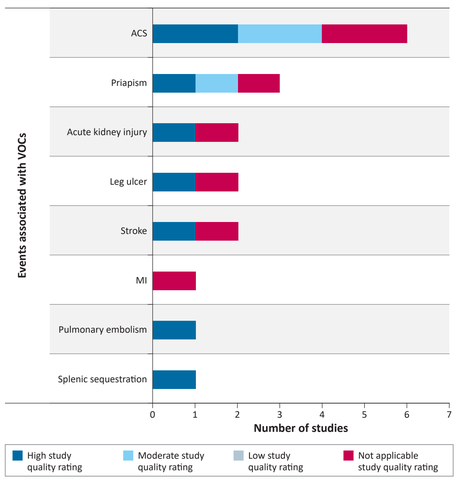
Figure 1. Number of Studies Investigating Select Events and Associated Complications in Patients With Sickle Cell Disease



AVN = avascular necrosis; CNS = central nervous system; MI = myocardial infarction; VTE = venous thromboembolism.

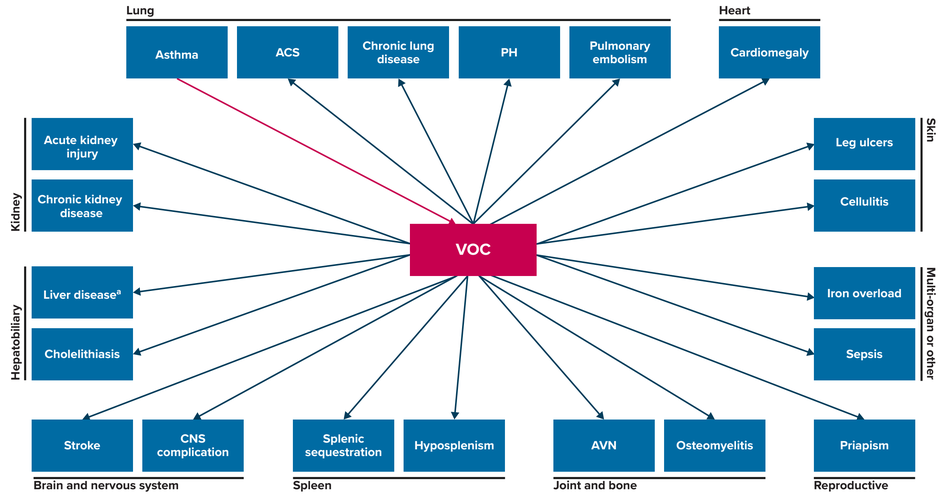
Note: Study quality ratings were not applicable for HTAs without original research and review articles. Studies reporting on multiple relationships were included in multiple categories in the figure. CNS complications included hemorrhage, infarction, and infection.

Figure 2. Number of Studies Investigating Select Events Associated With VOCs in Patients With Sickle Cell Disease



Note: Study quality ratings were not applicable for HTAs without original research or for review articles. Studies reporting on multiple relationships were included in multiple categories in the figure.

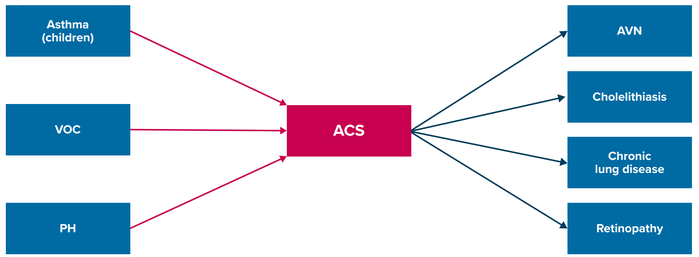
Figure 3. Vaso-occlusive Crises and Associations With Other Events and Complications



Note: The blue arrows indicate that VOC was found to be a risk factor for the indicated events and complications. The red arrow indicates that asthma was found to be a risk factor for VOC.

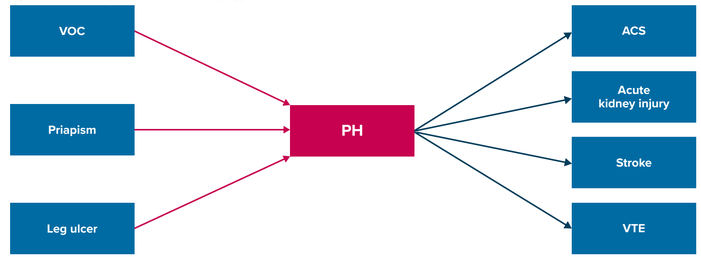
[a] Liver disease included chronic passive congestion and other specified disease.

Figure 4. Acute Chest Syndrome and Association With Other Events and Complications



Note: The blue arrows indicate that ACS was found to be a risk factor for the indicated events and complications. The red arrows indicates that these events and complications were found to be risk factors for ACS.

Figure 5. Relationships Between Pulmonary Hypertension and Select Events



Note: The blue arrows indicate that PH was found to be a risk factor for the indicated events and complications. The red arrows indicates that these events and complications were found to be risk factors for PH.

CONCLUSIONS

- The breadth of relationships identified in this review confirms a complex network of interactions among SCD events and related complications.
- Although VOCs and ACS are well-known drivers of acute medical care in SCD, associations involving more insidious events and complications, such as PH, are also important contributors to the downstream multisystem impacts of SCD.
- Our findings build a foundation for quantifying the interconnectedness of SCD events and complications that is relevant for health economic modeling, particularly when predicting lifetime outcomes for one-time therapies.
- With the possible near-term arrival of one-time gene therapies for SCD, it is essential that health economic models comprehensively reflect this interconnectedness when predicting the potential clinical, economic, and societal impacts of these therapies.

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DISCLOSURES

OMD, WLH, and DM are full-time employees of RTI Health Solutions, an independent research organization. MP was a full-time employee of RTI Health Solutions at the time the study was conducted. MG, AC, JWL are full-time employees and shareholders of bluebird bio. BA reports research funding from American Society of Hematology, Connecticut Department of Public Health, Forma Therapeutics, Global Blood Therapeutics, Hemanext, Health Resources and Services Administration, Imara, Novartis, and Patient-Centered Outcomes Research Institute. BA reports honorarium or consultancy fees from Afimmune, Agios, bluebird bio, CVS/Accordant, Emmaus, Forma Therapeutics, GlaxoSmithKline, Global Blood Therapeutics, Hemanext, Novartis, Novo Nordisk, and Vertex. This study was funded by bluebird bio. RTI Health Solutions contributed to the design and conducted the study under a research contract with bluebird bio.

SUPPLEMENTAL MATERIALS

Please refer to the Supplemental Materials for a detailed listing of the studies included in this review.

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