[0006] Antibodies that bind Factor XI and/or Factor XIa have been studied. For example, WO 2016/207858 describes one such anti-Factor XI and/or Factor XIa antibody, disclosed in Table 1 of the present application as Antibody 1. The present disclosure adds to these developments and provides further clinical methods, including dosage regimens, to treat patients with specific thromboembolic disorders with desired safety and efficacy. Furthermore, the present disclosure adds to the earlier developments in the field by providing formulations comprising such FXI and/or FXIa antibodies that are sufficiently stable and suitable for administration to patients.

SUMMARY OF THE DISCLOSURE

[0007] The present disclosure relates to methods for detection and measurement of anti-Factor XI and/or activated Factor XI (Factor XIa) antibodies, or antigen-binding fragments thereof.

[0008] Accordingly, in one aspect, provided herein is a method of detecting an anti-drug antibody (ADA) against an anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof, wherein the method comprises: (a) incubating a sample with an acid to dissociate anti-Factor XI and/or anti-Factor XIa antibody – antigen complexes and/or dissociate anti-Factor XI and/or anti-Factor XIa antibody – ADA complexes present in the sample to create an acid digest, (b) incubating the acid digest on a plate coated with the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof, (c) neutralizing the acid digest, and (d) detecting the presence of the ADA using a ruthenylated detector cocktail.

[0009] In some ~~embodiment~~examples, the sample is a sample from a subject. In some ~~embodiment~~examples, the sample is selected from the group consisting of blood, plasma, or serum from a subject. In some ~~embodiment~~examples, the method comprises an initial step of preparing the sample.

[0010] In some ~~embodiment~~examples, the acid is selected from the group consisting of acetic acid, citric acid, phosphoric acid, and mixtures thereof. In some ~~embodiment~~examples, the acid is acetic acid. In some ~~embodiment~~examples, the acetic acid is at a concentration of about 300 mM.

[0011] In some ~~embodiment~~examples, the antigen is Factor XI and/or Factor XIa. In some ~~embodiment~~examples, the plate is coated with streptavidin. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration selected from the group consisting of about 0.1 µg/ml, about 0.25 µg/ml, about

0.5 µg/ml, about 0.75 µg/ml, and about 1 µg/ml. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration of about 0.25 µg/ml.

[0012] In some ~~embodiment~~examples, the neutralizing allows for the ADA to bind the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the coated plate. In some ~~embodiment~~examples, the neutralizing uses a base at a pH of about 8.0. In some ~~embodiment~~examples, the neutralizing uses a base selected from the group consisting of Tris, Phosphate, HEPES, triethanolamine, and mixtures thereof. In some ~~embodiment~~examples, the base is Tris.

[0013] In some ~~embodiment~~examples, the ruthenylated detector cocktail comprises an antibody. In some ~~embodiment~~examples, the antibody is selected from the group consisting of an anti-human IgG, an anti-human IgM, an anti-human IgE, an anti-rabbit Ig, and any combination thereof. In some ~~embodiment~~examples, the detecting specifically detects the ADA and not Factor XI and/or Factor XIa.

[0014] In some ~~embodiment~~examples, the method further comprises a washing after the incubating.

[0015] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof is at a concentration of about 0.25 µg/mL.

[0016] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) comprising complementary determining regions HCDR1, HCDR2, and HCDR3 in SEQ ID NO: 9 or 29; and a light chain variable region (VL) comprising complementary determining regions LCDR1, LCDR2, LCDR3 in SEQ ID NO: 19 or 39.

[0017] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises: i. a heavy chain variable region CDR1 of SEQ ID NO: 23; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 25; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 34; and a light chain variable region CDR3 of SEQ ID NO: 35; ii. a heavy chain variable region CDR1 of SEQ ID NO: 26; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 28; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38; iii. a

heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 15; or iv. a heavy chain variable region CDR1 of SEQ ID NO: 46; a heavy chain variable region CDR2 of SEQ ID NO: 4; a heavy chain variable region CDR3 of SEQ ID NO: 5; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 14; and a light chain variable region CDR3 of SEQ ID NO: 15.

[0018] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9, 29, and a VH with 90% identity thereto; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19, 39, and a VL with 90% identity thereto. In certain ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9 and 29; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19 and 39.

[0019] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31, 11, and a heavy chain with 90% identity thereto; and a light chain comprising an amino acid sequence of SEQ ID NO: 41, 21, and a light chain with 90% identity thereto. In certain ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 and a light chain comprising an amino acid sequence of SEQ ID NO: 41.

[0020] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody is a human monoclonal antibody. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody is a human IgG1 isotype. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody comprises D265A and P329A substitutions in the Fc domain.

[0021] In another ~~aspect~~example, provided herein is a method of detecting an anti-drug antibody (ADA) against an anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof, wherein the antibody or antigen-binding fragment thereof comprises: i. a heavy chain variable region CDR1 of SEQ ID NO: 23; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 25; a light chain variable region

CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 34; and a light chain variable region CDR3 of SEQ ID NO: 35; ii. a heavy chain variable region CDR1 of SEQ ID NO: 26; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 28; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38; iii. a heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 15; or iv. a heavy chain variable region CDR1 of SEQ ID NO: 46; a heavy chain variable region CDR2 of SEQ ID NO: 4; a heavy chain variable region CDR3 of SEQ ID NO: 5; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 14; and a light chain variable region CDR3 of SEQ ID NO: 15 and wherein the method comprises: (a) incubating a sample with an acid to dissociate anti-Factor XI and/or anti-Factor XIa antibody – antigen complexes and/or dissociate anti-Factor XI and/or anti-Factor XIa antibody – ADA complexes present in the sample to create an acid digest, (b) incubating the acid digest on a plate coated with the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof, (c) neutralizing the acid digest, and (d) detecting the presence of the ADA using a ruthenylated detector cocktail.

[0022] In some ~~embodiment~~examples, the sample is a sample from a subject. In some ~~embodiment~~examples, the sample is selected from the group consisting of blood, plasma, or serum from a subject. In some ~~embodiment~~examples, the method comprises an initial step of preparing the sample.

[0023] In some ~~embodiment~~examples, the acid is selected from the group consisting of acetic acid, citric acid, phosphoric acid, and mixtures thereof. In some ~~embodiment~~examples, the acid is acetic acid. In some ~~embodiment~~examples, the acetic acid is at a concentration of about 300 mM.

[0024] In some ~~embodiment~~examples, the antigen is Factor XI and/or Factor XIa. In some ~~embodiment~~examples, the plate is coated with streptavidin. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration selected from the group consisting of about 0.1 µg/ml, about 0.25 µg/ml, about 0.5 µg/ml, about 0.75 µg/ml, and about 1 µg/ml. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration of about 0.25 µg/ml.

[0025] In some ~~embodiment~~examples, the neutralizing allows for the ADA to bind the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the coated plate. In some ~~embodiment~~examples, the neutralizing uses a base at a pH of about 8.0. In some ~~embodiment~~examples, the neutralizing uses a base selected from the group consisting of Tris, Phosphate, HEPES, triethanolamine, and mixtures thereof. In some ~~embodiment~~examples, the base is Tris.

[0026] In some ~~embodiment~~examples, the ruthenylated detector cocktail comprises an antibody. In some ~~embodiment~~examples, the antibody is selected from the group consisting of an anti-human IgG, an anti-human IgM, an anti-human IgE, an anti-rabbit Ig, and any combination thereof. In some ~~embodiment~~examples, the detecting specifically detects the ADA and not Factor XI and/or Factor XIa.

[0027] In some ~~embodiment~~examples, the method further comprises a washing after the incubating.

[0028] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof is at a concentration of about 0.25 µg/mL.

[0029] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9, 29, and a VH with 90% identity thereto; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19, 39, and a VL with 90% identity thereto. In certain ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9 and 29; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19 and 39.

[0030] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31, 11, and a heavy chain with 90% identity thereto; and a light chain comprising an amino acid sequence of SEQ ID NO: 41, 21, and a light chain with 90% identity thereto. In certain ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 and a light chain comprising an amino acid sequence of SEQ ID NO: 41.

[0031] In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody is a human monoclonal antibody. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor

XIa antibody is a human IgG1 isotype. In some ~~embodiment~~examples, the anti-Factor XI and/or anti-Factor XIa antibody comprises D265A and P329A substitutions in the Fc domain.

[0032] Other ~~embodiment~~examples and details of the disclosure are presented herein below.

BRIEF DESCRIPTION OF THE DRAWINGS

[0033] **FIG. 1** is a schematic depiction of the initial bridging assay for detection of anti-drug antibodies (ADA) in cynomolgus samples.

[0034] **FIG. 2** is a schematic depiction of the modified bridging assay with a Factor XI/Factor XIa depletion step for detection of ADA in cynomolgus samples.

[0035] **FIG. 3** is a schematic depiction of the modified bridging assay with a Ruthenylated anti-monkey Ig for detection of ADA in cynomolgus samples.

[0036] **FIG. 4** is a schematic depiction of the ADA assay for cynomolgus samples.

[0037] **FIG. 5** is a schematic depiction of the ADA assay for human samples.

DETAILED DESCRIPTION

Definitions

[0038] To facilitate an understanding of the present invention, a number of terms and phrases are defined below.

[0039] The terms “a” and “an” as used herein mean “one or more” and include the plural unless the context is inappropriate.

[0040] As used herein, the terms “FXI protein,” “FXI antigen,” and “FXI” are used interchangeably, and refers to the Factor XI protein in different species. Factor XI is the mammalian plasma coagulation factor XI, a glycoprotein present in human plasma at a concentration of 25-30 nM as a zymogen that when converted by limited proteolysis to an active serine protease, participates in the intrinsic pathway of blood coagulation.

[0041] The terms “FXIa protein,” “FXIa antigen,” and “FXIa”, are used interchangeably, and refers to the activated FXI protein in different species. The zymogen Factor XI is converted into its active form, the coagulation factor XIa (FXIa), either via the contact phase of blood coagulation or through thrombin-mediated activation on the platelet surface. During this activation of factor XI, an internal peptide bond is cleaved in each of the two chains, resulting in the activated factor XIa, a serine protease composed of two heavy and two light

CLAIMS

What is claimed is:

1. A method of detecting an anti-drug antibody (ADA) against an anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof, wherein the method comprises:

a. ~~Incubating~~ incubating a sample with an acid to dissociate anti-Factor XI and/or anti-Factor XIa antibody – antigen complexes and/or dissociate anti-Factor XI and/or anti-Factor XIa antibody – ADA complexes present in the sample to create an acid digest,

b. ~~Incubating~~ incubating the acid digest on a plate coated with the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof,

c. ~~Neutralizing~~ neutralizing the acid digest, and

d. ~~Detecting~~ detecting the presence of the ADA using a ruthenylated detector cocktail.

~~2. The method of claim 1, wherein the sample is a sample from a subject.~~

~~3.~~2. The method of claim 1 ~~or 2~~, wherein the sample is selected from the group consisting of human blood, plasma, or serum ~~from a subject~~.

~~4.~~3. The method of claim 1, wherein the method further comprises

a. an initial step of preparing the sample; and/or

b. a washing step after the incubating.

~~5.~~4. The method of any one of claims 1-~~4~~3, wherein:

a. the acid is selected from the group consisting of acetic acid, citric acid, phosphoric acid, and mixtures thereof;~~.~~

~~6. The method of claim 5, wherein the acid is acetic acid.~~

~~7. The method of claim 6, wherein the acetic acid is at a concentration of about 300 mM.~~

~~8. The method of any one of claims 1-7, wherein the antigen is Factor XI and/or Factor XIa.~~

~~9. The method of any one of claims 1-8, wherein the plate is coated with streptavidin.~~

~~10. The method of any one of claims 1-9, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration selected~~

~~from the group consisting of about 0.1 µg/ml, about 0.25 µg/ml, about 0.5 µg/ml, about 0.75 µg/ml, and about 1 µg/ml.~~

~~11. The method of claim 10, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration of about 0.25 µg/ml.~~

~~12. The method of any one of claims 1-11, wherein the neutralizing allows for the ADA to bind the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the coated plate.~~

~~13. The method of any one of claims 1-12, wherein the neutralizing uses a base at a pH of about 8.0.~~

~~14. The method of any one of claims 1-13, wherein~~

b. the neutralizing uses a base selected from the group consisting of Tris, Phosphate, HEPES, triethanolamine, and mixtures thereof, optionally at a pH of about 8.0; and/or;~~.~~

c. the ruthenylated detector cocktail comprises an antibody.

~~15.~~5. The method of claim ~~14~~4, wherein:

a. the acid is acetic acid, optionally at a concentration of about 300 mM; and/or

b. the base is Tris.

~~16. The method of any one of claims 1-14, wherein the ruthenylated detector cocktail comprises an antibody.~~

6. The method of any one of claims 1-3, wherein the plate is coated with streptavidin.

7. The method of any one of claims 1-3, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof is coated on the plate in a buffer at a concentration selected from the group consisting of about 0.1 µg/mL, about 0.25 µg/mL, about 0.5 µg/mL, about 0.75 µg/mL, and about 1 µg/mL, preferably about 0.25 µg/mL.

~~17.~~8. The method of claim ~~16~~5, wherein the antibody is selected from the group consisting of an anti-human IgG, an anti-human IgM, an anti-human IgE, an anti-rabbit Ig, and any combination thereof.

~~18. The method any one of claims 1-17, wherein the detecting specifically detects the ADA and not Factor XI and/or Factor XIa.~~

~~19. The method of any one of claims 1-18, further comprising a washing after the incubating.~~

~~20. The method of any one of claims 1-19, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof is at a concentration of about 0.25 µg/mL.~~

~~21. The method of any one of claims 1-20, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) comprising complementary determining regions HCDR1, HCDR2, and HCDR3 in SEQ ID NO: 9 or 29; and a light chain variable region (VL) comprising complementary determining regions LCDR1, LCDR2, LCDR3 in SEQ ID NO: 19 or 39.~~

~~22.~~9. The method of any one of claims 1-~~21~~3, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises:

i. a heavy chain variable region CDR1 of SEQ ID NO: 23; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 25; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 34; and a light chain variable region CDR3 of SEQ ID NO: 35;

ii. a heavy chain variable region CDR1 of SEQ ID NO: 26; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 28; a light chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38;

iii. a heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 15; or

iv. a heavy chain variable region CDR1 of SEQ ID NO: 46; a heavy chain variable region CDR2 of SEQ ID NO: 4; a heavy chain variable region CDR3 of SEQ ID NO: 5; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 14; and a light chain variable region CDR3 of SEQ ID NO: 15.

~~23.~~10. The method of any one of claims 1-~~22~~3, wherein the anti-Factor XI and/or anti-Factor Xia antibody or antigen-binding fragment thereof comprises:

a. a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9, 29, and a VH with 90% identity thereto; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19, 39, and a VL with 90% identity thereto; or~~.~~

~~24. The method of any one of claims 1-23, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises~~

b. a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9 and 29; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19 and 39.

~~25.~~11. The method of any one of claims 1-~~24~~3, wherein the anti-Factor XI and/or anti-Factor XIa antibody comprises:

a. a heavy chain comprising an amino acid sequence of SEQ ID NO: 31, 11, and a heavy chain with 90% identity thereto; and a light chain comprising an amino acid sequence of SEQ ID NOs: 41, 21, ~~and~~ or a light chain with 90% identity thereto; or~~.~~

~~26. The method of any one of claims 1-25, wherein the anti-Factor XI and/or anti-Factor XIa antibody comprises~~

b. a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 and a light chain comprising an amino acid sequence of SEQ ID NO: 41.

~~27.~~12. The method of any one of claims 1-~~26~~3, wherein the anti-Factor XI and/or anti-Factor XIa antibody is a human monoclonal antibody.

~~28.~~13. The method of claim ~~27~~12, wherein the anti-Factor XI and/or anti-Factor Xia antibody is a human IgG1 isotype~~.~~.

~~29. The method of claim 27 or 28, wherein the anti-Factor XI and/or anti-Factor XIa antibody~~ optionally comprises an antibody Fc domain comprising D265A and P329A substitutions ~~in the Fc domain~~.

~~30. A method of detecting an anti-drug antibody (ADA) against an anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof,~~

~~wherein the antibody or antigen-binding fragment thereof comprises:~~

~~i. a heavy chain variable region CDR1 of SEQ ID NO: 23; a heavy chain variable region CDR2 of SEQ ID NO: 24; a heavy chain variable region CDR3 of SEQ ID NO: 25; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 34; and a light chain variable region CDR3 of SEQ ID NO: 35;~~

~~ii. a heavy chain variable region CDR1 of SEQ ID NO: 26; a heavy chain variable region CDR2 of SEQ ID NO: 27; a heavy chain variable region CDR3 of SEQ ID NO: 28; a light~~

~~chain variable region CDR1 of SEQ ID NO: 36; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 38;~~

~~iii. a heavy chain variable region CDR1 of SEQ ID NO: 43; a heavy chain variable region CDR2 of SEQ ID NO: 44; a heavy chain variable region CDR3 of SEQ ID NO: 45; a light chain variable region CDR1 of SEQ ID NO: 47; a light chain variable region CDR2 of SEQ ID NO: 37; and a light chain variable region CDR3 of SEQ ID NO: 15; or~~

~~iv. a heavy chain variable region CDR1 of SEQ ID NO: 46; a heavy chain variable region CDR2 of SEQ ID NO: 4; a heavy chain variable region CDR3 of SEQ ID NO: 5; a light chain variable region CDR1 of SEQ ID NO: 33; a light chain variable region CDR2 of SEQ ID NO: 14; and a light chain variable region CDR3 of SEQ ID NO: 15~~

~~and wherein the method comprises:~~

~~a. Incubating a sample with an acid to dissociate anti-Factor XI and/or anti-Factor XIa antibody – antigen complexes and/or dissociate anti-Factor XI and/or anti-Factor XIa antibody – ADA complexes present in the sample to create an acid digest,~~

~~b. Incubating the acid digest on a plate coated with the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof,~~

~~c. Neutralizing the acid digest, and~~

~~d. Detecting the presence of the ADA using a ruthenylated detector cocktail.~~

~~31. The method of claim 30, wherein the sample is a sample from a subject.~~

~~32. The method of claim 30 or 31, wherein the sample is selected from the group consisting of blood, plasma, or serum from a subject.~~

~~33. The method of claim 30, wherein the method comprises an initial step of preparing the sample.~~

~~34. The method of any one of claims 30-33, wherein the acid is selected from the group consisting of acetic acid, citric acid, phosphoric acid, and mixtures thereof.~~

~~35. The method of claim 34, wherein the acid is acetic acid.~~

~~36. The method of claim 35, wherein the acetic acid is at a concentration of about 300 mM.~~

37. The method of any one of claims 30-36, wherein the antigen is Factor XI and/or Factor XIa.

38. The method of any one of claims 30-37, wherein the plate is coated with streptavidin.

39. The method of any one of claims 30-38, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration selected from the group consisting of about 0.1 µg/ml, about 0.25 µg/ml, about 0.5 µg/ml, about 0.75 µg/ml, and about 1 µg/ml.

40. The method of claim 39, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the plate is at a concentration of about 0.25 µg/ml.

41. The method of any one of claims 30-40, wherein the neutralizing allows for the ADA to bind the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof on the coated plate.

42. The method of any one of claims 30-41, wherein the neutralizing uses a base at a pH of about 8.0.

43. The method of any one of claims 30-42, wherein the neutralizing uses a base selected from the group consisting of Tris, Phosphate, HEPES, triethanolamine, and mixtures thereof.

44. The method of claim 43, wherein the base is Tris.

45. The method of any one of claims 30-44, wherein the ruthenylated detector cocktail comprises an antibody.

46. The method of claim 45, wherein the antibody is selected from the group consisting of an anti-human IgG, an anti-human IgM, an anti-human IgE, an anti-rabbit Ig, and any combination thereof.

47. The method any one of claims 30-46, wherein the detecting specifically detects the ADA and not Factor XI and/or Factor XIa.

48. The method of any one of claims 30-47, further comprising a washing after the incubating.

49. The method of any one of claims 30-48, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof is at a concentration of about 0.25 µg/mL.

50. The method of any one of claims 30-49, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region

(VH) selected from the group consisting of SEQ ID NO: 9, 29, and a VH with 90% identity thereto; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19, 39, and a VL with 90% identity thereto.

51. The method of any one of claims 30-50, wherein the anti-Factor XI and/or anti-Factor XIa antibody or antigen-binding fragment thereof comprises a heavy chain variable region (VH) selected from the group consisting of SEQ ID NO: 9 and 29; and a light chain variable region (VL) selected from the group consisting of SEQ ID NO: 19 and 39.

52. The method of any one of claims 30-51, wherein the anti-Factor XI and/or anti-Factor XIa antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31, 11, and a heavy chain with 90% identity thereto; and a light chain comprising an amino acid sequence of SEQ ID NO: 41, 21, and a light chain with 90% identity thereto.

53. The method of any one of claims 30-52, wherein the anti-Factor XI and/or anti-Factor XIa antibody comprises a heavy chain comprising an amino acid sequence of SEQ ID NO: 31 and a light chain comprising an amino acid sequence of SEQ ID NO: 41.

54. The method of any one of claims 30-53, wherein the anti-Factor XI and/or anti-Factor XIa antibody is a human monoclonal antibody.

55. The method of claim 54, wherein the anti-Factor XI and/or anti-Factor XIa antibody is a human IgG1 isotype.

56. The method of claim 54 or 55, wherein the anti-Factor XI and/or anti-Factor XIa antibody comprises D265A and P329A substitutions in the Fc domain.