CEVENFACTA®▼

Eptacog beta (activated)

Stop the bleed
Not the patient

Fast acting:
Median time of 3 hours to successfully treat bleeding episodes using the 225µg/kg initial dose*[1]

Sustained efficacy:
Primary endpoint met with 90.3% of bleeding episodes successfully treated at 12 hours using the 225µg/kg initial dose*[1]

Convenient for patients:
Median 1 injection required to successfully treat bleeding episodes using the 225µg/kg initial dose*[1]

CEVENFACTA® is indicated for the treatment of bleeding episodes and prevention of bleeding in adults and adolescents (≥12 years of age) undergoing surgery or invasive procedures:

- in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU));
- in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.

*: Data from PERSEPT 1, a phase 3 randomised, cross-over study of two initial dosing regimens for the on-demand early treatment and control of bleeding episodes in subjects with congenital haemophilia A or B with inhibitors. Primary endpoint was sustained clinical response (successfully treated bleeding episodes) at 12 hours after administration.[2]

PRESCRIBING INFORMATION

CEVENFACTA▼ (eptacog beta (activated)) 1mg/5mg Powder and 1.1mL/5.2mL solvent for solution for intravenous injection. This medicinal product is subject to additional monitoring to allow quick identification of new safety information.

Consult Summary of Product Characteristics (SmPC) before prescribing
Indications:

Treatment of bleeding episodes and prevention of bleeding in adults and adolescents (≥12 years of age) undergoing surgery or invasive procedures:

- in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU));
- in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.

Treatment should be initiated/supervised by a physician experienced in haemophilia. Dose and duration of treatment depend on location/severity of bleeding or type of surgery/procedure, need for urgent haemostasis, frequency of administration, known responsiveness to FVIIa-containing bypassing agents during prior bleeding events. Results of laboratory assessments of coagulation (PT, INR, aPTT, FVII:C) do not necessarily correlate with/predict haemostatic effectiveness of this medicine. Maximum tolerated doses have not been determined and cumulative daily doses >1025 µg/kg have not been studied. Initiate treatment as soon as bleeding occurs. For mild/moderate bleeding episodes, home therapy should not exceed 24 hours. If severe bleeding occurs in home setting, immediate medical care should be sought. To avoid treatment delay, an initial dose can be administered at home. If an adequate haemostatic response is not achieved e.g. within 24 hours for mild/moderate bleeding episodes, alternative therapies should be considered.

Dosage and administration:
Bleeding Episodes

Type of bleeding	Dosing Recommendation
Mild and moderate	75 µg/kg repeated every 3 hours until haemostasis is achieved. or 225 µg/kg initially. If haemostasis is not achieved within 9 hours, additional 75 µg/kg doses may be administered every 3 hours as needed to achieve haemostasis. Continue therapy to support healing and prevent recurrent haemorrhage after haemostasis to maintain haemostatic plug. Site and severity of bleeding should determine therapy duration.
Severe	225 µg/kg initially, followed if necessary 6 hours later with 75 µg/kg every 2 hours until haemostasis is achieved. Continue therapy to support healing and prevent recurrent haemorrhage. Site and severity of bleeding and use of other procoagulant therapies should determine treatment duration.

Perioperative Management

Type of surgical procedure	Dosing Recommendation
Minor	75 µg/kg immediately before surgery or start of invasive procedure; then 75 µg/kg repeated every 2 hours for the first 48 hours following the initial dose.
Major	200 µg/kg immediately before the surgery, followed by 75 µg/kg every 2 hours for the duration of the surgery. The following post-operative doses may be administered: • First 48 hours: 75 µg/kg every 2 hours • Days 3-4: 75 µg/kg every 2 to 4 hours • Days 5-6: 75 µg/kg every 2 to 6 hours • Days 7-10: 75 µg/kg every 2 to 8 hours • Day 11 onwards: 75 µg/kg every 2 to 12 hours

Following surgery, 75 mcg/kg also recommended prior to drain/suture removal or physical therapy.

Dosing regimen in elderly and in those with renal/hepatic impairment not yet established.

Method of administration: For reconstitution instructions, see SmPC. Administer as intravenous bolus injection over 2 minutes or less.

Contra-indications: Hypersensitivity to the active substance or excipients. Hypersensitivity to rabbits or rabbit proteins.

Warnings and Precautions: *Traceability:* Record name and batch number. *Thrombosis:* May be an increased risk of thromboembolic events if history of congenital or acquired haemophilia receiving concomitant treatment with aPCC/PCC or other haemostatic agents or with history of atherosclerosis, coronary artery disease, cerebrovascular disease, crush injury, septicaemia or thromboembolism. Monitor closely for signs or symptoms of activation of the coagulation system or thrombosis. If laboratory confirmation of intravascular coagulation or presence of thrombosis, reduce or stop Cevenfacta, depending on patient's condition. *Hypersensitivity reactions:* Hypersensitivity reactions, including anaphylaxis, may occur – treatment should be discontinued and immediate medical attention sought. Patients with known IgE-based hypersensitivity to casein may be at a higher risk of hypersensitivity reactions. *Neutralising antibodies:* If treatment does not result in adequate haemostasis, test for neutralising antibodies.

Interactions: None known. Clinical experience with other FVIIa products indicates elevated risk of thrombotic events when used simultaneously with aPCC. It is not recommended to combine this product with aPCC or rFXIII.

Pregnancy and lactation: No data. Avoid use during pregnancy. Discontinue breastfeeding or discontinue/abstain from Cevenfacta during breastfeeding.

Effects on driving/using machinery: Minor influence - dizziness may occur after administration.

Undesirable effects: Consult SmPC for full details. Common (>1/100 to <1/10): Injection site discomfort, injection site haematoma, post-procedural haematoma, injection-related reaction, body temperature increased, dizziness and headache.

Legal Category: POM

Package Quantities and Basic NHS Price: 1mg vial £525.20, 5mg vial £2626

Marketing Authorisation Holder:
Laboratoire français du Fractionnement et des Biotechnologies, Tour W, 102 Terrasse Boieldieu 19ème Étage, 92800 Puteaux, France

Marketing Authorisation Number: PLGB 17469/0011 (1mg), PLGB 17469/0013 (5mg)

Further information is available from LFB Biopharmaceuticals Limited, Suite 104, Spirella Building, Bridge Road, Letchworth Garden City, SG6 4ET Tel: +44(0) 1462 558844

Date of preparation: September 2022

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information, Pharmalex, Tel: 01628 531171 medinfo.uk@pharmalex.com

1. CEVENFACTA® Summary of Product Characteristics.
2. Wang M. *et al*. *Haemophilia*. 2017;23:832–843.

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ORIGINAL ARTICLE

The impact of ankle haemarthropathy in patients with moderate haemophilia

Richard A. Wilkins[1,2] | Heidi J. Siddle[1] | Graham J. Chapman[3] | Elizabeth Horn[2] | Rebecca Walwyn[4] | Anthony C. Redmond[1,5]

[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine (LIRMM), University of Leeds, Leeds, UK

[2]Leeds Haemophilia Comprehensive Care Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK

[3]School of Sport and Health Sciences, University of Central Lancashire, Preston, UK

[4]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK

[5]NIHR Leeds Biomedical Research Centre, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Correspondence
Richard A. Wilkins, Section of Clinical Biomechanics and Physical Medicine, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, UK.
Email: r.a.wilkins@leeds.ac.uk

Abstract

Introduction: Moderate haemophilia has traditionally been associated with less complications than severe haemophilia. Changes in treatment recommendations have highlighted the burden of moderate haemophilia with a subset of patients with a severe bleeding phenotype. The ankle joint is disproportionally affected by ankle haemarthropathy however the impact has not been evaluated in moderate haemophilia, nor the effect on health related quality of life (HRQoL) or foot and ankle outcomes.

Aims: To establish the impact of ankle haemarthropathy in patients with moderate haemophilia.

Methods: A multicentre questionnaire study recruited patients from 11 haemophilia centres in England, Scotland and Wales. The HAEMO-QoL-A and Manchester-Oxford foot and ankle questionnaire (MOXFQ) with total and domain scores measured impact. Measures of pain and ankle haemophilia joint health (HJHS) scores were also collected.

Results: Twenty-nine participants were recruited. HAEMO-QoL A mean (SD) total scores of 10.8 (5.2) of 100 (best health) and foot and ankle specific MOXFQ total scores of 45.5 (24.7) above zero (best outcome) indicate poor HRQoL and foot and ankle outcomes. Average ankle pain over past 6 months of (0–10) 5.5 (SD2.5) was reported and median (IQR) ankle HJHS of 3.0 (1;12.5) to 4.5 (0;9.5) for the left and right ankles.

Conclusion: HRQoL and foot and ankle specific outcomes are poor in patients with moderate haemophilia and ankle haemarthropathy, driven by chronic levels of ankle joint pain. Despite moderate haemophilia being considered less affected by haemarthrosis and haemarthropathy, patients with a bleeding or haemarthropathy phenotype are clinically similar to patients with severe haemophilia A.

KEYWORDS
ankles, haemarthropathy, haemarthrosis, moderate haemophilia, pain

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1 | INTRODUCTION

Haemarthropathy is an inherent clinical feature of severe haemophilia.[1] Clinically moderate haemophilia is less severe in presentation however, those with a bleeding phenotype are reported to have similar or higher bleed rates than patients with severe haemophilia. European studies of treatment in moderate haemophilia report median annual bleed rate 2–8 compared to 1–4 in severe haemophilia.[2,3] In addition, examination of annual joint bleed rates (AJBR) from the United Kingdom Haemophilia's Doctors Organisation (UKHCDO) national haemophilia database report patients with moderate haemophilia had median AJBR between 1 and 5.[2] In the UK treatment of moderate haemophilia has been placed on the clinical burden of haemarthrosis in moderate haemophilia.[4–6] Recently published recommendations by the UKHCDO now endorse the initiation of haemostatic management with prophylaxis treatment regimens if moderate haemophilia patients experience haemarthrosis or clinically significant bleeding.[7] Despite this advancement in treatment recommendations prevention of joints disease is paramount in delaying or halting joint disease.

In adults with severe haemophilia AJBR of the most affected joints of the ankles, elbows and knees are similar, however the ankle joint is disproportionally affected by haemarthropathy.[8] It is not fully understood why the ankle is disproportionately affected by haemarthropathy. Haemarthrosis has been shown to cause synovitis and functional joint change resulting in articular cartilage degeneration, bone damage, loss of joint space which leading to chronic end-stage haemarthropathy.[9–11] Changes to ankle joint structure and function are thought to expose the ankle joint to high contact and shearing forces, however no definitive evidence has been established for this hypothesis.[12–14] The advancements in novel factor and non-factor treatments are yet to be utilised or realised in the management of moderate haemophilia, and therefore the risk of joint disease remains an inherent clinical feature of their haemophilia status.[7]

Health related quality of life (HRQoL) of patients with moderate haemophilia is comparable to the general population in Netherlands, however a subset of patients (23%/ $n = 39$) have been identified who have more frequent episodes of bleeding and haemarthrosis.[3] Worse orthopaedic complications were reported in27% ($n = 46$) of patients who reported joint impairment, chronic pain ($n = 26$ /15%) and the need for orthopaedic aids ($n = 41$ /24%).[3] Similarly a recent Nordic study of joint health and treatment modalities in moderate haemophilia identified generally good joint health, but a proportion ($n = 36$ /25%) of patients with moderate haemophilia had severe haemarthropathy.[6] In adults with severe haemophilia the ankle joint is often cited as the main site of haemarthropathy and pain when compared to the most commonly affected joints of the elbows and knees. The impact of ankle haemarthropathy on overall musculoskeletal health, including foot and ankle outcomes in moderate haemophilia has not been reported.[16–19]

A subset of patients experience worse outcomes than the general moderate haemophilia population and the ankle is disproportionately affected by haemarthropathy in patients with severe haemophilia. Therefore, it was the aim of this paper to quantify the impact of ankle haemarthropathy of patients with moderate haemophilia investigating health related quality of life (HRQoL) and foot and ankle patient-reported outcome measures (PROMs). Secondly, we aimed to report the clinical measures of ankle haemarthropathy, ankle AJBR and levels of patient reported chronic ankle pain.

2 | METHODS

A cross-sectional multi-centre questionnaire was distributed to 18 national sites consisting of 13 haemophilia comprehensive care centres (CCC) and five haemophilia treatment centres (HC). Section A was completed by patients and comprised the validated haemophilia-specific quality of life (QoL) questionnaire for adults (Haemo-QoL-A), and foot and ankle specific outcome measure, the Manchester-Oxford Foot Questionnaire (MOxFQ, foot and ankle) (see Supplementary file A).

The HAEMO-QoL-A is a HRQoL tool consisting of 41 questions scored in subscales of functional activity, role function, worry, consequences of bleeding and emotional impact and treatment concerns.[20,21] Higher scores indicate better health, with raw scores combined to produce a total score with 0 indicating worst health and 100 best possible health.[22] The MOxFQ (foot and ankle) is a PROM used to evaluate foot and ankle pain, consisting of three domains of walking/ standing pain and social interactions. A higher total index score (0–100) indicates worse severity.[23–26]

Demographic details including disease characteristics (haemophilia type, severity), ankle pain status over six months using a numerical pain rating scale (NPRS) (Pain in your ankle over the last 6 months; How painful has your ankle been over the past six months? 0 = No Pain, 10 = Pain as bad as you can imagine)[27] and the presence of haemarthropathy at the most affected joints of the ankles, elbows, and knees. Section B was completed by the centre nurse, allied health professional (AHP) or doctor and included confirmation of disease characteristics, current treatment regime and a recent haemophilia joint health score (HJHS) for the ankles only, collected by the centre specialist haemophilia physiotherapist at the participants clinical review and point of data collection.

3 | STUDY POPULATION

Patients aged 18 and over with moderate haemophilia (A&B) with a consultant diagnosis of ankle haemarthropathy, confirmed by X-ray or magnetic resonance imaging were included. Patients were excluded from the study if they were female or had a different bleeding disorder such as Von Willebrand's disease. Patients with significant co-morbidities such as diabetes or inflammatory arthritis that might lead to altered foot and ankle biomechanics or neurological deficit and pain/ altered sensation were excluded, as were patients with severe haemophilia. Patients with mild haemophilia A and B were excluded as spontaneous bleeding is not reported.[1] Health professionals identified patients at the associated haemophilia CCC or HC. Informed written consent, in line with Good Clinical Practice guidelines, was

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TABLE 1 patient characteristics

Age (years)	48.4 (SD 15.9)
BMI (kg/m^2)	26.4 (SD 6.6)
Haemophilia A (yes)	25 (86.2%)
On demand treatment	14 (48.3%)
Prophylaxis	15 (51.7%)

Values are reported as mean (SD) unless otherwise stated BMI = Body Mass Index, SD = Standard deviation IQR = Interquartile range (25 and 75 percentile).

obtained before completion of the questionnaire. Ethical approval was obtained (IRAS:206141, R&D:PD16/227) and recruitment was undertaken across England, Scotland and Wales, with support from the National Institute for Health Research (NIHR) clinical research network (non-malignant haematology).

4 | DATA ANALYSIS

Data were analysed using Statistical Package for the Social Sciences (SPSS) version 26 (Armonk, NY: IBM Corp). Descriptive analyses are reported as mean and standard deviation, and data not meeting the criteria for normalcy are presented as the median and interquartile range (25th and 75th) for the primary outcomes the Haemo-QoL-A and MOxFQ (foot and ankle) scores and secondary outcomes.

5 | RESULTS

A total of 29 patients with moderate haemophilia were recruited from 11 haemophilia centres across the United Kingdom. Distribution amongst centres consisted of one participant at three centres, two participants at three centres and above three at five centres. Patient characteristics are presented in Table 1. The majority of participants had haemophilia A with four patents (13.8%) having haemophilia B. Mean BMI of 26.4 (SD 6.6) kg/m^2 indicate that patients were overweight (25.0–29.0 kg/m^2).[28] Prophylaxis and on demand treatment were similarly distributed amongst patients.

Details of patient reported haemarthropathy and ankle haemarthrosis rates and ankle NPRS over a 6 month period are presented in Table 2. In patients reporting ankle haemarthrosis patients reporting ankle haemarthrosis reported a median rate of 3.5 (IQR 2;6) for combined left and right ankles. A large proportion of patients reported bilateral ankle haemarthropathy (13/ 44.8%). Multi-joint haemarthropathy was reported in 12 (41.4%) participants reported ankle and knee, nine (31.0%) participants reported ankle and elbow, and four (13.8%) participants had ankle elbow and knee haemarthropathy.

5.1 | HRQoL and PROMs

The individual domain scores of the HAEMO-QoL-A and MOxFQ are presented in Figures 1 and 2, respectively. Patients with moderate haemophilia appear to report low scores across the domains of role function, worry and consequence of bleeding and treatment concerns.

The MOxFQ (foot and ankle) PROM (Figure 2) report higher scores for the walking/ standing domain indicating worse physical function followed by pain.

Total and index scores of the HAEMO-QoL-A and MOxFQ are presented in Table 3. Total scores for the HAEMO-QoL-A were low indicating worse HRQoL. The MOxFQ (foot and ankle) index were similar for combined scores, no haemarthrosis and patients reporting ankle haemarthrosis over the previous 12 months. Both HAEMO-QoL-A and MOxFQ confidence intervals were within the boundaries of each condition (total, no bleed, bleed).

6 | DISCUSSION

This study has provided insight to the burden of moderate haemophilia in a cohort of patients with ankle joint haemarthropathy. HRQoL and foot and ankle outcomes were poor and driven by chronic levels of ankle joint pain. Multi-joint haemarthropathy was reported in 72.4% (n = 21) of patients which suggest that in moderate haemophilia patients with a bleeding or haemarthropathy phenotype have similar musculoskeletal complications to severe haemophilia A.

The HRQoL of patients with moderate haemophilia in the Netherlands report majority of patients had few physical limitations measured using the haemophilia activities list and QoL to the general population.[15] SF-36 scores were similar to the general population across all domains of the SF-36, however a subset of patients were more affected by joint disease with worse QoL.[15] In comparison the moderate patients in this study were recruited because they had ankle joint haemarthropathy and therefore worse joint disease than the general moderate haemophilia population. Patients with ankle haemarthropathy had poor HRQoL with low total and domain scores of the HAEMO-QoL-A with the patient's particular affected by concerns of role function, worry, consequence of disease and treatment concerns. This reflects the historical treatment of moderate haemophilia where prophylaxis factor treatments were more likely to be offered to severe haemophilia. Similarly having moderate haemophilia was considered the clinical the equivalent of having severe haemophilia and treated by prophylaxis.[7] Therefore worry about treatment access and self-management and the long term consequence are a problem for patients with moderate haemophilia.

Historically patients with severe haemophilia were treated within the range of moderate factor levels by maintaining trough levels above 1IU/dl and tailoring prophylaxis to activities affording great protection against bleeding.[28] More recently patients with moderate haemophilia and factor levels between 1–3 IU/dl have a more severe clinical phenotype and those with levels of 3–5 IU/dl were less affected by bleed complications.[3] Patients within this impact study with moderate haemophilia may not have had access to prophylaxis in early years (below five years of age) or are still treated by on demand do not have the same factor cover and therefore the risk of bleeding during

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TABLE 2 Clinical characteristics

Annual ankle joint bleed rate	2.9 (SD 5.0)/ 1 (IQR 0; 4)
Ankle joint bleed over 12 m period (yes)/rate (mean SD/ median)	N = 16 (55%) 2.9 (SD 5.0) 3.5[2,6]
Average ankle pain over the past six months (0-10)	5.5 (SD,2.5)
Ankle HJHS (median, IQR)	Left 6.5 (SD 6.1), 4.5 (1; 12.5) Right 5.3 (SD 6.1), 3.0 (0 9.5)
History of ankle surgery (yes)	6 (20.7%)
Ankle haemarthropathy one/ both	16 (55.2%)/ 13 (44.8%)
Elbow haemarthropathy one/both	7 (24.1%)/ 3 (10.3%)
Knee haemarthropathy one/ both	8 (27.6%)/ 4 (13.8%)

Values are reported as mean (SD) and/or median (IQR), SD = Standard deviation IQR = Interquartile range (25 and 75 percentile), HJHS = haemophilia joint health score.

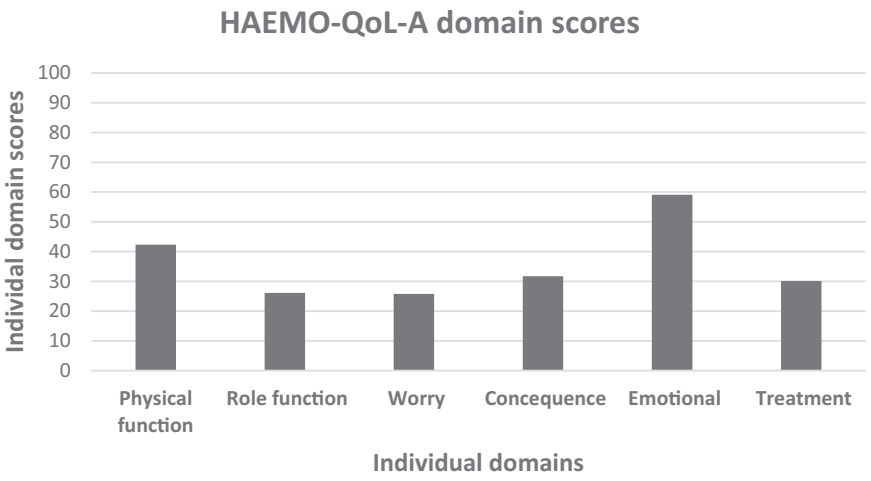

FIGURE 1 Mean HEAMO-QoL-A domain scores

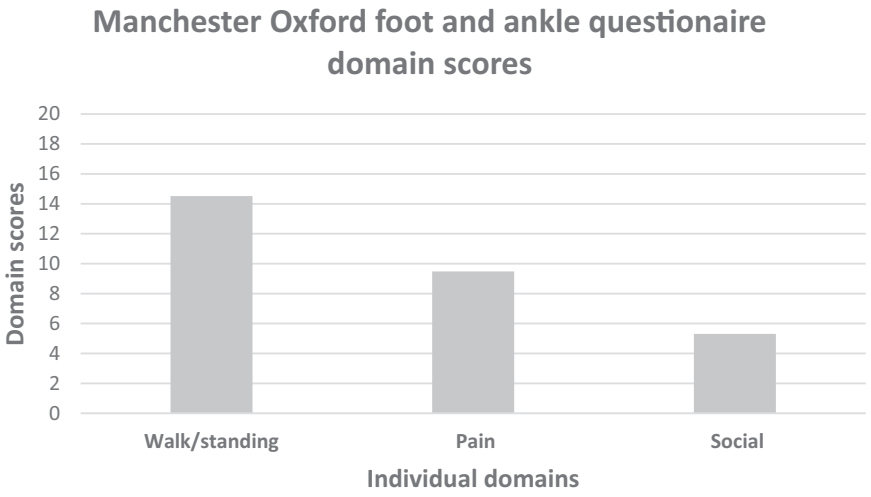

FIGURE 2 Mean MOxFQ (foot and ankle) domain scores

activities of daily living (ADL) are at risk of bleeding, or treatment after a bleed event.[7]

AJBR was only reported for the ankle in this study, as we aimed to take particular focus on the ankle joint based on the disproportionate levels of ankle haemarthropathy reported in severe haemophilia. Patient reported AJBR were high when compared to Scott et al (2019) study of treatment and outcomes in severe and moderate haemophilia with total median (IQR) AJBR 2.0 (.0–5.0) in those reporting prophylaxis and 5.0 (2.0-–15.3) on demand treatment.[2] Over the previous 12 months 55% (n = 16) reported a bleed over the previous six months with median ankle AJBR in this study of 1.0 (0–4). Whilst the number was low a single significant or repeated minor haemarthrosis is known to damage cartilage and trigger the development of haemarthropathy.[29-31]

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TABLE 3 Total and index score of the HAEMO-QoL-A and the MOxFQ (foot and ankle)

HAEMO-QoL-A[†] Mean (SD)/ Median (IQR)	Physical function	42.3 (13.9)/ 44.4 (36.7; 48.9)
	Role Function	26.1 (23.3)/ 18.2 (12.8; 32.7)
	Worry	25.8 (26.0)/ 20.0 (2.0; 38.0)
	Consequence of bleeding	31.7 (26.5)/ 22.6 (11.4; 42.9)
	Emotional impact	59.1 (19.7)/ 63.3 (46.7; 73.3)
	Treatment concerns	30.1 (30.5)/ 26.7 (6.7; 46.7)
	Total score	**35.8 (17.4)/ 32.8 (25.1; 41.1)**
	Bleed 12 m (n = 16)	**36.7 (20.8)/ 28.7 (24.6; 45.1)**
	No bleed 12 m (n = 13)	**34.8 (12.6)/ 33.0 (26.2; 36.7)**
MOXFQ (foot and ankle)[‡] Mean (SD)/ Median (IQR)	Walking/ standing	14.5 (8.0)/ 15.0 (11.5; 20.0)
	Pain	9.5 (5.1)/ 11.0 (6.0; 12.5)
	Social	5.3 (4.0)/ 4.0 (2.5; 7.5)
	Total score	**45.8 (24.7)/ 45.3 (36.7; 57.8)**
	Bleed 12 m (n = 16)	**50.5 (27.4)/ 51.6 (42.6; 57.8)**
	No bleed 12 m (n = 13)	**40.0 (23.4)/ 40.6 (25.0; 52.3)**

Values are reported as mean (SD) *and/or median (IQR)* [†]*best health related quality of life (HAEMO-QoL-A) is equal to 100 for each domain and total score,* [‡]*Best PROMs (MOXFQ) are equal to zero.*

Patients with moderate haemophilia are considered to be less affected by the complications of bleeding such as haemarthropathy when compared to severe haemophilia, but this was not the case in this study. The sample recruited to this study (n = 29) is a relatively small sample size, or findings are similar to De Juili et al. (2014), who in a much larger sample (n = 75) identified that whilst the majority of those with moderate haemophilia have fewer bleeds and lower bleed-related complications a proportion of patients are severely affected by haemarthrosis, disability and reduced HRQoL.[28] Måseide et al also identified a subgroup of patients with more severe joint haemarthropathy in Nordic haemophilia patients with moderate haemophilia A and B.[6] In this impact study we aimed to recruit this proportion of patients with ankle haemarthropathy, therefore it would be expected that they would represent a more affected cohort with poor HRQoL and Foot and ankle PROMs than previously reported.

The foot and ankle PROMs of patients in this study were equivalent to OA cohorts awaiting ankle fusion and arthroplasty surgery MOXFQ total scores and individual domains of walking/ standing pain and social interactions indicating chronic joint pain and disability.[32] There are few studies that report specific foot and ankle PROMs in haemophilia and patients with moderate haemophilia only reported in one study with a small number of moderate patients (n = 3).[12] Both studies report that moderate levels of haemarthropathy correlated with moderate impact using a recognised foot and ankle PROM.[16,17] In the presence of established joint haemarthropathy has been reported to "burn out" as the levels of joint disease become chronic and the rates of joint haemarthrosis decline.[33] In this study the median ankle HJHS were between 3.0 and 4.5 which suggest the patients had moderate levels of haemarthropathy. Therefore, the rates of ankle haemarthrosis represent joints that are pathological with ongoing synovial hypertrophy that is more likely to be damaged due to abnormal ankle joint biomechanics and pathological joint changes which predispose the joint to increased risk of bleeding. The findings of this study indicate that patients are moderate in disease type, however joint disease is similar to patients with severe haemophilia and ankle haemarthropathy as well as patients reporting elbow (24.1%) and knee (27.6%) haemarthropathy suggesting that patients in this study have multi-joint haemarthropathy.[6]

Ankle pain in this study were comparable to a large American survey of the experience of pain and haemarthropathy reported a mean (SD) NPRS (0–10) patient-reported persistent pain of 4.32 of 10 (SD, 2.53) in moderate and 4.25 of 10 (SD, 1.90) in those with severe haemophilia.[32] The level of haemarthropathy was not directly reported in the American study and whilst the healthcare system differs from the UK, scores were similar to this studies patients. This would suggest our data is representative of haemophilia in both acute and chronic pain, driven by synovitis, and chronic joint disease despite the less severe haemophilia classification.[32]

Ankle joint pain in problematic in clinical practice accounting for 45% of joint pain in haemophilia and multi-joint haemarthropathy.[18] Unlike the other affected joints of the knees and elbows the complexities of the ankle expose the joint to high forces during the loading phase of the gait cycle with ground reaction forces up to five times the patient's body weight.[34] The high ground reaction forces combined with limitations in ankle range of motions caused by ankle haemarthropathy make offloading difficult during ADL.[16,34]

It is now recommended that patients with moderate haemophilia should be offered prophylaxis if they experience clinically significant bleeds or joint bleeding to prevent joint haemarthropathy.[35,36] Similarly in the UK it is recommended that patients with moderate haemophilia are assessed by a specialist physiotherapist at the same

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frequency as those with severe haemophilia to detect joint pathology in children, monitor joint health in adults and direct prophylaxis treatment.[35]

The ankle joint is clinically difficult to assess with only access to the anterior and posterior margins with the HJHS reported to only moderate correlate with pathological changes identified using magnetic resonance imaging (MRI).[37] At the ankle it is recommend that where a patient presents with early ankle joint disease and a HJHS of less than 3 additional imaging such as MRI or musculoskeletal ultrasound (US) imaging should be considered.[37] The use of imaging modalities such as point of care US provides a cheap and repeatable addition to clinical assessment and have been shown to be effective at identifying early joint changes at the most affected joints of the ankles, elbows and knees.[38]

The study findings advocate the need for targeted pharmacological and non-pharmacological interventions in moderate haemophilia. A recent systematic review of pain management highlighted that studies involving physiotherapy interventions lacked methodological trial designs to make any conclusive recommendations for pain management.[39] Similarly, there is some low-quality evidence that the use of foot orthoses and footwear interventions reduce pain, however currently, there is no conclusive evidence sufficient to change clinical management and guidance.[40]

7 | LIMITATIONS

This study is limited by the sample size, whist patients were recruited from multiple sites our finding suggest only a small proportion of patients report ankle haemarthropathy, however we aimed to recruit patients with ankle haemarthropathy and our sample size is similarly to subsets in other studies with patients who have worse haemarthropathy.[3,6] Trough levels and treatment levels were not reported in this study which may have provided further clinical relevance to findings, however the patient reported in this study already have haemarthropathy and compilations related to haemarthrosis. The finding of this study do however, support recently published recommendations on the initiation of primary and secondary prophylaxis treatment of moderate haemophilia to prevent haemarthrosis and prevent or delay the progression of haemarthropathy.[7]

8 | CONCLUSION

Moderate haemophilia with a bleeding phenotype displays similarities to severe haemophilia in the development of haemarthropathy. This study demonstrates that a subset of patients with moderate haemophilia and ankle haemarthropathy who report poor HRQoL, marked increase in foot and ankle PROMs, and ankle pain similar to patients with severe haemophilia A. AJBR remain similar to the UK THUNDER study and whist levels of joint damage are lower than severe haemophilia, the age of the patients in this study suggest joint disease is delayed and driven by repeated haemarthrosis. The findings of this study highlight the need for early initiation of pharmacological treatment regimens, closer monitoring of joint health in moderate haemophilia and target pharmacological and non-pharmacological interventions for the management of ankle haemarthropathy in haemophilia.

AUTHOR CONTRIBUTIONS

The study was conceived by RAW, AR, GC and HS. Analysis was undertaken by RAW and RW. The manuscript was written by RAW. Subsequent drafts were edited and approved by all authors.

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CONFLICT OF INTERESTS

RAW has received conference registration fees and support for travel from Roche. RAW has received an HEE/NIHR clinical doctoral research fellowship which funded this work and is a current NIHR development skills enhancement award holder. ACR is an NIHR Senior Investigator and has received funding from NIHR who also funded this research. HJS is an NIHR Senior Clinical lecturer and has received funding from NIHR who also funded this research.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Richard A. Wilkins https://orcid.org/0000-0003-1885-5472
Heidi J. Siddle https://orcid.org/0000-0002-6015-332X
Graham J. Chapman https://orcid.org/0000-0003-3983-6641

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Elizabeth Horn https://orcid.org/0000-0001-5394-6324

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agement of ankle haemarthrosis and haemarthropathy in haemophilia. *Haemophilia*. 2022;28(3):422-436.

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