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# Current challenges for men and women with mild-to-moderate haemophilia

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**Abstract**

Current treatments in the field of haemophilia are changing the phenotype of many patients with severe haemophilia to that of mild haemophilia. Despite this improvement, those with mild-to-moderate haemophilia A and B continue to experience unmet needs. Whereas some patients with mild-to-moderate haemophilia experience similar complications to those of patients with severe haemophilia, they possess several unique attributes. These include a challenging diagnosis and variability in bleeding symptoms and treatment needs. In addition, haemophilia is an under-recognized condition in women even though many women with mild-to-moderate haemophilia experience the same symptoms and complications as men with haemophilia. These women also have their own unique challenges with this disease. This supplement highlights many of the unmet needs in men and women with mild-to-moderate haemophilia. The conclusions of each of these papers reinforce the need for additional research and resources for this patient population.

**Keywords:** haemophilia A, haemophilia B, non-severe haemophilia



*Introduction*

Current treatments in the field of haemophilia are changing the phenotype of many patients with severe haemophilia to that of mild haemophilia. Although this has the potential to improve the quality of life of these patients (1), many unmet needs remain in patients with mild-to-moderate haemophilia. Bleeding phenotypes in patients with mild-to-moderate haemophilia A, especially those with high-moderate haemophilia (factor VIII [FVIII] levels >2%), are variable; many patients only experience bleeding after trauma (2). Therefore, these individuals may lack the ability to recognize a bleed and to self-infuse factor treatments, leading to musculoskeletal complications, including poor joint outcomes. Importantly, patients with mild-to-moderate haemophilia A or B are often not included in or a focus of clinical trials (3); thus, there is a need for large, prospective studies to assess which patients could benefit from innovative treatments and to identify outcomes for this patient population.

*Unique attributes of patients with mild-to-moderate haemophilia*

Patients with mild-to-moderate haemophilia possess several unique attributes, including a challenging diagnosis, variability in bleeding symptoms and treatment needs, and disease complications. Diagnosis of mild-to-moderate haemophilia A is often difficult, owing to significant variability in FVIII levels and bleeding symptoms (4). Notably, the diagnosis may be missed or delayed as a consequence of normal screening test results (3,5). Therefore, many patients with mild-to-moderate haemophilia are diagnosed at an older age than those with severe haemophilia; diagnosis usually occurs after a trauma or surgery (4,5). In patients with moderate and severe haemophilia A, FVIII levels are generally concordant when measured by one-stage or chromogenic clotting factor assays. However, in approximately 30% of patients with mild haemophilia A, discrepancy in the one-stage and chromogenic assays may be seen (6). This discrepancy can occur both ways (ie, either the one-stage or the chromogenic FVIII assay may be higher), and thus, the use of both assays for the measurement of FVIII levels in all patients with mild haemophilia A is recommended. Genetic screening is also an important diagnostic step and can help differentiate between bleeding disorders and avoid misdiagnosis (3).

Owing to the bleeding phenotype in patients with mild-to-moderate haemophilia A and B, some bleeding episodes may not be obvious (7). Therefore, patients are evaluated less frequently in haemophilia treatment centres (HTCs) (4); they tend to seek care only when they experience major bleeding episodes or persistent symptoms. Many patients with mild haemophilia are not able to self-administer factor concentrates, which often results in delays in the management of bleeding episodes. These delays can lead to musculoskeletal complications, including haemophilic arthropathy, leading to pain and decreased range of motion in the affected joints (4,8) even after a single bleeding episode in some cases (9). In addition, the benefits of prophylaxis in this group of patients are unknown and there are no set guidelines or recommendations for participation in different recreational activities or sports due to wide variation in the risk of bleeding (10). Bleeding episodes are less frequent in the majority of patients with moderate haemophilia; however, a subpopulation of these patients has a more severe phenotype. These patients experience joint bleeds and impairment, and most report using prophylactic

treatment at some point during their lifetime (11,12). Some also report joint pain and the use of aids such as crutches or canes (12).

Although it is well known that patients with mild-to-moderate haemophilia A are at a lower risk for the development of inhibitors (3,10,13) than those with severe haemophilia A, certain genetic mutations may indeed be associated with a higher risk. In contrast to patients with severe haemophilia, A, the risk of inhibitor development may not plateau after the first 50 exposure days and patients with mild-to-moderate haemophilia A may carry a lifetime risk of inhibitor development. Furthermore, the development of an inhibitor is associated with a decrease in intrinsic FVIII level as well as loss of response to transfused factor. Moreover, immune tolerance induction regimens have been shown to be less successful in patients with mild haemophilia A (14,15).

*Women with haemophilia*

Women are an important subpopulation of patients with mild-to-moderate haemophilia. Haemophilia is an under-recognized condition in women, but they likely experience the same symptoms and complications as men with haemophilia and they have their own unique challenges with this disease (16,17). Similar to affected men, women with haemophilia experience bleeding episodes after trauma and surgery (18) and can also rarely develop inhibitors (19). Women also face additional challenges with heavy menstrual bleeding (16,18) and an increased risk of bleeding during pregnancy and the postpartum period (17).

*Addressing unmet needs in mild-to-moderate haemophilia*

Each of the articles included in this supplement highlights data on men and women with mild-to-moderate haemophilia from several sources, including 4 surveys and a roundtable meeting of haemophilia experts. This information was presented during the roundtable; unmet needs were identified, and potential solutions were discussed.

The Pain, Functional Impairment, and Quality of Life (P-FiQ) study and the Bridging Hemophilia B Experiences, Results and Opportunities Into Solutions (B-HERO-S) study both examined data across haemophilia severities, with a focus on

patient-reported outcome measures of functional ability, pain, and quality of life. Issues related to access to treatment and decision-making around treatment were identified, as well as problems with mobility and joints. Haemophilia A and B had a significant impact on quality of life, including issues with anxiety and depression, disclosure and bullying, and a limited ability to participate in recreational activities (20).

The Patient Reported Outcomes, Burdens, and Experiences (PROBE) article highlights self-reported survey data focused on three domains: pain, activities of daily living, and quality of life in men and women with non-severe haemophilia. The PROBE study also compared the data from this group with data from men and women with no bleeding disorder. This study identified issues with pain, joint range of motion, and activities of daily living. Importantly, problems with access to treatment for women were also found (21).

The final article summarizes the results of a roundtable meeting attended by a group of haemophilia experts. The participants defined challenges and potential solutions for patients with mild-to-moderate haemophilia. Challenges that were discussed included a lack of haemophilia knowledge among patients, including both the recognition and treatment of bleeding, and some health care providers' disbelief that women can have haemophilia and experience haemophilia-related bleeding. Other challenges were a lack of engagement with the HTC community; issues with access to treatment, disclosure, activities of daily living, and recreational activities; and lost days from school and work. Potential solutions to these challenges were improved diagnostic guidelines, enhanced educational materials for patients, additional studies and scientific publications, and revised transition guidelines (22).

The conclusions of each of these articles reinforce the need for further research on mild-to-moderate haemophilia in both men and women and underscore the necessity for additional resources for this patient population.

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