Joint replacement for the management of haemophilic arthropathy in patients with inhibitors: A long-term experience at a single Haemophilia centre

Christian Carulli1 | Matteo Innocenti1 | Silvia Linari2 | Massimo Morfini3 | Giancarlo Castaman2 | Massimo Innocenti1

1Department of Orthopaedic Surgery, University Hospital of Florence, Florence, Italy
2Center for Bleeding Disorders and Coagulation, University Hospital of Florence, Florence, Italy
3Italian Association of Haemophilia Centres (AICE), Italy

Correspondence
Matteo Innocenti, Department of Orthopaedic Surgery, University Hospital of Florence, Largo Palagi 1 50139 Florence, Italy.
Email: innocenti.matteo11@gmail.com

Abstract
Introduction: The association between haemophilia and the so-called ‘inhibitors’, alloantibodies against the infused factor able to neutralize its clotting activity, is a very rare condition. Those sporadic patients suffer of an even more severe arthropathy and performing primary or revision arthroplasty become truly challenging. Literature about this topic is scarce, consisting in small case series, high rates of complications and mid-term follow-ups.

Aim: The purpose of this study is the assessment of the long-term outcomes of primary and revision arthroplasty performed in a population of patients with inhibitors, the more consistent to date reported at a single haemophilia centre.

Methods: We reviewed the records of 18 patients with inhibitors (26 procedures) between 1999 and 2017, divided in two groups. Group A [primary total Knee-Hip arthroplasty (TKA-THA)]: 13 patients underwent 19TKA and 2THA; and B (revision): 5 subjects underwent 3rTKA and 2rTHA. All patients received the same haematological prophylaxis (rFVIIa). Haemophilic Joint Health score and VAS, and X-rays were recorded pre- and postoperatively. The survival rate of all primary implants was assessed.

Results: The median follow-up was 12.2 years (3-21) for group A, 8.6 years (4-12) for B. Few complications have been reported; the overall survival rate was 94.7% at 15 years. All patients reported satisfaction, pain reduction and improved functional ability.

Conclusion: Primary and revision TKA/THA in haemophilic subjects and inhibitors may be nowadays considered safe and effective if performed in dedicated multi-disciplinary centres. The use of continuous infusion of rFVIIa showed an adequate haemostatic effect and low rate of complications. As expected, revisions are more prone to complications compared to primary arthroplasty.

KEYWORDS
haemophilia, hip arthroplasty, infection, inhibitors, knee arthroplasty, loosening, oxidized zirconium, revision
1 | INTRODUCTION

Rare diseases are challenging conditions for patients, physicians and society: among these pathologies, one of the most frequent is haemophilia. Haemophilia is a X-linked bleeding disorder due to the deficiency of coagulation factor VIII (haemophilia A) and IX (haemophilia B), in the past associated to high morbidity and mortality. The hallmark of the disease is represented by recurrent joint bleeding, with the inherent risk of early haemophilic arthropathy, a severe type of secondary arthritis, which causes significant morbidity and impacts on the quality of life. After the introduction of the modern haematological care, based on prophylaxis approach, that is the periodic administrations of plasma-derived or recombinant coagulation factors to prevent rather than to treat bleeding, this complication has significantly decreased. However, the negative effects of joint bleeding occurring before this modern approach are still present in a significant proportion of adult patients. Haemophilic arthropathy begins with the first joint bleedings, either spontaneous or traumatic, usually during the first years of life. It consists in progressive and irreversible alterations produced by the direct and indirect toxicity of the free blood in the joint space, triggering synovium hypertrophy and inducing cartilage damages: knee, ankle and elbows are the most frequent involved joints, due to their high representation of synovial tissue. The results of frequent bleedings are pain, swelling, flexion contractures, chondral erosions, malalignment and finally severe deformity with functional disability and worsening of quality of life.

Until few decades ago, the orthopaedic treatment of haemophilic arthropathy usually consisted in a limited number of procedures: open synovectomy, joint arthroplasty, fusion and even amputation in severely complicated cases. Much more is nowadays feasible under the supervision of multidisciplinary teams dedicated to haemophilia. The modern haematological management, the early detection of joint alterations by periodic visits and ultrasound (US) evaluation, the subjects’ education for a safe lifestyle since childhood and the outcomes of conservative orthopaedic approaches have improved both the results of such disease and the quality of life of these generally young patients. Unfortunately, some patients develop the so-called ‘inhibitors’, which are alloantibodies against coagulative factors used for treatment (generally after the first 10-20 infusions), and able to neutralize their clotting activity. Thus, in persons with haemophilia (PWH) and inhibitors generally replacement therapy does not work, and by-passing agents must be used instead, with lesser efficacy in controlling bleeding episodes. As a consequence, these patients have a more severe arthropathy with an earlier onset compared to subjects of the same age and worse quality of life. Orthopaedic approaches to PWH and inhibitors have been more carefully performed than those without inhibitors. The most common surgery is joint replacement, in particular Total Knee Arthroplasty (TKA) due to the usually more severe arthropathy of the knee with respect to other target joints. Less common is the end-stage haemophilic arthropathy affecting the hip joint, and often PWH and inhibitors undergoing a THA have already received a previous TKA. As a matter of fact, the number of patients and procedures reported in the few papers dealing with this surgery is very limited compared to subjects without inhibitors. Despite good functional outcomes, such procedure has been usually associated to high rates of complications, mostly related to septic loosening and recurrent postoperative bleedings. Furthermore, long-term follow-up results have rarely been reported.

The aim of the present study is the assessment of the long-term outcomes of joint arthroplasties performed in a population of PWH with inhibitors, the more consistent to date reported at a single haemophilia centre.

2 | MATERIALS AND METHODS

2.1 | Patient selection

We retrospectively reviewed the medical records of all PWH followed at the authors’ institution from 1999 to 2017. The institutional Review Board approved the study, and all patients were informed of characteristics of the study and follow-up at the time of surgery, giving their consent. The study population included adult PWH and inhibitors (inhibitors titre > 5.0 Bethesda units/mL) who underwent joint replacement or revision arthroplasty with a follow-up of at least 3 years. The overall population of patients with inhibitors was represented by 22 PWH (30 procedures). Two cases (one primary hip replacement and one revision knee arthroplasty) were excluded because of a short follow-up (less than 3 years of follow-up); two further cases were excluded because surgery was performed by using an experimental haematological prophylaxis with activated recombinant factor VII (rFVIIa) and emicizumab (a recently introduced humanized bispecific monoclonal antibody). Thus, the final population consisted of 18 PWH for a total of 26 procedures. Depending on the type of orthopaedic approach, the study population was then divided in two groups (group A and group B) in order to obtain a homogeneous evaluation, and to avoid bias in the assessment of clinical outcomes.

Group A consisted of 13 adult patients undergoing primary joint replacement: they underwent 19 Total Knee Arthroplasties (TKA) and 2 Total Hip Arthroplasties (THA) (Table 1). Group B was composed of 5 patients treated by revision arthroplasty. In 3 cases, a revision of a knee arthroplasty (rTKA) was performed, while in 2 cases a revision of a hip arthroplasty (rTHA) was made. The reasons for revising were deep infection in three cases (2 rTKA, 1 rTHA) and aseptic loosening in the remaining two cases (1 rTKA, 1 rTHA) (Table 2).

2.2 | Surgical procedures

Group A: all TKA were Genesis II® Posterior Stabilized implants with oxidized zirconium femoral components and in selected cases with cementless stems (Smith & Nephew), while all THA were Regenerex®/Taperloc® with ceramic femoral heads (Zimmer Biomet). Seven patients had bilateral staged procedures, while
one had a staged TKA and THA. Three patients undergoing TKA had a previous open synovectomy during childhood. In these subjects, surgery was performed using the previous scar, in all cases a medial parapatellar approach; the remainders were operated by a longitudinal incision with deep medial parapatellar approach. The patients undergoing THA were operated by a modified lateral direct approach (with a minimal split of gluteus medius muscle, without any osteotomy). In no case, a tibial tuberosity osteotomy was needed. Tourniquets were used for TKA. In no case, drains were used.

Group B: Legion Revision® Posterior Stabilized implants with oxidized zirconium femoral components, cementless stems and cemented wedges (Smith & Nephew) were used in all rTKA cases except one. This latter patient underwent a revision surgery procedure
with a rotating hinge implant with cementless stems and a cemented trabecular metal femoral cone (Zimmer Biomet), after being operated for primary arthroplasty at the authors’ Institution (Figure 1), while all the other procedures were carried out in subjects treated elsewhere for the first operation. The previous surgical scars were used for all the patients, and no other surgical step to expose the joint was carried out. Drains were used only in the single case of rTHA and removed 24 hours after surgery. The rTHA were performed using a Link system (Waldemar Link GmbH); Partial Pelvic Replacement (PPR) ring with a cemented Bi-mobile dual mobility cup within it at the acetabular side, and the MP Reconstruction System at the femoral side. In both cases, the previous surgical scar was used with a postero-later surgical approach.

2.3 | Haematological prophylaxis

From the haematological point of view, all patients were treated by a continuous intravenous of rFVIIa (Novoseven®, Novo Nordisk). A preoperative bolus of rFVIIa (90-150 µg/kg b.w.) was administered thirty minutes before general anaesthesia, and every 2 hours until wound suturing, followed by continuous infusion using 50 µg/kg days 1-3, 30 µg/kg days 4-9 and 15 µg/kg days 10-14 after surgery.

2.4 | Clinical and radiological evaluation

All patients were followed at our haemophilia centre, involving a dedicated multidisciplinary team including haematologists, orthopaedic surgeons, anaesthesiologists, physiatrists, physical therapists and nurses.

Patients were clinically evaluated for range of motion (ROM) and by Visual Analogic Scale (VAS 0-100 mm), Haemophilia Joint Health Score (HJHS), X-rays for Petterson’s score and Magnetic Resonance Imaging (MRI) in case of primary arthroplasty. Subjects undergoing revision arthroplasty were also evaluated by standard radiology, Computerized Tomography (CT) and blood examinations to ascertain any septic condition (C reactive protein—CRP, Erythrocyte Sedimentation rate—ESR). Finally, in selected surgical cases with a clinical suspicion of infection regardless borderline CRP/ESR levels, a joint aspiration for both bacterial culture and assessment of synovial with blood cell count, synovial neutrophil percentage and leukocyte esterase were performed.

Clinical and radiographic parameters were evaluated preoperatively and after surgery at specific intervals. Intraoperative parameters were recorded (blood and bone loss, use of grafts or devices, type of implant and fixation, time of surgery, time of pneumatic tourniquet). Similarly, all complications, both intraoperatively and in the postoperative period, were evaluated. Postoperative major bleeding was defined as an unexpected or prolonged bleeding causing haemodynamic instability (reduction of haemoglobin level of 20 g/L-1.24 mmol/L-1): in case of further reduction of the haemoglobin level, packed red cell transfusions were provided. Areas of osteolysis or radiolucency and the presence of periarticular ossifications were also evaluated at every X-ray after surgery. After the admission for a period of 7-10 days in the orthopaedic ward, all patients were moved to the in-patient rehabilitative section at the same hospital, for at least two other weeks, in order to complete the rehabilitation following an internal dedicated protocol.

2.5 | Statistical analysis

Statistical analysis was performed using SPSS® statistics software (IBM®). The non-parametric Kaplan-Meier estimator was used to assess the survival rate of all primary implants, considering aseptic or septic loosening requiring revision as endpoint. A subjective analysis to assess the outcome of subjective evaluation was performed using Fisher’s exact test to allow the comparison cohorts with small sample sizes and so to avoid inadequate approximation, taking P-values

FIGURE 1 Left TKA in a 46-y-old PWH and high-titre inhibitors operated by a PS primary implant with oxidized zirconium femoral component and a cementless tibial stem (A). After recurrent bleedings (despite his haematological prophylaxis), an aseptic failure of the femoral component and at the tip of tibial stem (white arrows) were recorded (B). A revision was then performed with a rotating hinge implant, using a cemented trabecular metal femoral cone and cementless stems with good clinical outcomes (C, D)
of <.05 as statistically significant with a 95% confidence interval. A multivariate logistic regression model was constructed using primary arthroplasties and revision arthroplasties to assess the risk factors for both major bleedings and global ROM < 70° (the latest only for primary and revision knee arthroplasties).

3 | RESULTS

No patient was lost at follow-up. The median follow-up was of 12.2 years (range: 3-21) and 8.6 years (range: 4-12) for groups A and B, respectively. Group A: The median age at the time of surgery was 32 years (range: 25-56); the median Petterson's score was 11 (range: 10-12) (Table 1). Group B: The median age at the time of surgery was 49 years (range: 37-51 years); the median interval from the index operation and revision was 5.2 years (range: 4-11 years) (Table 2). The overall median hospital stay (orthopaedics ward plus in-patient rehabilitation) was 28 days (range: 23-41) for group A and 36 days (range: 26-49) for group B. All patients reported satisfaction, pain reduction and improved functional ability, in terms of VAS and HJHS for both hips and knees and in terms of ROM for knees (P < .005; Table 3).

3.1 | Complications and relative treatments

Five complications were reported. Two in group A: a case of non-fatal pulmonary embolism the day after a TKA (managed by intensive therapy unit monitoring and short-term low molecular weight heparin treatment), and a postoperative major bleeding after a TKA (managed by increasing the dose of rFVIIa administration, not requiring blood transfusion). Three postoperative bleedings occurred in group B (2 rTHA and 1 rTKA); two managed by increasing rFVIIa dosing and one requiring blood transfusions. No intraoperative haemorrhages were recorded; no septic complications were reported in both groups. No adverse events or intolerance was recorded for the haematological prophylaxis. No case of progressive area of osteolysis was found at the radiologic follow-up; however, radiolucency lines <2 mm were found after 3 years in 4 TKA (mostly in the medial tibial plateau and anterior femoral cortex) without apparent increase over the years. No significant radiolucent lines were found in the revision arthroplasties. No periarticular ossifications were recorded. A single TKA failed for aseptic loosening 4 years after surgery and a rTKA was performed, with global satisfaction of the patient (shifting from group A to group B).

3.2 | All-cause survivorship

The Kaplan-Meier curve showed a satisfactory survival rate of prosthesis in group A with an overall survival of 94.7% and a SD of 0.051 (Figure 2). No failures or indications for a new revision were recorded in group B.

Multivariate logistic modelling showed that revision arthroplasty was a statistically significant contributor to both postoperative ROM and postoperative bleeding (Table 4). Indeed, revision arthroplasty in PWH and inhibitors was a negative risk factor for both parameters (odds ratio: 0.946 for ROM; 0.977 for bleeding).

4 | DISCUSSION

In the present study, the long-term clinical results and implants’ survivals of primary and revision hip and knee arthroplasties in PWH and inhibitors over a period of almost 20 years are reported. At the best of our knowledge, this is the most consistent study performed in such complex and rare disease, with a low percentage of complications and the longest follow-up. A great variety of conservative and surgical orthopaedic procedures in haemophilic patients with mild to moderate arthropathy have shown noteworthy results during last decades, when performed in dedicated facilities.15,16,19,22–26,28–30 Differently, surgery in PWH and inhibitors has been more rarely performed and associated to high risk of complications, mainly bleedings and infections, even in specialized centres.6,15,19,22 A specific surgical procedure proposed decades ago in underage and young PWH and inhibitors was the open synovectomy.33 Such operation consisted in the full removal of synovial tissue (usually from knees, elbows and ankles34) by an arthrotomy, usually followed by the application of a cast for at least three or four weeks. From a side, bleedings stopped immediately after surgery, with a good pain relief; on the other side, the early violation of a joint in very young subjects, the secondary

TABLE 3 Clinical outcomes

<table>
<thead>
<tr>
<th></th>
<th>VASa</th>
<th>HJHSa</th>
<th>ROMb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group A</td>
<td>Group B</td>
<td>Group A</td>
</tr>
<tr>
<td>Pre-op</td>
<td>68 mm (54-86 mm)</td>
<td>72 mm (67-84 mm)</td>
<td>14 (12-18)</td>
</tr>
<tr>
<td>Postop</td>
<td>18 mm (12-26 mm)</td>
<td>26 mm (24-30 mm)</td>
<td>6 (4-8)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;.005</td>
<td>&lt;.005</td>
<td>&lt;.005</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: HJHS, Haemophilic Joint Health Score; VAS, Visual Analogic Scale in mm (0-100 mm).

aFor both knee and hip primary/revision arthroplasties.

bOnly for knee primary/revision arthroplasties.
stiffness due to the use of the cast and the new formation of synovial tissue in a couple of months, have historically been implicated in the recurrence of the conditions and an even worse progression of the arthropathy in PWH and inhibitors. 35 Recently, Mingo-Robinet et al. reported the long-term outcomes of ankle’s open synovectomy in young haemophilic patients, confirming first the improvement in clinical scores and second the better control of future recurrent bleedings. They indeed noticed that, even if recurrence of bleedings is frequent, it is less severe, less painful and requiring less factors replacement. But, at the same time, those authors confirmed that open synovectomy does not stop the progression of the arthropathy but just slightly retards it. These facts, in combination with the usually worse target joint conditions compared to subjects without inhibitors and the high costs of replacement therapy with by-passing agents, prompted orthopaedic surgeons for many years to discourage such patients from orthopaedic treatments. Thus, the quality of life of subjects with inhibitors has been reported to be rather poor.12-14,36

Key improvements in the multidisciplinary management of PWH and inhibitors now allow to perform several procedures with good efficacy and safety. Also, in children with symptomatic synovitis or early arthropathy, intra-articular injections (viscosupplementation, synoviorthesis) have been effectively associated with good outcomes in terms of pain relief, functional recovery and reduction of bleedings.7-11 Very young or adult patients with mild to moderate painful arthropathy associated with recurrence of bleedings related to inhibitors have found relief with some minimally invasive procedures as arthroscopic synovectomy and debridement, in order to delay a more invasive procedure.15,19,21,22 Nevertheless, primary arthroplasty (hip, knee, ankle) with modern implants may now allow pain resolution, restoration of static and dynamic function, and a longer survivorship of the device with respect to the early generation of implants also in PWH and inhibitors.18,23,27,29,37,38 Moreover, complications of TKA and THA may be managed by revision or joint fusion, definitely better alternatives than amputation. Such procedures, even if usually technically demanding and sometimes very close to limb salvage surgery, have more than acceptable outcomes.6,27,39

Modern orthopaedic surgery’s procedures have been associated to good clinical outcomes: this is undoubtedly related to the introduction of rFVIIa and aPCC that have significantly improved the management of patients with inhibitors, by an efficient control of coagulation during and after major surgery.13,14,19,20,22,24,30,40,41 Particularly, around 400 procedures have been reported as successful using rFVIIa,24 and recently more than 200 using aPCC with a reported efficacy rates of about 87% to 100% and 57% to 79% respectively.30,42 Therefore, despite their costs, major orthopaedic procedures have more probability to be successfully managed in terms of satisfactory haemostasis during the intra- and postoperative period.17,19,20,24,30,36,40,43

Rodriguez-Merchan et al.44 firstly reported data from nine centres collecting results of 51 patients with inhibitors undergoing 108 orthopaedic procedures: however, only 6 were TKA and 2THA. A protocol with rFVIIa was used during surgery (boluses with a mean dose 150 μg/kg; range 90-200 μg/kg), at the same dosage every 2 hours for 24 hours postoperatively and then by continuous infusion (45 μg/kg/h) for 4-7days. While THA showed good results with no complication or bleeding, two to six TKA showed poor outcomes, mainly related to postoperative bleeding requiring open surgical drainage. Despite those two patients, it was the first study to confirm that major elective orthopaedic surgery could be satisfactorily performed in PWH with inhibitors. A similar experience was described by Takedani et al.29 who added an antifibrinolytic agent (tranexamic acid) during the peri-operative period for all patients. Good outcomes in 2 TKA and 2 THA were reported, and the mean measured blood loss was 120 and 610 mL for TKA, and 1056 and 519 mL for THA. A complication was also reported: a massive

TABLE 4 Multivariate logistic modelling of risk factors for both postoperative Global ROM < 70° and Mayor bleeding

<table>
<thead>
<tr>
<th>Independent variables</th>
<th>Postop Global ROM &lt; 70°</th>
<th>Postop mayor bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>P value</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>Primary arthroplasty</td>
<td>.683</td>
<td>0.127</td>
</tr>
<tr>
<td>Revision arthroplasty</td>
<td>.012</td>
<td>0.946</td>
</tr>
</tbody>
</table>

Note: When analysing ROM, only TKAs or rTKAs were taken into account.
Abbreviations: rTKA, revision knee arthroplasty; TKA, total knee arthroplasty.
bleeding in a patient undergoing a THA, managed by administration of boluses of rFVIIa at 2-hour intervals.

A partially different protocol was adopted by Solimeno et al.\(^\text{18}\) using continuous infusion of rFVIIa, followed 5 days after by boluses in case of anamnestic response to FVIII in a series of 116 PWH. They identified 7 patients with inhibitors followed with a mean follow-up of 5.1 years. Despite the overall satisfactory outcome in patients with inhibitors, bleeding episodes occurred more frequently (28% vs 2%) compared with non-inhibitors patients.

They found a higher risk of septic complications in subjects with inhibitors undergoing TKA compared to haemophilic patients without inhibitors (33% vs 5%).

Atilla et al.\(^\text{45}\) reported their series of 14 PWH undergoing 21 TKA, of whom 4 had inhibitors. One of these developed an infection after a traumatic bleeding, 2 had massive haemorrhages after surgery. The haematological protocol consisted in a standard factor concentrate infusion with rFVIIa administered only in case of high-titre inhibitors. Postoperative bleedings were the most common complication also in our experience, particularly in the group of revision arthroplasty. However, no sequelae were recorded for such haemorrhagic events which were usually managed by additional rFVIIa boluses.

On the other hand, it is clear that such surgery has a high risk of complications, with a short- to mid-survival rate of implants\(^\text{18}\). In our experience only 1 TKA patient underwent a revision after the index operation, due to bleeding issues leading to early aseptic loosening.

Another crucial aspect related to the prevention of bleeding in major orthopaedic surgery is the rehabilitative period.\(^\text{25,46}\) The efficacy of rFVIIa and aPCC allows early mobilization of patients, usually from the first postoperative day (in case of primary joint replacement) and in two or three days after surgery (in case of revisions) without an increased risk of bleeding. These aspects are essential also to shorten hospital stay and to reduce the overall costs. Recently, Danielson et al.\(^\text{47}\) clearly described the impact in terms of costs of joint replacements in PWH and inhibitors. Their cost analysis reveals that surgery in such patients is not only highly technical demanding but also expensive, varying between 350 900 and 500 400 €, mostly related to factor replacement (87%-94%). In the group of PWH without or low-titre inhibitors, costs were lower (47 200 to 103,200 €), with factor replacement therapy covering the 59%-81% of total cost. The series of PWH and inhibitors was represented by 6 patients (15 joint replacements: 8 TKA, 3 rTKA, one THA, 2 ankle replacements and 1 glenohumeral replacement). With a mean follow-up of 7.3 years, the authors recorded substantially good results: however, 1 patient needed revision after an infection, and another reported a severe contracture flexion. Furthermore, two major bleedings were reported, occurring also months after surgery. Factor replacement consisted in the use of cryoprecipitates or factor VIII in case of low-titre inhibitors, and either aPCC or rFVIIa in high-titre inhibitors. The common basis of all experiences related to the rehabilitative principles in haemophilia after a major orthopaedic surgery is the need of the factor infusion before the session and a closely tailored approach: this task may be obtained only after a daily orthopaedic evaluation to assess the general and local status of the patient, specifically focused not only for the operated side, but also for the other target joints.

This study has several limitations. It is a retrospective analysis, without control group, and with a small cohort of patients, specifically for the group of revision arthroplasty. On the other hand, the strength of the present analysis comes from the consistency of the study population and the noteworthy clinical outcomes with respect to the other series, with the longest follow-up reported in literature regarding knee and hip arthroplasty in PWH and inhibitors.

5 | CONCLUSION

Primary and revision arthroplasties in patients with haemophilia and inhibitors may be nowadays considered safe and effective if performed in dedicated multidisciplinary haemophilia centres. In our series, the use of continuous infusion of rFVIIa showed an adequate haemostatic effect, ensuring good long-term results and low rates of complications with respect to the other published and limited series. The recent introduction of specific biological drugs with dramatically positive short-term effects may represent a further attempt to improve the management of subjects with inhibitors undergoing major orthopaedic surgery.

DISCLOSURES

The authors declare that they have no conflicts of interest.

AUTHORS’ CONTRIBUTIONS

Christian Carulli and Matteo Innocenti are the two Authors who made both the conception and the design of the work as well as they drafted the first version of the work. Each author has made substantial contributions to the design of the work as well as to the acquisition, analysis and interpretation of data. All authors have also substantively revised the work and has approved the submitted version (and any substantially modified version that involves the author’s contribution to the study) and have agreed both to be personally accountable for the author’s own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved and the resolution documented in the literature.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All patients accepted the proposed treatment and follow-up after an adequate information and written consent. The study and follow-up, respecting the criteria of the Declaration of Helsinki, have been approved by Institutional Review Board of Azienda Ospedaliera Universitaria Careggi (AOUC) Department of Surgery and Translational Medicine. The Institutional Review Board accepted the proposal of the study, and all selected patients were properly informed before surgery about the treatment and follow-up visits after discharge.
REFERENCES


24. Valentino L.A., Cooper D.L., Goldstein B. Surgical experience with rFVIIa (NovoSeven) in congenital haemophilia A and B patients with inhibitors to factors VIII or IX. Haemophilia. 2011;17(4):579-589.


How to cite this article: Carulli C, Innocenti M, Linari S, Morfini M, Castaman G, Innocenti M. Joint replacement for the management of haemophilic arthropathy in patients with inhibitors: A long-term experience at a single Haemophilia centre. Haemophilia. 2020;00:1–9. https://doi.org/10.1111/hae.14169