INTRODUCTION

Patients with haemophilia A experience recurrent bleeding episodes that can be treated with the replacement of factor VIII (FVIII) and prevented with regular prophylactic administrations of FVIII concentrates. The development of neutralizing antibodies (inhibitors) against FVIII remains the most severe and challenging complication of FVIII replacement therapy in patients with haemophilia A. Neutralizing antibodies can render treatment ineffective and can lead to frequent and severe bleeding episodes, even with high doses of FVIII. The eradication of the inhibitor through immune tolerance induction (ITI) remains the most effective strategy for managing these patients. Bypassing agents can be used to help restore haemostasis in inhibitor patients. Several novel agents have recently been developed, such as the FVIII mimetic agent emicizumab, which has been effective in reducing the annualized bleeding rate in haemophilia A patients with inhibitors. When coadministered with repetitive high doses of activated prothrombin complex concentrate (ie >100 U/kg/d for ≥24 hours), emicizumab was associated with thrombotic microangiopathy and thrombosis events. As a consequence the United Kingdom Haemophilia Centres Doctors’ Organisation (UKHCDO) issued the first guidance on the treatment of bleeding episodes in patients receiving emicizumab. To build on and extend this work, a panel of German haemophilia specialists met to discuss the UK guidance, review current evidence and provide additional guidance for German healthcare professionals on how to optimize the management of patients with haemophilia A receiving emicizumab. Recommendations are provided on the use of bypassing and other agents to manage breakthrough bleeding, ITI in the emicizumab era, haemostatic support during surgery and issues relating to laboratory monitoring.

KEYWORDS
bypassing agents, emicizumab, factor VIII, haemophilia A, immune tolerance induction, inhibitor
haemophilia A, affecting approximately 20%-40% of previously untreated patients with severe FVIII deficiency in the first 50 exposure days with FVIII. The presence of inhibitors makes the treatment and prevention of bleeds difficult, particularly for patients with high-responding (high-titre >5 Bethesda units [BU]) inhibitors, which increases mortality; the risk for chronic morbidity, particularly joint disease, pain and physical disability; and decreases quality of life. Eradication of inhibitors is therefore the most important goal for these patients—thereby making it possible for patients to continue with regular FVIII therapy to prevent and treat bleeding episodes, and to maintain joint health. Patients with low-responding (low-titre ≤5 BU) inhibitors generally experience fewer clinical problems and can usually be managed with higher doses and/or shorter intervals of FVIII concentrates to saturate the inhibitor and promote haemostasis.

1.1 | Immune tolerance induction

Eradication of inhibitors using immune tolerance induction (ITI) therapy is considered to be the most effective approach to managing the majority of patients with severe haemophilia A (FVIII <1% of normal) who develop inhibitors, with overall success rates ranging from 50% to 80% in registry studies. ITI therapy generally consists of regular and long-term administration of FVIII concentrate to downregulate the anti-FVIII antibody response, resulting in immune tolerance. There are two frequently applied ITI protocols. The 'Bonn Protocol' exhibiting a high FVIII dose of 100-150 IU/kg bodyweight (BW) twice daily or 200 IU/kg BW once daily, while the ‘van Creveld Protocol’ uses a lower dose of 50 IU/kg BW every other day or three times per week. Several factors may influence the likelihood of ITI success, including treatment- and disease-related factors. The most relevant parameter is the maximum inhibitor titre. In the international ITI study, the ITI success was lowered by 50% when the maximum inhibitor titre was higher than 36 BU. Of the treatment-related factors, the type of FVIII concentrate used for ITI might be relevant. In particular, there is some data suggesting that plasma-derived products containing von Willebrand factor (VWF) or rFVIII:Fc may induce rapid ITI success or reverse ITI failure in single-cohort studies.

1.2 | Bypassing agents

The management of bleeding episodes in patients with severe haemophilia A and inhibitors has historically relied on the episodic or prophylactic use of bypassing agents such as activated prothrombin complex concentrates (aPCCs) and recombinant activated factor VII (rFVIIa). These products can generally achieve an adequate level of bleed control in most patients with inhibitors, but their haemostatic efficacy is not as effective as that of specific factor replacement in patients without inhibitors. In recent years, however, several novel, non-factor therapies have emerged as promising new treatments for patients with haemophilia A and inhibitors, including emicizumab (activated FVIII [FVIIa] mimetic bispecific antibody), ffitusiran (antithrombin inhibitor through RNA interference) and concizumab (antithrombin inhibitor antibody).

1.3 | Emicizumab

Emicizumab (Hemlibra®; Roche Pharma AG) is the first of the non-factor agents which has been approved for the prophylactic treatment of patients with haemophilia A with and without inhibitors. Emicizumab has been initially approved for routine prophylaxis of bleeding episodes in patients with haemophilia A with FVIII inhibitors who are not receiving ITI. The approval of emicizumab in this indication was based on the results of the HAVEN 1 study in adolescents/adults and the ongoing HAVEN 2 study in paediatrics. Emicizumab prophylaxis, when administered subcutaneously once weekly, significantly reduced the number of bleeding episodes in patients with inhibitors. However, when emicizumab was coadministered with high doses of aPCC three patients in HAVEN 1 developed thrombotic microangiopathy (TMA) and two patients showed venous thromboembolism. No other cases of TMA or thrombosis have been reported in emicizumab clinical studies following the implementation of strict guidance on treating breakthrough bleeding with concomitant aPCC. However, a few more cases have been reported in the use of emicizumab after licensing.

Moreover, data from the pooled HAVEN clinical trials reported that 3.5% (14/398) of patients developed antidrug antibodies (ADAs) to emicizumab. Of these 14 ADAs, three were neutralizing (based on declining pharmacokinetics). One patient experienced complete loss of efficacy after 5 weeks of treatment, resulting in a very low overall rate of clinical loss of efficacy (1/398).

The challenges with the use of emicizumab prompted the United Kingdom Haemophilia Centres Doctors’ Organisation (UKHCDO) to produce the first set of consensus recommendations on the treatment of bleeding episodes in patients with haemophilia A and inhibitors receiving emicizumab. In light of the benefits offered by emicizumab for these difficult-to-treat patients, and because there are still unanswered questions about how to optimize the management of patients receiving emicizumab, a panel of German haemophilia specialists met to discuss the new UK guidance, review current evidence, and provide recommendations and guidance for German healthcare professionals in relation to the issues covered in the UK guidance and other key management issues, including ITI. These recommendations and guidance are applicable to the current clinical situation in Germany and may not take into account variations in laboratory and treatment availability worldwide. The panel’s discussion and consensus form the basis of this review article.

2 | GENERAL ADVICE ON THE USE OF EMICIZUMAB AND BYPASSING AGENTS

Bypassing agents are the standard of care for treating and preventing bleeding episodes in patients with haemophilia A and inhibitors...
However, the use of bypassing agents should be carefully followed during emicizumab treatment, especially because of the risk of aPCC with respect to TMA and thrombosis. As part of its consensus recommendations, the UKHCDO has issued general guidance on the use of emicizumab and bypassing agents in patients with haemophilia A and inhibitors. This advice was reviewed and broadly endorsed by the German panel (Table 1).

### 3 | TREATMENT OF BLEEDING EPISODES

Emicizumab prophylaxis results in a remarkable reduction in the number of bleeds compared with standard of care. In the HAVEN 1 study, about one-third of patients required bypassing agents to control breakthrough bleeding or managing unplanned surgery. Bypassing agents will therefore continue to play an important role in the management of bleeding episodes and surgery in patients receiving emicizumab treatment. Therefore, the UKHCDO guidance in relation to their appropriate use is timely and welcome.

The UK guidance (Table 2) emphasizes that aPCC should not be used in patients receiving emicizumab unless no other alternative is available—a recommendation endorsed by the German panel. Where aPCC is required, the German panel agrees with the UK guidance that a reduced dose should be used. However, although the initial recommended dose is 25-50 U/kg, recent preliminary evidence suggests that aPCC doses of 15-25 U/kg might be a viable and safe therapeutic strategy worthy of further exploration in patients receiving emicizumab who require aPCC treatment.56

The German panel endorses all UK recommendations relating to the choice of drugs, dosing and proposed escalation schemes for the management of bleeding episodes (Table 2). Additional clarification has been provided by the panel on the recommended dosing interval for rFVIIa, favouring the 90 µg/kg and emphasizing the need to adjust this interval based on the severity of the bleed and/or threat to life with no safety concerns if the cumulative dosing is consistent with the approved labelling.57 (see also Table 2). If the bleed has not resolved with optimized rFVIIa treatment, the panel favours the use of human FVIII (with regular inhibitor monitoring), providing the inhibitor titres are low. Porcine FVIII may represent an alternative, when the inhibitor is higher and bleed control cannot be achieved with human FVIII. If severe bleeding does not respond to 90 µg/kg rFVIIa or other treatment options, or if rFVIIa is not available, low-dose FEIBA may be administered with close follow-up and management by experienced healthcare providers.

### 4 | IMMUNE TOLERANCE INDUCTION: IS IT STILL NECESSARY IN THE EMICIZUMAB AGE?

The German panel agreed that ITI is still the first treatment of choice to eradicate inhibitors and is likely to retain an important role in the management of inhibitor patients55 (see Table 3). German and other national guidelines suggest that all patients with severe haemophilia A with inhibitors—and particularly those with high-responding inhibitors—should be offered at least one opportunity to become inhibitor free with ITI therapy.10,13,15,43,48,49 Initiating ITI immediately after high-titre inhibitors have been diagnosed has been standard practice in Germany. However, non-factor replacement agents, such as emicizumab, may be effective in the prophylactic treatment of bleeds in haemophilia A patients with inhibitors. The unprecedented efficacy and relative ease of use of emicizumab have led the panel to question whether ITI is still optimal.

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Consensus recommendations on the use of emicizumab in patients with haemophilia A and inhibitors: general advice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>UKHCDO</strong>43</td>
<td><strong>German expert panel</strong></td>
</tr>
<tr>
<td>Emicizumab should only be prescribed by Comprehensive Care Haemophilia Centres (CCC)</td>
<td>In Germany, emicizumab can be prescribed by Haemophilia Treatment Centres in addition to CCCs</td>
</tr>
<tr>
<td>Patients receiving emicizumab should have 24-h access to clinicians with expertise in treating haemophilia with an inhibitor for advice on treating bleeding episodes</td>
<td>Consensus</td>
</tr>
<tr>
<td>Bypassing agents should be stopped 24 h before emicizumab is started</td>
<td>Consensus for aPCC. rFVIIa can be given with an overlap</td>
</tr>
<tr>
<td>All aPCCs should be removed from the patient's home and returned to the CCC before emicizumab is started</td>
<td>Consensus. Patients should also be educated on the risks associated with the coadministration of an aPCC and emicizumab</td>
</tr>
<tr>
<td>Antihuman and antiporcine FVIII inhibitor titres should be measured before emicizumab is started</td>
<td>Antiporcine FVIII inhibitors should be tested before and after using porcine rFVII</td>
</tr>
<tr>
<td>All treatment with emicizumab, rFVIIa, aPCC and FVIII should be recorded</td>
<td>Consensus</td>
</tr>
<tr>
<td>Adverse events must be reported to regulators and other appropriate authorities</td>
<td>Consensus</td>
</tr>
<tr>
<td>Due to the long half-life of emicizumab, these treatment recommendations should be followed for 6 mo after the drug has been stopped</td>
<td>Consensus</td>
</tr>
</tbody>
</table>

Abbreviations: aPCC, activated prothrombin complex concentrates; FVIII, factor VIII; rFVIIa, recombinant activated factor VII; rFVIII, recombinant factor VIII.
At the same time preserving joint health.

However, with emicizumab prophylaxis the panel notes it is possible to postpone ITI until the patient is older, potentially evading the need for a central venous access device in very young children, while remaining candidates for immediate ITI therapy. Other authors have recently suggested that emicizumab prophylaxis should be used in patients who wish to delay ITI to allow the inhibitor titre to fall to below 10 BU/mL, in very young patients who find daily infusions burdensome, in those with poor venous access and/or poor compliance, or in those who have not responded to previous courses of ITI.

To help stratify patients, the panel recommends that those with a high bleeding rate (ie those who continue to experience bleeding episodes, particularly severe bleeding, such as intracranial bleeds, or repeated joint bleeds) and a suboptimal response to rFVIIa, would remain candidates for immediate ITI therapy. Other authors have recently suggested that emicizumab prophylaxis should be used in patients who wish to delay ITI to allow the inhibitor titre to fall to below 10 BU/mL, in very young patients who find daily infusions burdensome, in those with poor venous access and/or poor compliance, or in those who have not responded to previous courses of ITI.

In patients proceeding to ITI, should emicizumab also be prescribed to prevent bleeding episodes? Opinions on this differ. The recent UKHCDO guidance highlights a lack of evidence supporting the use of emicizumab prophylaxis to prevent bleeding episodes during ITI and recommend that emicizumab should only be considered during ITI for patients with significant and frequent bleeds. Others believe that it may be preferable to prescribe emicizumab when initiating ITI, since it has been shown that the bleeding rate during ITI is highest in the first months of treatment. Le Quellec and Négrier argue that emicizumab should be prescribed independently of ITI, suggesting that the use of emicizumab would not only prevent bleeding episodes during ITI compared with the use of bypassing agents, but that it might also enable the use of low-dose ITI regimens that would reduce the need for central venous access devices and their related complications.

### TABLE 2 Consensus recommendations for the treatment of bleeding episodes in patients receiving emicizumab

<table>
<thead>
<tr>
<th>UKHCDO</th>
<th>German expert panel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleeding episodes should not be treated with aPCC unless no other option is available</td>
<td>• See recommendation of aPCC doses of 15-25 U/kg as given below</td>
</tr>
<tr>
<td>• If used, the initial dose of aPCC should not exceed 50 U/kg</td>
<td>• Early kidney damage due to TMA may be detected using microhaematuria/proteinuria dipstick testing in patients receiving emicizumab who require aPCC treatment. Further analytical methods could be applied if necessary</td>
</tr>
<tr>
<td>• If a second dose of aPCC is required, the patient should be admitted to hospital for TMA surveillance</td>
<td></td>
</tr>
<tr>
<td>First-line treatment of bleeds should be with rFVIIa</td>
<td>Recommendation:</td>
</tr>
<tr>
<td>• The initial dose of rFVIIa should not exceed 90 µg/kg</td>
<td>• Start with 90 µg/kg (based on decades of experience with this dose without complications)</td>
</tr>
<tr>
<td>• Doses of 45 µg/kg every 4 h may be efficacious for some bleeds</td>
<td>• A second dose of 90 µg/kg rFVIIa should be given after 4-6 h, but should be individualized based on the clinical presentation (shorter intervals may also be appropriate in some cases)</td>
</tr>
<tr>
<td>• If lower doses or frequencies of rFVIIa do not result in adequate haemostasis, rFVIIa should be increased to 90 µg/kg every 2 h before it is assumed to have failed</td>
<td></td>
</tr>
<tr>
<td>Human FVIII may be a treatment option if the bleed does not resolve with rFVIIa and the human inhibitor titres are low</td>
<td>Consensus</td>
</tr>
<tr>
<td>Porcine rFVIII may be a treatment option if the bleed does not resolve with rFVIIa and the porcine inhibitor titres are low</td>
<td>Use of porcine FVIII when rFVIIa and human FVIII are not efficacious and the porcine inhibitor titres are low</td>
</tr>
<tr>
<td>If a severe bleed does not respond to rFVIIa and other treatment options are not available, aPCC may be administered at an initial dose of ≤50 U/kg (25 U/kg may be efficacious for some bleeds)</td>
<td>• If a severe bleed does not respond to 90 µg/kg rFVIIa or other treatment options, aPCC at doses of 15-25 U/kg may be used to control bleeds. Alternatively, low-dose FEIBA may be administered with close follow-up and management by experience healthcare providers</td>
</tr>
<tr>
<td>• A second dose of 25-50 U/kg may be considered on Day 1 if necessary</td>
<td></td>
</tr>
<tr>
<td>• The cumulative dose should not exceed 100 U/kg/day</td>
<td></td>
</tr>
</tbody>
</table>

### TABLE 3 Consensus recommendations on immune tolerance induction (ITI) in haemophilia A patients with inhibitors who receive emicizumab

ITI should be used to treat patients with haemophilia A who develop an inhibitor, regardless of whether they are receiving prophylaxis with emicizumab. The use of emicizumab would not influence the choice of FVIII replacement therapy (recombinant or plasma-derived) used to conduct ITI

For high-titre inhibitors >50 BU, a high-dose ITI protocol should be used

ITI should be started immediately after inhibitor detection, if it is feasible

Factor VIII replacement therapy should be avoided between the time from inhibitor diagnosis and start of ITI

Abbreviations: FVIII, factor VIII; rFVIIa, recombinant activated factor VII; rFVIII, recombinant factor VIII; TMA, thrombotic microangiopathy.

*Porcine rFVIII is currently (09/2019) only approved for acquired haemophilia and is approved in Germany for in-patient administration only.

To help stratify patients, the panel recommends that those with a high bleeding rate (ie those who continue to experience bleeding episodes, particularly severe bleeding, such as intracranial bleeds, or repeated joint bleeds) and a suboptimal response to rFVIIa, would remain candidates for immediate ITI therapy. Other authors have recently suggested that emicizumab prophylaxis should be used in patients who wish to delay ITI to allow the inhibitor titre to fall to below 10 BU/mL, in very young patients who find daily infusions burdensome, in those with poor venous access and/or poor compliance, or in those who have not responded to previous courses of ITI.

In patients proceeding to ITI, should emicizumab also be prescribed to prevent bleeding episodes? Opinions on this differ. The recent UKHCDO guidance highlights a lack of evidence supporting the use of emicizumab prophylaxis to prevent bleeding episodes during ITI and recommend that emicizumab should only be considered during ITI for patients with significant and frequent bleeds. Others believe that it may be preferable to prescribe emicizumab when initiating ITI, since it has been shown that the bleeding rate during ITI is highest in the first months of treatment. Le Quellec and Négrier argue that emicizumab should be prescribed independently of ITI, suggesting that the use of emicizumab would not only prevent bleeding episodes during ITI compared with the use of bypassing agents, but that it might also enable the use of low-dose ITI regimens that would reduce the need for central venous access devices and their related complications. In the
opinion of the panel, emicizumab prophylaxis offers the potential to reduce bleeds during ITI—particularly during the first phase of treatment when inhibitors are still measurable—which could improve the chances of ITI success, while at the same time conserving the joints. However, the lack of evidence on the benefit of ITI in patients receiving ITI should be noted. Future research should evaluate this important issue more fully, and patients receiving ITI and emicizumab should be included in clinical studies/registries so that the evidence for ITI can be fully evaluated.

Two main protocol options exist for ITI in patients with haemophilia A with inhibitors. Low-dose ITI is generally recommended by the panel for patients with clinically relevant (inhibitory activity which interferes with regular prophylaxis treatment), low-titre, low-responding inhibitors, as is standard in German treatment centres, while high-dose ITI is recommended for those with high-titre, high-responding inhibitors (Table 3). A novel ITI protocol (the Atlanta Protocol) that uses both FVIII and emicizumab has recently been proposed and evaluated in seven patients aged 21 months to 12 years with an active inhibitor ≥0.6 BU/mL. The protocol involves administering emicizumab for four weekly loading doses followed by the initiation of ITI with plasma-derived or recombinant FVIII at a dose of 100 U/kg three times per week. Recent data suggest that the dual protocol can be administered safely and leads to progressive improvements in clinical indicators of tolerance. However, the report represents an interim analysis during ongoing ITI in all patients. Further results using this novel ITI approach are awaited with interest.

Finally, the question remains as to which prophylactic approach should be used after successful ITI in these patients. The panel highlighted three distinct approaches, each with their own benefits and challenges:

1. Ongoing prophylaxis with emicizumab after FVIII is gradually withdrawn
2. Ongoing prophylaxis with emicizumab in addition to low frequent FVIII to maintain tolerance. However, there is only little evidence on the ideal dosing regimen for FVIII
3. Discontinuation of emicizumab prophylaxis and prophylaxis with FVIII only.

Using the first approach, it is unclear how long tolerance will persist in the absence of FVIII exposure and what will happen to patients with anti-FVIII antibodies receiving emicizumab upon subsequent exposure to FVIII. The panel recommends that, if the first approach is selected, FVIII should be gradually withdrawn following an individualized approach once negative inhibitors and normal pharmacokinetic properties have been achieved. Under all circumstances, slow reduction of FVIII is advised. In addition, by administering only emicizumab, patients may lose their ability to self-administer iv drugs, which poses a risk in emergency situations. The second approach has the benefit of retaining both tolerance and competence to self-administer iv drugs. Regular exposure to FVIII after successful ITI is likely to be needed; however, there is no experience and so it is hard to recommend an interval or dose. FVIII dosing should be individualized, but in the panel’s opinion a suggested protocol could be emicizumab plus FVIII once weekly or every 14 days. For the third approach, again, patients would retain both tolerance and competence to self-administer iv drugs. However, this approach would not take advantage of the easy s.c. administration at long intervals of emicizumab, while exhibiting a high efficacy in bleed prevention. Should the decision be taken to discontinue emicizumab, the panel recommends that FVIII trough levels are >3%-5% prior to treatment withdrawal and that FVIII administration continues at a frequency of at least thrice weekly/every other day when using standard half-life FVIII.

5 | SURGERY

The surgical setting with bypassing agents represents a challenge for the management of patients with haemophilia and inhibitors. As such, there is ongoing debate regarding the safe conduct of surgery in patients with inhibitors receiving emicizumab prophylaxis. To date, fewer than 40 surgical procedures have been reported in patients receiving emicizumab prophylaxis. The German panel agrees with the UKHCDO that there is scant published evidence on which to base consensus recommendations and that consideration should be given to delaying non-urgent major surgery until further data are available. To minimize risk, the panel recommends that all surgical procedures in inhibitor patients receiving emicizumab should be performed in a haemophilia treatment centre and should include haemostatic support that is planned, based on patient history and inhibitor status (Table 4). An initial dose of rFVIIa 90 μg/kg with a second dose after 2-4 hours is proposed, with all additional treatment decisions made according to the clinical picture and type of surgical procedure planned. Factor VIII may be used as an alternative to rFVIIa in major surgery if inhibitor titres are low (<5 BU/mL). In the event of haemostatic failure despite the combination of emicizumab and rFVIIa, the panel proposes the following treatment approaches: if a low-titre inhibitor is present, FVIII treatment may be administered for haemostatic support. In patients with an inhibitor titre up to 15 BU/mL, recombinant porcine FVIII treatment may represent a treatment option to overcome the inhibitor if the cross-reactivity to porcine FVIII is <5 BU, although this would currently (9/2019) represent an off-label use. If a high-titre inhibitor is present, aPCC at a lower dose of 15-25 IU/kg BW should be administered. Further guidance will be required when the evidence base allows. In general, the use of tranexamic acid may be considered; according to current knowledge, the presence of emicizumab does not affect the efficacy or safety of tranexamic acid.

6 | EMICIZUMAB AND LABORATORY MONITORING

Accurate measurement of FVIII activity levels is critical for the diagnosis, classification and therapeutic monitoring of patients with...
TABLE 4 Consensus recommendations on the conduct of surgery in a patient with haemophilia A and inhibitors receiving emicizumab

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery</td>
<td>An initial dose of rFVIIa 90 µg/kg with subsequent doses every 2-4 h is recommended. Depending on wound size, postoperative bleeding and cardiovascular risk, dosing intervals of rFVIIa can be increased.</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>Decision for additional treatment should be based on the individual assessment of the treating physician. If necessary, an initial dose of rFVIIa (90 µg/kg) is recommended, followed by a second dose 2-6 h after surgery; additional doses may be required based on wound size and postoperative bleedings.</td>
</tr>
<tr>
<td>Supportive treatment</td>
<td>Tranexamic acid should be given until wound healing is completed. FVIII may be used as an alternative if prompt monitoring is available and the inhibitor titre is low.</td>
</tr>
<tr>
<td>In the event of haemostatic failure despite rFVIIa</td>
<td>Human FVIII should be used: if antihuman titre is low (≤5 BU) Porcine FVIII: if antiporcine titre is low (≤5 BU) and antihuman FVIII titre is high (&gt;5 BU) aPCC. The cumulative amount of activated prothrombin complex concentrate (aPCC) applied must be &lt;100 U/kg/24 h. Regimens, for example 15-25 U/kg up to 6 h can be considered</td>
</tr>
</tbody>
</table>

Abbreviations: aPCC, activated prothrombin complex concentrate; CCC, comprehensive care centre; FVIII, factor VIII; rFVIIa, recombinant factor VIIa.

haemophilia A with inhibitors. However, current laboratory assays may have limited utility for patients receiving treatment with emicizumab. Standard laboratory tests of coagulation measure total clotting time, including the time needed for activation of FVIII to FVIIIa by thrombin. Since emicizumab does not require activation by thrombin, intrinsic pathway-based laboratory tests, such as activated clotting time and activated partial thromboplastin time (aPTT), yield overly shortened (normalized) clotting times with emicizumab, which then disturb all single-factor assays based on aPTT, including the one-stage FVIII activity assay and the clotting-based Bethesda assay, independent of the aPTT reagent used (Table 5). This means that measurement of FVIII levels, as well as inhibitor titres, will not be reliable using these assays and may result in inappropriate treatment and serious adverse outcomes.

The new UKHCDO guidance recommends the use of bovine chromogenic assays to monitor FVIII replacement and to measure inhibitor titres. The German panel supports this recommendation. For further details see Table 5.

TABLE 5 Current status and recommendations for coagulation testing and monitoring of haemophilia A patients with inhibitors receiving emicizumab treatment

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major surgery</td>
<td>The current inhibitor titre should be known.</td>
</tr>
<tr>
<td>Minor surgery</td>
<td>The presence of emicizumab does not affect the use of tranexamic acid.</td>
</tr>
<tr>
<td>Supportive treatment</td>
<td>Tranexamic acid should be given until wound healing is completed. FVIII may be used as an alternative if prompt monitoring is available and the inhibitor titre is low.</td>
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<td>In the event of haemostatic failure despite rFVIIa</td>
<td>Human FVIII should be used: if antihuman titre is low (≤5 BU) Porcine FVIII: if antiporcine titre is low (≤5 BU) and antihuman FVIII titre is high (&gt;5 BU) aPCC. The cumulative amount of activated prothrombin complex concentrate (aPCC) applied must be &lt;100 U/kg/24 h. Regimens, for example 15-25 U/kg up to 6 h can be considered</td>
</tr>
</tbody>
</table>

Abbreviations: aPCC, activated prothrombin complex concentrate; CCC, comprehensive care centre; FVIII, factor VIII; rFVIIa, recombinant factor VIIa.

In an attempt to overcome these laboratory monitoring issues, investigators have recently used anti-emicizumab monoclonal antibodies to eliminate the effects of emicizumab on aPTT and facilitate the accurate determination of FVIII activity and inhibitor titres using clotting-based assays in plasma from patients with haemophilia A with and without inhibitors. The same research group is also examining different methodologies, including modified clot waveform analysis and rotational thromboelastometry, in an attempt to measure the whole coagulation potential of plasma in the presence of emicizumab. Other researchers are investigating a novel point-of-care whole blood coagulation assay to monitor emicizumab therapy.

The thrombin generation assay (TGA) has also been under the spotlight recently as a potential means to assess global coagulation potential and monitor the effects of bypassing treatment in haemophilia patients with inhibitors receiving emicizumab. Dargaud et al demonstrated successful tailoring of bypassing therapy in inhibitor patients undergoing surgery and have recently proposed that TGA may enable clinicians to personalize bypassing therapy in patients receiving emicizumab who experience breakthrough bleeds. The panel's recommendations for laboratory testing during emicizumab treatment are outlined in Table 5.

7 WHAT DOES THE FUTURE HOLD?

For haemophilia A patients with inhibitors, ITI is still the most effective approach to eradicating inhibitors and is likely to retain an important role in managing inhibitor patients in the era of emicizumab. As emicizumab becomes more fully integrated into clinical practice
and greater experience is gained, further guidance may be needed on how to optimize ITI therapy.

Much has been learnt in the short time that emicizumab has been available; however, many unresolved issues remain, and further clarification is required in several areas, including:

- The mode of interaction between emicizumab and FVIII and bypassing agents
- The long-term safety of emicizumab, such as effects on joint health and unforeseen side effects
- The optimal way to manage bleeds and undertake surgery, including how to dose bypassing agents
- The relative roles of emicizumab and ITI therapy
- How to optimize ITI in the emicizumab era
- How to use novel techniques for monitoring patients receiving emicizumab
- If, and how, to use emicizumab in previously untreated patients (PUPs)
- The (self-) management of emergency events

The management of bleeds in PUPs is particularly important owing to both the increased risks of inhibitor development with early intensive treatment (ie high-frequency treatment or surgical procedure) and also the risk of developing haemophilic arthropathy in later life. It will therefore be interesting to see if, and how, these risks and their management change with the emergence of novel non-factor replacement agents. The recent approval of emicizumab in haemophilia A patients without inhibitors means that even more patients with haemophilia A are now eligible to receive this treatment option. Nevertheless, clinical controversies remain regarding the optimal treatment approach and long-term outcomes and safety—emicizumab does not normalize coagulation and therefore may not provide effective haemostatic coverage for very active patients, such as those who participate in sports, and breakthrough bleeding may still occur and so treatment with coagulation factor replacement products will be required. Although there is still a journey ahead in terms of learning how to optimize the management of haemophilia A patients with (and without) inhibitors who are receiving emicizumab, the panel hopes that clinicians and other practitioners involved in the care of these patients will find this initial guidance helpful.

ACKNOWLEDGEMENTS
The authors would like to thank Professor Andreas Tiede for his input in discussions and support with recommendations. Authors attended a consensus meeting funded by CSL Behring. Editorial support was provided by Meridian HealthComms, funded by CSL Behring. Open access funding enabled and organized by Projekt DEAL.

DISCLOSURES
G Auerswald has received reimbursement for speaker’s fees at symposia by CSL. C Escuriola-Ettingshausen has acted as a consultant and received speaker’s fees and/or research funding from the following companies: Bayer Healthcare, Biotest, CSL Behring, Grifols, Octapharma, Novo Nordisk, Shire/Takeda, Sobi, Roche/Chugai, Alnylam and Kedrion. R Klamroth has received funding for research from Bayer, CSL Behring, LEO, Novo Nordisk and Takeda and acted as a paid consultant for Bayer, Biomarin, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Roche, Sanofi, Takeda and SOBI. C Königs has acted as consultant or has been part of the speakers’ bureau of Bayer, BFSH, Biotest, Bioverativ, CSL Behring, MSD, Novo Nordisk, Pfizer, Roche, Shire, Sobi; his institution has received research funding (including the GEPHARD registry) from the EU (IMI, FP7), DFG, BMBF, FSKK-Foundation, Bayer, Biotest, Bioverativ/Sanofi, CSL Behring, Intersero, Novo Nordisk, Pfizer, Roche/Chugai, Shire/Takeda, Sobi. K Kurnik reports grants and personal fees from Bayer, and personal fees from Biotest, CSL Behring, Novo Nordisk, Roche, Sobi and Shire/Takeda. J Oldenburg reports grants and personal fees from Bayer, Biotest, CSL Behring, Novo Nordisk, Octapharma, and Shire/Takeda; and personal fees from Chugai, Grifols, Pfizer, Roche, and SOBI, outside the submitted work. Personal fees were received for travel support, participation in Advisory Boards and participating in symposia as chair or speaker. U Scholz reports research support from Bayer Vital GmbH, Werfen Group and Siemens AG; consultancy for Novo Nordisk Pharma GmbH and Pfizer GmbH; honoraria from CSL Behring GmbH, Pfizer GmbH, Biotest AG, Bayer Vital GmbH and Roche Diagnostics Deutschland GmbH.

AUTHOR CONTRIBUTIONS
All authors were involved in the analysis and discussion of the published literature; preparation and critical review of the manuscript; and final approval of the submitted version.

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**How to cite this article:** Escuriola-Ettingshausen C, Auerswald G, Königs C, et al. Optimizing the management of patients with haemophilia A and inhibitors in the era of emicizumab: Recommendations from a German expert panel. *Haemophilia*. 2020;00:1–9. https://doi.org/10.1111/hae.14010