The prospective, open-label, single-group ANNEXA-4 study is currently evaluating the efficacy and safety of andexanet alfa in patients with factor Xa inhibitor-associated acute major bleeding. The first 67 patients enrolled in the study have been included in an interim report.[71] Andexanet alfa was administered as a bolus (15–30 min) followed by a 2-h infusion. A bolus dose of 400 mg and an infusion dose of 480 mg were used for patients on apixaban or known to have taken rivaroxaban more than 7 h before administration of andexanet alfa, whereas patients on enoxaparin or edoxaban and those who had taken rivaroxaban 7 h or less before administration of andexanet alfa or at an unknown time received a bolus dose of 800 mg and an infusion dose of 960 mg. The two co-primary efficacy outcomes were the percent change in anti-factor Xa activity and the rate of excellent or good haemostatic efficacy 12 h after the infusion. Median anti-factor Xa activity decreased by 89% (95% CI, 58–94) amongst rivaroxaban-treated patients and by 93% (95% CI, 87–94) amongst apixaban-treated patients. Clinical haemostasis 12 h after the infusion was rated as excellent or good in 79% (95% CI, 64–89) of the 47 patients included in the efficacy analysis. Thrombotic events occurred in 12 patients (18%) during the 30-day follow-up.

Ciraparantag

Ciraparantag (Perosphere Pharmaceuticals, Danbury, CT, USA) is a small, synthetic, water-soluble, cationic molecule which reverses unfractionated heparin, low-molecular-weight heparin and fondaparinux through non-covalent hydrogen binding and charge–charge interactions, and NOACs through non-covalent hydrogen binding.[72] In thromboelastographic studies and animal models, ciraparantag was shown to reverse the anticoagulant effect of all NOACs. In healthy volunteers, a single i.v. dose of ciraparantag within 3 h after administration of 60 mg of edoxaban decreased whole-blood clotting time to within 10% above the baseline value in 10 min or less.[72]

Management of bleeding in patients treated with NOACs

In the absence of high-quality evidence from randomized trials to guide clinical practice, current recommendations for the management of bleeding in patients treated with NOACs are based on expert opinion and limited clinical experience (Fig. 1). The European Heart Rhythm Association has published a practical guide on the use of NOACs in patients with NVAF, updated in 2015, which includes a section on bleeding management.[3] Practical guidance has also been provided by several expert groups.[27,54,73–76]

The management of bleeding in patients on NOAC therapy should be tailored according to the severity and location of the haemorrhage. Medical history taking is required to identify comorbidities and concomitant treatments associated with an increased bleeding risk and to assess which NOAC is taken, which dose regimen is used, and when the last dose was taken. A renal function test is important to evaluate when

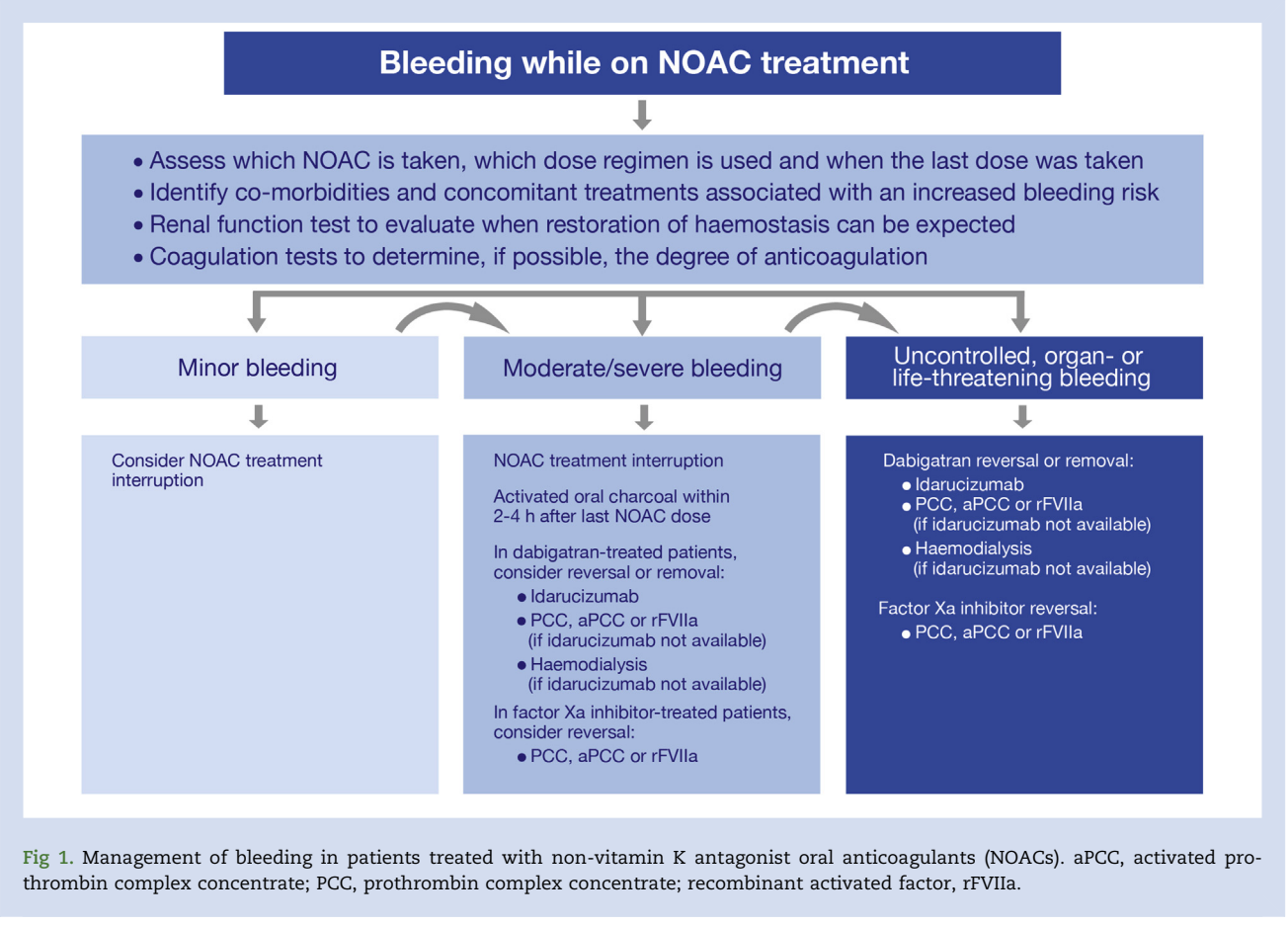

Fig 1. Management of bleeding in patients treated with non-vitamin K antagonist oral anticoagulants (NOACs). aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; recombinant activated factor, rFVIIa.

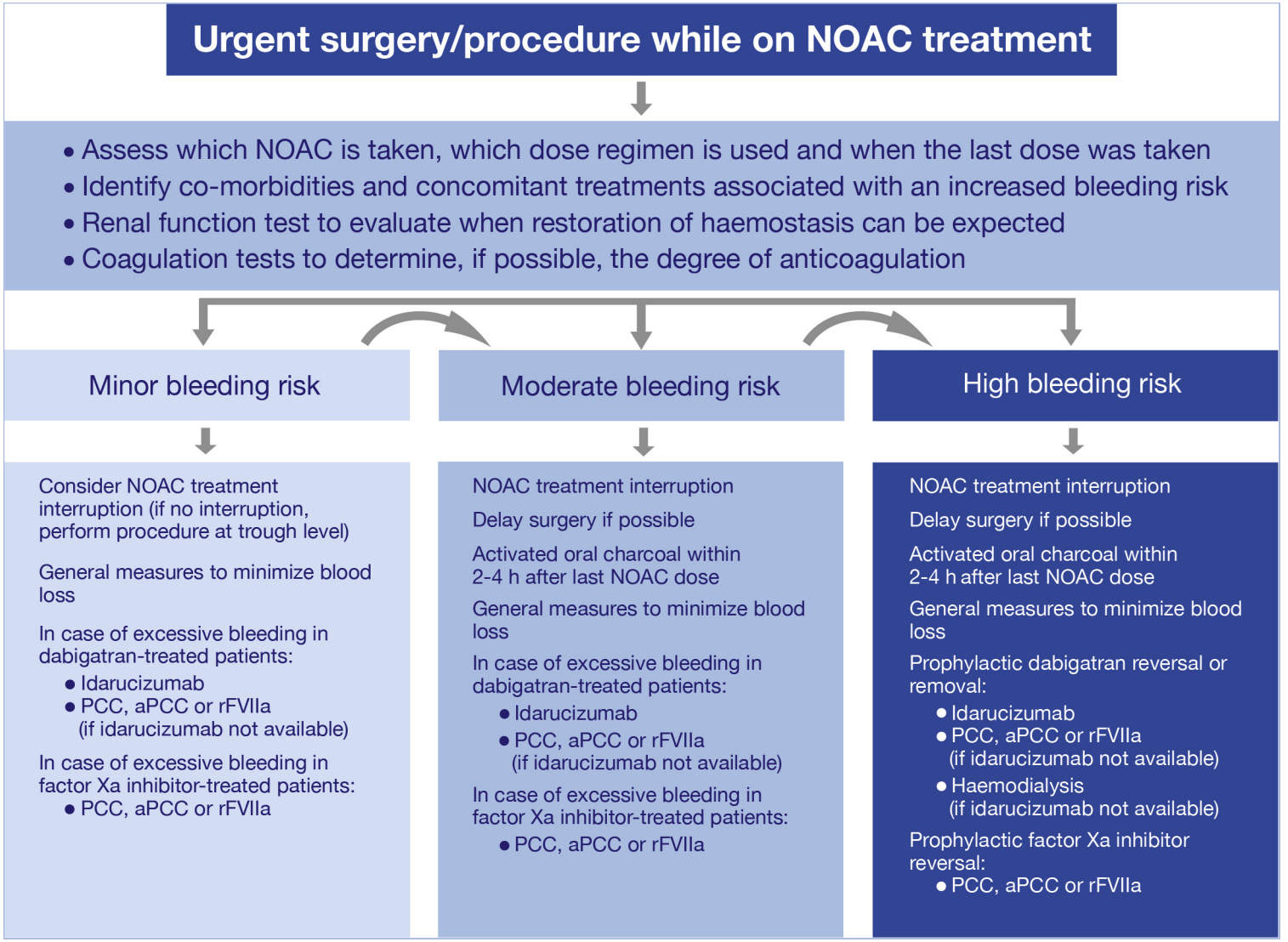

Fig 2. Management of non-vitamin K antagonist oral anticoagulant (NOAC)-treated patients who require an emergency surgical or invasive procedure. aPCC, activated prothrombin complex concentrate; PCC, prothrombin complex concentrate; recombinant activated factor, rFVIIa.