FVIIa or a combination of fibrinogen and FII, optionally further in combination with FX and FVIIa. The haemostatic agent(s) can be recombinant human factors, for example, rhFII, rhFX and rhVIIa, or rhFII alone. In some embodiments, an effective treatment of a haemostatic disorder can consist of administering FII or co-administering FII, FX and FVIIa, or co-administering fibrinogen with FII, and optionally further co-administering FX and FVIIa, where FII, FX and/or FVIIa can be recombinantly produced human factors.

[0035] The treatment or normalization or haemostasis can be performed without substantial supplementation of any other clotting factor. In some embodiments, a treatment of a haemostatic disorder may consist of FII or co-administration of fibrinogen and FII, where the FII can be recombinant human FII (rhFII).

[0036] The term "substantial supplementation" refers to the addition of other components, such as clotting factors in addition to those described in the present invention, in an amount whereby the effect of the one or more haemostatic agents when supplemented with such additional clotting factors is considerably different to that of the effect of administering the one or more haemostatic agents without supplementation.

[0037] As used herein, "recombinant" proteins include those proteins made by recombinant techniques. Such proteins include those which resemble the natural protein as well as those modified to enhance activity, protein half-life, protein stability, protein localization, and efficacy. *See*, U.S. Patent Application Publication No. US 2005/0164367~~, which is hereby incorporated by reference herein~~.

[0038] As used herein, "treatment" is a method for obtaining beneficial or desired clinical results. Beneficial or desired clinical results include, but are not limited to,

~~WHAT IS CLAIMED IS:~~

1. Use of a clotting factor treatment selected from the group consisting of (1) FII, (2) a combination of FII, FVIIa, and FX, (3) fibrinogen and a combination of FII, FVIIa, and FX, and (4) fibrinogen and FII in the manufacture of a medicament for normalizing impaired haemostasis in a mammal in need thereof.

2. Use of a clotting factor treatment selected from the group consisting of (1) FII, (2) a combination of FII, FVIIa, and FX, (3) fibrinogen and a combination of FII, FVIIa, and FX, and (4) fibrinogen and FII in the manufacture of a medicament for increasing maximum clot firmness (MCF) in a mammal having impaired haemostasis.

3. Use of a clotting factor treatment selected from the group consisting of (1) FII, (2) a combination of FII, FVIIa, and FX, (3) fibrinogen and a combination of FII, FVIIa, and FX, and (4) fibrinogen and FII in the manufacture of a medicament for reducing coagulation time (CT) in a mammal having impaired haemostasis.

4. Use of a clotting factor treatment selected from the group consisting of (1) FII, (2) a combination of FII, FVIIa, and FX, (3) fibrinogen and a combination of FII, FVIIa, and FX, and (4) fibrinogen and FII in the manufacture of a medicament for improving thrombin generation in a mammal having impaired haemostasis.

5. The use of any of claims 1-4, wherein said impaired haemostasis is associated with a bleeding disorder, hemorrhage, massive blood loss or a traumatic bleeding event.

6. The use of claim 5, wherein said massive blood loss is associated with coagulopathy.

7. The use of claim 5, wherein said bleeding disorder is haemophilia.

8. The use of claim 5, wherein said hemorrhage or traumatic bleeding event is associated with peri-surgical bleeding, post-surgical bleeding or postpartum hemorrhage.

9. The use of any of claims 1-8, wherein said FII is recombinant human FII (rhFII).

10. The use of any of claims 1-9, wherein said FVIIa is recombinant human FVIIa (rhVIIa).

11. The use of any of claims 1-10, wherein said FX is recombinant human FX (rhFX).

12. The use of any of claims 1-11, wherein the mammal in need of treatment has a blood fibrinogen concentration level of less than about 2 g/L, less than about 1 g/L, or less than about 0.5 g/L,

13. The use of any of claims 1-11, wherein the mammal in need of treatment has a blood fibrinogen concentration level of less than about 200 mg/dL, less than about 150 mg/dL, less than about 100 mg/dL, or less than about 50 mg/dL g/L.

14. The use of any one of claims 1-13, wherein said impaired haemostasis is associated with a blood loss of greater than about 30%, greater than about 40%, greater than about 50%, greater than about 60%, greater than about 70% , greater than about 80% or greater than about 85% of the estimated total blood volume of a mammal.

15. The use of claim 6, wherein said coagulopathy is dilutional coagulopathy that results from reestablishment of normovolemia or haemodynamic stabilization.

16. The use of any one of claims 1-15, wherein fibrinogen is to be administered in an amount sufficient to raise the blood fibrinogen concentration above about 0.5 g/L, above about 1 g/L, above about 1.5 g/L, or above about 2 mg/L.

~~17. The use of any one of claims 1-16, wherein fibrinogen is to be administered at~~ a dose of 12.5 to 200 mg/kg.

18. The use of any one of claims 1-17, wherein the FII is rhFII and is to be administered at a dose of 1 to 10 mg/kg..

19. The use of any one of claims 1-18, wherein the clotting factor treatment is to be administered at a dose that reduces clotting time by about 40 seconds to about 60 seconds

20. The use of any one of claims 1-19, wherein the clotting factor treatment is to be administered at a dose that increases maximum clot firmness to about 10 mm to about 30 mm.

21. The use of any one of claims 1-20, wherein administration of said clotting factor treatment results in the maintenance of normalized coagulation for at least two hours after administration.

22. The use of any of claims 1-21, wherein said clotting factor treatment is (1) FII, or (2) fibrinogen and FII; and wherein said clotting factor treatment is to be co-administered with FVIIa.

23. The use of any of claims 1-21, wherein said clotting factor treatment is (1) the combination of FII, FVIIa, and FX, or (2) the combination of FII, FVIIa, and FX with fibrinogen; and wherein FII and FVIIa are to be administered in a ratio of at least 1:90.

24. The use of any one of claims 1-21, wherein said clotting factor treatment is (1) FII, or (2) fibrinogen and FII; and wherein administration of said clotting factor treatment is performed without co-administration of any other coagulation factors from among the coagulation factors FV-FXIII.

WHAT IS CLAIMED IS:

1. Use of a composition selected from the group consisting of (1) FII and (2) a combination of fibrinogen and FII in the manufacture of a medicament for normalizing impaired haemostasis in a mammal in need thereof.

2. Use of a composition selected from the group consisting of (1) FII and (2) a combination of fibrinogen and FII in the manufacture of a medicament for increasing maximum clot firmness (MCF) in a mammal having impaired haemostasis.

3. Use of a composition selected from the group consisting of (1) FII, and (2) a combination of fibrinogen and FII in the manufacture of a medicament for reducing coagulation time (CT) in a mammal having impaired haemostasis.

4. Use of a composition selected from the group consisting of (1) FII and (2) a combination of fibrinogen and FII in the manufacture of a medicament for improving thrombin generation in a mammal having impaired haemostasis.

5. The use of any of claims 1-4, wherein said impaired haemostasis is associated with a bleeding disorder, hemorrhage, massive blood loss or a traumatic bleeding event.

6. The use of claim 5, wherein said massive blood loss is associated with coagulopathy.

7. The use of claim 5, wherein said bleeding disorder is haemophilia.

8. The use of claim 5, wherein said hemorrhage or traumatic bleeding event is associated with peri-surgical bleeding, post-surgical bleeding or postpartum hemorrhage.

9. The use of any of claims 1-8, wherein said FII is recombinant human FII (rhFII).

10. The use of any of claims 1-9, wherein the mammal in need of treatment has a blood fibrinogen concentration level of less than 2 g/L, less than 1 g/L, or less than 0.5 g/L.

11. The use of any of claims 1-9, wherein the mammal in need of treatment has a blood fibrinogen concentration level of less than 200 mg/dL, less than 150 mg/dL, less than 100 mg/dL, or less than 50 mg/dL.

12. The use of any one of claims 1-11, wherein said impaired haemostasis is associated with a blood loss of greater than 30%, greater than 40%, greater than 50%, greater than 60%, greater than 70% , greater than 80% or greater than 85% of the estimated total blood volume of a mammal.

13. The use of claim 6, wherein said coagulopathy is dilutional coagulopathy that results from reestablishment of normovolemia or haemodynamic stabilization.

14. The use of any one of claims 1-13, wherein fibrinogen is to be administered in an amount sufficient to raise the blood fibrinogen concentration above 0.5 g/L, above 1 g/L, above 1.5 g/L, or 2 mg/L.

15. The use of any one of claims 1-14, wherein fibrinogen is to be administered at a dose of 12.5 to 200 mg/kg.

16. The use of any one of claims 1-15, wherein the FII is rhFII and is to be administered at a dose of 1 to 10 mg/kg.

17. The use of any one of claims 1-16, wherein the composition is to be administered at a dose that reduces clotting time by 40 seconds to 60 seconds

18. The use of any one of claims 1-17, wherein the composition is to be administered at a dose that increases maximum clot firmness to 10 mm to 30 mm.

19. The use of any one of claims 1-18, wherein administration of said composition results in the maintenance of normalized coagulation for at least two hours after administration.

ABSTRACT

The present invention relates to normalizing impaired haemostasis comprising administering a clotting factor treatment selected from the group consisting of (1) FII; (2) PCC; and (3) a three factor combination of FII, FX, and FVIIa. The clotting factor treatment can be administered in combination with fibrinogen. The clotting factor(s) can be recombinant human clotting factor(s).